Improving Quality of Care in Inflammatory Bowel Disease: Treatment Targets and Body Composition

By

Robert Venning Bryant

MBBS FRACP MScR (Oxon)

A1068490

A thesis submitted for the degree of

Doctor of Philosophy

University of Adelaide

THE UNIVERSITY of ADELAIDE

School of Medicine

Faculty of Health Sciences

June 2018

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

Figures

Tables

PUBLICATION CITATIONS

Articles published

1. Robert V Bryant[1], Daniel C Burger, Joseph Delo, Alissa J Walsh, Sally Thomas, Axel von Herbay, Otto C Buchel, Lydia White, Oliver Brain, Satish Keshav, Bryan F Warren, Simon PL Travis. **Beyond endoscopic mucosal healing in ulcerative colitis: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up.** Gut 2016; 65: 408-414.
2. Robert V Bryant, Samuel P Costello, Scott Schoeman, Dharshan Sathananthan, Emma Knight, Su-Yin Lau, Mark N Schoeman, Reme Mountifield, Derrick Tee, Simon PL Travis, Jane M Andrews. **Limited uptake of ulcerative colitis 'treat to target' recommendations in real-world practice.** Journal of Gastroenterology and Hepatology 2018; 33: 599-607.
3. Bryant RV, Ooi S, Schultz, CG, Goess C, Grafton R, Hughes, J, Lim A, Bartholomeusz FD, Andrews JM. **Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease.** Alimentary Pharmacology and Therapeutics 2015; 41: 895-906.
4. Robert V. Bryant*, Alissa J. Walsh* and Simon P. L. Travis. **Current best practice for disease activity assessment in IBD.** Nature Reviews Gastroenterology and Hepatology 2016; 42 (12): 567-79. *Joint first authors.

Articles in submission or under revision

1. Bryant RV, Schultz CG, Ooi S, Goess C, Costello SP, Vincent AD, Schoeman S, Lim A, Bartholomeusz FD, Travis SPL, Andrews JM. **Obesity in inflammatory bowel disease: gains in adiposity despite high prevalence of myopenia and osteopenia.** Submitted to American Journal of Clinical Nutrition June 2018.
2. Bryant RV, Schultz CG, Ooi S, Goess C, Costello SP, Vincent AD, Schoeman S, Lim A, Bartholomeusz FD, Travis SPL, Andrews JM. **Visceral adipose tissue is associated with stricturing Crohn's disease behaviour, faecal calprotectin and quality of life.** Under revision, Inflammatory Bowel Diseases June 2018.

ABBREVIATIONS

ASMI	Appendicular skeletal muscle index
BIA	Bioelectrical impedance analysis
BMD	Bone mineral density
BMI	Body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
DXA	Dual energy x-ray absorptiometry
EIM	Extra-intestinal manifestations
ELISA	Enzyme-linked immunosorbent assay
FC	Faecal calprotectin
FDA	Food and Drug Administration
FFM	Fat-free mass
FM	Fat mass
FMI	Fat mass index
GWAS	Genome wide association studies
HR	Hazard ratio
IBD	Inflammatory bowel diseases

IHD	Ischaemic heart disease
IBS	Irritable bowel syndrome
LM	Lean mass
LMI	Lean mass index
MRI	Magnetic resonance imaging
PROM	Patient reported outcome measure
PSC	Primary sclerosing cholangitis
QoL	Quality of life
QI	Quality indicators
SAT	Subcutaneous adipose tissue
STRIDE	Selecting Therapeutic Targets in IBD
T2T	Treat to Target
TNF	Tumour necrosis factor
UC	Ulcerative colitis
VAT	Visceral adipose tissue
VHI	Visceral adipose tissue: height index
VTE	Venous thromboembolic disease
WHO	World Health Organisation
WHR	Waist:Hip ratio

ABSTRACT

Introduction

Quality care for people with inflammatory bowel disease (IBD) aims to modify the course of disease and normalise quality of life (QoL). Treatment directed at objective inflammation has been shown to improve outcomes in IBD, yet represents a paradigm shift for clinicians trained to manage symptoms alone. Beyond conventional treatment targets, abnormal body composition is often overlooked in clinical practice, yet is likely to influence morbidity in IBD. Although seemingly unrelated aspects of management, both treatment targets and evaluation of body composition are important for the delivery of quality IBD care.

Aims

The aims of this thesis were to:

1. Explore treatment targets in IBD
2. Determine the prevalence and impact of abnormal body composition in IBD.

Methods

A systematic review of disease activity assessment indices in IBD was performed. Following this, a prospective observational study was undertaken to explore the concordance between and prognostic benefits of measures of remission in IBD, so as to help define the 'optimal' treatment target. Thereafter, a cross-sectional study assessed attainment of IBD treatment targets in routine clinical practice, alongside clinician perceptions and potential barriers. Prospective evaluation of body composition in patients with IBD was undertaken, so as to describe rates of abnormal body composition, evolution of body composition over time, influencing factors, and the impact of body composition on outcomes in IBD.

Results

Multiple indices of disease activity assessment in IBD were identified, most of which were confounded by complexity and lack of validation. Measures of disease activity in IBD were observed to be distinct and discordant, with the greatest disparity between symptoms and objective assessments of mucosal inflammation. Histological remission was found to impart prognostic benefit beyond endoscopic remission in ulcerative colitis (UC), predicting lower rates of steroid usage and hospitalisation over 6 years of follow-up. In routine IBD practice,

attainment of treatment targets was identified to be modest and limited by clinician-dependent practice behaviours, with only one-third of patients attaining combined clinical and endoscopic remission.

There was a high prevalence of abnormal body composition in patients with IBD. Rising rates of obesity were exposed, with gains in BMI related to increases in adiposity, whilst lean mass declined over time. Accordingly, myopenia and sarcopenia were prevalent (21% and 12% respectively). Visceral adipose tissue, rather than overall adiposity, was associated with stricturing Crohn's disease behaviour, as well as disease activity and QoL in a disease distribution-dependent manner. Metabolic bone disease was prevalent in patients with IBD (37%), despite protocolised management of bone health.

Conclusions

Incorporation of objective treatment targets into routine practice stands to benefit patients with IBD, but further work is required to simplify disease activity indices, define optimal treatment targets, and assess feasibility in practice. Beyond conventional treatment targets, body composition is frequently abnormal in patients with IBD yet may go unrecognised and is important because it is associated with morbidity. Treatment targets and body composition are disparate but important aspects of the same challenge: to improve the quality of care in IBD.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Dr Robert Venning Bryant

ACKNOWLEDGEMENTS

I would first like to thank Professor Jane Andrews for her guidance and mentorship, not only throughout my PhD, but during my entire training in Gastroenterology. I am eternally grateful to Jane for all of her time, energy, and effort invested in me, as well as for the numerous career-shaping opportunities she has afforded me. I am inspired by her forthright approach, dedication to patients, and zest for life. I look forward to many future years of working together.

I would like to sincerely thank Professor Simon Travis for his steadfast support, counsel, and leadership since my Fellowship in Oxford. Simon has had such an enormous and valuable influence on both my career and life outlook during the past 5 formative years. So much so, that this is the second post-graduate degree that he has supervised! I cherish our ongoing friendship, even from afar, and hope that this will continue for many years to come.

I would like to thank the dedicated and talented group of collaborators, both from Oxford and Adelaide, with whom I have been lucky to work during this degree. To my collaborators at the John Radcliffe Hospital in Oxford, in particular Australian ex-pats Daniel Burger and Alissa Walsh, I am grateful to have worked with you and have benefited from your experience and input. To the wonderful IBD team at the Royal Adelaide Hospital, in particular Charlotte Goess, Rachel Grafton, and Julie Hughes, thank you for all of your hard work, support and friendship over the course of this degree. I know it is not easy facing a 'hurricane' in the workplace, and I am ever grateful for your patience and calmness throughout. To the Nuclear Medicine group at the Royal Adelaide Hospital, in particular Chris Schultz and Dylan Bartholomeusz, thank you for your support of the body composition project. I am grateful for the countless hours that you have spent performing the scans, analysing the data, and for your ongoing enthusiasm to undertake body composition studies. I would like to individually thank Sam Costello, my 'other life-partner', who has given so much of his time to listen, encourage, and steer me over recent years.

I would like to thank the Royal Adelaide Hospital Research Foundation for their generous support through the AR Clarkson Scholarship, without which I would not have had the means to pursue this degree.

I would like to thank all of the patients with IBD who took part in our studies. Without their selfless participation in research, none of this would have been possible.

I would like to thank the Bryant family, in particular my mum Caroline, for all of the unwavering love, support, (and babysitting) over this degree. Mum's endless interest in my research, even the seemingly mundane, is a great source of motivation and I am ever grateful for her insights and enthusiasm.

Lastly, I would like to thank my amazing wife Maddie. So much has happened over the span of this degree; a move between countries, home renovations, periods of ill-health, and the birth of our beautiful daughter Florence. Throughout all of this, your patient love and steadfastness has kept us afloat. Thank you for bearing with me, pacifying my rants and frustrations, and for tolerating a second thesis write-up

The thesis was edited by Elite Editing and editing intervention was restricted to Standards D and E of the *Australian Standards for Editing Practice*.

CHAPTER 1: OVERVIEW

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is a lifelong inflammatory disease affecting the gut.[1] The aetiology of IBD remains unclear, although likely results from a complex interplay between predisposing genetics, intestinal microbiota, immune dysregulation, and environmental factors.[2, 3] The global prevalence of IBD has risen sharply over the last three decades and despite the advent of more effective medical therapies, there remains no cure for IBD.[4, 5]

Therapeutic advances in the medical management of IBD have evolved treatment targets. The goal of therapy for IBD is now to modify the course of disease, so as to improve quality of life and avoid disability, whilst balancing the risks associated with therapy.[1] A 'treat to target' approach in IBD advocates striving for not only resolution of symptoms, but also objective resolution of inflammation.[6] Consensus guidelines define the target of therapy in IBD as both clinical and endoscopic remission.[6] Endoscopic remission has been associated with improved outcomes in IBD, including reduced rates of hospitalisation, corticosteroid use, and surgery.[7-13] However, due to the heterogeneous nature of IBD and multiple ways to assess disease activity, the optimal treatment target is not yet established.[14, 15] Moreover, the uptake of a 'treat to target' approach in routine clinical practice remains unexplored.

Quality IBD care requires management of factors not captured by a conventional 'treat to target' approach.[16, 17] Many of these factors are un-promoted areas of care in IBD that are yet associated with significant morbidity, including abnormal body composition, metabolic bone disease, cardiovascular disease, and venous thromboembolic disease.[18] These factors have a substantial bearing on outcomes including QoL, social or occupational function, and mortality. Clinicians who focus on managing inflammation alone may neglect these factors in routine care, leaving patients at risk of potentially avoidable morbidity.

Metabolic bone disease, osteopenia and osteoporosis, affects more than one-third of patients with IBD.[19, 20] Although data are limited, reduced bone density may be associated with an increased risk of pathological fractures, which is especially relevant given the young demographic affected by IBD.[21] Body composition, described in terms of fat and fat-free mass, may also be abnormal in many patients with IBD, however data are limited.[19] Small studies have shown that sarcopenia, defined as low muscle mass and reduced strength, is associated with poor outcomes in IBD.[22-24] High rates of obesity have also been reported in

patients with IBD, although there are conflicting reports on the impact of obesity on IBD disease course and susceptibility.[25] Perhaps more important is visceral adipose tissue (VAT), increases in which have been associated with a more severe CD phenotype and disease course in cross-sectional studies.[26-29] Despite the intuitive importance of body composition as key factor in IBD care, there has been a dearth of quality prospective data in this area.

Thus, in optimising outcomes for patients with IBD using a 'treat to target' approach, both inflammatory burden and patient factors such as body composition need to be considered. Accordingly, this body of work set out to explore both conventional treatment targets and body composition in patients with IBD, as disparate but key elements of quality of care.

A systematic review of conventional indices used in the assessment of disease activity in IBD was performed to explore the multifaceted nature of clinical and objective assessments within a heterogeneous disease entity. This study is presented in Appendix 1: Manuscript: Bryant RV & Walsh A, Travis SPL. "Current best practice for disease activity assessment in IBD", published in *Nature Reviews Gastroenterology and Hepatology*, 2016 [impact factor (IF) 2016 13.678].

Given the multiple domains of disease activity assessment in IBD, a prospective study was undertaken to evaluate the optimal target of therapy in UC. Contemporaneous assessment of clinical, endoscopic, and histological UC disease activity, coupled with longitudinal follow-up capturing hospitalisation and surgery, allowed for analysis of prognostic benefits associated with the various measures of remission. This study is presented in Chapter 3: Manuscript: Bryant *et al*. "Beyond endoscopic musical healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up", published in *Gut*, 2015 [IF 2016 16.658].

A multicentre study was undertaken to evaluate the extent to which clinical, endoscopic and histologic treatment targets are achieved in 'real-world' clinical practice in UC. Clinicians' perceptions of treatment targets were explored via survey and potential challenges of implementation of a 'treat to target' approach in practice were appraised. This study is presented in Chapter 4: Manuscript: Bryant RV *et al*. "Limited uptake of ulcerative colitis 'treat to target' recommendations in practice", published in *Journal Gastroenterology and Hepatology*, 2017 [IF 2016 2.152].

Looking beyond conventional treatment targets in IBD, comprehensive evaluation of body composition in patients with IBD was undertaken. Cross-sectional evaluation was initially undertaken to explore rates of abnormal body composition in IBD, in particular sarcopenia and osteopenia. Clinical predictors of abnormal body composition were carefully examined as well as the correlation between anthropometric assessments and direct measures of body composition to better inform clinical practice. This study is presented in Chapter 5: Manuscript: Bryant *et al*. "Low lean mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease", published in *Alimentary Pharmacology and Therapeutics*, 2015 [IF 2016 7.286].

Prospective evaluation of body composition in patients with IBD over time was then performed, with serial measurements over 24 months of follow-up. Concurrent assessment of IBD-related and lifestyle factors was performed to allow analysis of influences on body composition over time. This study is presented in Chapter 6: Bryant *et al*. "Obesity in inflammatory bowel disease: gains in adiposity despite high prevalence of myopenia and osteopenia", submitted to *American Journal of Clinical Nutrition*, 2018 [IF 2016 6.77].

The impact of body composition on outcomes in CD, in particular obesity and visceral adipose tissue (VAT), was then prospectively assessed. Comprehensive analysis taking into account IBD-related and lifestyle factors was performed to determine whether obesity and/or VAT influenced CD activity, quality of life, and rates of surgery and hospitalisation. The study is presented in Chapter 7: Bryant *et al*. "Visceral adipose tissue is associated with structuring Crohn's disease behaviour, faecal calprotectin and quality of life", under revision *Inflammatory Bowel Diseases*, 2018 [IF 2016 4.525].

Finally, a discussion is presented summarising and integrating the findings of the thesis (Chapter 8). Strategies to optimise outcomes in patients with IBD in clinical practice are proposed, incorporating both a 'treat to target' approach alongside routine measurement of body composition. Issues with the current body of evidence are discussed and future research directions outlined, so as to place the thesis within the contextual framework of current and future research, with the ultimate aim of improving the quality of care for patients with IBD.

REFERENCES

1. Allen PB, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. Current opinion in gastroenterology. 2013 Jul;29(4):397-404.
2. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011 Jun 16;474(7351):307-17.
3. Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. Gut. 2013 Oct;62(10):1505-10.
4. Cosnes J, Gower-Rousseau C, Seksik P*, et al.* Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011 May;140(6):1785-94.
5. Molodecky NA, Soon IS, Rabi DM*, et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.
6. Peyrin-Biroulet L, Sandborn W, Sands BE*, et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Sep;110(9):1324-38.
7. Baert F, Moortgat L, Van Assche G*, et al.* Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010 Feb;138(2):463-8.
8. Colombel JF, Rutgeerts P, Reinisch W*, et al.* Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011 Oct;141(4):1194-201.
9. D'Haens G, Baert F, van Assche G*, et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008 Feb 23;371(9613):660-7.
10. De Cruz P, Kamm MA, Prideaux L*, et al.* Mucosal healing in Crohn's disease: a systematic review. Inflammatory bowel diseases. 2013 Feb;19(2):429-44.
11. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012 Nov;61(11):1619-35.
12. Rutgeerts P, Diamond RH, Bala M*, et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointestinal endoscopy. 2006 Mar;63(3):433-42.

13. Schnitzler F, Fidder H, Ferrante M*, et al.* Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflammatory bowel diseases. 2009 Sep;15(9):1295-301.
14. Walsh AJ, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. Nature reviews Gastroenterology & hepatology. 2016 Oct;13(10):567-79.
15. Walsh AJ, Ghosh A, Brain AO*, et al.* Comparing disease activity indices in ulcerative colitis. Journal of Crohn's & colitis. 2014 Apr 1;8(4):318-25.
16. Melmed GY, Siegel CA, Spiegel BM*, et al.* Quality indicators for inflammatory bowel disease: development of process and outcome measures. Inflammatory bowel diseases. 2013 Mar;19(3):662-8.
17. Kim AH, Roberts C, Feagan BG*, et al.* Developing a Standard Set of Patient-Centred Outcomes for Inflammatory Bowel Disease - an International, Cross-disciplinary Consensus. Journal of Crohn's & colitis. 2017; 12: 408-418.
18. Bryant RV, Brain O, Travis SP. Conventional drug therapy for inflammatory bowel disease. Scandinavian journal of gastroenterology. 2015 Jan;50(1):90-112.
19. Bryant RV, Trott MJ, Bartholomeusz FD*, et al.* Systematic review: body composition in adults with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Aug;38(3):213-25.
20. Harbord M, Annese V, Vavricka SR*, et al.* The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2016 Mar;10(3):239-54.
21. Bernstein CN, Blanchard JF, Leslie W*, et al.* The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Annals of internal medicine. 2000 Nov 21;133(10):795-9.
22. Adams DW, Gurwara S, Silver HJ*, et al.* Sarcopenia Is Common in Overweight Patients with Inflammatory Bowel Disease and May Predict Need for Surgery. Inflammatory bowel diseases. 2017 Jul;23(7):1182-6.
23. Bamba S, Sasaki M, Takaoka A*, et al.* Sarcopenia is a predictive factor for intestinal resection in admitted patients with Crohn's disease. PloS one. 2017;12(6):e0180036.
24. Pedersen M, Cromwell J, Nau P. Sarcopenia is a Predictor of Surgical Morbidity in Inflammatory Bowel Disease. Inflammatory bowel diseases. 2017 Oct;23(10):1867-72.

25. Singh S, Dulai PS, Zarrinpar A*, et al.* Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nature reviews Gastroenterology & hepatology. 2017 Feb;14(2):110-21.
26. Buning C, von Kraft C, Hermsdorf M*, et al.* Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. Inflammatory bowel diseases. 2015 Nov;21(11):2590-7.
27. Erhayiem B, Dhingsa R, Hawkey CJ*, et al.* Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. Clinical gastroenterology and hepatology. 2011 Aug;9(8):684-7.
28. Holt DQ, Moore GT, Strauss BJ*, et al.* Visceral adiposity predicts post-operative Crohn's disease recurrence. Alimentary pharmacology & therapeutics. 2017 May;45(9):1255-64.
29. Van Der Sloot KW, Joshi AD, Bellavance DR*, et al.* Visceral Adiposity, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. Inflammatory bowel diseases. 2017 Jan;23(1):82-8.

CHAPTER 2: INTRODUCTION

Definitions, clinical presentation, and diagnosis of IBD

Definitions. The term IBD encompasses both UC and CD. UC is characterised by chronic non-granulomatous inflammation that is limited to the colonic mucosa, typically involving the rectum and a variable proximal extent of the colon in continuity.[1] CD is characterised by transmural, often granulomatous, inflammation that can involve any part of the gastrointestinal tract from the mouth to the anus.[2, 3] IBD unclassified (IBDU) is a term used in a small proportion of patients in whom a definitive distinction between UC and CD cannot be made.[1] Indeterminate colitis is a histopathological term that is used to describe a colectomy specimen that has overlapping features of both UC and CD.[1]

Clinical presentation. The clinical presentation of UC is characterised by bloody diarrhoea with associated urgency, tenesmus, and lower abdominal pain.[1] CD most frequently involves the terminal ileum and perianal regions, and stricturing and fistulising disease are common. The clinical presentation of CD varies widely according to disease distribution, but is typically one of abdominal pain, diarrhoea, and weight loss.[2, 3] Extra-intestinal manifestations (EIMs) of IBD affect up to 50% of patients, typically in parallel with disease activity, and are more common in CD than in UC.[4] The range of EIM's of IBD is broad, including arthropathy, venous thromboembolic disease, metabolic bone disease, uveitis and scleritis, and skin disease (pyoderma granulosum, erythema nodosum). Primary sclerosing cholangitis (PSC) is a hepatobiliary manifestation of IBD, affecting up to 5% of patients with IBD, which carries a high risk of progression to cholangiocarcinoma and liver transplantation.[5, 6] IBD patients are also at increased risk of intestinal dysplasia and malignancy, in particular those with extensive colitis for whom colonoscopic surveillance is recommended.[2,7]

Diagnosis. There is no gold-standard for the diagnosis of IBD. Rather, it is based on a composite assessment, incorporating clinical, endoscopic, histological, and radiological factors.[1, 3] For UC, a diagnosis is established using colonoscopy, with consistent features including continuous and confluent rectal and colonic mucosal friability, spontaneous bleeding and ulceration.[1] Mucosal biopsy features of UC include changes of chronicity, basal plasmacytosis, cryptitis, and crypt abscess formation. Colonoscopy will also establish a diagnosis of CD, with consistent features including discontinuous inflammation,

cobblestoning, anal lesions, and ileal involvement of disease.[7] Mucosal biopsies in CD typically show features of chronicity with crypt architectural distortion, patchy inflammation, and the presence of granulomas.[7] Cross-sectional imaging is important to evaluate for involvement of CD in the small bowel, beyond the reaches of the colonoscope, with magnetic resonance enterography (MRE) particularly helpful.

IBD pathogenesis, epidemiology, natural history, classification and burden

Pathogenesis. The aetiology of IBD is complex, multifactorial and incompletely understood.[8, 9] Factors thought to play a role in the pathogenesis of IBD are host genetics, immune dysregulation, abnormal composition and function of the microbiome (dysbiosis), and environmental factors.[8, 9] Meta-analyses of genome wide association studies (GWAS) have identified > 230 IBD-associated risk loci, many of which are shared between CD and UC, as well as other autoimmune conditions and pathogen-defence pathways.[10] Rare and private genetic variants may explain some of the 'missing heritability' in IBD, in particular early onset IBD.[11, 12] Studies have consistently characterised the luminal microbiota in active IBD to show a reduced diversity of microbial communities compared to healthy individuals.[13] There has also been increasing recognition of altered function of the microbiome in patients with IBD through the study of metabolomics.[14] Dysbiosis of the gut microbiome in IBD is thought to have a bidirectional relationship with host genetics and the immune system.[15] Key pathways in the interaction between the immune system and intestinal microflora include epithelial barrier function, microbial handling, and regulation of innate and adaptive immunity.[8] Multiple putative environmental factors ('the exposome') influence both susceptibility and natural history of IBD, including dietary intake, enteric infections, medications, and lifestyle factors (such as stress and sleep deprivation).[16]

Epidemiology. IBD typically presents in late adolescence to early adulthood, although there is a small rise in incidence in later life.[17] The global prevalence of IBD has risen sharply over the last three decades, with a trebling of incidence and prevalence in this relatively short time-period.[17-19] The prevalence of IBD is highest in developed countries. Australia has one of the highest rates of IBD in the world; as many as 1:250 Australians are estimated to be affected.[19] There has also been a rapid increase in the incidence of IBD in developing countries, where environmental factors and adoption of a Western lifestyle are implicated in observed trends.[20, 21] Accordingly, migration studies have shown that children of immigrants from a low-risk to a high-risk IBD country assume the same incidence of IBD as children of

non-immigrants and that a younger age of immigration is associated with a higher risk of developing IBD after arrival.[22]

Natural history. The natural history of IBD is one of relapsing and remitting disease, although some patients experience an unremitting disease course from the outset.[23] Half of patients with CD will experience a stricturing or penetrating intestinal complication within 20 years of diagnosis, and more than half will undergo surgery in a similar time period.[24, 25] Proximal extension occurs in around 30% of patients with UC and around 10% will undergo colectomy within 10 years of diagnosis.[26-28]

Classification. IBD can be classified according to the age of onset, natural history of disease, distribution of disease, activity of disease, and response to therapy.[29] The Montreal Classification and its later Paris modification for the paediatric group are the most widely used classification systems for IBD, incorporating age of onset, disease distribution, and phenotype (behaviour).[30, 31] Most current classification systems only take into account disease activity at a moment in time and fail to account for the long-term burden of disease.[32, 33] Thus, current classification systems do not capture overall disease severity and are therefore poor measures of outcomes in IBD. Moreover, existing classification systems were developed by clinicians and do not reflect patient reported measures of disease severity.[34]

Socioeconomic burden. The socioeconomic burden of IBD on affected individuals, their family units/communities and the healthcare system is substantial. Although patients with IBD have a normal life expectancy, they are burdened with physical and psychological morbidity, with accordingly high rates of disability and loss of work-related productivity.[35-37] The overall cost of IBD to healthcare systems is driven by healthcare, surgery and hospitalisation as well as the high cost of biologic therapies.[38] Taking into account both direct and indirect costs, it is estimated that IBD in Australia cost $AUD 3.18 billion annually (Price Waterhouse Coopers, Crohn's and Colitis Australia 2013).

Evaluating outcomes of care in IBD

Typically, outcomes of care in IBD are measured using burden of inflammation following initiation of therapy.[39] Clinical symptoms have long been used as a surrogate for inflammation in IBD, and most clinical trials to date have defined therapeutic outcomes by either clinical improvement or remission. However, objective evidence of inflammation has replaced clinical symptoms as the outcome of interest in recent IBD trials, with incorporation

of endoscopic and biomarker endpoints. Although current burden of inflammation is useful to interpret anti-inflammatory efficacy of a therapy, it is a flawed outcome measure that fails to account for true longitudinal disease 'severity'. Disease severity should take into account cumulative disability, necessity for surgery and hospitalisation, corticosteroid use, and the impact of IBD on the patient socially, emotionally, and occupationally.[32, 33] Integration of current severity indices into IBD clinical practice and trials has been limited by complexity.[35, 40]

Conventional clinician evaluation of outcomes in IBD fails to consider the patient's perspective. This has led to the development of patient reported outcome measures (PROMs). PROMs are direct reports from patients about how they feel in relation to a health condition and its therapy, without interpretation by healthcare professionals. PROMs are favoured by the US Food and Drug Administration (FDA) as clinical trial outcome measures in IBD and interim PROMs are being developed.[41]

QoL is an increasingly acknowledged outcome metric in IBD. Complexity of tools has limited feasibility of formal QoL assessment in clinical practice, but new instruments have been developed (such as the IBD-Control Questionnaire) that are simple to use and well-validated.[42]

Quality of care in IBD

IBD care is complex and expensive, incorporating medical, surgical and allied health management delivered in both ambulatory and inpatient settings by a multidisciplinary team.[43] There is significant worldwide variation in the delivery of IBD care, which has prompted care improvement initiatives and the development of quality indicators (QIs) in IBD.[43, 44] QIs measure the structure, processes and outcomes of health care delivery in IBD.[45] QIs are intended to be measurable and represent the minimal acceptable standard of care, to allow objective assessment of quality of care across disparate settings.[43]

Several professional organisations have produced QIs for IBD, including Crohn's and Colitis Australia, American Gastroenterology Association, Crohn's and Colitis Foundation, and Canadian Emerging Practice of IBD Collaborative (EPIC).[45-48] Common themes include avoidance of long-term corticosteroids, mitigating potential complications of therapy by screening (such as tuberculosis screening or thiopurine methyltransferase (TPMT) testing) and prevention (appropriate vaccination schedules), and undertaking appropriate surveillance.

These QIs have been limited by lack of inclusion of patients as key stakeholders in their development.

A standard set of patient-centred outcomes measures has been proposed by an international working group of *both* patients and clinicians (International Consortium for Health Outcomes Measurement (ICHOM, www.ichom.org)).[34] Key outcome metrics were survival, disease control, treatment-related complications, healthcare utilisation, and PROM's. The ICHOM initiative is the first to generate a unified set of outcome measures for use in clinical trials and practice.

The development of QIs exemplifies the importance of a multifaceted approach to evaluation of outcomes in IBD, taking into account factors beyond disease activity alone.

Un-promoted areas of care in IBD

Recognition and management of the corollary of chronic illness are a key part of quality care in IBD (***Table 2.1***).[49] These are un-promoted areas of care in IBD and oft overlooked in clinical practice when the sole focus is on intestinal inflammation.[29] The prevalence of these comorbidities in patients with IBD is poorly researched, as they are not incorporated into clinical trial methodology. Therefore, their impact on morbidity and outcomes in IBD remains largely uninvestigated, and the possible benefit of their mitigation, unexplored.

Table 2.1. Un-promoted areas of care in IBD

Domain		Description
Body composition	Metabolic bone disease	- Osteopenia/osteoporosis > 30% of patients with IBD and may impart increased risk of pathological fracture[4]
	Low muscle mass (myopenia and sarcopenia)	- Low muscle mass has been associated with increased need for surgery as well as non-response to biologic therapy in IBD[50-52]
	Obesity	- Obesity has been associated with worse outcomes in IBD[53]
Venous thromboembolic disease (VTE)		- Active IBD is a risk factor for incident and recurrent VTE[54]
Cardiovascular (CVS) disease		-IBD associated with increased risk of cerebrovascular and ischaemic heart disease[55]
Opportunistic infections (OI's)		- Immunosuppression associated with

Domain	Description
	increased risk of infection in IBD[56]
Vitamin D deficiency	- Vitamin D deficiency is associated with IBD disease activity and contributes to fatigue[57-59]
Anxiety and depression	- Mental health issue are common and may affect clinical outcomes[60]
Opioid use in patients with IBD	- Contributes to mortality in IBD[61]
Fatigue	- Fatigue is common and debilitating in IBD[62] - Treatable causes include nutritional deficiencies, anemia, and adrenal suppression after corticosteroid use

Fatigue is common in patients with IBD and may relate to remediable factors such as nutritional deficiencies, alterations in thyroid or adrenal function, or changes in muscle function associated with IBD, which may be improved by establishment of regular exercise.[59, 62, 63] Rates of anxiety and depression are high in the IBD cohort, and yet frequently go unrecognised in routine clinical practice.[60] Restrictive dietary practices and eating disorders are also prevalent in patients with IBD, and can contribute to the high rates of malnutrition observed in this group.[64] Vitamin D deficiency is common amongst patients with IBD, and beyond risk of metabolic bone disease, may be associated with disease activity and poorer QoL outcomes.[57, 65] Risk of opportunistic infection, particularly amongst immunosuppressed patients, may be reduced by adherence to appropriate screening and vaccination guidelines.[56] Akin to other chronic inflammatory conditions, IBD patients are at increased risk of ischaemic heart disease (IHD), cerebrovascular disease, and arterial thrombotic events. [37) 55, 66, 67] Both hospitalised and ambulatory patients with IBD have an increased risk of venous thromboembolic disease (VTE), however appropriate use of thromboprophylaxis is variable amongst treating clinicians.[54, 68]

There is also a small body of evidence to suggest that abnormal body composition may be common in patients with IBD, including obesity, sarcopenia, and metabolic bone disease (discussed further below).[50]

Conventional management of IBD

Corticosteroid therapy was the first therapy trialled in IBD in the 1950s and despite potential harm associated with use, corticosteroids remain an important option for induction of remission in IBD.[69] Aminosalicylates, including sulfasalazine and mesalazine, are anti-inflammatory therapies that are the foundation of therapy for UC. Many patients with IBD require immunomodulator therapy, the most commonly used of which are the thiopurines (azathioprine or mercaptopurine) and methotrexate. Exclusive enteral nutrition (EEN) involves intake of only medical formulas with exclusion of table foods for a defined period.[2] EEN is useful for remission induction in luminal CD, especially in the paediatric cohort, in which setting it has superior efficacy to corticosteroids.[2]

The advent of effective biologic therapies, in particular the anti-tumour necrosis factor-alpha (anti-TNF) agents, has revolutionised the management of IBD. Since the arrival of anti-TNF's, there have been further biological therapies showing efficacy in IBD, including anti-integrin therapies (such as vedolizumab) and cytokine inhibitors (such as IL12-IL23 pathway inhibitor ustekinumab). New therapies directed at novel molecular targets are on the horizon for IBD, which will increase the complexity of therapeutic choices and necessitate better markers for predicting response.[70] Unfortunately, despite improved medical therapies, surgery is unavoidable for many patients with IBD.[17, 24]

A detailed summary of medical therapy for IBD is provided in Bryant RV *et al*. "Conventional medical therapy for inflammatory bowel disease". *Scandinavian Journal of Gastroenterology*. 2015; 50: 90-112.

Therapeutic considerations in IBD

Most patients with IBD require lifelong medical therapy, and treatment decisions must be strategic, balancing drug efficacy, side-effects, and the likely duration of therapy.[29] Therapeutic strategies in IBD go beyond mere treatment choice. Timing of therapy is key and early combined immunosuppression, delivered as a 'top-down' or 'accelerated step-up' approach, may be appropriate early in disease course, especially for patients predicted to have a severe disease phenotype.[71, 72] Management decisions in IBD are ultimately guided by patient-, disease-, and medication-related factors.[29, 73]

Patient factors. Treatment decisions in IBD are best personalised and tailored to individual goals and treatment acceptability.[29] Shared decision-making between doctors and patients leads to better patient understanding of treatment choices and improved adherence to therapy.[74]

Disease-related factors. Clinical classification of IBD is pertinent to therapeutic decision-making.[29] Disease distribution informs therapeutic choices; perianal and ileal CD and extensive UC are associated with a higher risk of complicated disease.[25, 28] Prior surgery should also be taken into account, such as ileocolic resection, along with environmental factors, such as tobacco smoking and habitual diet, which have been shown to influence IBD disease course.[75-78] Age at diagnosis is also important; patients diagnosed as children frequently suffer from more complicated disease than those diagnosed at an older age.[79, 80] Prognostic factors at diagnosis should also be considered, including weight loss (> 5 kg), requirement for corticosteroids, and a stricturing phenotype or perianal disease.[81, 82] Extra-intestinal manifestations also need to be considered, in particular PSC, which is associated with risk of colorectal cancer.[6]

IBD disease activity is an important determinant of therapy (discussed further below). There are multiple domains of disease activity assessment in IBD, both clinical and objective.[73]

Medication-related factors. The efficacy and potential side-effect profile of any medication must be considered in light of patient factors.[29]

Conventional disease activity assessment in IBD

Disease activity in IBD may be measured using clinical, endoscopic, histological, or radiological assessment tools, as well as using biomarkers and QoL.[73] Each of the domains of disease activity assessment in IBD has its merits, although none are perfect.[73] Moreover, disease activity metrics capture a snapshot of inflammation in time, but fail to account for longitudinal disease course, complications, and impact of the disease, and therein are poor measures of true disease severity.[32, 33] To further complicate matters, within each domain of assessment, there are multiple indices, many of which are confounded by lack of validation, confusing terminology and abbreviations, and composite use of symptoms with objective measures of inflammation or quality of life.[73]

Nonetheless, indices of disease activity are important metrics in IBD care, in that they are repeatable and responsive to change and thereby allow objective longitudinal interpretation of therapeutic efficacy. Inflammatory burden, QoL and clinical symptoms in IBD are distinct from one another yet overlapping (***Figure 1***).

A detailed systematic review of disease activity indices in IBD is presented as part of this thesis (Appendix 1. Bryant RV & Walsh A, Travis SPL. "Current best practice for disease activity assessment in IBD". *Nature Reviews in Gastroenterology and Hepatology* 2016; 13: 567-79).[73]

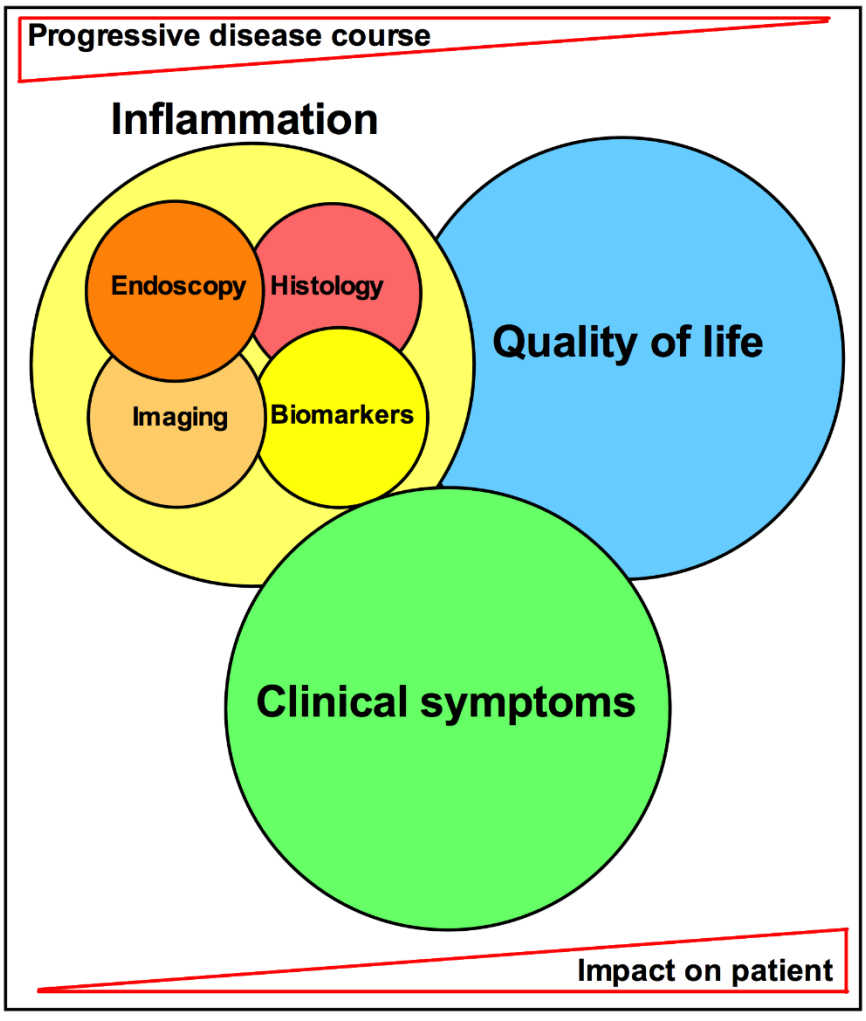


Figure 2.1: Distinct but overlapping domains of disease activity assessment in IBD *(adapted from [73])*

‘Treat to target’ in IBD

Therapeutic advances in the medical management of IBD have evolved treatment targets. The primary endpoint for early randomised trials using cortisone for acute severe UC was mortality.[69] Commensurate with the therapeutic revolution in IBD, treatment expectations have been raised from merely ‘saving a life’, past achieving symptomatic remission, and now toward extinguishing inflammation without the use of corticosteroids so as to normalise QoL.

For many decades, management of IBD was centred on achieving symptomatic control.[83] However, clinical symptoms are known to correlate poorly with objective measures of inflammation in IBD.[84] Up to 40% of patients with IBD suffer from concurrent irritable bowel syndrome (IBS), which leads to symptoms in the absence of inflammation.[85, 86] Conversely, insidious progression of IBD can occur in the absence of symptoms.[29] Treating patients with only clinical symptoms in mind does not modify the course of IBD and therapeutic decisions are best made incorporating objective measures of inflammatory activity.[83, 87]

A ‘treat to target’ approach has thus been proposed for IBD, which advocates striving not only for resolution of symptoms, but objective resolution of inflammation.[83, 88] The driving principle of a ‘treat to target’ strategy is incorporation of objective assessment of disease activity to guide subsequent treatment decisions.[88] Although novel in IBD, the principle of ‘treat to target’ is not a new concept in medicine. Objective (often numerical) measures of disease control have long been applied to cardio-metabolic illnesses such as hypertension and diabetes mellitus, as well as other chronic inflammatory diseases such as rheumatoid arthritis.[89] Although IBD metrics may be more complex, this represents a frame-shift in thinking for many clinicians trained to make therapeutic decisions based on symptoms alone.

Due to the heterogeneous nature of IBD and multiple domains of disease activity assessment, there is no single perfect target in IBD.[73] The Selecting Therapeutic Targets in IBD (STRIDE) initiative set out to achieve international consensus on evidence-based treatment targets that could be used in routine practice.[88] Systematic review of each domain of disease activity assessment in IBD was performed and a modified Delphi process amongst IBD specialists was then undertaken for formulation of guidelines.[88] The group agreed upon 12 recommendations for both UC and CD, including an overall target of therapy for IBD.

Clinical targets. Clinical targets for IBD were defined using both traditional indices of assessment as well as PROM's. The clinical/PROM target for UC was defined as resolution of rectal bleeding and normalisation of bowel habit, whereas for CD, the target was resolution of abdominal pain and normalisation of bowel habit.[88] Resolution of symptoms alone was deemed an insufficient target.

Endoscopic targets. In UC, endoscopic mucosal healing, variably defined as lack of visible mucosal inflammation or ulceration at endoscopy, has been associated with reduced rates of clinical relapse, hospitalisation, and colectomy.[71, 84, 90-93] Accordingly, a Mayo endoscopic subscore of 0 was defined as the optimal target, with a subscore of 1 as the minimum target.[88] In CD, mucosal healing, as defined by resolution of ulceration at endoscopy, has been associated with decreased need for surgery, hospitalisation and corticosteroids and was defined as the target.[93-95]

Histological targets. Histological remission in UC is distinct from endoscopic mucosal healing; persistent microscopic inflammation is common in the setting of endoscopically quiescent disease and is likely to represent a harbinger of residual inflammation.[96] Accordingly, persistent histological inflammation in UC is associated with an increased risk of relapse, hospitalisation and colectomy, as well as an increased risk of colorectal neoplasia.[97-105] However, although a sensitive measure of inflammation, histopathology was not considered a target in UC, nor in CD where less evidence exists.[88, 106]

Imaging targets. Cross-sectional imaging, in particular magnetic resonance imaging (MRI), is complementary to endoscopy in assessment inflammation in CD. The MaRIA Score is a system for reporting disease activity on MRI that has been shown to closely correlate with endoscopic remission.[107, 108] Therefore, cross-sectional imaging was proposed as a target in CD where inflammation could not be adequately assessed using endoscopy.[88]

Biomarker targets. Biomarkers, typically derived from blood or stool, represent a non-invasive means of measuring inflammatory activity in IBD. The most commonly used biomarkers in IBD are C-reactive protein (CRP) and faecal calprotectin (FC). CRP has been shown to be useful in CD, where levels have been shown to correlate with clinical response to therapy and predict relapse.[109-117] In UC, CRP has been shown to predict risk of colectomy in patients with acute severe ulcerative colitis.[118] However, CRP correlates only modestly with endoscopic inflammation in both UC and CD.[73] Although a sensitive and accurate measure

of inflammation, FC varies widely between stools on a daily basis, is subject to assay variability and disease distribution, and a broad range of cut-off values have been described ranging from < 50 μg/g to < 250 μg/g.[73, 119-121] Therefore, biomarkers of inflammation were not considered treatment targets and rather adjunctive measures of monitoring inflammation in IBD.[88]

Composite targets. The composite target of therapy in IBD has been proposed as *both* clinical/PROM and endoscopic remission, with the overarching goal to modify the course of disease so as to improve quality of life and avoid disability, whilst balancing the risks associated with therapy.[33, 88, 122]

How often to assess targets? A shorter interval between endoscopic evaluation of disease activity in IBD, coupled with appropriate titration of therapy, has been shown to increase the likelihood of achieving endoscopic mucosal healing.[123] It has been proposed that in the active phase of disease, clinical assessment should be performed at 3-monthly intervals, coupled with endoscopic assessment 3-monthly in UC and 6-9 monthly in CD.[88]

Potential issues with a 'treat to target' approach in IBD clinical practice

The proposition of treatment targets for IBD represents a substantial step forward for the field, however there are challenges facing implementation in clinical practice (***Table 2.2***).

First and foremost, the 'treat to target' approach is based on data that correlate measures of remission with outcomes in IBD, largely from clinical trials and observational studies. Although the principles are sound, there is a paucity of data showing the benefit of actually treating to a target beyond symptom control, with sequential therapeutic escalation until the target is reached. Therein, the benefit of escalating therapy to achieve endoscopic remission in an asymptomatic patient has not been shown. Only the 'CALM' RCT in Crohn's disease approximates a modified 'treat to target' strategy in practice, finding escalation of therapy based on clinical symptoms and biomarkers, as compared to symptoms alone, led to higher rates of endoscopic mucosal healing at 48 weeks (without an increase in adverse events).[124] Whether aggressive treatment to a defined target, such as endoscopic mucosal healing or even histological healing, modifies the course of IBD is unproven. Moreover, patient factors may play a substantial role in selection of treatment targets in IBD, such as age, duration of disease, comorbidities, and drug tolerance. Therein, beyond expert consensus and associations, the 'optimal' target of therapy in IBD remains elusive.

Based on data from randomised clinical trials (RCT's), composite clinical and endoscopic remission is achievable in up to two-thirds of patients on biological therapy.[91, 125, 126] However, trials are poorly reflective of clinical practice and most real-life patients are ineligible for trial enrolment.[127] Moreover, many patients do not qualify for biological therapy within the constraints of healthcare systems. Implementation of a 'treat to target' strategy in IBD will require higher upstream healthcare costs, related to intensification of therapy and frequent endoscopic investigations. Although downstream savings related to less surgery and hospitalisation are presumed, current data are lacking.

Guidelines are impotent if there is failure of uptake by key stakeholders: patients and clinicians. Despite the potential benefits of a 'treat to target' approach in IBD, it remains to be seen whether patients will accept intensive and invasive monitoring, or whether they will adhere to proposed medication strategies and accept the potential toxicities of therapy. It must be noted that patients were not involved in the development of the STRIDE guidelines. The optimal treatment target for any patient is a personal choice. Clinician uptake of a 'treat to target' strategy requires not only knowledge of the guidelines, but an evidence-based conviction that guidelines will better patient outcomes. A 'gap' between guidelines and practice can emerge, as has been observed in rheumatology practice (***Figure 2***).[128]

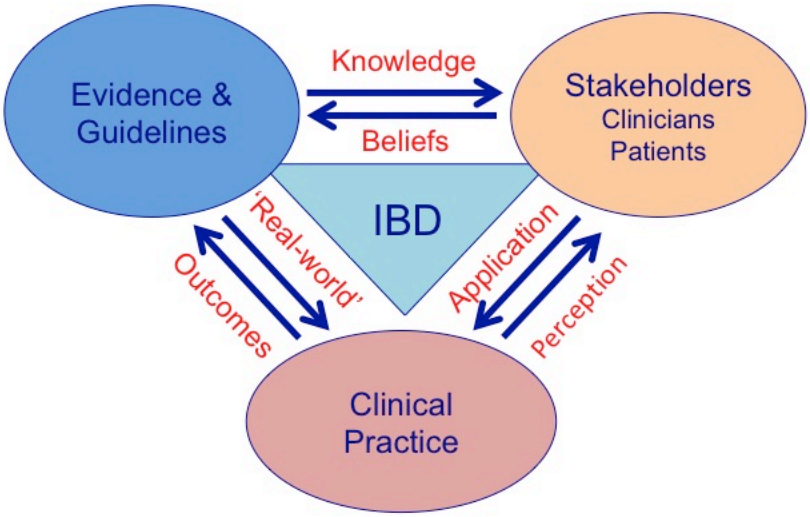


Figure 2.2. Potential 'gap' between guidelines and clinical practice in IBD

Table 2.2. Challenges for the current 'treat to target' approach in IBD

Issue		Description
Lack of evidence for benefit of a 'treat to target' approach		There are no clinical trials showing that therapeutic escalation to achieve mucosal healing in an asymptomatic patient improves outcomes
Feasibility in clinical practice	Patient acceptance of intensive therapy and monitoring	Lack of patient involvement in development of STRIDE guidelines
	Healthcare and patient costs	Health economic rationale for intensive therapy and monitoring unproven
	Clinician uptake	Traditional training toward treating symptoms and lack of current evidence to escalate therapy in asymptomatic patients
Optimal treatment target in IBD is unclear		Optimal target is unclear and patients were not involved in defining targets
Failure to measure other factors associated with quality of care in IBD		Conventional disease activity assessment does not measure other factors associated with morbidity in IBD, including body composition

Body composition in IBD: an un-promoted area of care

Body composition analysis divides the body into bone, fat and fat-free (lean mass) compartments.[50] There are few quality studies exploring body composition in patients with IBD.[50]

Systematic review of body composition in adult patients with IBD identified a total of 19 studies reporting on 926 subjects with IBD compared to healthy age- and sex- matched controls.[50, 129-147] All studies were cross-sectional, aside from a single study of patients with UC in remission at 6 years of follow-up.[145] Overall, the findings were heterogeneous and although meaningful conclusions were difficult to draw, high rates of disturbances in body composition were observed in patients with IBD compared to controls.[50] In patients with CD (n = 631), around one-third of patients had altered body composition, characterised by reduced body mass index (BMI), fat mass (FM) and fat-free mass (FFM). Body composition was abnormal in a smaller proportion (13%) of patients with UC (n = 295), in whom reduced FM and FFM was evident. Small sample sizes, lack of standardisation of confounding

variables, and variable techniques used to measure body composition limit the quality of systematic review data on body composition in adult patients with IBD.[50] Moreover, analysis of the prevailing influences on body composition was not possible due to the heterogeneity of findings, in particular IBD disease activity, therapy, phenotype, and smoking.

Metabolic bone disease. More than 30% of patients with IBD are affected by metabolic bone disease.[4] Osteopenia and/or osteoporosis have been reported in 20–50% of patients.[4, 148-152] Reduced BMD is associated with risk of pathological fractures and associated morbidity, which is particularly relevant given the young demographic affected by IBD.[150, 153, 154] The pathogenesis of metabolic bone disease in IBD is thought to be multifactorial, relating to chronic inflammation, corticosteroid therapy, nutritional deficiencies, and reduced physical activity.[50, 137, 155-157]

Few prospective studies have evaluated longitudinal changes in BMD in IBD.[145, 158, 159] Moreover, the influence of IBD-related factors and body composition on bone density over time remains poorly explored. Accordingly, there are no consistent international recommendations for osteoporosis screening in IBD, and as a consequence, screening practices vary widely and patients with low BMD may go unrecognised and without therapy.[160]

Sarcopenia. The term sarcopenia, correctly used, incorporates both anatomical and functional assessment and is defined as loss of skeletal muscle coupled with loss of strength.[50, 161] In elderly populations, sarcopenia is associated with poor QoL, hospitalisation, falls, and even death.[162-164] In patients with IBD, premature 'accelerated' sarcopenia may develop, related to factors including chronic inflammation, malnutrition, corticosteroid use, immobility, and surgery.[155, 157, 165] In both human and mouse models, inflammatory pathways and cytokine release (NF-κβ, tumour necrosis factor, and interleukin-6) lead to inflammatory muscle wasting and fatigue.[59, 62, 166]

Rates of sarcopenia in patients with IBD, contributing factors and the influence of sarcopenia on outcomes and QoL are poorly understood. Several studies reporting on sarcopenia in IBD have not used the true anatomical and functional definition.[50, 161] Systematic review identified only four studies reporting on both muscle mass and function in IBD,[130, 135, 146, 147] one of which identified a higher prevalence sarcopenia in IBD patients in remission (n = 144) than controls.[50, 146] A subsequent study reported sarcopenia in 53% of patients with intestinal

insufficiency and failure, many of whom had underlying IBD.[167] Other studies have rather reported on myopenia, defined as lean mass deficits without assessment of strength or performance.[51, 52, 142, 168] Sample size and heterogeneity of measurement tools further limit assessment of the true prevalence of sarcopenia in IBD.

Although current data are scarce, both myopenia and sarcopenia are likely to be of clinical significance in patients with IBD. Lean mass is better associated with BMD than the equivalent weight of fat mass, as muscle contraction applies stress to bones and thereby precipitates bone deposition and remodelling.[169-171] Furthermore, muscle function has been associated with fatigability and QoL in patients with CD.[59, 172] Myopenia has also been shown to be predictive of need for surgery in patients with IBD, particularly in those with an overweight or obese range BMI.[51, 52] Myopenia may be associated with primary non-response and a shorter time to treatment failure after commencement of anti-TNF therapy.[173, 174] Conversely, reversal of skeletal muscle deficits in patients with active CD was demonstrated using quadriceps MRI following infliximab induction therapy, which correlated with a reduction in IL-6 levels.[175, 176] Detection of lean muscle deficits may be limited by conventional anthropometric tests alone; BMI has been shown to correlate poorly with lean mass in IBD patients.[137, 177, 178]

Obesity. The prevalence of overweight and obese adults has reached epidemic proportions worldwide.[179] In Australia, the 2014–2015 National Health Survey found that 63.4% of Australian adults (11.2 million people) were either overweight or obese, 35.5% overweight (6.3 million people) and 27.9% obese (4.9 million people).[180] Comparatively, in the United States, 35.7% of adults are obese.[181]

In parallel, the incidence and prevalence of IBD is rising globally, with a rapidly rising incidence in newly industrialised countries.[18, 20, 182] Obesity has been shown to impart an increased risk of other autoimmune illnesses, including rheumatoid arthritis and psoriasis.[183, 184] Current data on obesity and IBD susceptibility are inconsistent and limited by use of BMI alone, which does not distinguish between visceral and subcutaneous fat compartments with distinct metabolic profiles.[53, 185] In IBD, large prospective cohort studies including the Nurses' Health Study and Danish National Birth Cohort have reported an association between development of Crohn's disease and premorbid obesity.[185-187] Obesity is recognised as a state of low-grade inflammation, and mesenteric fat has been shown to secrete pro-inflammatory cytokines, chemokines, and adipokines.[53, 188, 189]

There are emerging data on the growing prevalence of obesity amongst patients with IBD.[53] Recent cross-sectional studies report that 15–40% of adult patients with IBD are obese and 20–40% are overweight.[190-196] Current rates of obesity in IBD are higher than those reported prior to the turn of the century and accordingly the weight of CD subjects entering clinical trials has dramatically increased from 1991 to 2008.[197, 198] The high prevalence of obesity in IBD prompts speculation that IBD could impart risk of developing obesity.[53] Dysbiosis and aberrations in intestinal microbial metabolism may act through a variety of mechanisms to potentiate metabolic disturbance and obesity in the setting of IBD.[189, 199, 200]

There are conflicting data on the influence of overweight and obesity on disease outcomes and complications in patients in IBD (***Table 2.3***). In a large retrospective study (n = 846), obesity was associated with a reduced risk of penetrating complications in patients with CD.[191] In another study, obese patients with IBD were less likely to receive anti-TNF therapy, undergo surgery, or require hospitalisation.[190] In contrast, obese patients with IBD have been shown to have a poorer health-related QoL, and a higher rate of surgery in those with UC.[192, 201] Increasing BMI may also adversely affect surgical outcomes in patients with IBD; a higher BMI has been shown to increase perioperative morbidity in patients with CD and obesity has been shown to increase the complexity of laparoscopic surgery in IBD patients.[202, 203]

There are data to suggest that obesity may influence response to therapy in IBD. Network meta-analyses and observational comparative data report lower rates of IBD-related hospitalisation and surgery in patients with CD who receive weight-based dosed infliximab as compared to empirically dosed adalimumab.[204, 205] Accordingly, BMI has been shown to be a predictor of need for dose-escalation of adalimumab in patients with CD.[206] Pharmacokinetic studies of all available biologic agents used in IBD have shown high body weight as a risk factor for increased drug clearance, short half-life, and low drug trough levels.[53]

Overall, current data on obesity in IBD are limited by a lack of prospective data, which limits capacity to interpret causal directionality in IBD susceptibility and natural history. Current studies also do not sufficiently adjust for confounding variables such as disease activity and medications.

Table 2.3. Overweight/obese patients with IBD: influence on phenotype and outcomes

Author and year	Study design	Patient number	Assessment method	Results
Pringle *et al* 2015[191]	Prospective Registry data (retrospective analysis)	n = 846 CD	BMI	- Obese patients had lower risk of penetrating disease and no increase in perianal, stricturing disease or surgery compared to normal weight individuals
Flores A *et al* 2015[190]	Retrospective study	n = 581 IBD	BMI	- Obese patients were less likely to receive anti-TNF therapy, undergo surgery, or hospitalisation than normal weight individuals
Seminerio *et al* 2015[192]	Retrospective study	n = 1494 IBD	BMI	- No difference in risk of surgery, hospitalisation, or emergency attendance between obese, overweight, and normal weight individuals - Obesity associated with higher CRP and lower QoL - Increasing BMI associated with increased rates of diabetes, hypertension and hyperlipidaemia
Hass DJ *et al* 2006[207]	Retrospective study	n = 138 CD	BMI	- No difference in surgery or escalation of medical therapy in normal weight vs. overweight/obese patients - Time to first surgery shorter in overweight as compared to underweight patients
Nic Suibhne T *et al* 2013[193]	Prospective case-control study	n = 100 CD	BMI	- Higher BMI associated with lower disease activity
Steed *et al* 2009[201]	Retrospective study	n = 489	BMI	- Overweight and obese patients with UC had a higher risk of surgery, whereas the converse was true of patients with CD

Visceral adipose tissue (VAT). Body fat is distributed into two main compartments with distinct metabolic characteristics: subcutaneous adipose tissue (SAT) and VAT.[208] Intestinal mesenteric fat wrapping or 'creeping fat' was first described by Burrill Crohn and colleagues as a disease-specific feature of 'regional ileitis'.[209] Mesenteric fat accumulation occurs early in the course of CD and is evident in most small bowel resection specimens.[210, 211] More than an innocent bystander, mesenteric adipocytes are a key source of pro-inflammatory cytokines in CD, including tumour necrosis factor-alpha (TNF-α), peroxisome proliferator-activating receptor-gamma, and interleukin-6.[188, 210-212] Secretion of pro-inflammatory cytokines by VAT may act to amplify inflammation in CD.[213]

The clinical significance of VAT as a biomarker for disease severity and outcomes has been evaluated in a number of studies, albeit with conflicting results (***Table 2.4***).[210, 211, 214-219] An increase in VAT has been associated with a complex CD behaviour (stricturing and fistulising disease), an increased likelihood of post-operative CD recurrence and post-operative morbidity, and adverse pouch outcomes.[214-219] Existing studies are limited by small sample sizes and retrospective study design. Moreover, heterogeneity in the techniques used to evaluate VAT, as well as the VAT metric reported, limit meaningful interpretation of results. Whole body dual energy X-ray absorptiometry (DXA) is an accurate means of assessing VAT and incurs minimal additional radiation or time to standard BMD DXA assessment, yet has not been evaluated in patients with CD.[220-223]

Table 2.4. Studies of VAT in CD

Author and year	Study design	Patient number	VAT method VAT metric	Results
Van der Sloot *et al* 2017[224]	Retrospective analysis (prospective data)	n = 482 (CD)	- CT - VAT area	-VAT volume associated with increased risk of penetrating (but not stricturing disease) and risk of surgery
Holt DQ *et al* 2017[218]	Retrospective post-hoc analysis (or prospective study)	n = 44 (CD)	- CT or MRI - VHI (VAT area/height)^2	-VHI > 1.5x gender-specific mean increased risk of post-operative CD recurrence (RR 2.1, CI 1.5-3.0, p = 0.012) -VAT:SAT and MFI not associated with outcome variables

Author and year	Study design	Patient number	VAT method VAT metric	Results
Connelly *et al* 2014[215]	Retrospective study	n = 143 (CD)	- CT scan - VAT:SAT ratio	-VAT:SAT but not VAT area or abdominal circumference was predictive of surgical morbidity
Buning *et al* 2015[214]	Prospective study (Retrospective evaluation of clinical characteristics)	n = 31 (CD) n = 19 (controls)	- Air-displacement plethysmography (FM) and MRI (VAT) - VAT: FM ratio	-VAT:FM ratio associated with increased inflammatory markers (leptin, Il-6) -Patients with structuring/fistulising CD phenotype had a higher VAT:FM ratio than inflammatory phenotype -Higher VAT:FM at baseline associated with higher clinical disease activity at follow-up
Erhayiem *et al* 2011[217]	Retrospective study	CD n = 50	- CT scan - Mesenteric fat index (MFI) VAT:SAT ratio	-MFI significantly higher in patients with complicated disease (stricturing and fistulising) - MFI cut-off of 0.29 was 93.7% sensitive and 81% specific for detecting complicated disease behaviour
Desreumaux *et al* 1999[211]	Prospective study	CD n = 38 (17 post-operative)	- MRI - VAT:SAT	-VAT:SAT higher in CD than in controls -No correlation between VAT:SAT and CDAI, duration disease and corticosteroid use
Ding *et al* 2015[216]	Retrospective study	CD n = 164	- CT scan - VAT area	-VAT area associated with a high rate of post-operative complications (< 30 days) following primary CD surgery -BMI not associated with surgical outcomes

Tools for evaluation of body composition

There are a variety of methods that have been employed to measure body composition in patients with IBD, the pros and cons of which are outlined in ***Table 2.5***.[50, 225]

Anthropometric assessments. Commonly used anthropometric assessment tools include BMI, skin-fold thickness, and measurement of calf, mid-arm, waist, and hip circumference. Anthropometric tests are quick and easy to perform in the ambulatory setting without expensive equipment, however they are a blunt tool for measuring body composition.[50] BMI has been shown to correlate poorly with lean mass in patients with IBD, and an over-representation of fat mass may mask deficits in lean mass with consequent failure of recognition of malnutrition.[50, 137, 177, 178, 226] Although not performed routinely, measurement of hip and waist circumference are helpful in evaluating fat distribution, in particular distinguishing between VAT and SAT compartments.[227]

Anthropometric testing should optimally incorporate evaluation of muscle function.[161] Muscle strength can be evaluated using isometric hand-grip strength, shown to be correlate with lower limb power.[228] Other tests of physical performance including the 'Short Physical Performance Battery', 'timed get-up-and-go' test, and usual gait speed have been evaluated as useful measures of dynamic muscle function in elderly populations.[161]

Cross-sectional imaging. MRI is an accurate modality for assessment of body composition and provides information on both muscle mass and quality, however its use is limited by expense and availability.[161, 208, 229] CT is also accurate for assessment of body composition, however use is limited by ionising radiation exposure.[161, 208, 225]

Dual-energy X-ray absorptiometry. DXA measures the attenuation of two energies to distinguish between fat, lean, and bone mineral compartments. DXA is recommended in the routine care of IBD patients for assessment of BMD and is associated with a very small dose of ionising radiation.[4] Whole body composition analysis adds little to the time taken or radiation exposure of a BMD DXA scan, yet provides accurate and regional body composition information.[50] DXA is considered a gold-standard tool for assessment of body composition in research and clinical practice.[225] DXA has also been shown to be as accurate as CT scanning in the assessment of VAT and SAT.[220, 230]

Bioelectrical impedance analysis (BIA) and other tools. BIA measurement of body composition is based on the principle that electrolyte-rich fluids (body water) pose least impedance to electrical current as compared to those enriched with lipids (adipose tissue).[225] BIA is portable, inexpensive, and reproducible; however, accuracy may be limited by hydration, body position, and ambient and skin temperature. Moreover, BIA cannot distinguish between VAT and SAT.[208, 231]

Ultrasound relies on quantification of thickness of tissues and can be a useful tool for evaluation of body composition at the bedside but is limited by operator dependence.[208, 225, 232] Other tests, including total body water measurement (hydrodensitometry) and total body potassium measurement, are infrequently used in clinical practice.

In summary, BMI is a poor surrogate for direct measures of body composition in IBD, but incorporation of addition anthropometric tests such as waist hip circumference and performance testing may increase accuracy. DXA is an underused modality for assessment of body composition in IBD, given that it is accurate, available, and is in routine use for evaluation of BMD.

Table 2.5. Tools for evaluation of body composition

Assessment tool	Pros	Cons	Summary
Magnetic resonance imaging (MRI)	- Accurate for fat mass (FM) and fat-free mass (FFM) - Additional data on muscle quality - No radiation exposure	- High cost - Limited availability - Lack of standardisation of data acquisition	- Accurate and useful in research setting but limited by expensive and availability for routine assessment of body composition in clinical practice
Computed tomography (CT)	- Accurate for FM and fat-free mass FFM - Additional data on muscle quality -	- Ionising radiation exposure - Single slice analysis may VAT accuracy	- Accurate and useful in research setting but limited by ionising radiation for routine assessment of body composition in clinical practice
Dual energy X-ray absorptiometry (DXA)	- Accurate for bone, FM and FFM - Minimal radiation - Recommended in routine care for BMD	- Small dose of ionising radiation - Non-portable and availability can be limited - Limited information on muscle quality	- Where available and in routine use for IBD care (regular BMD assessment), DXA is an accurate and repeatable modality for assessment of body composition
Bioelectrical impedance (BIA)	- Portable, inexpensive and reproducible - Accurate in standard conditions	- Accuracy limited by clinical factors - Limited capacity to differentiate between fat compartments	- Useful tool for the ambulatory setting, particularly for FFM, but may be inaccurate in non-standard conditions and unable to evaluate adipose compartments
Ultrasound	- Portable, inexpensive - Non-invasive - No radiation	- Operator-dependent, poor reproducibility - Limited utility for visceral fat	- Not yet a viable tool for routine assessment of body composition

Research question

Rationale. Therapeutic advances in the medical management of IBD have evolved treatment targets. A 'treat to target' strategy has been proposed, but the 'optimal' target in IBD remains elusive. Beyond clinical trials, the feasibility of a 'treat to target' approach and proportions of patients achieving targets in routine clinical practice remain unexplored.

Quality care in IBD necessitates management of factors beyond inflammatory burden alone. Aberrant body composition may contribute to morbidity in patients with IBD, yet has been poorly researched and often overlooked in clinical practice.

Overarching aims of this thesis. The overarching aim of this thesis is to explore both conventional treatment targets as well as body composition in IBD, toward improving quality of care for patients with IBD.

Research objectives

1. To evaluate conventional indices of disease activity assessment in IBD.
2. To explore the relationship between conventional measures of disease activity assessment in IBD.
3. To evaluate the prognostic benefits of achieving clinical, endoscopic, and histological measures of remission in IBD, so as to help define the 'optimal' treatment target.
4. To explore the extent to which treatment targets are achieved in IBD clinical practice, alongside clinician perceptions and potential barriers to a 'treat to target' approach.
5. To explore body composition in patients with IBD, so as to describe rates of aberrant body composition, evolution of body composition over time, influencing factors, and correlation with anthropometric tools of assessment.
6. To evaluate the impact of body composition, in particular obesity and VAT, on outcomes in patients with IBD.

Research process

Several studies were conducted to address the overarching aim set out for this thesis. The research presented in this thesis was undertaken in both Adelaide, South Australia and Oxford, United Kingdom. The research performed may be broadly divided into 3 inter-related work-streams along with a systematic review, the time-lines for which were overlapping over the course of candidature.

Project 1. The first work-stream set out to evaluate the concordance between treatment targets and as well as the 'optimal' treatment target in IBD (Oxford, UK).

Project 2. The second work-stream involved evaluation of treatment targets achieved and potential barriers to attainment in routine clinical care (Adelaide, SA).

Project 3. The third work-stream involved cross-sectional and longitudinal evaluation of body composition in an IBD cohort (Adelaide, SA).

REFERENCES

1. Dignass A, Eliakim R, Magro F*, et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. Journal of Crohn's & colitis. 2012 Dec;6(10):965-90.
2. Dignass A, Van Assche G, Lindsay JO*, et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. Journal of Crohn's & colitis. 2010 Feb;4(1):28-62.
3. Van Assche G, Dignass A, Panes J*, et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. Journal of Crohn's & colitis. 2010 Feb;4(1):7-27.
4. Harbord M, Annese V, Vavricka SR*, et al.* The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2016 Mar;10(3):239-54.
5. Chapman RW, Williamson KD. Are Dominant Strictures in Primary Sclerosing Cholangitis a Risk Factor for Cholangiocarcinoma? Current hepatology reports. 2017;16(2):124-9.
6. Hirschfield GM, Karlsen TH, Lindor KD*, et al.* Primary sclerosing cholangitis. Lancet. 2013 Nov 09;382(9904):1587-99.
7. Van Assche G, Dignass A, Bokemeyer B*, et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. Journal of Crohn's & colitis. 2013 Feb;7(1):1-33.
8. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011 Jun 16;474(7351):307-17.
9. Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. Gut. 2013 Oct;62(10):1505-10.
10. Jostins L, Ripke S, Weersma RK*, et al.* Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491(7422):119-24.
11. Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. Gut. 2013 Dec;62(12):1795-805.

12. Uhlig HH, Schwerd T, Koletzko S*, et al.* The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014 Nov;147(5):990-1007.
13. De Cruz P, Prideaux L, Wagner J*, et al.* Characterization of the gastrointestinal microbiota in health and inflammatory bowel disease. Inflammatory bowel diseases. 2012 Feb;18(2):372-90.
14. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology. 2014 May;146(6):1489-99.
15. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. Gastroenterology. 2011 May;140(6):1704-12.
16. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nature reviews Gastroenterology & hepatology. 2015 Apr;12(4):205-17.
17. Cosnes J, Gower-Rousseau C, Seksik P*, et al.* Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011 May;140(6):1785-94.
18. Molodecky NA, Soon IS, Rabi DM*, et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.
19. Australia CsaC. The Economic Costs of Crohn's Disease and Ulcerative Colitis.
20. Ng SC, Tang W, Ching JY*, et al.* Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology. 2013 Jul;145(1):158-65.
21. Ng SC, Tang W, Leong RW*, et al.* Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. Gut. 2015 Jul;64(7):1063-71.
22. Benchimol EI, Mack DR, Guttmann A*, et al.* Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. The American journal of gastroenterology. 2015 Apr;110(4):553-63.
23. Abraham C, Cho JH. Inflammatory bowel disease. The New England journal of medicine. 2009 Nov 19;361(21):2066-78.
24. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF*, et al.* The natural history of adult Crohn's disease in population-based cohorts. The American journal of gastroenterology. 2010 Feb;105(2):289-97.

25. Thia KT, Sandborn WJ, Harmsen WS*, et al.* Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterology. 2010 Oct;139(4):1147-55.
26. Solberg IC, Lygren I, Jahnsen J*, et al.* Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scandinavian journal of gastroenterology. 2009;44(4):431-40.
27. Langholz E, Munkholm P, Davidsen M*, et al.* Changes in extent of ulcerative colitis: a study on the course and prognostic factors. Scandinavian journal of gastroenterology. 1996 Mar;31(3):260-6.
28. Torres J, Billioud V, Sachar DB*, et al.* Ulcerative colitis as a progressive disease: the forgotten evidence. Inflammatory bowel diseases. 2012 Jul;18(7):1356-63.
29. Bryant RV, Brain O, Travis SP. Conventional drug therapy for inflammatory bowel disease. Scandinavian journal of gastroenterology. 2015 Jan;50(1):90-112.
30. Satsangi J, Silverberg MS, Vermeire S*, et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749-53.
31. Levine A, Griffiths A, Markowitz J*, et al.* Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflammatory bowel diseases. 2011 Jun;17(6):1314-21.
32. Siegel CA, Whitman CB, Spiegel BMR*, et al.* Development of an index to define overall disease severity in IBD. Gut. 2018 Feb;67(2):244-54.
33. Peyrin-Biroulet L, Panes J, Sandborn WJ*, et al.* Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clinical gastroenterology and hepatology. 2015 Jun 11.
34. Kim AH, Roberts C, Feagan BG*, et al.* Developing a Standard Set of Patient-Centred Outcomes for Inflammatory Bowel Disease - an International, Cross-disciplinary Consensus. Journal of Crohn's & colitis. 2017 Dec 5.
35. Peyrin-Biroulet L, Cieza A, Sandborn WJ*, et al.* Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. Gut. 2012 Feb;61(2):241-7.
36. Ramos A, Calvet X, Sicilia B*, et al.* IBD-related work disability in the community: Prevalence, severity and predictive factors. A cross-sectional study. United European gastroenterology journal. 2015 Aug;3(4):335-42.

37. Selinger CP, Andrews J, Dent OF*, et al.* Cause-specific mortality and 30-year relative survival of Crohn's disease and ulcerative colitis. Inflammatory bowel diseases. 2013 Aug;19(9):1880-8.
38. Limsrivilai J, Stidham RW, Govani SM*, et al.* Factors That Predict High Health Care Utilization and Costs for Patients With Inflammatory Bowel Diseases. Clinical gastroenterology and hepatology. 2017 Mar;15(3):385-92.e2.
39. Sands BE, Abreu MT, Ferry GD*, et al.* Design issues and outcomes in IBD clinical trials. Inflammatory bowel diseases. 2005 Nov;11 Suppl 1:S22-8.
40. Pariente B, Cosnes J, Danese S*, et al.* Development of the Crohn's disease digestive damage score, the Lemann score. Inflammatory bowel diseases. 2011 Jun;17(6):1415-22.
41. Jairath V, Khanna R, Zou GY*, et al.* Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. Alimentary pharmacology & therapeutics. 2015 Nov;42(10):1200-10.
42. Bodger K, Ormerod C, Shackcloth D*, et al.* Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. Gut. 2014 Jul;63(7):1092-102.
43. Berry SK, Siegel CA, Melmed GY. Quality Improvement Initiatives in Inflammatory Bowel Disease. Current gastroenterology reports. 2017 Aug;19(8):41.
44. Esrailian E, Spiegel BM, Targownik LE*, et al.* Differences in the management of Crohn's disease among experts and community providers, based on a national survey of sample case vignettes. Alimentary pharmacology & therapeutics. 2007 Oct 1;26(7):1005-18.
45. Melmed GY, Siegel CA, Spiegel BM*, et al.* Quality indicators for inflammatory bowel disease: development of process and outcome measures. Inflammatory bowel diseases. 2013 Mar;19(3):662-8.
46. Nguyen GC, Boland K, Afif W*, et al.* Modified Delphi Process for the Development of Choosing Wisely for Inflammatory Bowel Disease. Inflammatory bowel diseases. 2017 Jun;23(6):858-65.
47. Nguyen GC, Devlin SM, Afif W*, et al.* Defining quality indicators for best-practice management of inflammatory bowel disease in Canada. Canadian journal of gastroenterology & hepatology. 2014 May;28(5):275-85.

48. Siegel CA, Allen JI, Melmed GY. Translating improved quality of care into an improved quality of life for patients with inflammatory bowel disease. Clinical gastroenterology and hepatology. 2013 Aug;11(8):908-12.
49. Melmed GY, Siegel CA. Quality improvement in inflammatory bowel disease. Gastroenterology & hepatology. 2013 May;9(5):286-92.
50. Bryant RV, Trott MJ, Bartholomeusz FD*, et al.* Systematic review: body composition in adults with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Aug;38(3):213-25.
51. Adams DW, Gurwara S, Silver HJ*, et al.* Sarcopenia Is Common in Overweight Patients with Inflammatory Bowel Disease and May Predict Need for Surgery. Inflammatory bowel diseases. 2017 Jul;23(7):1182-6.
52. Bamba S, Sasaki M, Takaoka A*, et al.* Sarcopenia is a predictive factor for intestinal resection in admitted patients with Crohn's disease. PloS one. 2017;12(6):e0180036.
53. Singh S, Dulai PS, Zarrinpar A*, et al.* Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nature reviews Gastroenterology & hepatology. 2017 Feb;14(2):110-21.
54. Bryant RV, Jairath V, Curry N*, et al.* Thrombosis in inflammatory bowel disease: are we tailoring prophylaxis to those most at risk? Journal of Crohn's & colitis. 2014 Feb;8(2):166-71.
55. Singh S, Singh H, Loftus EV, Jr.*, et al.* Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clinical gastroenterology and hepatology. 2014 Mar;12(3):382-93.
56. Rahier JF, Magro F, Abreu C*, et al.* Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's & colitis. 2014; 8(6): 443-68.
57. Ulitsky A, Ananthakrishnan AN, Naik A*, et al.* Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. JPEN Journal of parenteral and enteral nutrition. 2011 May;35(3):308-16.
58. Garg M, Hendy P, Ding JN*, et al.* The effect of vitamin D on intestinal inflammation and faecal microbiota in patients with ulcerative colitis. Journal of Crohn's & colitis. 2018 May (epub ahead of print).

59. van Langenberg DR, Gatta PD, Hill B*, et al.* Delving into disability in Crohn's disease: Dysregulation of molecular pathways may explain skeletal muscle loss in Crohn's disease. Journal of Crohn's & colitis. 2014;8 (7):626-34.
60. Byrne G, Rosenfeld G, Leung Y*, et al.* Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease. Canadian journal of gastroenterology & hepatology. 2017;2017:6496727.
61. Targownik LE, Nugent Z, Singh H*, et al.* The prevalence and predictors of opioid use in inflammatory bowel disease: a population-based analysis. The American journal of gastroenterology. 2014 Oct;109(10):1613-20.
62. van Langenberg DR, Della Gatta P, Warmington SA*, et al.* Objectively measured muscle fatigue in Crohn's disease: correlation with self-reported fatigue and associated factors for clinical application. Journal of Crohn's & colitis. 2014 Feb;8(2):137-46.
63. Loudon CP, Corroll V, Butcher J*, et al.* The effects of physical exercise on patients with Crohn's disease. Am J Gastroenterol. 1999 Mar;94(3):697-703.
64. Halmos EP, Gibson PR. Dietary management of IBD--insights and advice. Nature reviews Gastroenterology & hepatology. 2015 Mar;12(3):133-46.
65. Bakker SF, Dik VK, Witte BI*, et al.* Increase in bone mineral density in strictly treated Crohn's disease patients with concomitant calcium and vitamin D supplementation. Journal of Crohn's & colitis. 2013 Jun;7(5):377-84.
66. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clinical gastroenterology and hepatology. 2008 Jan;6(1):41-5.
67. Hansen PR. Chronic inflammatory diseases and atherosclerotic cardiovascular disease: Innocent bystanders or partners in crime? Current pharmaceutical design. 2018; 24(3): 281-290.
68. Bernstein CN, Blanchard JF, Houston DS*, et al.* The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thrombosis and haemostasis. 2001 Mar;85(3):430-4.
69. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. British medical journal. 1955 Oct 29;2(4947):1041-8.
70. Danese S, Fiocchi C, Panes J. Drug development in IBD: from novel target identification to early clinical trials. Gut. 2016 Aug;65(8):1233-9.

71. D'Haens G, Baert F, van Assche G*, et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008 Feb 23;371(9613):660-7.
72. Khanna R, Bressler B, Levesque BG*, et al.* Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet. 2015 Nov 7;386(10006):1825-34.
73. Walsh AJ, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. Nature reviews Gastroenterology & hepatology. 2016 Oct;13(10):567-79.
74. Siegel CA. Shared decision making in inflammatory bowel disease: helping patients understand the tradeoffs between treatment options. Gut. 2012 Mar;61(3):459-65.
75. Jowett SL, Seal CJ, Pearce MS*, et al.* Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut. 2004 Oct;53(10):1479-84.
76. Parkes GC, Whelan K, Lindsay JO. Smoking in inflammatory bowel disease: Impact on disease course and insights into the aetiology of its effect. Journal of Crohn's & colitis. 2014; 8(8): 717-725.
77. Torres J, Caprioli F, Katsanos KH*, et al.* Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases. Journal of Crohn's & colitis. 2016 Dec;10(12):1385-94.
78. De Cruz P, Kamm MA, Hamilton AL*, et al.* Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015 Apr 11;385(9976):1406-17.
79. Duricova D, Fumery M, Annese V*, et al.* The natural history of Crohn's disease in children: a review of population-based studies. European journal of gastroenterology & hepatology. 2017 Feb;29(2):125-34.
80. Fries W, Viola A, Manetti N*, et al.* Disease patterns in late-onset ulcerative colitis: Results from the IG-IBD "AGED study". Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2017 Jan;49(1):17-23.
81. Beaugerie L, Seksik P, Nion-Larmurier I*, et al.* Predictors of Crohn's disease. Gastroenterology. 2006 Mar;130(3):650-6.
82. Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. Scandinavian journal of gastroenterology. 2008 Aug;43(8):948-54.
83. Bouguen G, Levesque BG, Feagan BG*, et al.* Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease. Clinical gastroenterology and hepatology. 2013 Sep 10;13(6):1042-50.

84. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012 Nov;61(11):1619-35.
85. Burgell R, Asthana A, Gibson PR. Irritable bowel syndrome in patients with quiescent inflammatory bowel disease. A review. Minerva gastroenterologica e dietologica. 2015; 61(4):201-213.
86. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. The American journal of gastroenterology. 2012 Oct;107(10):1474-82.
87. Landi B, Anh TN, Cortot A*, et al.* Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gastroenterology. 1992 May;102(5):1647-53.
88. Peyrin-Biroulet L, Sandborn W, Sands BE*, et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Sep;110(9):1324-38.
89. Smolen JS, Aletaha D, Bijlsma JW*, et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the rheumatic diseases. 2010 Apr;69(4):631-7.
90. Baert F, Moortgat L, Van Assche G*, et al.* Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010 Feb;138(2):463-8.
91. Colombel JF, Rutgeerts P, Reinisch W*, et al.* Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011 Oct;141(4):1194-201.
92. Rutgeerts P, Diamond RH, Bala M*, et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointestinal endoscopy. 2006 Mar;63(3):433-42.
93. Schnitzler F, Fidder H, Ferrante M*, et al.* Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflammatory bowel diseases. 2009 Sep;15(9):1295-301.
94. Froslie KF, Jahnsen J, Moum BA*, et al.* Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007 Aug;133(2):412-22.

95. Rutgeerts P, Geboes K, Vantrappen G*, et al.* Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990 Oct;99(4):956-63.
96. Bryant RV, Winer S, Travis SP*, et al.* Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's & colitis. 2014 Dec 1;8(12):1582-97.
97. Azad S, Sood N, Sood A. Biological and histological parameters as predictors of relapse in ulcerative colitis: a prospective study. Saudi journal of gastroenterology. 2011 May-Jun;17(3):194-8.
98. Bessissow T, Lemmens B, Ferrante M*, et al.* Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. The American journal of gastroenterology. 2012 Nov;107(11):1684-92.
99. Bitton A, Peppercorn MA, Antonioli DA*, et al.* Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001 Jan;120(1):13-20.
100. Gupta RB, Harpaz N, Itzkowitz S*, et al.* Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007 Oct;133(4):1099-105.
101. Hefti MM, Chessin DB, Harpaz NH*, et al.* Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Diseases of the colon and rectum. 2009 Feb;52(2):193-7.
102. Riley SA, Mani V, Goodman MJ*, et al.* Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991 Feb;32(2):174-8.
103. Rubin DT HD, Hetzel JT et al Increased degree of histological inflammation predicts colectomy and hospitalisation in patients with ulcerative colitis. Gut. 2007;132 (Suppl. 1):A-19 (Abstract 103).
104. Rutter M, Saunders B, Wilkinson K*, et al.* Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004 Feb;126(2):451-9.
105. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. The American journal of digestive diseases. 1966 Nov;11(11):847-57.
106. Baars JE, Nuij VJ, Oldenburg B*, et al.* Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflammatory bowel diseases. 2012 Sep;18(9):1634-40.

107. Rimola J, Ordas I, Rodriguez S*, et al.* Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. Inflammatory bowel diseases. 2011 Aug;17(8):1759-68.
108. Rimola J, Rodriguez S, Garcia-Bosch O*, et al.* Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut. 2009 Aug;58(8):1113-20.
109. Kiss LS, Szamosi T, Molnar T*, et al.* Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. Alimentary pharmacology & therapeutics. 2011 Oct;34(8):911-22.
110. Hanauer SB, Sandborn WJ, Rutgeerts P*, et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006 Feb;130(2):323-33.
111. Lamireau T, Cezard JP, Dabadie A*, et al.* Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. Inflammatory bowel diseases. 2004 Nov;10(6):745-50.
112. Rutgeerts P, D'Haens G, Targan S*, et al.* Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology. 1999 Oct;117(4):761-9.
113. Targan SR, Hanauer SB, van Deventer SJ*, et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. The New England journal of medicine. 1997 Oct 9;337(15):1029-35.
114. Reinisch W, Colombel JF, Sandborn WJ*, et al.* Factors associated with short- and long-term outcomes of therapy for Crohn's disease. Clinical gastroenterology and hepatology. 2015 Mar;13(3):539-47.e2.
115. Sipponen T, Bjorkesten CG, Farkkila M*, et al.* Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scandinavian journal of gastroenterology. 2010 Mar;45(3):325-31.
116. Kiss LS, Papp M, Lovasz BD*, et al.* High-sensitivity C-reactive protein for identification of disease phenotype, active disease, and clinical relapses in Crohn's disease: a marker for patient classification? Inflammatory bowel diseases. 2012 Sep;18(9):1647-54.

117. Henderson P, Kennedy NA, Van Limbergen JE*, et al.* Serum C-reactive protein and CRP genotype in pediatric inflammatory bowel disease: influence on phenotype, natural history, and response to therapy. Inflammatory bowel diseases. 2015 Mar;21(3):596-605.
118. Travis SP, Farrant JM, Ricketts C*, et al.* Predicting outcome in severe ulcerative colitis. Gut. 1996 Jun;38(6):905-10.
119. Falvey JD, Hoskin T, Meijer B*, et al.* Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. Inflammatory bowel diseases. 2015 Apr;21(4):824-31.
120. Mosli MH, Zou G, Garg SK*, et al.* C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. The American journal of gastroenterology. 2015 Jun;110(6):802-19.
121. Calafat M, Cabre E, Manosa M*, et al.* High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what is the best timing for stool sampling? Inflammatory bowel diseases. 2015 May;21(5):1072-6.
122. Allen PB, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. Current opinion in gastroenterology. 2013 Jul;29(4):397-404.
123. Bouguen G, Levesque BG, Pola S*, et al.* Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clinical gastroenterology and hepatology. 2014 Jun;12(6):978-85.
124. Colombel JF, Panaccione R, Bossuyt P*, et al.* Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2018; 390(10114):2779-2789.
125. Colombel JF, Sandborn WJ, Reinisch W*, et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. The New England journal of medicine. 2010 Apr 15;362(15):1383-95.
126. Sandborn WJ, van Assche G, Reinisch W*, et al.* Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65 e1-3.
127. Ha C, Ullman TA, Siegel CA*, et al.* Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clinical gastroenterology and hepatology. 2012 Sep;10(9):1002-7.

128. Vermeer M, Kuper HH, Bernelot Moens HJ*, et al.* Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. Arthritis research & therapy. 2012 Nov 23;14(6):R254.
129. Capristo E, Addolorato G, Mingrone G*, et al.* Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. Am J Gastroenterol. [Research Support, Non-U.S. Gov't]. 1998;93(12):2411-9.
130. Capristo E, Mingrone G, Addolorato G*, et al.* Metabolic features of inflammatory bowel disease in a remission phase of the disease activity. J Intern Med. 1998;243(5):339-47.
131. Capristo E, Mingrone G, Addolorato G*, et al.* Glucose metabolism and insulin sensitivity in inactive inflammatory bowel disease. Aliment Pharmacol Ther. 1999;13(2):209-17.
132. Cuoco L, Vescovo G, Castaman R*, et al.* Skeletal muscle wastage in Crohn's disease: a pathway shared with heart failure? Int J Cardiol. 2008;127(2):219-27.
133. Filippi J, Al-Jaouni R, Wiroth JB*, et al.* Nutritional deficiencies in patients with Crohn's disease in remission. Inflamm Bowel Dis. 2006;12(3):185-91.
134. Geerling BJ, Badart-Smook A, Stockbrugger RW*, et al.* Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. Am J Clin Nutr. 1998;67(5):919-26.
135. Geerling BJ, Badart-Smook A, Stockbrugger RW*, et al.* Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. Eur J Clin Nutr. 2000;54(6):514-21.
136. Geerling BJ, Lichtenbelt WD, Stockbrugger RW*, et al.* Gender specific alterations of body composition in patients with inflammatory bowel disease compared with controls. Eur J Clin Nutr. 1999;53(6):479-85.
137. Jahnsen J, Falch JA, Mowinckel P*, et al.* Body composition in patients with inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2003;98(7):1556-62.
138. Katznelson L, Fairfield WP, Zeizafoun N*, et al.* Effects of growth hormone secretion on body composition in patients with Crohn's disease. The Journal of clinical endocrinology and metabolism. 2003 Nov;88(11):5468-72.
139. Mingrone G, Benedetti G, Capristo E*, et al.* Twenty-four-hour energy balance in Crohn disease patients: metabolic implications of steroid treatment. Am J Clin Nutr. 1998;67(1):118-23.

140. Mingrone G, Capristo E, Greco AV*, et al.* Elevated diet-induced thermogenesis and lipid oxidation rate in Crohn disease. Am J Clin Nutr. 1999;69(2):325-30.
141. Mingrone G, Greco AV, Benedetti G*, et al.* Increased resting lipid oxidation in Crohn's disease. Dig Dis Sci. 1996;41(1):72-6.
142. Schneider SM, Al-Jaouni R, Filippi J*, et al.* Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008;14(11):1562-8.
143. Tjellesen L, Nielsen PK, Staun M. Body composition by dual-energy X-ray absorptiometry in patients with Crohn's disease. Scand J Gastroenterol. 1998;33(9):956-60.
144. Ulivieri FM, Lisciandrano D, Ranzi T*, et al.* Bone mineral density and body composition in patients with ulcerative colitis. Am J Gastroenterol. 2000;95(6):1491-4.
145. Ulivieri FM, Piodi LP, Taioli E*, et al.* Bone mineral density and body composition in ulcerative colitis: a six-year follow-up. Osteoporos Int. 2001;12(5):343-8.
146. Valentini L, Schaper L, Buning C*, et al.* Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition. 2008;24(7-8):694-702.
147. Wiroth JB, Filippi J, Schneider SM*, et al.* Muscle performance in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2005;11(3):296-303.
148. Siffledeen JS, Fedorak RN, Siminoski K*, et al.* Bones and Crohn's: risk factors associated with low bone mineral density in patients with Crohn's disease. Inflammatory bowel diseases. 2004 May;10(3):220-8.
149. Goodhand JR, Kamperidis N, Nguyen H*, et al.* Application of the WHO fracture risk assessment tool (FRAX) to predict need for DEXA scanning and treatment in patients with inflammatory bowel disease at risk of osteoporosis. Aliment Pharmacol Ther. 2011 Mar;33(5):551-8.
150. Targownik LE, Bernstein CN, Nugent Z*, et al.* Inflammatory bowel disease and the risk of fracture after controlling for FRAX. J Bone Miner Res. 2013 May;28(5):1007-13.
151. Targownik LE, Bernstein CN, Nugent Z*, et al.* Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clinical gastroenterology and hepatology. 2013 Mar;11(3):278-85.

152. Wada Y, Hisamatsu T, Naganuma M*, et al.* Risk factors for decreased bone mineral density in inflammatory bowel disease: A cross-sectional study. Clinical nutrition (Edinburgh, Scotland). 2015 Dec;34(6):1202-9.
153. Bernstein CN. Osteoporosis in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2006;4(2):152-6.
154. Bernstein CN, Blanchard JF, Leslie W*, et al.* The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Annals of internal medicine. 2000 Nov 21;133(10):795-9.
155. Sousa Guerreiro C, Cravo M, Costa AR*, et al.* A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. Am J Gastroenterol. 2007;102(11):2551-6.
156. Steiner SJ, Noe JD, Denne SC. Corticosteroids increase protein breakdown and loss in newly diagnosed pediatric Crohn disease. Pediatr Res. 2011;70(5):484-8.
157. Valentini L, Schulzke JD. Mundane, yet challenging: the assessment of malnutrition in inflammatory bowel disease. European journal of internal medicine. 2011 Feb;22(1):13-5.
158. Casals-Seoane F, Chaparro M, Mate J*, et al.* Clinical Course of Bone Metabolism Disorders in Patients with Inflammatory Bowel Disease: A 5-Year Prospective Study. Inflammatory bowel diseases. 2016 Aug;22(8):1929-36.
159. Targownik LE, Leslie WD, Carr R*, et al.* Longitudinal change in bone mineral density in a population-based cohort of patients with inflammatory bowel disease. Calcified tissue international. 2012 Nov;91(5):356-63.
160. Schule S, Rossel JB, Frey D*, et al.* Widely differing screening and treatment practice for osteoporosis in patients with inflammatory bowel diseases in the Swiss IBD cohort study. Medicine. 2017 Jun;96(22):e6788.
161. Cruz-Jentoft AJ, Baeyens JP, Bauer JM*, et al.* Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010 Jul;39(4):412-23.
162. Janssen I, Baumgartner RN, Ross R*, et al.* Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol. 2004;159(4):413-21.
163. Woo J, Ho SC, Sham A. Longitudinal changes in body mass index and body composition over 3 years and relationship to health outcomes in Hong Kong Chinese age 70 and older. J Am Geriatr Soc. 2001;49(6):737-46.

164. Beaudart C, Zaaria M, Pasleau F*, et al.* Health Outcomes of Sarcopenia: A Systematic Review and Meta-Analysis. PloS one. 2017;12(1):e0169548.
165. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. Journal of human nutrition and dietetics. 2011 Aug;24(4):313-26.
166. Tang K, Murano G, Wagner H*, et al.* Impaired exercise capacity and skeletal muscle function in a mouse model of pulmonary inflammation. Journal of applied physiology (Bethesda, Md : 1985). 2013 May;114(9):1340-50.
167. Skallerup A, Nygaard L, Olesen SS*, et al.* The prevalence of sarcopenia is markedly increased in patients with intestinal failure and associates with several risk factors. Clinical nutrition (Edinburgh, Scotland). 2017 (epub before print).
168. Zhang T, Ding C, Xie T*, et al.* Skeletal muscle depletion correlates with disease activity in ulcerative colitis and is reversed after colectomy. Clinical nutrition (Edinburgh, Scotland). 2017 Dec;36(6):1586-92.
169. Lee N, Radford-Smith GL, Forwood M*, et al.* Body composition and muscle strength as predictors of bone mineral density in Crohn's disease. J Bone Miner Metab. 2009;27(4):456-63.
170. Mauro M, Armstrong D. Evaluation of densitometric bone-muscle relationships in Crohn's disease. Bone. 2007;40(6):1610-4.
171. Leslie WD, Miller N, Rogala L*, et al.* Body mass and composition affect bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. Inflamm Bowel Dis. 2009;15(1):39-46.
172. van Langenberg DR, Della Gatta P, Warmington SA*, et al.* Objectively measured muscle fatigue in Crohn's disease: Correlation with self-reported fatigue and associated factors for clinical application. Journal of Crohn's & colitis. 2014;8(2):137-46.
173. Ding NS, Malietzis G, Lung PFC*, et al.* The body composition profile is associated with response to anti-TNF therapy in Crohn's disease and may offer an alternative dosing paradigm. Alimentary pharmacology & therapeutics. 2017 Nov;46(9):883-91.
174. Holt DQ, Varma P, Strauss BJG*, et al.* Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis. European journal of clinical nutrition. 2017 Jun;71(6):773-7.
175. Molfino A, Amabile MI, Rossi Fanelli F*, et al.* Novel therapeutic options for cachexia and sarcopenia. Expert opinion on biological therapy. 2016 Oct;16(10):1239-44.

176. Subramaniam K, Fallon K, Ruut T, *et al.* Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015 Mar;41(5):419-28.

177. Sylvester FA, Leopold S, Lincoln M, *et al.* A two-year longitudinal study of persistent lean tissue deficits in children with Crohn's disease. Clin Gastroenterol Hepatol. 2009;7(4):452-5.

178. Wiskin AE, Wootton SA, Hunt TM, *et al.* Body composition in childhood inflammatory bowel disease. Clin Nutr. 2011;30(1):112-5.

179. Ng M, Fleming T, Robinson M, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 Aug 30;384(9945):766-81.

180. National Health Survey: First Results, 2014-2015 [database on the Internet]2015 [cited 10/01/2018]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by Subject/4364.0.55.001~2014-15~Main Features~Overweight and obesity~22

181. Finkelstein EA, Trogdon JG, Cohen JW, *et al.* Annual medical spending attributable to obesity: payer-and service-specific estimates. Health affairs (Project Hope). 2009 Sep-Oct;28(5):w822-31.

182. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. Gastroenterology. 2017 Feb;152(2):313-21.e2.

183. Qin B, Yang M, Fu H, *et al.* Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis research & therapy. 2015 Mar 29;17:86.

184. Sterry W, Strober BE, Menter A. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. The British journal of dermatology. 2007 Oct;157(4):649-55.

185. Chan SS, Luben R, Olsen A, *et al.* Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). The American journal of gastroenterology. 2013 Apr;108(4):575-82.

186. Harpsoe MC, Basit S, Andersson M, *et al.* Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. International journal of epidemiology. 2014 Jun;43(3):843-55.

187. Khalili H, Ananthakrishnan AN, Konijeti GG*, et al.* Measures of obesity and risk of Crohn's disease and ulcerative colitis. Inflammatory bowel diseases. 2015 Feb;21(2):361-8.
188. Fink C, Karagiannides I, Bakirtzi K*, et al.* Adipose tissue and inflammatory bowel disease pathogenesis. Inflammatory bowel diseases. 2012 Aug;18(8):1550-7.
189. Winer DA, Luck H, Tsai S*, et al.* The Intestinal Immune System in Obesity and Insulin Resistance. Cell metabolism. 2016 Mar 8;23(3):413-26.
190. Flores A, Burstein E, Cipher DJ*, et al.* Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. Digestive diseases and sciences. 2015 Aug;60(8):2436-45.
191. Pringle PL, Stewart KO, Peloquin JM*, et al.* Body Mass Index, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. Inflammatory bowel diseases. 2015 Oct;21(10):2304-10.
192. Seminerio JL, Koutroubakis IE, Ramos-Rivers C*, et al.* Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. Inflammatory bowel diseases. 2015 Dec;21(12):2857-63.
193. Nic Suibhne T, Raftery TC, McMahon O*, et al.* High prevalence of overweight and obesity in adults with Crohn's disease: Associations with disease and lifestyle factors. Journal of Crohn's & colitis. 2013; 7(7):e241-8.
194. Mendall MA, Gunasekera AV, John BJ*, et al.* Is obesity a risk factor for Crohn's disease? Digestive diseases and sciences. 2011 Mar;56(3):837-44.
195. Stabroth-Akil D, Leifeld L, Pfutzer R*, et al.* The effect of body weight on the severity and clinical course of ulcerative colitis. International journal of colorectal disease. 2015 Feb;30(2):237-42.
196. Back IR, Marcon SS, Gaino NM*, et al.* Body composition in patients with crohn's disease and ulcerative colitis. Arquivos de gastroenterologia. 2017 Apr-Jun;54(2):109-14.
197. Blain A, Cattan S, Beaugerie L*, et al.* Crohn's disease clinical course and severity in obese patients. Clinical nutrition (Edinburgh, Scotland). 2002 Feb;21(1):51-7.
198. Moran GW, Dubeau MF, Kaplan GG*, et al.* The increasing weight of Crohn's disease subjects in clinical trials: a hypothesis-generatings time-trend analysis. Inflammatory bowel diseases. 2013 Dec;19(13):2949-56.
199. Zietek T, Rath E. Inflammation Meets Metabolic Disease: Gut Feeling Mediated by GLP-1. Frontiers in immunology. 2016;7:154.

200. Karmiris K, Koutroubakis IE, Xidakis C*, et al.* Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflammatory bowel diseases. 2006 Feb;12(2):100-5.
201. Steed H, Walsh S, Reynolds N. A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. Obesity facts. 2009;2(6):370-2.
202. Causey MW, Johnson EK, Miller S*, et al.* The impact of obesity on outcomes following major surgery for Crohn's disease: an American College of Surgeons National Surgical Quality Improvement Program assessment. Dis Colon Rectum. 2011 Dec;54(12):1488-95.
203. Krane MK, Allaix ME, Zoccali M*, et al.* Does morbid obesity change outcomes after laparoscopic surgery for inflammatory bowel disease? Review of 626 consecutive cases. J Am Coll Surg. 2013 May;216(5):986-96.
204. Singh S, Fumery M, Sandborn WJ*, et al.* Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Alimentary pharmacology & therapeutics. 2018 Jan;47(2):162-75.
205. Singh S, Heien HC, Sangaralingham LR*, et al.* Comparative Effectiveness and Safety of Anti-Tumor Necrosis Factor Agents in Biologic-Naive Patients With Crohn's Disease. Clinical gastroenterology and hepatology. 2016 Aug;14(8):1120-9.e6.
206. Bultman E, de Haar C, van Liere-Baron A*, et al.* Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. Aliment Pharmacol Ther. 2012 Feb;35(3):335-41.
207. Hass DJ, Brensinger CM, Lewis JD*, et al.* The impact of increased body mass index on the clinical course of Crohn's disease. Clinical gastroenterology and hepatology. 2006 Apr;4(4):482-8.
208. Shuster A, Patlas M, Pinthus JH*, et al.* The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. The British journal of radiology. 2012 Jan;85(1009):1-10.
209. Crohn BB, Ginzburg L, Oppenheimer GD. Landmark article Oct 15, 1932. Regional ileitis. A pathological and clinical entity. By Burril B. Crohn, Leon Ginzburg, and Gordon D. Oppenheimer. Jama. 1984 Jan 06;251(1):73-9.
210. Sheehan AL, Warren BF, Gear MW*, et al.* Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. The British journal of surgery. 1992 Sep;79(9):955-8.

211. Desreumaux P, Ernst O, Geboes K*, et al.* Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. Gastroenterology. 1999 Jul;117(1):73-81.
212. Schaffler A, Herfarth H. Creeping fat in Crohn's disease: travelling in a creeper lane of research? Gut. 2005 Jun;54(6):742-4.
213. Peyrin-Biroulet L, Chamaillard M, Gonzalez F*, et al.* Mesenteric fat in Crohn's disease: a pathogenetic hallmark or an innocent bystander? Gut. 2007 Apr;56(4):577-83.
214. Buning C, von Kraft C, Hermsdorf M*, et al.* Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. Inflammatory bowel diseases. 2015 Nov;21(11):2590-7.
215. Connelly TM, Juza RM, Sangster W*, et al.* Volumetric fat ratio and not body mass index is predictive of ileocolectomy outcomes in Crohn's disease patients. Digestive surgery. 2014;31(3):219-24.
216. Ding Z, Wu XR, Remer EM*, et al.* Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. Colorectal disease. 2016 Feb;18(2):163-72.
217. Erhayiem B, Dhingsa R, Hawkey CJ*, et al.* Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. Clinical gastroenterology and hepatology. 2011 Aug;9(8):684-7.e1.
218. Holt DQ, Moore GT, Strauss BJ*, et al.* Visceral adiposity predicts post-operative Crohn's disease recurrence. Alimentary pharmacology & therapeutics. 2017 May;45(9):1255-64.
219. Liu G, Wu X, Li Y*, et al.* Postoperative excessive gain in visceral adipose tissue as well as body mass index are associated with adverse outcomes of an ileal pouch. Gastroenterology report. 2016 Sep 25 (epub ahead of print).
220. Kaul S, Rothney MP, Peters DM*, et al.* Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring, Md). 2012 Jun;20(6):1313-8.
221. Miazgowski T, Krzyzanowska-Swiniarska B, Dziwura-Ogonowska J*, et al.* The associations between cardiometabolic risk factors and visceral fat measured by a new dual-energy X-ray absorptiometry-derived method in lean healthy Caucasian women. Endocrine. 2014 Nov;47(2):500-5.
222. Direk K, Cecelja M, Astle W*, et al.* The relationship between DXA-based and anthropometric measures of visceral fat and morbidity in women. BMC cardiovascular disorders. 2013 Apr 03;13:25.

223. Rothney MP, Catapano AL, Xia J*, et al.* Abdominal visceral fat measurement using dual-energy X-ray: association with cardiometabolic risk factors. Obesity (Silver Spring, Md). 2013 Sep;21(9):1798-802.
224. Van Der Sloot KW, Joshi AD, Bellavance DR*, et al.* Visceral Adiposity, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. Inflammatory bowel diseases. 2017 Jan;23(1):82-8.
225. Tosato M, Marzetti E, Cesari M*, et al.* Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. Aging clinical and experimental research. 2017 Feb;29(1):19-27.
226. Bin CM, Flores C, Alvares-da-Silva MR*, et al.* Comparison between handgrip strength, subjective global assessment, anthropometry, and biochemical markers in assessing nutritional status of patients with Crohn's disease in clinical remission. Dig Dis Sci. [Comparative Study]. 2010;55(1):137-44.
227. Kullberg J, von Below C, Lonn L*, et al.* Practical approach for estimation of subcutaneous and visceral adipose tissue. Clinical physiology and functional imaging. 2007 May;27(3):148-53.
228. Lauretani F, Russo CR, Bandinelli S*, et al.* Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. Journal of applied physiology (Bethesda, Md : 1985). 2003 Nov;95(5):1851-60.
229. Marzetti E, Lees HA, Manini TM*, et al.* Skeletal muscle apoptotic signaling predicts thigh muscle volume and gait speed in community-dwelling older persons: an exploratory study. PloS one. 2012;7(2):e32829.
230. Holt DQ, Strauss BJ, Lau KK*, et al.* Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's Disease. Scandinavian journal of gastroenterology. 2016 Jul;51(7):842-7.
231. Panel NE. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. The American journal of clinical nutrition. 1996 Sep;64(3 Suppl):524s-32s.
232. Bellisari A, Roche AF, Siervogel RM. Reliability of B-mode ultrasonic measurements of subcutaneous adipose tissue and intra-abdominal depth: comparisons with skinfold thicknesses. International journal of obesity and related metabolic disorders. 1993 Aug;17(8):475-80.

CHAPTER 3: WHAT IS THE OPTIMAL TREATMENT TARGET IN UC?

Background

Establishing treatment targets is fundamental to delivering quality care in IBD. The ideology of a 'treat to target' approach in IBD is to venture beyond clinical symptoms to assess and treat objective inflammation, with the aim of retarding disease progression and preventing structural damage or disability. Endoscopic mucosal healing is an established target for patients with UC, since it is associated with reduced rates of clinical relapse, colectomy and hospitalisation. Consensus guidelines have therefore proposed a composite target of both clinical *and* endoscopic remission in UC.[1]

Persistent histological inflammation is common in the setting of endoscopic mucosal healing. Nevertheless, there has been little systematic analysis of the concordance between indices of remission in UC.[2] Observational data suggest that persistent histological inflammation in patients with UC predicts worse clinical outcomes and even risk of colorectal neoplastic.[3, 4] The question may then be posed as to whether histological remission is in fact the 'optimal' treatment target in UC.

This prospective observational study evaluated the concordance between and comparative prognostic benefits associated with attainment of clinical, endoscopic, and histological measures of remission in UC. Clinical outcomes of corticosteroid use, hospitalisation, and colectomy were captured over 6 years of follow-up under routine clinical care conditions.

Presented in this chapter is the manuscript published in Gut 2016; 65 (3): 408-14.

Specific author contributions

Title of Paper	Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up.
Publication Status	Published
Publication Details	Gut. 2016; 65 (3): 408-14. Impact factor: 16.6

Name of Principal Author (Candidate)	Robert Venning Bryant		
Contribution to the Paper	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	18/11/2015

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Daniel Burger
Contribution to the Paper 12%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article

Signature		Date	9/11/2015

Name of Co-Author	Joseph Delo		
Contribution to the Paper 3%	Data acquisition and management		
Signature		Date	3/11/2015

Name of Co-Author	Alissa Walsh		
Contribution to the Paper 3%	Conception and design of the project Data acquisition and management		
Signature		Date	3/11/2015

Name of Co-Author	Sally Thomas		
Contribution to the Paper 3%	Data acquisition and management		
Signature		Date	4/11/2015

Name of Co-Author	Axel von Herbay		
Contribution to the Paper 3%	Data acquisition and management Analysis and interpretation of research data		
Signature		Date	17/11/2015

Name of Co-Author	Otto Buchel
Contribution to the Paper 3%	Data acquisition and management

Signature		Date	4/11/2015

Name of Co-Author	Lydia White		
Contribution to the Paper 3%	Data acquisition and management		
Signature		Date	3/11/2015

Name of Co-Author	Oliver Brain		
Contribution to the Paper 3%	Conception and design of the project Data acquisition and management		
Signature		Date	3/11/2015

Name of Co-Author	Satish Keshav		
Contribution to the Paper 3%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	3/11/2015

Name of Co-Author	Brian Warren		
Contribution to the Paper 3%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data		
Signature	Posthumous signature not possible	Date	NA

Name of Co-Author	Simon PL Travis (Corresponding author)
Contribution to the Paper 11%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data

	Drafting and revision of article		
Signature		Date	2/11/2015

[Manuscript 1] Beyond endoscopic mucosal healing in ulcerative colitis: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up.

Short title: Histological healing in UC

Robert V Bryant[1,2], Daniel C Burger[1], Joseph Delo[1], Alissa J Walsh[1], Sally Thomas[1], Axel von Herbay[1], Otto C Buchel[1], Lydia White[1], Oliver Brain[1], Satish Keshav[1], Bryan F Warren[1], Simon PL Travis[1].

[1]Translational Gastroenterology Unit and Department of Cellular Pathology, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

[2]School of Medicine, Faculty of Health Sciences, University of Adelaide, South Australia

Corresponding author

Simon PL Travis DPhil FRCP
Translational Gastroenterology Unit,
John Radcliffe Hospital,
Oxford, OX3 9DU,
United Kingdom.
simon.travis@ndm.ox.ac.uk
Tel: +44 1865 228753

Acknowledgements

The authors gratefully acknowledge the assistance of Paul Bassett in the statistical analyses and the willingness of our patients to contribute to the study. The untimely death of Professor Bryan Warren, friend, tireless teacher and mentor to many, has been a loss to Medicine and to patient care, let alone to the field of Gastrointestinal Pathology in which he was a world expert.

Grant support and writing assistance

No funding was received for this study. No writing assistance was provided for the manuscript.

Conflicts of interest and personal interests

There is no competing interest to be reported by any author of the manuscript.

Abstract

Background: Endoscopic mucosal healing is an established treatment target for ulcerative colitis (UC), yet the value of achieving histological remission remains unclear.

Aims: To evaluate histological remission compared to endoscopic mucosal healing for predicting patient outcomes in UC.

Methods: Blinded assessment of endoscopic and histological measures of disease activity was performed on patients with established UC at baseline. Concordance and prognostic values of endoscopic mucosal healing (defined by Baron score ≤ 1) and histological remission (defined by Truelove and Richards' index) for predicting outcomes of corticosteroid use, hospitalisation and colectomy were determined over a median 6 years, including kappa statistics and Cox regression multivariate analysis.

Results: Some 91 patients with UC were followed for a median 72 months (interquartile range 54–75 months). Overall, concordance between endoscopic and histological remission was moderate (kappa 0.56, 95% CI 0.36–0.77); 24% patients had persistent inflammation despite endoscopic remission. Histological remission predicted corticosteroid use and acute severe colitis requiring hospitalisation over the follow-up period (hazard ratio (HR) 0.42 (0.2–0.9), p = 0.02; HR 0.21 (0.1–0.7), p = 0.02; respectively), whereas endoscopic mucosal healing did not (HR 0.86, 95% CI 0.5–1.7, p = 0.65; HR 0.83 95% CI 0.3–2.4, p = 0.74; respectively).

Conclusions: Histological remission is a target distinct from endoscopic mucosal healing in UC and better predicts lower rates of corticosteroid use and acute severe colitis requiring hospitalisation, over a median of 6 years. Our findings support the inclusion of histological indices in both UC clinical trials and practice, toward a target of 'complete remission'.

Key words

Ulcerative colitis, remission, disease activity, mucosal healing, histological healing, histopathology

Introduction

Therapeutic advances in the medical management of ulcerative colitis (UC) have altered treatment targets.[5-7] Consensus guidelines for clinical practice and trial endpoints recommend striving beyond resolution of clinical symptoms, to achieve endoscopic mucosal healing.[6, 8-11] Endoscopic mucosal healing in inflammatory bowel disease (IBD) is defined by resolution of visible mucosal inflammation and ulceration. This has been associated with prolonged clinical remission, lower rates of hospitalisation and lower rates of colectomy.[12-17] The term 'deep remission' has evolved as a treatment target in the era of biological therapy for IBD, currently defined as the combination of clinical remission and endoscopic mucosal healing.[18, 19] The unanswered question is whether mucosal biopsies, taken at the time of endoscopy for evaluation of microscopic mucosal healing, add sufficient therapeutic value to constitute a further target: 'complete remission'.[20]

Expert opinion aside, there is no gold-standard for assessing or defining disease remission in UC.[5, 6] Histological remission represents a target distinct from endoscopic mucosal healing, since many studies have shown that endoscopic mucosal healing does not necessarily reflect histological mucosal healing in UC.[4, 20-22] Multiple histological scoring systems to assess disease activity in UC have been described since the 1950s, though none are fully validated.[4, 20, 23-25] As a consequence of multiple scoring systems, there currently exists no standard definition for histological remission in UC.[20, 24] Definitions of histological remission range from residual inflammation with architectural distortion to complete normalisation of the colonic mucosa. This lack of consensus has limited incorporation of histopathological endpoints into clinical trials in UC, although this does not diminish the intuitive importance of controlling inflammation and persistent microscopic inflammation for predicting the future course of UC.

Observational studies have shown that persistent histological inflammation in UC is associated with an increased risk of relapse, hospitalisation and colectomy, as well as an increased risk of colorectal neoplasia.[3, 4, 26-32] Despite such evidence suggesting the importance of microscopic inflammation as a harbinger of disease activity, histological remission is not yet recommended as a therapeutic endpoint either for clinical trials or practice in UC.[5, 6, 33] As a consequence, there is currently no evidence from randomised controlled trials in support of treatment intensification to achieve histological healing in UC. Few studies have assessed the histological response to immunomodulator or biological

therapy.[19, 34, 35] Nevertheless, this situation is bound to change since the Food and Drug Administration (FDA) has recently insisted on documentation of histological disease activity at both inclusion and as an outcome measure in clinical trials.

The aim of this study was to prospectively analyse the value of histological remission compared to endoscopic remission, for predicting outcomes of steroid use, hospitalisation, or colectomy in patients with UC over a long period of follow-up. Concordance between measures of remission was systematically evaluated.

Materials and methods

Patients

Outpatients with an established diagnosis of UC according to conventional criteria,[36] were recruited from the IBD Clinic of the Translational Gastroenterology Unit at the John Radcliffe Hospital, Oxford. Subjects were initially invited to participate in a study of inter-observer variation for the assessment of disease activity between November 2007 and March 2008.[2] Subjects were recruited regardless of degree of clinical disease activity.

Baseline characteristics were recorded, including demographics, disease duration, extent and current medications. The Simple Clinical Colitis Activity Index (SCCAI) was calculated for each patient.[37] An SCCAI < 2 was used to define clinical remission.[5] The SCCAI was selected as a validated index of clinical activity,[7, 38] since it solely depends on symptoms with a defined inter-observer variation,[2] without the need for endoscopy or laboratory tests. The Montreal criteria were used to define disease extent.[39]

Patients subsequently received standard clinical care[9, 36] at the recruiting hospital, with regular outpatient follow-up (maximum interval 12 months between appointments) to assess clinical outcomes.

Baseline assessment

Endoscopic

At the baseline visit, patients underwent a video sigmoidoscopy according to a standard technique[40] by a single clinician (OCB), who was blinded to the clinical activity score. The extent of examination was to the sigmoid-descending junction or to descending colon, as tolerated by the patient. A trained central reader (AJW) later scored endoscopic disease

activity for the most severely affected area, using the Baron index.[41] In the absence of a validated endoscopic index of activity at the time of assessment, a Baron score < 1 without mucosal friability was used to define endoscopic remission.[6] Small patient numbers precluded further analysis within Baron score subgroups.

Histological

Mucosal biopsies were routinely taken from the sigmoid colon and rectum, targeting the area where the colitis was endoscopically most active, as well as any other areas of interest. A single specialised gastrointestinal histopathologist (AvH) scored the worst affected area using Truelove and Richards' index,[25] blinded to the clinical and endoscopic scores. The index was selected as a clinically applicable grading system, where the category 'no significant inflammation' defines histological remission and refers to architectural changes in the absence of erosions, crypt abscesses or neutrophilic infiltration. It groups activity into domains (remission/mild–moderate/severe) that could be compared directly with clinical and endoscopic activity, and tested over time. Truelove and Richards' index is one of few partially validated histological indices in UC.[20, 24] The best validated histological index of disease activity (Geboes index)[23] does not use a summative scale and avoids classification by activity tertiles.

Clinical outcomes

Patients' clinical records were audited in July 2014 for clinical outcomes including oral corticosteroid use and requirement for escalation of therapy, hospitalisation, or colectomy since the baseline assessment. Standardised practice for oral corticosteroid use in patients with UC applied during the follow-up period. Oral corticosteroids were initiated through an IBD advice telephone service or outpatient clinic on the basis of a relapse of established UC, characterised by bloody diarrhoea and urgency, with or without endoscopic confirmation, in the absence of systemic features sufficient to meet a diagnosis of acute severe colitis,[36] generally after no response within 2 weeks to up-titration of 5-aminosalicylic acid therapy (oral and topical). Oral corticosteroids were initiated before escalation of therapy to immunomodulators (thiopurines, methotrexate) or biological therapy. The need for hospitalisation was defined by Truelove and Witts' criteria for acute severe colitis.[42] Colectomy was indicated in the instances of severe, treatment-refractory colitis, toxic megacolon, or malignancy complicating colitis.[43]

Statistical analysis

Descriptive statistics are expressed as medians and interquartile range. Fleiss' kappa was calculated to quantify agreement between the three measures of disease activity. Qualitative interpretation of kappa statistics used the convention of Landis and Koch,[44] where 0 indicates poor agreement, 0.0–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.0 almost complete agreement.

Since clinical outcomes (corticosteroid use/escalation of therapy, hospitalisation, or colectomy) did not occur in all patients, univariate and multivariate survival analysis with Cox regression was used to examine how endoscopic and histological measures of remission were associated with time to corticosteroid use or escalation of therapy, time to hospitalisation and time to colectomy. Kaplan Meier survival analysis was performed for outcomes. In addition, chi square analysis was used to compare categorical variables between groups. Analysis was performed using SPSS® (Version 22) software and Graphpad Prism®.

Ethical considerations

Subjects were invited to participate in the study comparing disease indices between November 2007 and March 2008 (approved by the Oxfordshire Research Ethics Committee LREC 536407Q1605/58ORH). Informed consent was obtained and participant information was stored in a confidential depersonalised database. Patients also consented to the Inflammatory Bowel Disease Cohort Study (Research Ethics Committee Reference 09/HI204/30), consenting to longitudinal follow-up of patient information.

Results

Patients

91 patients underwent baseline assessment, with clinical outcome data available on all patients over a median 72 months (6 years, interquartile range 54–75 months) of follow-up. Two patients died of causes unrelated to their UC during the follow-up period (ruptured abdominal aortic aneurysm and acute myocardial infarction). Baseline characteristics are shown in ***Table 3.1***.

Concordance between measures of disease activity at baseline

Disease activity was dichotomised into either remission or active disease on the basis of clinical, endoscopic, and histological indices. Overall concordance between the three measures for disease activity was 55% (50/91), consistent with moderate agreement (kappa = 0.43, 95% confidence interval (CI) 0.31–0.55) (***Figure 3.1***). Only 29% (26/91) of patients were in remission by all three measures of assessment.

Agreement between endoscopic and histological measures of remission was moderate (43% (42/91), kappa 0.56, 95% CI 0.36–0.77). In the setting of endoscopic mucosal healing, 75% (42/56) of patients were also in histological remission; 11% of patients appeared to have endoscopic activity despite histological remission.

The greatest disparity arose when clinical assessment was compared to endoscopic and histological measures of remission (kappa 0.29, 95% CI, 0.10–0.49; kappa 0.47, 95% CI 0.27–0.68; endoscopic and histological remission respectively).

Endoscopic vs. histological remission in predicting patient outcomes

Corticosteroid requirement

During the 6-year follow-up period, 63% (57/91) of patients received oral corticosteroids, with 33% (30/91) needing more than one course. In multivariate Cox regression analysis, a reduced corticosteroid requirement was predicted by histological remission (HR 0.42, (0.2–0.9), p = 0.02 respectively) (***Table 3.2***). Endoscopic remission however, did not predict a lower requirement for corticosteroids (HR 0.86 (0.5–1.7), p = 0.65). Numbers of patients with a more stringent endoscopic definition of remission (Baron score = 0) were too small for statistical analysis. ‘Complete remission’, as defined by both endoscopic and histological remission, predicted future corticosteroid requirement (HR 0.38, (0.2–0.9), p = 0.02). Amongst those patients in ‘complete remission’ at baseline, 43% required corticosteroids over the follow-up period, as opposed to 78% of those in endoscopic remission but with persistent histological activity (p = 0.02) (***Figure 3.2, Table 3.3***).

Hospitalisation

Over the 6-year follow-up period, 22% (20/91) patients were hospitalised with acute severe colitis. Disease extent and histological remission predicted reduced rates of hospitalisation in

multivariate analysis (HR 3.21 (1.1–8.6), p = 0.02; HR 0.21 (0.1–0.7), p = 0.02; respectively), whereas endoscopic remission did not (HR 0.83 (0.3–2.4). p = 0.74). 'Complete remission' also predicted lower rates of hospitalisation (HR 0.24 (0.1–0.9), p = 0.04). Amongst those in 'complete remission' at baseline, 12% were hospitalised over the follow-up period, as compared to 36% of those in endoscopic remission but with persistent histological activity (p = 0.04) (***Figure 3.2***, ***Table 3.3***).

Colectomy

Colectomy was an infrequent event over the 6-year follow-up period, occurring in only 12% (11/91) patients over the follow-up period. Only disease extent was a significant predictor of colectomy in multivariate analysis (HR 4.06 (1.3–16.2), p = 0.02).

Discussion

This study is the first to systematically analyse concordance between indices of remission in UC, as well as the value of endoscopic and histological remission in predicting patient outcomes over a long period of follow-up. Histological remission as a marker of 'complete' remission, was shown to be of more value than endoscopic remission in predicting requirement for corticosteroids, or hospitalisation for acute severe colitis over the 6-year follow-up. The findings are striking but intuitive, adding weight to calls to include histological remission in definitions of the depth of remission for UC.[21, 45, 46] In the current scramble for biomarkers that might predict the future pattern of disease, traditional measures such as histology merit re-appraisal.

Histological healing deserves distinction from endoscopic mucosal healing. We show moderate agreement between histological and endoscopic measures of remission (kappa 0.56, 95% CI 0.36–0.77). Microscopic inflammation persists in 25% of patients with endoscopic mucosal healing, illustrating that leukocyte infiltration is not seen using conventional endoscopy.[15, 47, 48] This is consistent with previous studies, although the large range (16–90%) reflects different definitions of remission and activity for endoscopy and histopathology.[4, 20, 22, 27, 28, 49-51] Histological remission in the presence of endoscopic activity may relate to discontinuous inflammation, but histopathology helps avoid over-interpretation of mucosal changes that may occur due to factors such as bowel preparation.[52] The greatest disparity between measures of remission occurred for clinical assessment, which is consistent with Truelove's original observations.[25] Symptoms in patients with endoscopic remission are

commonplace, often due to concurrent irritable bowel syndrome, medications, or infection. This is relevant both to clinical practice when trying to avoid unnecessary medical therapy and also to clinical trials, since clinical symptoms alone cannot be relied upon to judge disease activity.[53] This also emphasises the need for endoscopy along with mucosal biopsies to assess disease activity objectively. Histopathology is more likely to reflect inflammation than endoscopy, particularly in the presence of 'minimal' or 'mild' endoscopic activity.[22, 51] Better concordance between histology and endoscopy is reported for inactive or severely active disease,[51] but the potential for disproportionate intramural extension of inflammation in severe colitis is recognised.[54, 55] Both endoscopic and histological assessment are prone to inter-observer variability,[56] which has implications for clinical trials, indicating the need for independent evaluation by central reader of disease activity.[56-59]

Our study reveals the prognostic value of histological remission beyond that of endoscopic mucosal healing, over an extended follow-up period. Histological remission, but not endoscopic mucosal healing, was predictive of a lower requirement for corticosteroids (HR 0.42 (0.2–0.9), p = 0.02) over the 6-year follow-up. Histological remission, but not endoscopic mucosal healing, predicted lower rates of acute severe colitis requiring hospitalisation (HR 0.21 (0.1–0.7), p = 0.02). The rate of acute severe colitis over the follow-up period was 22%, consistent with the natural history of UC.[42] Extensive disease was the only predictive factor for colectomy; the lack of association with endoscopic and histological remission is likely to represent a Type 2 statistical error from small numbers.

Guidelines do not yet recommend histological remission as a therapeutic endpoint in clinical trials.[7] Paradoxically, this ignores long-standing evidence that histological inflammation may better predict clinical outcomes than clinical or endoscopic measures.[32] Riley *et al* showed that an acute inflammatory cell infiltrate, crypt abscesses, or mucin depletion on mucosal biopsy from patients in clinical and sigmoidoscopic remission was associated with higher relapse rates within 12 months.[4] Other studies have shown that the lamina propria inflammatory cell infiltrate or basal plasmacytosis predict a higher relapse rate within 12 months or colectomy in patients with quiescent clinical and endoscopic disease,[26-30] although not all studies concur.[49] Histological remission is also associated with a reduction in colorectal cancer risk.[3, 31]

No histological definition of remission exists despite many histological indices,[20] none of which are fully validated. This reflects discontinuous variation in histological activity as a

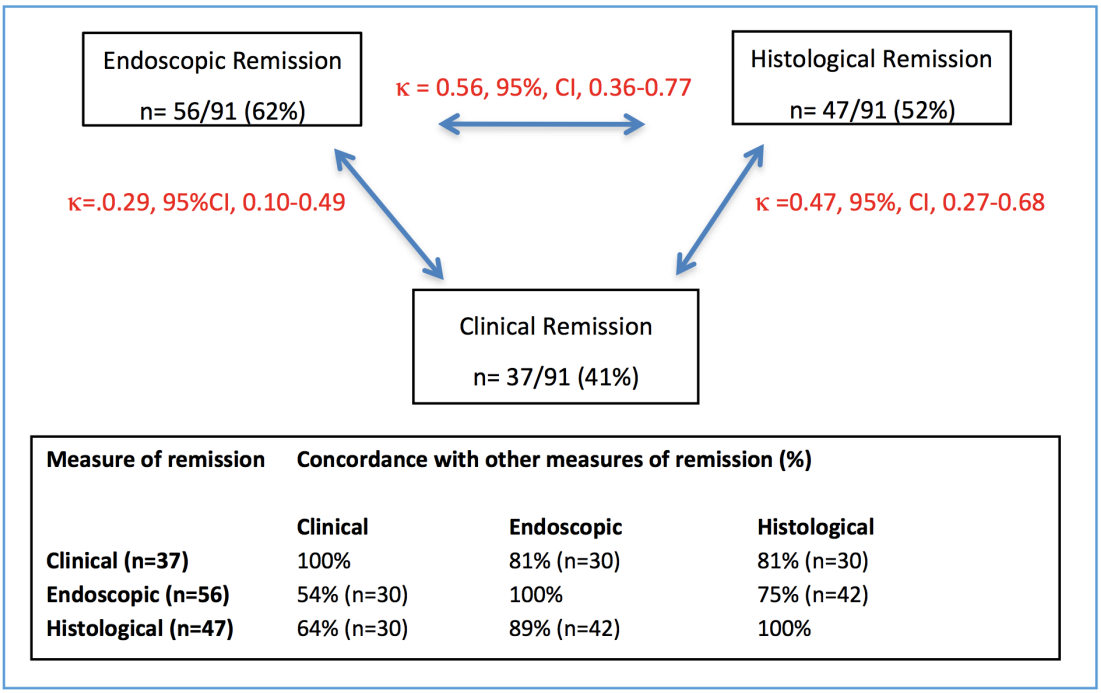
treatment effect and a reluctance for invasive investigation when the impact on outcomes is unclear. Our results provide some substance to the value of mucosal biopsy and histological assessment of the worst affected area. At the very least, they imply that maintenance therapy should not be decreased or stopped whilst microscopic inflammation persists.

Limitations of this study include the design and small number of patients, but these are mitigated by management consistency at a single centre and long duration of follow-up. The study was underpowered to detect differences with regard to colectomy. Further limitations include an unvalidated endoscopic index of severity (Baron score) that is subject to wide inter-observer variability, since the baseline assessment predated a validated index.[56, 59] Truelove and Richards' index for grading histological activity is prone to inter-observer variability, although is partially validated.[25] It also does not take into account features such as basal plasmacytosis that have been shown to predict patient outcomes. The index is however simple, reproducible and includes a summative scale, unlike the Geboes index.[23] Reproducibility of clinical, endoscopic and histological assessment of disease activity in the baseline cohort has been reported separately.[2] International initiatives to standardise histopathology for ulcerative colitis are beginning,[20] but variables such as the number of biopsies, number of sections and quality of processing need to be agreed.[60] Other factors such as intercurrent infection or drug-induced lesions may not be resolved by histopathology. Another limitation is dichotomisation of endoscopic and histologic indices into remission or active disease, given the lack of validation of a 'remission cut-off' and the lack of control over variables that may have influenced clinical outcomes during the follow-up period, including changes in maintenance therapy, disease extent, or smoking. Measurement of faecal calprotectin might have enhanced the study. However retrospective analysis of mucosal calprotectin in this cohort was not associated with outcomes,[61] and another group has been unable to correlate faecal calprotectin and histological activity, even if a low calprotectin was associated with a better clinical outcome.[62]

In spite of these limitations, we have demonstrated that histological remission represents a distinct target from endoscopic mucosal healing in UC, since it better predicts lower rates of corticosteroid use and acute severe colitis requiring hospitalisation over a median 6 years of follow-up. These data lend weight to the importance of developing standardised and validated scoring indices to measure histological remission. Our findings support the inclusion of

histopathology in both IBD clinical trials and practice, which will require a paradigm shift in thinking amongst clinicians, toward a treatment target of ‘complete remission’ in UC.[20]

Figures



Measure of remission	Concordance with other measures of remission (%)		
	Clinical	**Endoscopic**	**Histological**
Clinical (n=37)	100%	81% (n=30)	81% (n=30)
Endoscopic (n=56)	54% (n=30)	100%	75% (n=42)
Histological (n=47)	64% (n=30)	89% (n=42)	100%

Figure 3.1. Concordance between clinical, endoscopic and histological measures of remission in ulcerative colitis

Legend: *Kappa statistical analysis was used to assess concordance of clinical, endoscopic, and histological indices of remission.*

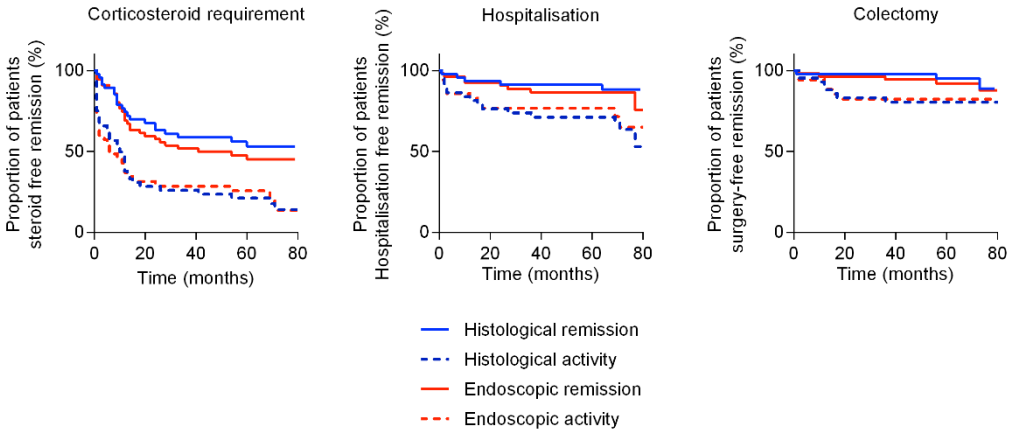


Figure 3.2. Kaplan-Meier graph of endoscopic and histologic remission and clinical outcomes in ulcerative colitis patients

Legend: *Kaplan Meier survival analysis of time to corticosteroid requirement, hospitalisation for acute severe colitis, or colectomy. Groups were divided on basis of endoscopic or histological healing. The numbers of patients in each group are shown in Figure 1. The curve for 'complete' (histological and endoscopic remission, n = 42) is almost identical to that of histological remission (n = 47) and is depicted by a single line.*

Tables

Table 3.1. Baseline Patient Characteristics

Baseline Clinical Characteristics	
Ulcerative colitis patients	91
Females	50 (55%)
Median age, years (IQR)	50 (36–63)
Median follow-up period, months (IQR)	72 (5–96)
Median duration of disease, years (IQR)	9 (3–17)
Disease extent (Montreal classification) Proctitis (E1) Distal (E2) Extensive (E3)	 27 (30%) 45 (49%) 19 (21%)
Clinical disease activity (SCCAI) 0–2 3–5 6–10 > 10	 37 (41%) 24 (26%) 25 (27%) 5 (6%)
Endoscopic disease activity (Baron index) 0 1 2 3	 13 (14%) 43 (47%) 23 (25%) 12 (13%)
Histological disease activity (Truelove and Richards index) No significant inflammation Mild to moderate inflammation Severe inflammation	 47 (52%) 27 (30%) 17 (18%)
Medications None 5-aminosalicylic acid (5-ASA) Immunosuppressant Immunosuppressant + 5-ASA Anti-tumour necrosis factor therapy (anti-TNF)	 10 (11%) 48 (53%) 11 (13%) 19 (21%) 3 (3%)

Table 3.2. Cox regression multivariate analyses for outcome measures in UC patients over a median 6-year follow-up

	Corticosteroid requirement		**Hospitalisation for acute severe colitis**		**Colectomy**	
Variable	**Univariate analysis^**	**Multivariate analysis^**	**Univariate analysis^**	**Multivariate analysis^**	**Univariate analysis^**	**Multivariate analysis^**
Age	0.96 (0.8–1.1), p=0.59		1.16 (0.9–1.5), p=0.29		1.37 (0.9–2.0), p=0.11	
Sex	0.70 (0.4–1.2), p=0.20		1.05 (0.4–2.6), p=0.91		2.52 (0.7–8.7), p=0.14	
Disease duration	**0.90 (0.8–1.0), p=0.05***	0.91 (0.8–1.1), p=0.36	0.92 (0.7–1.2), p=0.47		1.06 (0.8–1.4), p=0.65	
Disease extent	0.94 (0.5–1.8), p=0.86		**2.62 (1.0–6.7), p=0.04***	**3.21 (1.1–8.6), p=0.02***	**3.67 (1.1–12.1), p=0.03***	**4.06 (1.3–16.2), p=0.02***
Maintenance therapy • **5ASA** • **Other**	0.93 (0.4, 2.3), p=0.01[5] 2.08 (0.9–5.0)	0.72 (0.3–1.9) p=0.57[5] 0.98 (0.4–2.7)	0.78 (0.2–3.9), p=0.03[5] 1.70 (0.4–7.7)		0.46 (0.1–2.5), p=0.66[5] 0.69 (0.1–3.6)	
Histological remission	**0.35 (0.2–0.6), p < 0.001***	**0.42 (0.2– 0.9), p=0.02***	**0.22 (0.1–0.7), p=0.007***	**0.21 (0.1–0.7), p=0.02***	0.32 (0.1–1.2), p=0.10	0.36 (0.1–1.8), p=0.22
Endoscopic remission	**0.47 (0.3–0.8), p=0.005***	0.86 (0.5–1.7), p=0.65	0.48 (0.2–1.2), p=0.12	0.83 (0.3–2.4). p=0.74	0.50 (0.2–1.6), p=0.25	0.71 (0.2–3.0), p=0.64

Table 3.3. Risks of clinical outcomes in ulcerative colitis patients over a median of 6 years of follow-up

	Corticosteroid requirement	**Hospitalisation for acute severe colitis**	**Colectomy**
Overall (n = 91)	57 (63%)	20 (22%)	11 (12%)
Histology^			
Remission (n = 47)	21 (45%)	5 (11%)	3 (6%)
Active disease (n = 44)	36 (82%)	15 (34%)	8 (18%)
Endoscopy*			
Remission (n = 56)	29 (52%)	10 (18%)	5 (5%)
Active disease (n = 35)	28 (90%)	10 (29%)	6 (17%)
'Complete' remission			
Endoscopic and histological remission (n = 42)	18 (43%)	5 (12%)	3 (7%)
Endoscopic remission and histological activity (n = 14)	11 (79%)	5 (36%)	2 (14%)

^Histological remission defined by Truelove and Richards' index, architectural changes in the absence of erosions, crypt abscesses or neutrophilic infiltration.
**Endoscopic remission defined by Baron score $\leq$ 1 without mucosal friability.*

REFERENCES

1. Peyrin-Biroulet L, Sandborn W, Sands BE*, et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Sep;110(9):1324-38.
2. Walsh AJ, Ghosh A, Brain AO*, et al.* Comparing disease activity indices in ulcerative colitis. Journal of Crohn's & colitis. 2014 Apr 1;8(4):318-25.
3. Gupta RB, Harpaz N, Itzkowitz S*, et al.* Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007 Oct;133(4):1099-105; quiz 340-1.
4. Riley SA, Mani V, Goodman MJ*, et al.* Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991 Feb;32(2):174-8.
5. D'Haens G, Sandborn WJ, Feagan BG*, et al.* A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007 Feb;132(2):763-86.
6. Travis SP, Higgins PD, Orchard T*, et al.* Review article: defining remission in ulcerative colitis. Alimentary pharmacology & therapeutics. 2011 Jul;34(2):113-24.
7. Peyrin Biroulet L SW, Sands B, Reinisch W, *et al*. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. American Journal of Gastroenterology. 2015 Sep;110(9):1324-38.
8. Daperno M, Castiglione F, de Ridder L*, et al.* Results of the 2nd part Scientific Workshop of the ECCO. II: Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. Journal of Crohn's & colitis. 2011 Oct;5(5):484-98.
9. Dignass A, Lindsay JO, Sturm A*, et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's & colitis. 2012 Dec;6(10):991-1030.
10. Peyrin-Biroulet L, Ferrante M, Magro F*, et al.* Results from the 2nd Scientific Workshop of the ECCO. I: Impact of mucosal healing on the course of inflammatory bowel disease. Journal of Crohn's & colitis. 2011 Oct;5(5):477-83.
11. Reinisch W, Van Assche G, Befrits R*, et al.* Recommendations for the treatment of ulcerative colitis with infliximab: a gastroenterology expert group consensus. Journal of Crohn's & colitis. 2012 Mar;6(2):248-58.

12. Baert F, Moortgat L, Van Assche G*, et al.* Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010 Feb;138(2):463-8; quiz e10-1.
13. Colombel JF, Rutgeerts P, Reinisch W*, et al.* Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011 Oct;141(4):1194-201.
14. D'Haens G, Baert F, van Assche G*, et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008 Feb 23;371(9613):660-7.
15. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012 Nov;61(11):1619-35.
16. Rutgeerts P, Diamond RH, Bala M*, et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointestinal endoscopy. 2006 Mar;63(3):433-42.
17. Schnitzler F, Fidder H, Ferrante M*, et al.* Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflammatory bowel diseases. 2009 Sep;15(9):1295-301.
18. Colombel JF, Rutgeerts PJ, Sandborn WJ*, et al.* Adalimumab Induces Deep Remission in Patients With Crohn's Disease. Clinical gastroenterology and hepatology. 2013 Jul 12.
19. Molander P, Sipponen T, Kemppainen H*, et al.* Achievement of deep remission during scheduled maintenance therapy with TNFalpha-blocking agents in IBD. Journal of Crohn's & colitis. 2013 Oct;7(9):730-5.
20. Bryant RV, Winer S, Travis SP*, et al.* Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's & colitis. 2014 Dec 1;8(12):1582-97.
21. Korelitz BI. Mucosal healing as an index of colitis activity: back to histological healing for future indices. Inflammatory bowel diseases. 2010 Sep;16(9):1628-30.
22. Rosenberg L, Nanda KS, Zenlea T*, et al.* Histologic markers of inflammation in patients with ulcerative colitis in clinical remission. Clinical gastroenterology and hepatology. 2013 Aug;11(8):991-6.
23. Geboes K, Riddell R, Ost A*, et al.* A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000 Sep;47(3):404-9.

24. Mosli MH, Feagan BG, Sandborn WJ*, et al.* Histologic evaluation of ulcerative colitis: a systematic review of disease activity indices. Inflammatory bowel diseases. 2014 Mar;20(3):564-75.
25. Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. British medical journal. 1956 Jun 9;1(4979):1315-8.
26. Azad S, Sood N, Sood A. Biological and histological parameters as predictors of relapse in ulcerative colitis: a prospective study. Saudi journal of gastroenterology. 2011 May-Jun;17(3):194-8.
27. Bessissow T, Lemmens B, Ferrante M*, et al.* Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. The American journal of gastroenterology. 2012 Nov;107(11):1684-92.
28. Bitton A, Peppercorn MA, Antonioli DA*, et al.* Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001 Jan;120(1):13-20.
29. Hefti MM, Chessin DB, Harpaz NH*, et al.* Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Diseases of the colon and rectum. 2009 Feb;52(2):193-7.
30. Rubin DT HD, Hetzel JT et al Increased degree of histological inflammation predicts colectomy and hospitalisation in patients with ulcerative colitis. Gut. 2007;132 (Suppl. 1):A-19 (Abstract 103).
31. Rutter M, Saunders B, Wilkinson K*, et al.* Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004 Feb;126(2):451-9.
32. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. The American journal of digestive diseases. 1966 Nov;11(11):847-57.
33. Daperno M, Castiglione F, de Ridder L*, et al.* Results of the 2nd part Scientific Workshop of the ECCO. II: Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. Journal of Crohn's & colitis. 2011 Oct;5(5):484-98.
34. Chey WY. Infliximab for patients with refractory ulcerative colitis. Inflammatory bowel diseases. 2001 May;7 Suppl 1:S30-3.
35. Paoluzi OA, Pica R, Marcheggiano A*, et al.* Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis:

results of an open-label study on efficacy and tolerability in inducing and maintaining remission. Alimentary pharmacology & therapeutics. 2002 Oct;16(10):1751-9.

36. Dignass A, Eliakim R, Magro F*, et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. Journal of Crohn's & colitis. 2012 Dec;6(10):965-90.
37. Walmsley RS, Ayres RC, Pounder RE*, et al.* A simple clinical colitis activity index. Gut. 1998 Jul;43(1):29-32.
38. Turner D, Seow CH, Greenberg GR*, et al.* A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. Clinical gastroenterology and hepatology. 2009 Oct;7(10):1081-8.
39. Satsangi J, Silverberg MS, Vermeire S*, et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749-53.
40. Sandborn WJ, Korzenik J, Lashner B*, et al.* Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. Gastroenterology. 2010 Apr;138(4):1286-96, 96 e1-3.
41. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. British medical journal. 1964 Jan 11;1(5375):89-92.
42. Dinesen LC, Walsh AJ, Protic MN*, et al.* The pattern and outcome of acute severe colitis. Journal of Crohn's & colitis. 2010 Oct;4(4):431-7.
43. Brain O, Travis SP. Therapy of ulcerative colitis: state of the art. Current opinion in gastroenterology. 2008 Jul;24(4):469-74.
44. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74.
45. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic Remission: The Ultimate Therapeutic Goal in Ulcerative Colitis? Clinical gastroenterology and hepatology. 2013 Aug 1.
46. Villanacci V, Antonelli E, Geboes K*, et al.* Histological healing in inflammatory bowel disease: a still unfulfilled promise. World journal of gastroenterology : WJG. [Editorial]. 2013 Feb 21;19(7):968-78.
47. Kiesslich R, Fritsch J, Holtmann M*, et al.* Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003 Apr;124(4):880-8.

48. Tontini GE, Vecchi M, Neurath MF*, et al.* Review article: newer optical and digital chromoendoscopy techniques vs. dye-based chromoendoscopy for diagnosis and surveillance in inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Nov;38(10):1198-208.
49. Baars JE, Nuij VJ, Oldenburg B*, et al.* Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflammatory bowel diseases. 2012 Sep;18(9):1634-40.
50. Gomes P, du Boulay C, Smith CL*, et al.* Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986 Jan;27(1):92-5.
51. Lemmens B, Arijs I, Van Assche G*, et al.* Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. Inflammatory bowel diseases. 2013 May;19(6):1194-201.
52. Leriche M, Devroede G, Sanchez G*, et al.* Changes in the rectal mucosa induced by hypertonic enemas. Diseases of the colon and rectum. 1978 May-Jun;21(4):227-36.
53. Travis SP, Danese S, Kupcinskas L*, et al.* Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut. 2014;63 (3):433-41..
54. Seldenrijk CA, Morson BC, Meuwissen SG*, et al.* Histopathological evaluation of colonic mucosal biopsy specimens in chronic inflammatory bowel disease: diagnostic implications. Gut. 1991 Dec;32(12):1514-20.
55. von Herbay A, Gebbers JO, Otto HF. Immunopathology of ulcerative colitis: a review. Hepato-gastroenterology. 1990 Feb;37(1):99-107.
56. Travis SP, Schnell D, Krzeski P*, et al.* Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012 Apr;61(4):535-42.
57. Feagan BG, Sandborn WJ, D'Haens G*, et al.* The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013 Jul;145(1):149-57 e2.
58. Magro F, Langner C, Driessen A*, et al.* European consensus on the histopathology of inflammatory bowel disease. Journal of Crohn's & colitis. 2013;7(10):827-851.
59. Travis SP, Schnell D, Krzeski P*, et al.* Reliability and Initial Validation of the Ulcerative Colitis Endoscopic Index of Severity. Gastroenterology. 2013;145(5):987-995.

60. Langner C, Magro F, Driessen A*, et al.* The histopathological approach to inflammatory bowel disease: a practice guide. Virchows Archiv : an international journal of pathology. 2014 May;464(5):511-27.
61. Guirgis M WE, Wang LM, Burger D, Kent A, Adamson R, Travis SPL, Keshav S. Intestinal mucosal calprotectin in ulcerative colitis (UC): measuring disease activity, defining remission and predicting clinical outcome. Journal of Crohn's and Colitis. 2013;7:P168.
62. Mooiweer E, Severs M, Schipper ME*, et al.* Low fecal calprotectin predicts sustained clinical remission in inflammatory bowel disease patients: a plea for deep remission. Journal of Crohn's & colitis. 2015 Jan;9(1):50-5.

CHAPTER 4: TREATMENT TARGETS ACHIEVED IN 'REAL-WORLD' CLINICAL PRACTICE IN ULCERATIVE COLITIS

Background

In Chapter 3 of this thesis, objective remission of inflammation was shown to be associated with reduced corticosteroid usage and hospitalisation in patients with UC. Whether the optimal target in UC is endoscopic mucosal or histological remission remains unclear, but the rationale for use of objective measures of disease to guide therapy is resounding.

Accordingly, a 'treat to target' approach in IBD advocates striving for not only resolution of symptoms, but objective resolution of inflammation. Consensus guidelines have defined the goal of therapy in IBD as *both* endoscopic and clinical remission. This represents a frame-shift in thinking for many clinicians, trained to manage symptoms alone.

Despite the potential benefits of a 'treat to target' approach in IBD, the uptake of these guidelines in 'real-world' IBD practice remains unexplored. Akin to rheumatology practice, evaluation of clinicians' perceptions of guidelines is key to application in practice.

This multicentre cross-sectional study evaluated the extent to which proposed remission targets are achieved in outpatients with UC in routine clinical practice in South Australia. Factors predicting attainment of the composite clinical and endoscopic treatment target were explored, alongside clinician assessment of objective disease activity in routine care. An anonymous online survey was sent to all practicing Gastroenterologists working across teaching hospitals in South Australia to evaluate perceptions of proposed 'treat to target' guidelines in UC. The study allowed identification of potential challenges to implementation of a 'treat to target' approach in 'real-world' practice.

Presented in this chapter is the manuscript published in Journal of Gastroenterology and Hepatology 2018; 33: 599-607.

Specific Author Contributions

Title of Paper	Limited uptake of ulcerative colitis 'treat to target' recommendations in real-world practice
Publication Status	Published
Publication Details	Journal of Gastroenterology and Hepatology. 2018; 33 (3): 599-607. Impact factor: 3.5

Name of Principal Author (Candidate)	Robert Venning Bryant		
Contribution to the Paper	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21/2/2018

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Samuel Paul Costello		
Contribution to the Paper 4%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	20/2/2018

Name of Co-Author	Dharshan Sathananthan		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	20/2/2018

Name of Co-Author	Su Yin Lau		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	16/2/2018

Name of Co-Author	Scott Schoeman		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	19/2/2018

Name of Co-Author	Emma Knight		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	15/2/2018

Name of Co-Author	Mark Schoeman		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	14/2/2018

Name of Co-Author	Reme Mountifield		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	1/4/2018

Name of Co-Author	Derrick Tee		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	13/2/2018

Name of Co-Author	Simon PL Travis		
Contribution to the Paper 4%	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	12/2/2018

Name of Co-Author	Jane M Andrews		
Contribution to the Paper 14%	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	12/2/2018

[Manuscript 2] Limited uptake of ulcerative colitis 'treat to target' recommendations in real-world practice

Short title: Treat to Target in UC

Robert V Bryant[1,2], Samuel P Costello[1,2], Scott Schoeman[3], Dharshan Sathananthan[3], Emma Knight[1], Su-Yin Lau[2], Mark N Schoeman[3], Reme Mountifield[4], Derrick Tee[5], Simon PL Travis[6], Jane M Andrews[1,3]

[1]School of Medicine, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia

[2]Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Adelaide, Australia.

[3]IBD Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, Australia

[4]Department of Gastroenterology and Hepatology, Flinders Medical Centre, Adelaide, Australia

[5]Department of Gastroenterology and Hepatology, Lyell McEwin Hospital, Adelaide, Australia

[6]Translational Gastroenterology Unit, Oxford University Hospitals, Oxford, United Kingdom

Correspondence

Dr Robert V Bryant

Address: Department of Gastroenterology, The Queen Elizabeth Hospital, 30 Woodville Rd Woodville South, Adelaide, South Australia 5011

Email: robert.bryant@sa.gov.au

Phone: (+61) 08 82226000

Acknowledgements

Royal Adelaide Hospital IBD Nurses, Rachel Grafton, Julie Hughes, and Lucy Cronin, for their kind assistance and contribution to the database.

Grant support and writing assistance

No funding was received for this study. RVB was the recipient of the AR Clarkson Scholarship through the Royal Adelaide Hospital Research Fund. No writing assistance was provided for the manuscript.

Conflicts of interest and personal interests

The authors have no conflicts of interest to declare.

Abstract

Background and aims

A 'treat to target' (T2T) approach has been proposed for ulcerative colitis (UC), with a target of combined clinical and endoscopic remission. The aim of the study was to evaluate the extent to which proposed targets are achieved in real-world care, along with clinician perceptions and potential challenges.

Methods

A multicentre, retrospective, cross-sectional review of patients with UC attending outpatient services in South Australia was conducted. Clinical and objective assessment of disease activity (endoscopy, histology, and/or biomarkers) was recorded. A survey evaluated Gastroenterologists' perceptions of T2T in UC. Statistical analysis included logistic regression and Fisher's exact tests.

Results

Of 246 patients with UC, 61% were in clinical remission (normal bowel habit and no rectal bleeding), 35% in clinical *and* endoscopic remission (Mayo endoscopic subscore ≤ 1), and 16% in concordant clinical, endoscopic and histological (Truelove and Richards' index) remission. Rather than *disease*-related factors (extent/activity), clinician-related factors dominated outcomes. Hospital location and the choice of therapy predicted combined clinical and endoscopic remission (OR 3.6, 95% CI 1.6–8.7, $p < 0.001$; OR 3.3, 95% CI 1.1–12.5, $p = 0.04$, respectively). Clinicians used C-reactive protein (CRP) more often than endoscopy as a biomarker for disease activity (75% vs. 47%, $p < 0.001$). In the survey, 45/61 Gastroenterologists responded, with significant disparity between clinician estimates of targets achieved in practice and real-world data ($p < 0.001$ for clinical and endoscopic remission).

Conclusions

Most patients with UC do not achieve composite clinical and endoscopic remission in 'real-world' practice. Clinician uptake of proposed 'treat to target' guidelines is a challenge to their implementation.

Key words

Ulcerative colitis, inflammatory bowel disease, treat to target, mucosal healing

Introduction

Therapeutic advances in the medical management of ulcerative colitis (UC) have evolved to treatment targets. The goal of therapy for UC is now to modify the course of disease, so as to improve quality of life and avoid disability, whilst balancing the risks associated with therapy.[1] A 'treat to target' approach has been proposed for UC, wherein objective measures of disease activity are actively sought and used to guide subsequent management.[2, 3] Accordingly, consensus guidelines for clinical practice in UC advocate striving not only for resolution of symptoms, but for resolution of inflammation.[2, 4-6] This approach has long been used in other chronic inflammatory diseases, but represents a novel strategy for IBD, necessitating a paradigm shift in thinking for most clinicians.[7]

Targets for treatment of UC have been defined as clinical and endoscopic remission.[2] This is underpinned by the knowledge that clinical remission together with endoscopic mucosal healing ('deep remission'), with mucosal healing defined as lack of visible mucosal inflammation or ulceration at endoscopy (variably a Mayo endoscopic subscore of 0 or 1), is associated with reduced rates of clinical relapse, hospitalisation, and colectomy.[8-13] Moreover, a short interval between endoscopic evaluation of disease activity in IBD has been shown to increase the likelihood of achieving endoscopic mucosal healing.[14] Consensus guidelines recommend endoscopic evaluation of disease at 3-monthly intervals during active UC, and within 3-6 months after a change in therapy.[2]

Data from clinical trials estimate that up to two-thirds of patients with UC achieve both clinical remission and endoscopic mucosal healing with intensive therapy.[9, 15, 16] However, most patients with IBD are ineligible for clinical trial enrolment and therefore the proportion of patients in whom these goals are achieved in 'real-world' practice remains unclear.[17] Furthermore, implementation of guidelines requires clinician uptake, adherence and implementation within a healthcare system. These are hard taskmasters, constrained by healthcare system resources and capacity. It is thus no surprise that the feasibility of a 'treat to target' strategy in UC has yet to be evaluated in routine clinical practice.

We therefore set out to:

- assess the extent to which proposed 'Treat to Target' goals are achieved in UC
- examine how and when UC disease activity is assessed
- evaluate potential challenges to achieving these targets during routine care.

Concurrently, we explored treating Gastroenterologists' perceptions of 'treat to target' in UC and documented their clinical behaviour.

Materials and methods

Multicentre cross-sectional data collection

A retrospective cross-sectional review of patients with UC attending inflammatory bowel disease (IBD) outpatient services between 1 July 2013 and 1 November 2015 at three South Australian teaching hospitals (Royal Adelaide Hospital (RAH), The Queen Elizabeth Hospital (TQEH), and Lyell McEwin Hospital (LMH)) was conducted (***Figure 4.1***).

All patients with an established diagnosis of UC were identified from IBD databases and hospital records. All cases with disease duration of 6 months or more, with an outpatient review during the study period, were included. Patients were excluded if they underwent colectomy or ileal pouch-anal anastomosis surgery prior to or during the study period, or had their diagnosis amended to either IBD-unclassified (IBD-U) or Crohn's disease (CD). The outpatient encounter selected for cross-sectional analysis was that within the eligible time period, closest to the time of data collection. At least 6 months of observation on either side of the outpatient encounter was allowed to capture evaluation of disease activity undertaken by the clinician, resulting in a total study duration of 1 January 2013 to 1 May 2016 (***Figure 4.1***). Disease activity assessment was captured at the closest time interval to the cross-sectional outpatient encounter (before and/or after), including endoscopy, histopathology and/or biomarkers. If assessment was performed both before and after the outpatient encounter, data from after the encounter were included to better reflect clinical strategy and outcomes.

Demographic and IBD-specific data were collected from multiples sources, including an IBD database, patient case-notes and clinic letters. Data on clinical decision-making, medication or appointment non-compliance, or medication intolerance were extracted from patient case-notes and clinic letters where available. Endoscopic data were collected from an electronic endoscopy reporting system (Provation®). Colonic mucosal histopathology, C-reactive

protein (CRP), and faecal calprotectin (FC) data were extracted from electronic clinical software (Oacis®).

UC disease activity assessments and definitions

Clinical assessment of UC disease activity (rectal bleeding and stool frequency) were collected from a cross-sectional, outpatient encounter recorded by the treating clinician (***Figure 4.1***). Clinical remission was defined as the absence of rectal bleeding and normal stool frequency (rated as 'normal' by the reviewing clinician or reported as ≤ 3 bowel actions per day).

Endoscopic and histological examinations were performed for the purposes of disease activity assessment, at the closest time interval (before and/or after) the index outpatient encounter. Investigations performed for the purposes of surveillance were excluded from the analysis. Endoscopic disease activity, assessed at either colonoscopy or flexible sigmoidoscopy, was scored using the Mayo endoscopic subscore, reported prospectively by the endoscopist (26%) or retrospectively derived from procedural photographs and/or description (74%).[18] Endoscopic remission was defined as a Mayo endoscopic subscore of ≤ 1.[2] Histological disease activity was retrospectively scored from histopathology reporting of the most severely affected colonic mucosal biopsy specimen, using Truelove and Richards' index (TRI).[19] The TRI was chosen as a simple partially validated score that has been widely used in randomised controlled trials in UC.[20] As per the TRI, histologic remission was defined as an absence of erosions, crypt abscesses, or neutrophilic inflammation (with or without architectural distortion).

Biomarker (CRP and FC) results were selected from the time-point nearest the index outpatient encounter. CRP remission was defined as CRP < 5 mg/L performed by high sensitivity enzyme-linked immunosorbent assay (ELISA). FC remission was defined as < 100 mcg/g, using a CALPRO® ELISA test.

Clinical decision-making and therapeutic strategy at the outpatient encounter was evaluated from entries in the case-notes, including escalation or de-escalation of therapy and therapeutic drug monitoring (TDM).

Clinician survey

An anonymous online survey was sent to all practicing Gastroenterologists working across 4 teaching hospitals in South Australia (RAH, TQEH, LMH, and Flinders Medical Centre (FMC)) using a Survey Monkey® platform (***Supplementary Table 4.1***). The 14-question survey assessed the duration and nature of clinicians' IBD clinical practice, and familiarity with a 'Treat to Target' approach to UC management and its perceived relevance were explored using Likert scales. Clinicians' perceptions of their current use of objective measures of disease activity to guide management, optimal treatment targets in UC, and the proportion of their patients in which these targets are currently achieved were evaluated.

Statistical analysis

A power calculation was not performed as this was a convenience sample and the intent was to sample all eligible patients with UC at three participating hospitals, as well as all practicing Gastroenterologists, Fellows, and Trainees at four participating hospitals in South Australia. For non-normally distributed data, median and interquartile range (IQR) are presented. Comparisons between non-normally distributed data were made using non-parametric t-tests, and comparisons between proportions were made using Fisher's exact tests. A linear mixed model for log (time to assessment) was fitted to compare the time interval between outpatient review and objective assessment. Cochran's Q test and post-hoc pairwise McNemar's tests were used to compare proportions undergoing objective assessment within 3 months of their outpatient review. Logistic regression analyses were used to examine for variables that may have been associated with achieving combined clinical and endoscopic remission, as well as clinician factors related to the use of objective measures of disease activity to guide treatment decisions. A p-value of < 0.05 was considered statistically significant.

Ethical considerations

The research was conducted under the auspices of clinical performance audit. Specific ethics approval was considered unnecessary by the RAH Ethics Committee since the study met criteria for clinical audit, used retrospective data, did not interfere with patient management and did not involve any direct patient contact. Data collected for the study were stored on a central server, in an encrypted de-identified form to protect confidentiality. For the clinician survey, completion of the survey was taken as consent as per usual practice.

Results

Patient characteristics

Of 501 patients with UC assessed for eligibility, 246 (49%) were included in the final analysis (CONSORT diagram and reasons for exclusion, ***Figure 4.1***). 53% were male, median age 44 years (interquartile range (IQR) 31–58), age at UC diagnosis 32 years (IQR 23–44), and median UC disease duration of 95 months (IQR 35–168) (***Table 4.1***). UC disease distribution was extensive (E3) in 38%, left-sided (E2) in 42%, and proctitis (E1) in 20% of included patients. Some 20% had a history of acute severe colitis (ASUC), while 226/246 (92%) were on therapy for UC: 81% 5-aminosalicylic acid therapy (5-ASA), 35% immunosuppressant therapy, 7% biological therapy, 14% oral prednisolone, and 5% faecal microbiota transplant (FMT) therapy (as part of a clinical trial).[21] Observation within the study period was performed for a median 785 (IQR 554–903) days before and 267 days (IQR 157–506) after the index outpatient encounter.

Are proposed UC treatment targets assessed and/or attained in real-world practice?

Documentation of clinical disease activity at the index outpatient encounter was sufficient to allow characterisation of clinical disease activity in all cases, although in 4%, patients either rectal bleeding or stool frequency went unrecorded. Endoscopic assessment was performed in 218/246 (89%) patients over the study period, histological assessment in 190 (77%), CRP in 204 (83%), and FC in 22 (9%) (***Supplementary Table 4.2***).

Clinical remission (normal stool frequency and no rectal bleeding) was documented in 149/246 (61%) of patients at the time of the index outpatient encounter, of whom 85/149 (57%) were also in endoscopic remission (Mayo endoscopic subscore ≤ 1). Overall, 85/246 (35%) of patients were documented to be in combined clinical and endoscopic remission (17% in Mayo 0 endoscopic subscore remission). Of those patients in clinical and endoscopic remission, 39/85 (46%) were also in histologic remission (Truelove and Richards' index) (***Table 4.2, Figure 4.2A***). Overall, 39/246 (16%) patients were documented as being in combined clinical, endoscopic, and histological remission.

How and when is objective UC disease activity assessment performed in real-world practice?

Where clinicians documented clinically active disease (n = 97), endoscopy was performed within 3 months of the outpatient encounter in 46/97 (47%) patients, with a significantly higher proportion undergoing assessment of disease activity using CRP (73/97 (75%), $p < 0.001$). FC was used to assess disease activity in only 6 (6%) patients within 3 months of the clinical encounter (***Figure 4.2B, Supplementary Table 3***). In those patients with clinically active disease, the time to endoscopy (84 days; IQR 29–180) was significantly longer than the time to CRP (13 days; IQR 4–40) (estimated difference in means of 16.9 days, 95% CI 7.9–36.6, $p < 0.001$) (***Figure 2C***). Similar findings were observed for those with clinically quiescent disease, although the median time to endoscopy was longer (***Supplementary Table 4.3, Figure 4.2B, 4.2C***).

After making a clinical assessment of disease activity, how do clinicians act?

Medical therapy for UC was escalated following the outpatient encounter in 82/246 (34%) patients overall (54/82 (56%) of those with clinically active disease), de-escalated in 13/246 (5%) patients, and unchanged in 150/246 (61%) patients (***Supplementary Table 4.4***). Therapeutic escalation included up-titration within therapeutic class in 46/246 (19%) patients (8 of whom underwent pre-testing of therapeutic drug levels), and a change in therapeutic class in 37/246 (15%) patients. Therapeutic strategy employed by clinicians was broadly in keeping with conventional recommended guidelines,[6] although in 19 (12%) of patients, clinically active disease was evident and there was failure of objective disease activity assessment and/or therapeutic escalation.

Predictive factors for achieving combined clinical and endoscopic remission?

IBD-specific factors such as disease extent or duration did not predict achievement of combined clinical and endoscopic remission during the study period (***Table 4.3)***. Rather, therapeutic factors, including taking any therapy for UC (OR 3.3, 95% CI 1.1–12.5, p 0.04; as compared no therapy), use of a 5-ASA alone (OR 3.5, 95% CI 1.1–13.5, p 0.04), and use of immunosuppressant therapy (OR 4.8, 95% CI 1.3–20.4, 0.02; with or without 5-ASA therapy), as well as the hospital at which IBD care was delivered (OR 3.6, 95% CI 1.6–8.7, $p < 0.001$; inter-hospital comparison) were each significantly associated with achieving combined clinical and endoscopic remission (***Table 4.3***).

What are the challenges of implementing a 'Treat to Target' strategy for UC in real-world practice?

Potential challenges facing a 'Treat to Target' strategy in practice were examined in those patients who were not in clinical and endoscopic remission (n = 161). A single issue was identified in 139/161 (86%) and > 1 issue in 22 (14%) (***Table 4.4***). Clinician-related factors were the most frequently identified issues limiting attainment of composite remission, affecting 101/161 patients (63%); specifically, failure to evaluate patients endoscopically to document disease activity, either to confirm clinical remission or to assess effectiveness following escalation of UC therapy (***Table 4.4***). Patient-related factors, including appointment or medication non-compliance, were documented in 28/161 (17%) patients. Truly treatment-resistant disease, defined as failure to achieve clinical and objective remission despite treating to target with appropriate use of therapy and objective monitoring of response, was uncommon and evident in only 25/161 (16%) patients.

Clinician survey of Treat to Target in UC: perceptions vs. reality

Of 61 practicing Gastroenterologists surveyed, 45 (74%) returned the questionnaire, of whom 32 (71%) were Consultants, 10 (22%) were Registrars, and 3 (7%) were Fellows (***Supplementary Table 4.5***). Some 80% of respondents had heard of the 'Treat to Target' concept in UC, 61% were either familiar or very familiar with the concept, but only 64% considered it relevant to local clinical practice (***Supplementary Table 4.6)***. Familiarity with the concept of Treat to Target was significantly associated with perception of its relevance to practice (OR 5.5, 95% CI 1.5–20.4, p = 0.01). Most clinicians (78%) reported usually or always using objective measures of disease activity to guide treatment decisions in UC (***Supplementary Table 4.7***). Duration of clinical practice of 10 years of more was associated with a numerically lower likelihood of using objective measures of disease activity, although this did not reach statistical significance (OR 0.27 vs. < 10 years duration of practice, 95% CI 0.05–1.25, p = 0.09) (***Supplementary Table 4.8***). The single 'optimal treatment target' selected was histological healing by 51% of clinicians surveyed, followed by endoscopic (33%), and clinical remission (12%) (***Supplementary Table 4.9***). Clinicians estimated achieving clinical, endoscopic, and histologic remission in 73%, 59% and 52% of patients with UC in current clinical practice respectively, a perception significantly disparate from the real-world data (***Figure 4.2D and Supplementary Table 4.9***).

Discussion

This is the first study to evaluate the proposed 'treat to target' strategy in patients with UC in real-world practice, exploring potential challenges to its implementation along with the attitudes of treating clinicians. In this large multicentre South Australian cohort, one-third of patients were found to achieve the composite treatment target of clinical and endoscopic remission proposed by consensus guidelines, but only 17% attained the optimal treatment target of Mayo 0 endoscopic remission.[2] These findings illustrate a broad disparity between anticipated rates of remission derived from clinical data in highly selected trial patients, and actual remission targets achieved in routine practice.[9, 15-17] Therapeutic factors and the hospital at which IBD care was delivered were significantly associated with likelihood of attaining the composite treatment target, rather than disease- or patient-related factors.

The most frequently identified challenges to implementation of a 'Treat to Target' strategy in practice were clinician-dependent practice behaviours. In particular, lack of endoscopic assessment was common, both in the setting of clinical remission as well as following escalation of therapy. In contrast to consensus guidelines, which advocate for endoscopic evaluation at least at 3-monthly intervals during the active phase of UC, endoscopy was performed in only 47% of patients with clinically active disease within a time frame of 3 months, and in 68% within 6 months.[2]

Rather, it seems that clinicians rely on the convenience of CRP to assess disease activity, despite CRP not being a target of therapy, lacking sensitivity for detecting endoscopic remission in UC, and of limited value outside the setting of ASUC.[2, 22, 23] FC represents a more useful biomarker to monitor disease activity in UC, shown to predict persistent endoscopic inflammation, risk of relapse, and response to therapy.[24-29] Although not a treatment target *per se*, FC was underused in the examined UC cohort, performed in only 9% of patients during the study period, which perhaps reflects reimbursement conditions in Australia and an out-of-pocket cost incurred by patients to undertake the test.

The relatively small proportion of the patient cohort receiving biologic therapy for UC (7%) is likely to have truncated attainment of the composite clinical and endoscopic treatment target. However, a further 6 (2%) of patients were escalated to biologic therapy following the outpatient encounter. In Australia, access to biologic therapy requires failure of conventional therapy, which limits a 'top-down' approach to IBD management.[10] This may limit

generalisability of the findings internationally, yet this is reflective of the limitations of 'real-world' practice in Australia.

Although most clinicians had heard of 'treat to target' in UC, only two-thirds were familiar with the concept, and familiarity was significantly associated with perception of relevance to practice. Overall, only two-thirds of clinicians felt that a 'treat to target' strategy was relevant to their practice currently. Survey data also revealed that clinicians' perceptions of their practice and treatment targets achieved was incongruent with their own 'real-word' outcomes, and that estimates of care outcomes were overly optimistic. These data expose a gap between perception and practice, which represents a potential obstacle to improving care in IBD.

The identified failure to adhere to proposed 'treat to target' guidelines for UC may relate to a lack of clinician familiarity and perceived relevance as identified in the survey. Clinician uptake of guidelines in the 'real-world' setting is also constrained not only by limited healthcare resources, but by patients' needs, desires, and adherence. Moreover, despite the likely benefits of a 'treat to target' approach in UC, beyond consensus opinion and clinical trials, there is currently a paucity of robust data to support improved long-term patient outcomes in 'real-world' practice, particularly when balancing competing issues of costs and risks of therapy. Clinician education, along with evaluation of practice and patient outcomes have been integral to establishing practice recommendations in rheumatoid arthritis, and are essential sequelae to any guideline proposal, garnering more widespread uptake amongst clinicians.[7, 30-32]

Limitations of this study include the retrospective design, which introduces risk of bias in terms of retrospective interpretation of disease activity and clinical decision-making, as well as the potential for missing data. The time interval between disease activity assessments is also likely to introduce risk of bias. Functional symptomatology is known to affect around 40% patients with IBD, so a clinical decision not to undertake endoscopy or up-titrate therapy was difficult to evaluate in retrospect.[33] However, this work would not have been possible with a prospective study design given the potential to influence clinician behaviour. The median duration of UC in the examined cohort was almost 8 years, which may have influenced the prevalence of clinical symptoms within the cohort, given the propensity for structural damage with long-standing disease.[34] The clinician survey lacked sufficient power for subgroup analysis, but all clinicians at participating hospitals were distributed the questionnaire and a response rate of 74% was representative. Due to the anonymous nature of

the survey, further analysis into clinician attitudes as a potential factor behind the significant differences in rates of combined endoscopic and clinical remission between the included hospitals was not possible.

Our data from a multicentre Australian cohort of patients with UC and their treating clinicians has demonstrated that only one-third of patients are achieving proposed composite clinical and endoscopic treatment targets. The study exposes a gap between guidelines, clinician perceptions, and clinical practice in UC.

Figures

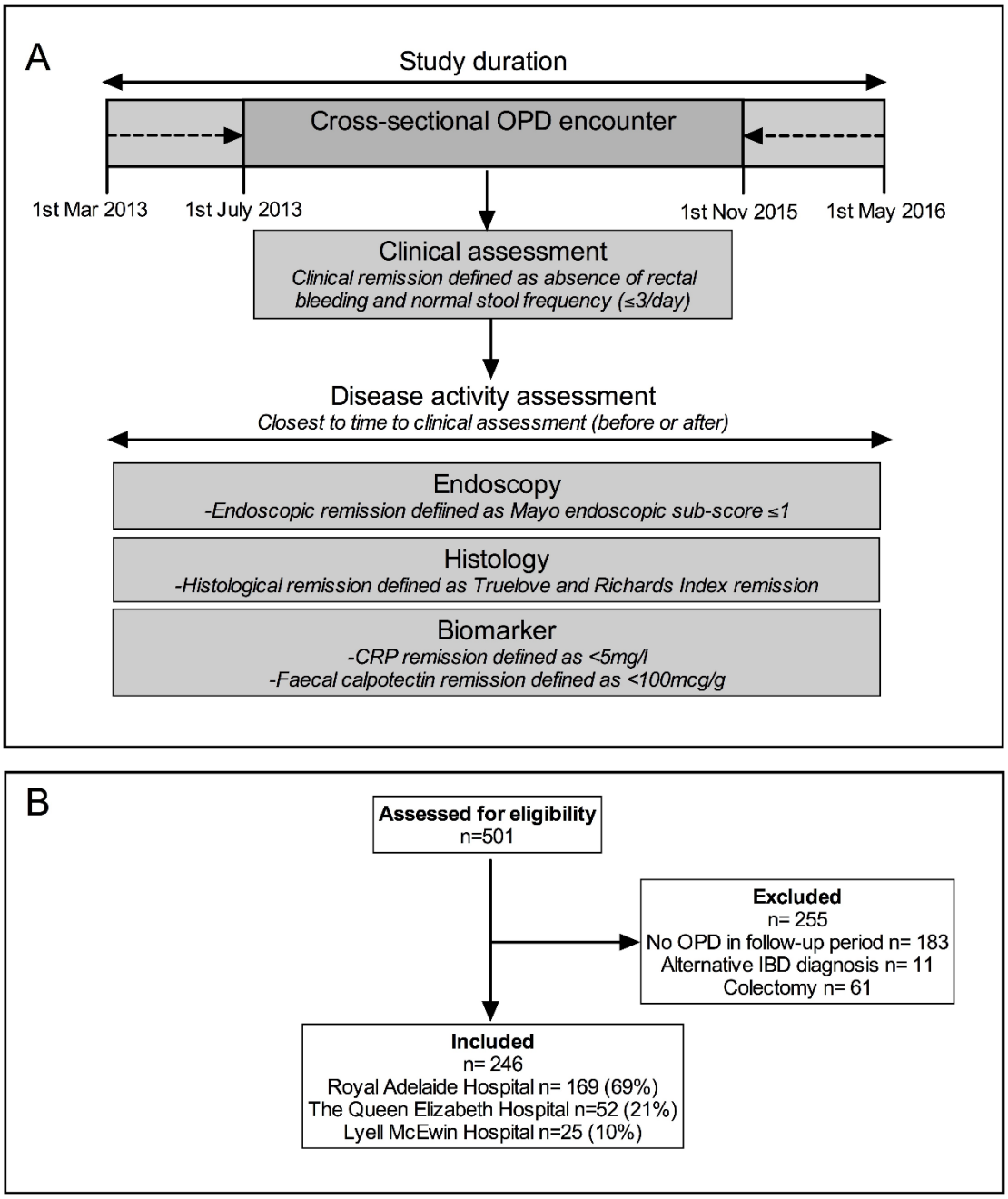


Figure 4.1. Treat to target in UC cross-sectional analysis: methods diagram and flow chart

Legend: ***A****. A retrospective cross-sectional review of patients with UC attending inflammatory bowel disease (IBD) outpatient (OPD) services between July 2013 and November 2015 at 3 South Australian teaching hospitals.* ***B.*** *Flow diagram.*

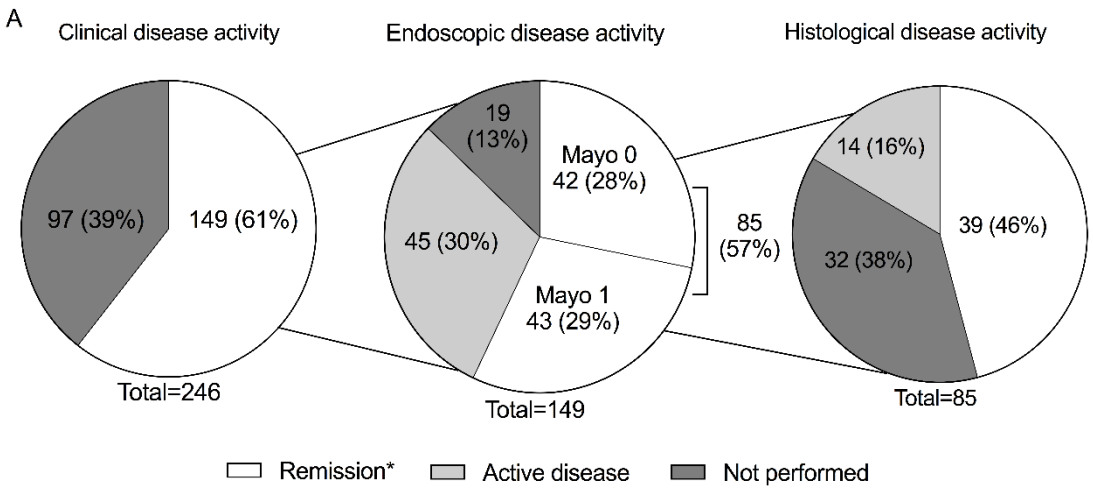


Figure 4.2A. UC treatment targets achieved in real-world practice

Legend: **Clinical remission defined as normal stool frequency and absence of rectal bleeding; endoscopic remission defined by Mayo endoscopic sub-scores of ≤ 1; histological remission defined by an absence of acute inflammatory cell infiltrate according to the Truelove and Richards' index.*

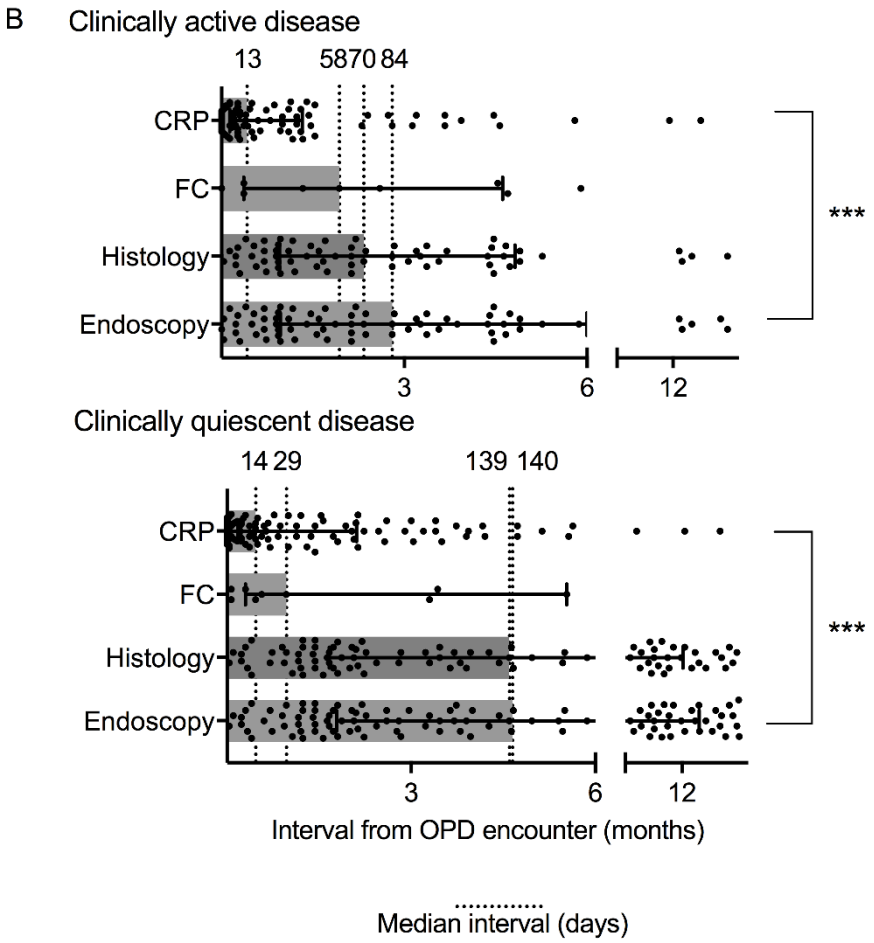


Figure 4.2B. Timing of UC disease activity assessment

Legend: *The interval between the index outpatient (OPD) encounter and disease activity assessment in patients with clinically active and quiescent disease at the OPD encounter. Statistical analysis mixed model for log (time to assessment).*

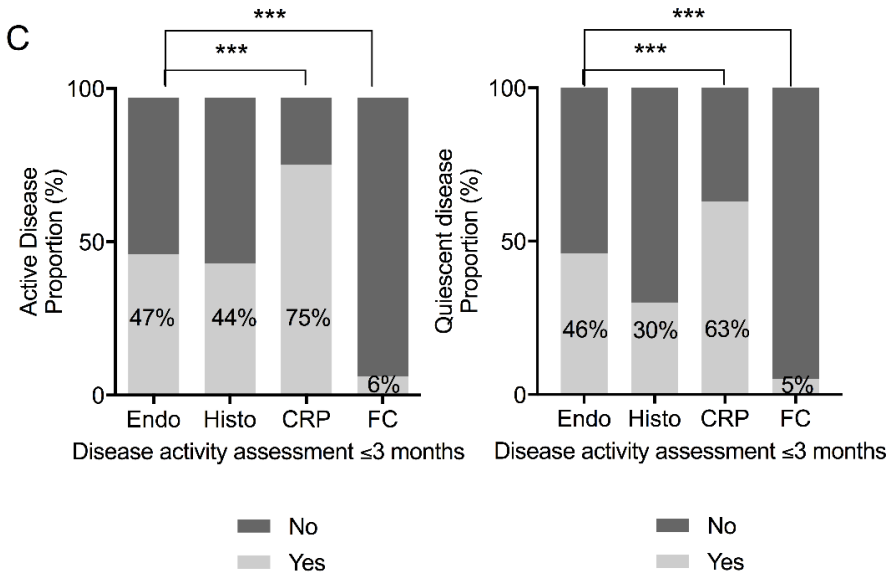


Figure 4.2C. UC disease activity assessment within 3 months of clinical encounter

Legend: *The proportion of patients with clinically active and quiescent disease at the time of the OPD encounter undergoing disease activity assessment within a 3-month time interval. CRP, C-reactive protein; FC, faecal calprotectin. Statistical analysis using Cochran's Q test along with post-hoc pairwise McNemar's test.*

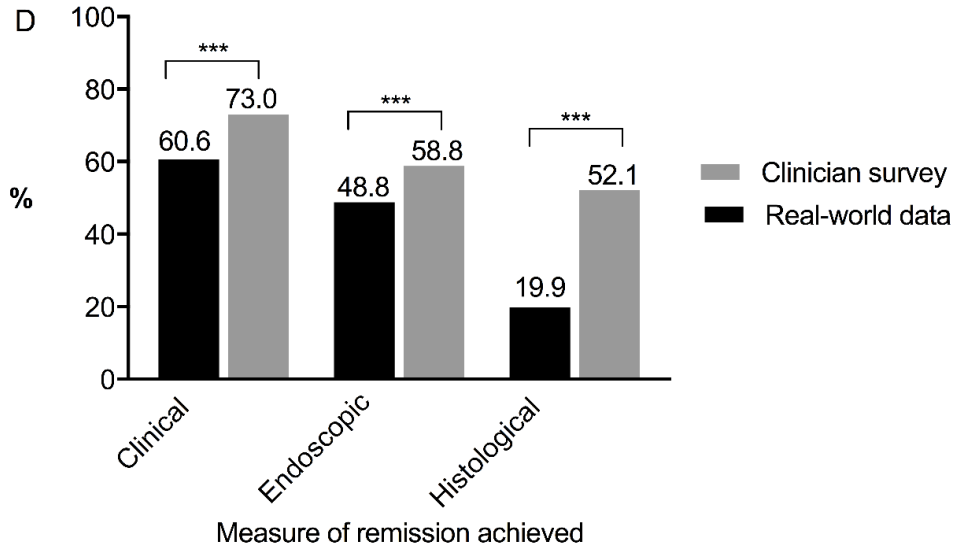


Figure 4.2D. Clinician reported achievement of treatment targets in UC vs. real-world data

Legend*: Real-world data from retrospective analysis of 246 patients UC across 3 hospital sites in South Australia compared with survey data on clinician perceptions of treatment targets achieved. Actual vs. expected proportions compared using a Fisher's exact test, with the expected frequency calculated using the mean of the mid-value for each 'bin' of the survey. *** p-value ≤ 0.001.*

Tables

Table 4.1. Demographics and IBD-related information of UC cohort

Variable		n (%)
Patient number		246
Hospital		RAH 169 (69) TQEH 52 (21) LMH 25 (10)
Gender (male)		131 (53)
Age (median, IQR)		44 (31–58)
Disease extent (Montreal criteria)	E1	48 (20)
	E2	104 (42)
	E3	94 (38)
Age at diagnosis	Median (IQR)	32 (23–44)
	Montreal age range A1	24 (10)
	A2	158 (64)
	A3	64 (26)
Disease duration (months, median, IQR)		95 (35–168)
Extra-intestinal manifestations IBD	Overall	29 (12)
	Arthropathy	17 (7)
	Primary sclerosing cholangitis	7 (3)
	Skin	4 (2)
	Eyes	2 (1)
Prior ASUC	Overall	50 (20)
ASUC rescue therapy	IFX	15 (30)
	CsA	7 (14)
Current therapy		
Any UC therapy		226 (92)
5-aminosalycilic acid (5-ASA)	Overall	200 (81)
	Oral 5-ASA	144 (59)
	Oral and topical 5-ASA	52 (21)
	Topical 5-ASA	4 (2)
	5-ASA therapy alone	97 (39)
Immunosuppressants	Overall	87 (35)
	Thiopurine (AZA or MP)	68 (28)
	Thiopurine (AZA or MP) + allopurinol	15 (6)
	Methotrexate	4 (2)
Biologic therapy	Overall	17 (7)
	Infliximab	15 (6)
	Vedolizumab	1 (< 1)
	Trial biologic therapy	1 (< 1)
Corticosteroid therapy	Oral prednisolone	35 (14)
	Topical corticosteroid	11 (4)
Other	Faecal microbiota therapy	13 (5)
	Tacrolimus	2 (1)

Legend: *ASUC, acute severe ulcerative colitis; RAH, Royal Adelaide Hospital; TQEH, The Queen Elizabeth Hospital; LMH, Lyell McEwin Hospital; IQR, interquartile range; AZA, azathioprine; MP, mercaptopurine; 5-ASA, 5-aminosalicylic acid.*

Table 4.2. UC treatment targets achieved in real-world practice

Treatment target		n (% overall)
Clinical remission (*Normal stool frequency <u>and</u> absence of PR bleeding*)		149 (60.6)
Clinical remission	Mayo ≤ 1	85 (34.6)
+ Endoscopic remission (*Mayo endoscopic sub-score of ≤1*)	Mayo 0	42 (17.1)
Clinical remission	Mayo ≤ 1	39 (15.9)
+ Endoscopic remission **+ Histological remission** (*Truelove and Richards' index remission*)	Mayo 0	31 (12.6)

Legend: *Overall proportions of patients in UC cohort (n=246) attaining remission.*

Table 4.3. Clinical factors associated with combined clinical and endoscopic remission

Variable		**OR**	**95% CI**	**p-value**
Age		1.0	0.9–1.0	0.81
Gender (male)		0.8	0.5–1.6	0.61
Disease extent (E2/E1 vs. E3)		1.4	0.5–3.7	0.69
Age of diagnosis of UC		1.0	0.3–3.6	0.99
Disease duration		1.0	0.9–1.0	0.07
Compliance with therapy and/or appointments		1.2	0.5–3.0	0.63
Therapy	Any therapy^	3.3	1.1–12.5	0.04*
	5-aminosalicylic acid alone	3.5	1.1–13.3	0.04*
	Immunosuppressant therapy	4.8	1.3–20.4	0.02*
	Biologic therapy	2.3	0.3–14.8	0.39
	Oral prednisolone	0.6	0.1–3.3	0.61
Consultant vs. Registrar OPD review		0.9	0.4–1.8	0.72
OPD Hospital	Hospital 1 (intercept)			< 0.001*
	Hospital 2	3.6	1.6–8.7	
	Hospital 3	0.4	0.1–1.3	

Legend: *Logistic regression analyses performed to assess factors associated with achieving composite of clinical and endoscopic remission. Analysis performed amongst 218 patients who underwent endoscopic assessment during follow-up period. Clinical remission defined as normal bowel habit and no rectal bleeding. Endoscopic remission defined as Mayo endoscopic sub-score 0 or 1. * $p < 0.05$ denoting statistical significance; OR, odds ratio; 95% CI, confidence interval. Age, age of diagnosis of UC, duration of disease continuous variables. Otherwise, unless stated, the comparator variable is the inverse of the variable presented. ^Any therapy analysed in a separate logistic regression model to other therapies as confounding.*

Table 4.4. Challenges of implementing a 'Treat to Target' strategy in UC in 'real-world' practice

Domain	Issue	n (%)*
Clinician-related factors	Clinical remission (and no change to therapy) • Failure to seek and confirm endoscopic remission	 52 (32)
	Clinically active disease • Escalation of UC therapy and failure to perform endoscopy to assess response to therapy • No escalation of UC therapy and failure to perform endoscopy to assess disease activity	 33 (20) 19 (12)
	Overall	101 (63)^
Patient-related factors	Appointment or medication non-compliance	28 (17)
	Ongoing (likely functional) symptoms despite endoscopic evidence of remission	29 (18)
	Overall	57 (35)
Disease-related factors	Treatment-resistant disease as defined by: • Failure to achieve clinical and endoscopic remission • Appropriate titration of therapy and objective assessment of response • Lack of documented patient non-compliance or non-attendance	25 (16)
Overall	Single issue identified Two issues identified	139 22

Legend: *Clinical remission defined as absence of rectal bleeding and normalisation of stool frequency. * Proportion (%) provided for 161 patients not meeting composite definition of clinical and endoscopic remission. ^ Concurrent appointment or medication non-compliance affecting 16/101 patients.*

Supplementary Table 4.1 'Treat to target' in ulcerative colitis Gastroenterologist survey questions

Treat to target in UC Gastroenterologist Survey
1. In what capacity do you practice Gastroenterology? a. Consultant b. Clinical Fellow c. Registrar
2. How long have you practiced in Gastroenterology? a. Fewer than 3 years b. 3–9 years c. 10–-19 years d. 20 years or more
3. How many hours do you spend performing clinical duties as a Gastroenterologist on average per WEEK?
4. What proportion of ***clinical duties*** do you undertake in private or public practice? Please provide as a percentage (0–100%) for each. a. Public practice b. Private practice
5. How many patients with inflammatory bowel disease (IBD) do you manage in an ambulatory or inpatient setting on an average WEEKLY basis? a. Fewer than 10 b. 10–25 c. 26–50 d. 51–75 e. 76 or more
6. How many IBD-specific educational sessions (e.g., ECCO, Australian IBD Symposium) have you attended in the past 12 months? a. 0 b. 1 c. 2 d. > 2
7. Have you heard of the concept of 'Treat to Target' in UC? a. Yes b. No
8. Please provide a rating of your familiarity with a definition of a 'Treat to Target' approach to UC management as defined below. *'Treat to Target' in IBD is an approach to therapy in which regular assessment of disease activity using objective measures is used to guide subsequent IBD treatment* *(Unfamiliar, somewhat familiar, familiar, very familiar)*
9. How relevant do you think a 'Treat to Target' approach for UC is in current clinical practice in Australia? *(Not at all, generally not, uncertain relevance, generally, very)*

Treat to target in UC Gastroenterologist Survey
a. Please could you provide the reasoning (in free-text) for your answer on the relevance of the 'Treat to Target' approach in current IBD practice in Australia?
10. Do you routinely use OBJECTIVE measures of disease activity to guide subsequent treatment in UC? *(Never, occasionally, sometimes, often, always)*
11. Which measures of disease activity do you use most frequently in routine practice to guide subsequent treatment in UC? Please provide an answer for each domain of assessment. *(Clinical, endoscopic, histological, biomarker (CRP or FC), quality of life assessment)*
12. What do you think is the current OPTIMAL treatment target in ulcerative colitis (UC) in current clinical practice? Please tick ONE box. b. Clinical remission (normal bowel frequency and no rectal bleeding) c. Endoscopic remission (absence of colonic mucosal ulceration or erosion) d. Histological remission (absence of acute inflammatory cell infiltrate on colonic mucosal biopsy) e. Biomarker remission (normalisation of CRP (CRP < 5) and/or faecal calprotectin (FC < 50) f. Normalisation of quality of life
13. Please could you provide your reasoning as to why you think this to be the OPTIMAL treatment target in UC?
14. In your current clinical practice, in what proportion of patients with UC do you think that you achieve the following treatment targets? g. Clinical remission h. Endoscopic remission i. Histological remission j. Biomarker remission k. Normalisation of quality of life

Supplementary Table 4.2. Disease activity assessment in the UC cohort

Domain	Assessment	n (%)
Clinical assessment	**Stool frequency** Increased	69 (28.1)
	Normal	172 (69.9)
	Not documented	5 (2.0)
	PR bleeding Present	63 (25.6)
	Absent	178 (72.4)
	Not documented	5 (2.0)
	Clinically quiescent disease	
	Normal stool frequency and no rectal bleeding	149 (60.6)
	Clinical active disease	
	Increased stool frequency AND/OR rectal bleeding	97 (39.4)
Endoscopic assessment	**Overall**	218 (88.6)
	Before/after outpatient encounter	157 (72%)/ 61 (28%)
	Colonoscopy	152 (61.8)
	Sigmoidoscopy	66 (26.8)
	No	28 (11.497)
	Endoscopic disease activity	
	Method of determining disease activity	
	Endoscopist-reported Mayo subscore	56 (25.7%)
	Mayo subscore derived from photos and report	125 (57.3%)
	Mayo subscore derived from report alone	37 (17.0%)
	Quiescent endoscopic disease	120 (55.1%)
	Mayo endoscopic subscore of 0	52 (23.9%)
	Mayo endoscopic subscore of 1	68 (31.2%)
	Active endoscopic disease	
	Mayo endoscopic subscore ≥ 2	98 (44.9%)
Histological assessment	**Biopsies taken for histopathology at endoscopic assessment** Yes	190 (77.2%)
	No	28 (12.8%)
	Before/after outpatient encounter	134 (71%)/ 56 (29%)
	Histological disease activity	
	Truelove and Richard's Score Remission	49 (25.8%)
	Active histological inflammation	141 (74.2%)
Biomarker assessment	**Overall**	204 (82.9%)
	C-reactive protein	198 (80.5%)
	Before/After outpatient encounter	112 (55%)/ 86 (45%)
	Faecal calprotectin	22 (8.9%)
	Before/After outpatient encounter	10 (45%)/12 (55%)
	No	42

Supplementary Table 4.3. Timing of UC disease activity assessment relative to outpatient encounter

Clinical assessment	Disease activity assessment		Timing of objective assessment relative to OPD encounter					
			Interval to assessment (median days, IQR)	< 1 month n (%)	≤ 3 months n (%)	≤ 6 months n (%)	≤ 1 year n (%)	During study period overall
				After				
Overall n = 246	**Endoscopic**		111.5 (43.8–339.8)	37 (15.0)	96 (39.0)	137 (55.7)	167 (67.9)	218 (89.0)
	Histologic		102.5 (42.8–304.3)	34 (13.8)	88 (35.8)	124 (50.4)	152 (61.8)	190 (77.2)
	Biomarker	**CRP**	14 (2.0–48.3)	126 (51.2)	167 (67.9)	190 (77.2)	193 (78.5)	198 (80.5)
		FC	49 (11.0–139.8)	10 (4.1%)	14 (5.7%)	22 (8.9)	22 (8.9)	22 (8.9)
Quiescent disease n = 149 (60.6%)	**Endoscopic**		139.5 (53.5–400.3)	14 (9.4)	69 (46.3)	90 (60.4)	113 (75.8)	130 (87.2)
	Histologic		138.0 (50.0–367.5)	13 (8.7)	45 (30.2)	63 (42.3)	85 (57.0)	113 (75.8)
	Biomarker	**CRP**	14.0 (1.0–63.3)	71 (47.7)	94 (63.1)	109 (73.2)	111 (74.5)	114 (76.5)
		FC	29.0 (9.0–166.0)	7 (4.7)	8 (5.4)	13 (8.7)	13 (8.7)	13 (8.7)
Active disease n = 97 (39.4%)	**Endoscopic**		84.0 (29.0–179.8)	23 (23.7%)	46 (47.4)	66 (68.0)	73 (75.3)	88 (90.7)
	Histologic		70.0 (28.5–144.5)	21 (21.6)	43 (44.3)	61 (62.9)	67 (69.1)	77 (79.4)
	Biomarker	**CRP**	12.5 (4.0–39.8)	55 (56.7)	73 (75.3)	82 (84.5)	82 (84.5)	84 (86.6)
		FC	58.0 (11.0–138.5)	3 (3.1)	6 (6.2)	9 (9.3)	9 (9.3)	9 (9.3)

Supplementary Table 4.4. UC therapeutic strategy following outpatient encounter

Therapy	Strategy	Details		N (%)*
Escalation	**Escalation within class**	**Overall**		**46 (19)**
		5-aminosalicylic acid (5-ASA)	Additional topical 5-ASA	16 (7)
			Increase oral 5-ASA dose	12 (5)
			Increase oral 5-ASA and additional topical 5-ASA	6 (2)
		Thiopurine therapy	Test levels and increase dose/addition allopurinol	8 (3)
			Empirical dose increase	3 (1)
		Biologic therapy	Empirical dose increase	1 (1)
	Escalation in therapeutic class	**Overall^**		**37 (15)**
		Corticosteroid therapy	Topical (budesonide oral or enema)	7 (3)
			Oral prednisolone	6 (2)
		5-aminosalicylic acid therapy		7 (3)
		Immunomodulator therapy		8 (3)
		Biologic therapy		6 (2)
		Faecal microbial therapy (FMT)		6 (2)
		Clinical trial		2 (1)
		Other (antibiotic therapy)		1 (1)
De-escalation of therapy		**Overall**		**13 (5)**
		5-aminosalicylic acid	Oral 5-ASA dose reduction	4 (2)
			Cessation topical 5-ASA	6 (2)
		Immunomodulator	Thiopurine dose reduction	2 (1)
			Thiopurine cessation	1 (1)

Legend: **Therapy was unchanged in 150 patients. Table provides information on therapeutic strategy on n=96 patients who underwent a change in therapy. ^ Note that 6 patients underwent escalation in more than one class of therapy.*

Supplementary Table 4.5. Clinician survey of 'treat to target' in UC: clinician-related information

Survey respondent	**n (%)**
Capacity of Gastroenterology practice (n, %)	
Consultant	32 (71)
Fellow	3 (7)
Registrar	10 (22)
Duration of Gastroenterology practice (n, %)	
< 3 years	14 (31.1)
3–9 years	11 (24.4)
10–19 years	9 (20.0)
20 or more years	11 (24.4)
Hours per week practicing Gastroenterology? (median, IQR)	35 (25–40)
Area of Gastroenterology practice? (%, median, IQR)	
Public	80 (32.5–100)
Private	20 (0.0–62.5)
IBD patients managed per week on ambulatory and/or inpatient basis? (n, %)	
< 2	10 (22.7)
2–5	12 (27.3)
6–10	13 (29.5)
11–20	7 (15.9)
> 20	2 (4.5)
IBD-specific educational sessions attended in the last 12 months? (n, %)	
0	15 (34.9)
1	13 (30.3)
2	8 (18.6)
> 2	7 (16.3)

Supplementary Table 4.6. Clinician survey of 'treat to target' in UC: familiarity and relevance to practice

Question	Response	n (%)
Have you heard of the concept of treat to target in UC?	Yes	35 (79.5)
	No	4 (9.1)
	Uncertain	5 (11.4)
Please provide a rating of your familiarity with a definition of a 'treat to target' in UC management?	Unfamiliar	4 (9.1)
	Vaguely familiar	13 (29.5)
	Familiar	19 (43.2)
	Very Familiar	8 (18.2)
How relevant do you think a 'treat to target' approach for UC is in current clinical practice in Australia?	Not at all	0 (0.0)
	Generally not	1 (2.3)
	Uncertain	15 (34.1)
	Generally	23 (52.3)
	Very	5 (11.4)

Supplementary Table 4.7. Clinician survey of 'treat to target' in ulcerative colitis: reported use of objective measures to guide UC treatment decisions

Question		**n (%)**				
		Never	**Occasionally**	**Sometimes**	**Mostly**	**Always**
Do you routinely use objective measures of disease activity to guide subsequent treatment in UC? (n, %)		1 (2.5)	2 (5.0)	6 (15.0)	20 (50.0)	11 (27.5)
Which measures of disease activity do you use most frequently to guide subsequent treatment in UC? (n, %)	Clinical	0 (0.0)	0 (0.0)	4 (9.5)	15 (35.7)	23 (54.8)
	Endoscopic	0 (0.0)	1 (2.4)	8 (19.5)	23 (56.1)	9 (22.0)
	Histological	1 (2.4)	1 (2.4)	7 (17.1)	26 (63.4)	6 (14.6)
	Biomarkers	0 (0.0)	0 (0.0)	3 (7.5)	28 (70.0)	9 (22.5)
	QoL	1 (2.8)	7 (19.4)	13 (36.1)	13 (36.1)	2 (5.5)

Supplementary Table 4.8. Clinician factors associated with survey reported use of objective measures of disease activity to guide subsequent therapy

Factor	OR	95% CI	P-value
Capacity of practice (Consultant vs. Registrar or Fellow)	1.05	0.19–4.91	0.95
Duration of practice (≥ 10 years vs. < 10 years)	0.27	0.05–1.25	0.09
Hours of clinical practice per week (Continuous variable)	0.97	0.97–1.02	0.28
Nature of practice (Public practice > 50% vs. private practice > 50%)	1.0	0.99–1.03	0.41
IBD patients per week (≤ 5 vs. > 5 patients)	0.41	0.07–1.86	0.25
Attendance at IBD-specific meeting in the last year (No meeting vs. any meeting)	0.53	0.07–2.74	0.46
Self-reported familiarity with concept of 'treat to target' in UC (Familiar vs. unfamiliar)	1.8	0.50–6.54	0.36
Perception of 'treat to target' in UC as 'relevant' to practice (Relevant vs. not relevant)	2.1	0.58–7.63	0.33

Legend: *Univariate analysis using logistic regression modelling (multivariate analysis not performed due to the presence of confounding variables).*

Supplementary Table 4.9. Clinician survey of 'treat to target' in ulcerative colitis: optimal treatment target and proportion achieved in practice

		Clinical remission	**Endoscopic remission**	**Histological remission**	**Biomarker remission**	**Normalisation of QoL**
Optimal treatment target in UC in current clinical practice? (n, %)		5 (11.6)	14 (32.6)	22 (51.2)	1 (2.3)	1 (2.3)
In current practice, what proportion of patients achieve the following targets?	< 25%	0 (0.0)	0 (0.0)	5 (12.2)	0 (0.0)	2 (4.8)
	26–50%	2 (4.8)	12 (29.3)	11 (26.8)	4 (9.5)	7 (16.7)
	51–75%	20 (47.6)	23 (56.1)	21 (51.2)	23 (54.8)	20 (47.6)
	> 75%	20 (47.6)	6 (14.6)	4 (9.8)	15 (35.7)	13 (30.9)

REFERENCES

1. Allen PB, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. Current opinion in gastroenterology. 2013 Jul;29(4):397-404.
2. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Aug 25;110(9):1324-38.
3. Bouguen G, Levesque BG, Feagan BG, *et al.* Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease. Clinical gastroenterology and hepatology. 2013 Sep 10;13(6):1042-50.
4. D'Haens G, Sandborn WJ, Feagan BG, *et al.* A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007 Feb;132(2):763-86.
5. Travis SP, Higgins PD, Orchard T, *et al.* Review article: defining remission in ulcerative colitis. Alimentary pharmacology & therapeutics. 2011 Jul;34(2):113-24.
6. Dignass A, Lindsay JO, Sturm A, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's & colitis. 2012 Dec;6(10):991-1030.
7. Smolen JS, Aletaha D, Bijlsma JW, *et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the rheumatic diseases. 2010 Apr;69(4):631-7.
8. Baert F, Moortgat L, Van Assche G, *et al.* Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010 Feb;138(2):463-8.
9. Colombel JF, Rutgeerts P, Reinisch W, *et al.* Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011 Oct;141(4):1194-201.
10. D'Haens G, Baert F, van Assche G, *et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008 Feb 23;371(9613):660-7.
11. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012 Nov;61(11):1619-35.

12. Rutgeerts P, Diamond RH, Bala M, *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointestinal endoscopy. 2006 Mar;63(3):433-42.
13. Schnitzler F, Fidder H, Ferrante M, *et al.* Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflammatory bowel diseases. 2009 Sep;15(9):1295-301.
14. Bouguen G, Levesque BG, Pola S, *et al*. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clinical gastroenterology and hepatology. 2014 Jun;12(6):978-85.
15. Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. The New England journal of medicine. 2010 Apr 15;362(15):1383-95.
16. Sandborn WJ, van Assche G, Reinisch W, *et al.* Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65 e1-3.
17. Ha C, Ullman TA, Siegel CA, *et al*. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clinical gastroenterology and hepatology. 2012 Sep;10(9):1002-7.
18. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. The New England journal of medicine. 1987 Dec 24;317(26):1625-9.
19. Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. British medical journal. 1956 Jun 9;1(4979):1315-8.
20. Bryant RV, Winer S, Travis SP, *et al*. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's & colitis. 2014 Dec 1;8(12):1582-97.
21. Costello SC, Bryant RV, Katsikeros R, *et al*. Short duration, low intensity pooled faecal microbiota transplantation induces remission in patients with mild-moderately active ulcerative colitis: a randomised controlled trial. Journal of Crohn's and Colitis. 2017; 11 ECCO abstract.
22. Travis SP, Farrant JM, Ricketts C, *et al.* Predicting outcome in severe ulcerative colitis. Gut. 1996 Jun;38(6):905-10.

23. Yoon JY, Park SJ, Hong SP, *et al*. Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. Digestive diseases and sciences. 2014 Apr;59(4):829-37.
24. De Vos M, Louis EJ, Jahnsen J, *et al.* Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. Inflammatory bowel diseases. 2013 Sep;19(10):2111-7.
25. Gisbert JP, Bermejo F, Perez-Calle JL, *et al.* Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflammatory bowel diseases. 2009 Aug;15(8):1190-8.
26. Guardiola J, Lobaton T, Rodriguez-Alonso L, *et al.* Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. Clinical gastroenterology and hepatology. 2014 Nov;12(11):1865-70.
27. Molander P, af Bjorkesten CG, Mustonen H*, et al.* Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFalpha blocking agents. Inflammatory bowel diseases. 2012 Nov;18(11):2011-7.
28. Theede K, Holck S, Ibsen P, *et al*. Level of Fecal Calprotectin Correlates With Endoscopic and Histologic Inflammation and Identifies Patients With Mucosal Healing in Ulcerative Colitis. Clinical gastroenterology and hepatology. 2015 Nov;13(11):1929-36.e1.
29. Yamamoto T, Shiraki M, Bamba T, *et al.* Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy. International journal of colorectal disease. 2014 Apr;29(4):485-91.
30. Haraoui B, Smolen JS, Aletaha D, *et al.* Treating Rheumatoid Arthritis to Target: multinational recommendations assessment questionnaire. Annals of the rheumatic diseases. 2011 Nov;70(11):1999-2002.
31. Tymms K, Zochling J, Scott J, *et al.* Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. Arthritis care & research. 2014 Feb;66(2):190-6.
32. Vermeer M, Kuper HH, Bernelot Moens HJ, *et al.* Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. Arthritis research & therapy. 2012 Nov 23;14(6):R254.

33. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. The American journal of gastroenterology. 2012 Oct;107(10):1474-82.
34. Torres J, Billioud V, Sachar DB, *et al*. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflammatory bowel diseases. 2012 Jul;18(7):1356-63.

CHAPTER 5: BEYOND CONVENTIONAL TREATMENT TARGETS: LOW LEAN MASS AND SARCOPENIA IN PATIENTS WITH IBD

Background

Incorporation of objective treatment targets to guide therapy in IBD stands to improve outcomes for patients. However, quality of care in IBD requires management of patient factors that are not captured by a conventional 'treat to target' approach alone.

Body composition refers to compartments of bone, fat mass, and fat-free (lean) mass in the body.

Abnormal body composition may be common in patients with IBD and an important contributor to morbidity, however there is limited data to inform current understanding. Metabolic bone disease is known to be prevalent in patients with IBD, however less is known about myopenia (reduced lean mass) and sarcopenia (reduced lean mass and strength). Abnormal body composition is an un-promoted area of care in IBD, warranting further study to better understand its influence on QoL and outcomes.

This single-centre prospective study comprehensively evaluated body composition in adult patients with IBD in routine care as compared to population-based sex- and age-matched controls. Both anthropometrics and DXA were used to assess body composition, alongside muscle performance testing using grip strength, in order to correctly define rates of myopenia and sarcopenia in the evaluated IBD cohort. Rigorous analysis of IBD-related factors, alongside nutritional and lifestyle factors such as exercise, allow identification of potential relationships between these factors and body composition in patients with IBD.

Presented in this chapter is the manuscript published in Alimentary Pharmacology and Therapeutics 2015; 41: 895-906.

Specific Author Contributions

Title of Paper	Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease
Publication Status	Published
Publication Details	Alimentary Pharmacology and Therapeutics. 2015; 41 (9): 895-906. Impact factor: 5.7

Name of Principal Author (Candidate)	Robert Venning Bryant		
Contribution to the Paper	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21/2/2018

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Soong Ooi
Contribution to the Paper 10%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article

Signature		Date	21/2/2018

Name of Co-Author	Chris Schultz		
Contribution to the Paper 10%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	14/2/2018

Name of Co-Author	Charlotte Goess		
Contribution to the Paper 3%	Data acquisition and management Drafting and revision of article		
Signature		Date	16/2/2018

Name of Co-Author	Rachel Grafton		
Contribution to the Paper 3%	Data acquisition and management Drafting and revision of article		
Signature		Date	26/2/2018

Name of Co-Author	Julie Hughes		
Contribution to the Paper 3%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	14/2/2018

Name of Co-Author	Amanda Lim		
Contribution to the Paper 3%	Data acquisition and management Drafting and revision of article		
Signature		Date	16/2/2018

Name of Co-Author	Francis D Bartholomeusz		
Contribution to the Paper 3%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	14/2/2018

Name of Co-Author	Jane M Andrews		
Contribution to the Paper 15%	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	12/2/2018

[Manuscript 3] Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease

Short title: Sarcopenia in IBD

Bryant RV[1,2], Ooi S[1,2], Schultz, CG[3], Goess C[1], Grafton R[1], Hughes, J[1], Lim A[2], Bartholomeusz FD[1,3], Andrews JM[1,2]

[1]Inflammatory Bowel Disease Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, South Australia.

[2]School of Medicine, University of Adelaide, South Australia.

[3]Department of Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital, South Australia.

Corresponding author

Professor Jane Andrews

Inflammatory Bowel Disease Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, North Terrace Adelaide, South Australia 5000.

Email: jane.andrews@health.sa.gov.au

Acknowledgements

Royal Adelaide Hospital IBD Nurses, Rachel Grafton, Julie Hughes, and Lucy Cronin, for their kind assistance and contribution to the database.

Grant support and writing assistance

No funding was received for the study. The Royal Adelaide Hospital (RAH) Research Fund, The RAH IBD Service Research Fund and the Department of Nuclear Medicine at the RAH each partially funded this study. No writing assistance was provided for the manuscript.

Conflicts of interest and personal interests

The authors have no personal conflicts of interest to declare.

Abstract

Background

Body composition is poorly studied in inflammatory bowel disease (IBD). Sarcopenia describes a loss of muscle mass and strength.

Aim

To assess the prevalence of low lean mass (LM), sarcopenia, and associated morbidity in an adult IBD cohort.

Methods

Cross-sectional data were gathered on pre-menopausal 18–50-year-old patients with IBD. Whole body dual energy X-ray absorptiometry, anthropometric assessment and grip strength were performed. Low LM was defined as ≥ 1standard deviation (SD) below the population mean for appendicular skeletal muscle index (ASMI, (kg)/height (m)²), and sarcopenia as both ASMI and grip strength ≥ 1 SD below population mean. Multivariate regression analyses were performed.

Results

Of 137 participants (mean age 32.2 years, BMI 26.2 kg/m^2), 56% were male and 69% had Crohn's disease (CD). Low LM and sarcopenia were observed in 21% and 12% of patients respectively and osteopenia/osteoporosis in 38% of patients (mean lumbar spine t-score −0.3 ± SD 1.1). Grip strength predicted low LM and sarcopenia better than body mass index (BMI) (OR 4.8 vs. OR 0.7 for low LM, $p < 0.05$ both). Normal BMI was falsely reassuring in 72% and 76% of patients with low ASMI and sarcopenia respectively. Low LM and sarcopenia (OR 3.6, p0.03; OR 6.3, $p = 0.02$; respectively), but not BMI nor fat mass, predicted osteopenia/osteoporosis.

Conclusions

Low LM and sarcopenia are common in patients with IBD, and important to recognise as they predict osteopenia/osteoporosis. Grip strength testing should be incorporated into routine clinical practice to detect LM deficits, which may go unrecognised using BMI alone.

Key words

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, body composition, osteopenia, osteoporosis, sarcopenia, muscle

Introduction

Body composition refers to proportions of bone, fat and fat-free (lean) mass in the body. Lean mass deficits lead to reduced muscle strength and endurance indices, and have been associated with demonstrable morbidity, mortality, and reduced quality of life (QoL) in elderly populations.[1-4] The term sarcopenia, correctly used, incorporates both anatomical and functional assessment and is defined as lean mass deficit coupled with loss of strength.[5] Premature and 'accelerated' development of sarcopenia has been described in other populations affected by factors such as chronic inflammation, malnutrition and immobility, which are relevant in inflammatory bowel disease (IBD).[6-9] Yet, despite the risks and potential consequences of low lean mass and sarcopenia in IBD, there is a paucity of quality data to inform our understanding of body composition in adult patients with IBD.[10]

Recent review of existing data on body composition in adult patients with IBD suggests that patients are affected by altered body composition compared to healthy matched controls.[10] However, the validity of available data is limited by considerable heterogeneity, due to small study populations and suboptimal control groups (not representative of population norm data), poor standardisation of clinical characteristics, and variable techniques used to measure body composition, which are prone to inaccuracy.[10-13] Moreover, rates of (appropriately defined) sarcopenia have not been previously described in an adult IBD cohort.

Lean mass is known to be more predictive of bone strength than the equivalent weight of fat mass, as it applies stress to bones, thereby encouraging bone deposition and remodelling.[14-16] Osteopenia and osteoporosis are often discussed issues for patients with IBD, however, surprisingly, rates are poorly characterised and conflicting reports exist. Existing data suggest that up to 30–48% of patients are affected.[17-22] Detection of lean mass deficits may be limited using BMI assessment alone in routine clinical practice. Small studies have shown that BMI does not correlate well with lean mass in patients with IBD, even amongst those in clinical remission.[10, 23-25] Furthermore, gains in BMI may relate to gains in fat mass, further masking underlying lean mass deficits.[24, 25] Beyond the potential to influence bone health, low lean mass and sarcopenia are likely surrogate markers of ill-health and inadequately controlled disease activity, and may be associated with fatigue and reduced quality of life in

patients with IBD.[10, 26-30] Yet, lean mass and body composition are still not routinely assessed in clinical IBD practice.

The aim of this study was to provide a comprehensive assessment of body composition in adult patients with IBD compared to a healthy population. We employed the use of the gold-standard technique of dual energy X-ray absorptiometry (DXA) coupled with assessment of muscle performance using grip strength testing;[31] a combined anatomical and functional assessment, which would allow for rates of sarcopenia to be characterised in patients with IBD. The study involved rigorous analysis of contemporaneous clinical and nutritional variables including physical activity and vitamin D levels, so as to identify potential relationships between these factors and body composition as well as possible management targets. Our hypothesis was that low lean mass is common and associated with sarcopenia and osteopenia in patients with IBD.

Materials and methods

Subjects

Between April 2012 and July 2013, consecutive eligible patients with IBD who had either an ambulatory or inpatient encounter with the IBD Service at the Royal Adelaide Hospital were invited to participate in the study. Men and women with both CD and ulcerative colitis (UC), between the ages of 20–50 (and pre-menopausal) were recruited. Following provision of an information sheet, informed consent was gained prior to enrolment. Exclusion criteria were current pregnancy, significant medical or surgical comorbidity other than IBD, and steroid use other than that required for IBD therapy. Recruitment of 140 patients with IBD was estimated to provide adequate power for multivariate analysis.

Subject data collection

Data were captured on enrolled subjects via self-reporting questionnaires along with case-note and IBD database corroboration by authors (CG, SO, AL). Case-note review included endoscopy, histopathology, pathology and radiology reports, along with prescription and medication history. Patients were contacted for clarification if there were any discrepancies between self-reporting and hospital-held data.

Demographic data included age, gender, racial background, smoking history, and alcohol use. For the purposes of statistical analysis, smoking history was dichotomised into ex or current

smokers versus those who had never smoked. Alcohol use was dichotomised into < 20 g/day versus ≥ 20 g/day on the basis of current alcohol consumption guidelines.[32, 33] IBD-related data collected included diagnosis, date of diagnosis, disease extent (Montreal criteria), current and past IBD medical therapy, and IBD-related surgery.[34] Data on medical and surgery comorbidities were collected, as well as non-IBD medications. Subjects' use of corticosteroids was collected in detail. Total lifetime duration of corticosteroid use (equivalent to prednisolone ≥ 10 mg/day) was established on the basis of patient self-reporting and exhaustive case-note and medication prescription review by the authors (CG, SO). Patients were dichotomised into those who had cumulative use of ≥ 12 months of steroids versus those having used < 12 months of steroids for statistical analysis, as this was median total duration of cumulative use within the cohort. The impact of current steroid therapy was also examined.

A composite assessment of IBD disease activity was used, incorporating clinical indices, biomarkers of inflammation, and most recent endoscopic or radiologic investigations. Clinical assessment incorporated the Crohn's Disease Activity Index (CDAI) for those with CD (CDAI < 150 considered inactive disease),[35] and the Partial (Clinical) Mayo Score for those with UC (a score of ≤ 1 and no rectal bleeding was considered inactive disease).[36] C-reactive protein (CRP) was used as a marker of systemic inflammation (< 5 miligrams/litre considered consistent with inactive disease). Faecal calprotectin (FC) as an objective marker of intestinal disease activity was also assessed using a CALPRO® enzyme-linked immunosorbent assay test (a stringent level of < 100micrograms/gram was considered consistent with inactive disease). Endoscopic/radiologic investigations were reviewed and incorporated into the overall assessment of disease activity when recent (within 3 months). IBD activity was dichotomised into inactive/quiescent disease versus active disease for the purposes of analysis. Where there was incongruity between measures of disease activity (4 cases overall), objective markers of disease activity took precedence over symptom scores.

Participants' habitual physical activity was assessed using a validated self-administered Short International Physical Activity Questionnaire (IPAQ).[37] Given the young age of the cohort, physical activity was dichotomised into normal (moderate to high categorical scale of IPAQ, > 600 MET-minutes/week) or low (< 600 MET-minutes/week). The validated Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was used to assess health-related quality of life (HRQoL).[38] Testing for exclusion of endocrinopathies was also performed

including testosterone, sex-hormone binding globulin, insulin-like growth factor 1 and thyroid function tests.

Body composition, anthropometric and nutritional assessment

Dual energy X-ray absorptiometry (DXA) for BMD of the lumbar spine, total femur and whole body was performed on enrolled subjects using a General Electric Lunar Prodigy Vision bone densitometer (Madison WI, US; system DF+13727; software version Encore 13.60) using standard manufacturer protocols conforming to International Society for Clinical Densitometry/International Osteoporosis Foundation guidelines.[39] A standard whole body DXA scan was performed to assess body composition. Height and weight were measured using standard Seca ® stadiometer and scale equipment at the time of DXA scanning. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres, squared. The appendicular skeletal muscle (ASM) mass is the sum of the lean mass of the arms and legs (kilograms) and is considered the functional lean mass.[12, 26, 40] Measurement of ASM compared with overall lean mass better reflects true muscle mass, as measurement of overall lean mass includes non-fat soft tissues such as organs, which are not muscle and have little influence on bone loading.[16, 26] Fat mass (FM) is the sum of body fat mass (kilograms).

Analogous to calculating the BMI, the appendicular skeletal muscle index (ASMI) is the ASM mass in kilograms divided by height in metres, squared.[40] The fat mass index (FMI) is calculated as the fat mass in kilograms divided by height in metres, squared.[40]

Population-based, age- and gender-matched, normative ASMI and FMI data from the National Health and Nutrition Examination Survey (NHANES) were used for comparison.[40] NHANES performs a continuous, nationally representative health survey of the civilian, non-institutionalised American population, collecting data on around 5000 people each year. Between 1999 and 2004, DXA data were gathered on body composition, stratified according to age, gender and ethnicity. DXA procedures were performed according to standard technique and calibration. The data were normalised via a process of division and power transformation. NHANES standard deviation values were used to calculate z-scores for ASMI and FMI. Low lean mass was defined as an ASMI greater than or equal to 1 SD below the age- and gender-matched ASMI mean.

World Health Organization population-based age- and sex-matched normative data of the lumbar spine (L2–L4) and total femur were used to calculate t-scores.[41] The lowest t-score of

either site was used to stratify patients as normal (> −1), osteopenic (≤ −1 > −2.5) or osteoporotic (≤ −2.5). Patients younger than 20 years of age were not included in analysis of BMD, as population-based normative data do not include this group.

Muscle function was measured by testing grip strength, a widely accepted robust surrogate measure of whole body strength,[16, 42] performed with a calibrated Jamar Digital Hand Dynamometer (2011, made in China). Testing was performed on the dominant arm, with subjects standing with the test arm held straight at their side. After a practice attempt, three recorded attempts were performed and the mean score and standard deviation recorded. Population-based age- and sex-matched normative data derived from 638 normal healthy adults were used for comparison and for calculation of z-scores.[43]

Sarcopenia was defined using a combined anatomical/functional definition;[5] both ASMI and grip strength > 1 SD below mean.

Concurrent measurement of nutritional indices was performed at a single laboratory affiliated with the Royal Adelaide Hospital and included albumin, 25(OH) vitamin D (measured using an automated chemiluminescent assay performed on an iSYS Automated Immunoassay System (IDS)), calcium, hemoglobin and mean cell volume, iron studies including ferritin and transferrin saturation, vitamin B12 and folate. Iron deficiency was defined as a ferritin < 30 ng/ml and a transferrin saturation of < 16% where CRP was normal (< 8 mg/l), and as a ferritin of < 100 and a transferrin saturation of < 16% where CRP was elevated (≥8 mg/l).[44] The World Health Organization (WHO) defines anemia as hemoglobin < 12 g/dl in non-pregnant women and < 130 g/dl in men.[44] Low vitamin D was defined according to Australian Guidelines as a serum 25(OH) vitamin D level of < 50 nmol/L.[45]

Statistical analysis

Results are expressed in means and standard deviations for normally distributed variables and in medians and interquartile range for non-normally distributed variables. Body composition data were normalised via the process of division by an independent variable (age) and power calculation.[40] SD values from population-based age- and sex-matched data were used to calculate z-scores (for FMI, ASMI and grip strength) and t-scores (for BMD). Univariate and multivariate logistic regression analyses were performed to determine the clinical features associated with ASMI, sarcopenia, and bone health. Pearson correlation coefficients were used to examine for any relationship between BMI and ASMI/FMI. Unpaired t-tests were

used to compare ASMI and disease activity with quality of life (QoL). Data were missing in < 5% of cases for any variable; complete case analysis is presented.[46]

Ethical considerations

The study was approved by the Royal Adelaide Hospital Research Ethics Committee (study approval number 120304, 02/03/2012) and each subject provided written informed consent. A baseline assessment of BMD using DXA along with blood tests for disease activity and nutritional analysis was considered within routine practice for patients with IBD. Whole body DXA does not confer significant additional radiation to that used for BMD assessment. A radiation safety report confirmed that the total radiation dose per visit for DXA scans was 2.56μSv.

Results

Some 180 patients with IBD were assessed for eligibility over the enrolment period; 43 were excluded (20 declined and 23 did not meet inclusion criteria due to significant medical or surgical comorbidity other than IBD, or steroid use other than that required for IBD therapy). A total of 137 participants were included in the final analysis; 95 (69%) with CD and 42 (31%) with UC (***Table 5.1***). Five patients were hospitalised at the time of study enrolment. The median disease duration was 7 years, and longer amongst patients with CD than UC (8 vs. 6 years, p = 0.01). At study entry, 78 (57%) patients had active disease using the described composite disease activity assessment. The median cumulative total duration of corticosteroid use amongst the group was 12 months, with a trend toward higher use in patients with CD than UC (12 vs. 6 months, p = 0.09). Six percent of patients had never received corticosteroids, 29% of patients were currently using corticosteroids, and 40% had cumulative use ≥ 12 months. Sixteen percent of the group were current smokers (21% and 5% of patients with CD and UC respectively), and only 4% used > 20 g of alcohol per day. Physical activity measured by the IPAQ was low (< 600 MET-minutes/week) in the majority of patients (53%). The median HRQoL score as assessed by the SIBDQ was 53/70, with no significant differences between CD and UC patients. HRQoL was significantly lower amongst those with active disease than those with inactive disease (SIBDQ median 50 vs. 55.5, p0.005).

Body composition and nutritional characteristics

The median BMI in the cohort was 26.2 (SD ± 5.6, median 25.2), ranging from underweight (BMI 16) to morbidly obese (BMI 43) (***Table 5.2***). The mean ASMI z-score was significantly lower than the age-matched control population (−0.38 ± 0.76, $p < 0.0001$). Overall, 29 (21%) patients had a low ASMI (≥ 1 SD below mean) (***Table 5.2***, ***Figure 5.1***): 18 (19%) patients with CD and 11 (26%) with UC; 19 (25%) males and 10 (16%) females (***Table 5.2***, ***Figure 5.2***). Fat mass was unaffected in the IBD population, as the mean FMI z-score was not significantly different to the control population (0.16 ± 1.3, p0.15).

The mean grip strength z-score was significantly lower than age-matched population normal data (−0.51 ± 1.0, $p < 0.01$); 40 (29%) patients overall and 29 (38%) males had a low grip strength (> 1 SD below mean).

Overall, 17 (12%) of patients with IBD fulfilled our combined anatomical/functional definition criteria for sarcopenia; 11 (12%) patients with CD, 6 (14%) patients with UC, 14 (18%) males and 3 females (5%). Amongst those with low ASMI, just over half (57%) also had low grip strength and therefore fulfilled criteria for sarcopenia.

Nutritional indices revealed 28% of participants to be iron deficient, though only 7 (5%) patients demonstrated current anemia. The mean serum 25-hydroxyvitamin D level in the cohort was normal (67 nmol/mL), although 28% of the cohort were deficient. Serum calcium levels were normal in all patients and no endocrinopathy was identified during screening.

Clinical predictors of low ASMI

Univariate analyses revealed that BMI was a negative predictor of low ASMI (OR 0.7, $p < 0.01$), whereas iron deficiency (OR 2.4, p0.05) and low grip strength (OR 5.7, $p < 0.01$) were positive predictors of low ASMI (***Table 5.3***). In multivariate analysis, BMI remained a negative predictor of low ASMI, and grip strength a positive predictor of low ASMI (OR 0.7, $p < 0.01$ vs. OR 4.8, p0.03; respectively). For every 1 kg/m^2 increase in BMI there was a 29% reduction in the odds of low ASMI. Unexpectedly, cumulative steroid use for ≥ 12 months and current or ex-smoking status were each associated with a lower likelihood of low ASMI (OR 0.2, $p = 0.04$; OR 0.3, p0.07; respectively). Current steroid use was not associated with low ASMI (OR 0.9, p0.83), nor was active disease (OR 1.1, p0.84).

Correlation coefficient analysis showed that BMI correlated well with fat mass index (r = 0.89, 95% CI 0.85–0.92), though only moderately with ASMI (r = 0.75, 95% CI 0.67–0.82). Of patients with a low ASMI and sarcopenia, 72% and 76% had a falsely reassuring normal BMI (> 20), respectively.

Consequences of low ASMI and sarcopenia

The mean BMD t-score was significantly reduced in patients with IBD (−0.3 ± 1.1, $p < 0.01$) (***Table 5.2***). Osteopenia was evident in 49 (36%) overall, while only 3 (2%) had osteoporosis; thus 52 (38%) had osteopenia or osteoporosis as a combined endpoint.

Multivariate analysis revealed that sarcopenia (ASMI and grip strength > 1 SD below mean) was the strongest predictor of the combined endpoint of osteopenia/osteoporosis with an OR of 6.3, followed by low ASMI alone (OR 3.6) and then disease duration (OR 1.1). BMI was not predictive of bone health (OR 0.95) (all data shown in ***Table 5.4***).

Health-related quality of life as assessed by the SIBDQ did not differ between patients with or without low ASMI or sarcopenia (SIBDQ median 53 vs. 51, p0.53; 50.5 vs. 53, p0.81 respectively).

Discussion

This cross-sectional study documents rates of sarcopenia in patients with IBD as compared to healthy population-based data, using an appropriate definition, incorporating assessment of both muscle mass and strength.[4] Appendicular skeletal muscle measurement, as assessed using the gold-standard reference method of DXA, best reflects functional muscle mass,[26] and grip strength is a well-validated measure of whole body muscle performance.[16, 42] Overall, 21% of this young IBD cohort demonstrated low lean mass and 12% were sarcopenic. Of particular concern was the finding that almost 20% of young male patients (mean 31 years) were sarcopenic.

Grip strength was a shown to be a better predictor of low lean mass and sarcopenia than BMI testing; BMI was shown to better correlate with fat mass than with lean mass. In fact, a normal BMI was falsely reassuring in 72% of patients who were demonstrated to have low lean mass. Low lean mass and sarcopenia were each shown to be independent predictors of poor bone health (osteopenia/osteoporosis), whereas BMI did not predict bone health at all. Thus, we propose that clinicians incorporate routine grip strength testing, alongside BMI, in

their clinical assessment of patients with IBD, to best to detect lean mass deficits, which are predictive of poor bone health and likely reflective of poorly controlled IBD. Measurement of grip strength is quick, cheap, and practically feasible within the confines of busy clinical practice.

Sarcopenia has been previously described in patients with IBD, though many prior studies have not incorporated appropriate testing of both muscle mass and performance into this definition.[26-29] Mechanisms of premature sarcopenia in patients with IBD, derived from both human and mouse models, are purported to involve inflammatory pathways and cytokine release (especially NF-κβ, tumour necrosis factor and interleukin-6 (IL-6)), which lead to inflammatory muscle wasting and fatigue.[28, 30, 47, 48] Malnutrition due to malabsorption, dietary restriction, surgery, or inflammation-related catabolism, along with corticosteroid use and lack of physical activity also likely contribute to the development of sarcopenia in patients with IBD.[7, 9, 49-55]

Sarcopenia is likely to represent a surrogate marker of ill-health and inadequately controlled IBD, and in keeping with this, we have demonstrated that sarcopenia is an independent predictor of osteopenia and osteoporosis. Given that BMI and fat mass do not predict bone health, our findings support the supposition that muscle contraction, over and above body weight or fat mass, applies stress to bone and thereby generates bone deposition and strength.[14-16, 26, 56-58] In keeping with existing literature, the combined outcome of osteopenia/osteoporosis was prevalent in the studied IBD cohort (38%), and is likely reflective of a high proportion of patients with active disease.[17-19, 59]

Recognition of sarcopenia is important amongst patients with IBD, given that sarcopenia may be amenable to management via adequate control of inflammation, correction of malnutrition, and physical activity. Reversal of sarcopenia amongst 19 patients with active CD was recently demonstrated following infliximab administration, which correlated with a reduction in serum IL-6.[30] Optimisation of nutritional status, in particular vitamin D, has an important role in muscle function.[48, 60-62] Small studies have shown that exercise may improve quality of life and clinical disease activity indices in outpatients with IBD.[63-65] Muscle function is associated with self-reported fatigability amongst patients with CD,[28] and survey data suggests that physical fatigue may be improved by establishment of regular exercise, a supposition supported by molecular work analysing muscle protein synthesis pathways.[48, 66] Given that consensus IBD guidelines support routine bone densitometry for patients with

IBD,[61, 62] a simultaneous request for whole body DXA would yield valuable information on lean mass, whilst adding little to patient radiation exposure or the time taken for the scan.

Limitations of this cross-sectional study were an inability to perform prospective correlations with clinically relevant outcomes such as clinical disease course, need for surgery, and cumulative disability. Longitudinal analysis is required. We were unable to show that body composition influences, or is influenced by, other meaningful clinical variables/outcomes or quality of life. This is likely reflective of Type 2 error and confounders present within this study. The high rate of active disease (57%) and concurrent steroid use (29%) is likely due to recruitment of sicker patients through a tertiary-level IBD centre. Despite the use of the validated IPAQ, self-reporting of physical activity is subjective. Furthermore, the overall low rates of habitual exercise amongst the cohort may be a confounding factor. Surprising was the finding that cigarette smoking was positively associated with lean mass, as although smoking has not been linked specifically to sarcopenia, it is known risk factor for osteoporosis. This may relate to dichotomisation of smoking status for statistical purposes, without accounting for a pack-year history. Further weaknesses include lack of control for dietary intake and disease extent in the statistical analysis.

Conclusions

Low muscle mass and sarcopenia are common in patients with IBD, and are unlikely to be recognised by routine clinical assessment with BMI alone. Detection of low lean mass is important, as it independently predicts osteopenia, and is a surrogate marker of ill-health and inadequately controlled IBD. Grip strength testing, alongside BMI, should be incorporated into the routine anthropometric assessment of patients with IBD given its strong correlation with low lean mass and sarcopenia.

The challenge remains for further research to identify management strategies for sarcopenia in IBD, as well as to assess whether addressing lean muscle deficits can improve endpoints including disease outcomes, bone health, fatigue, and quality of life in patients with IBD.

Figures

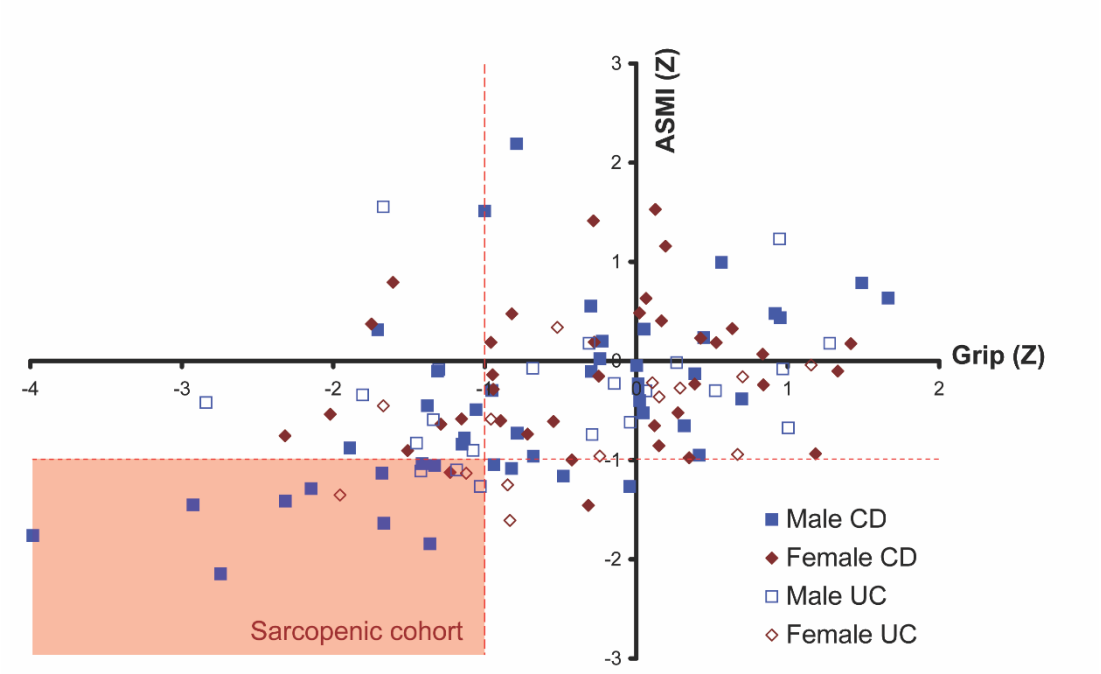


Figure 5.1 Grip strength z-score versus appendicular skeletal muscle index (ASMI) z-score

Legend: *ASMI and grip strength z-scores calculated using standard deviations derived from population-based healthy control datasets. Sarcopenia was defined using a combined anatomical/functional definition, with both ASMI and grip strength > 1 SD below mean (highlighted in red).*

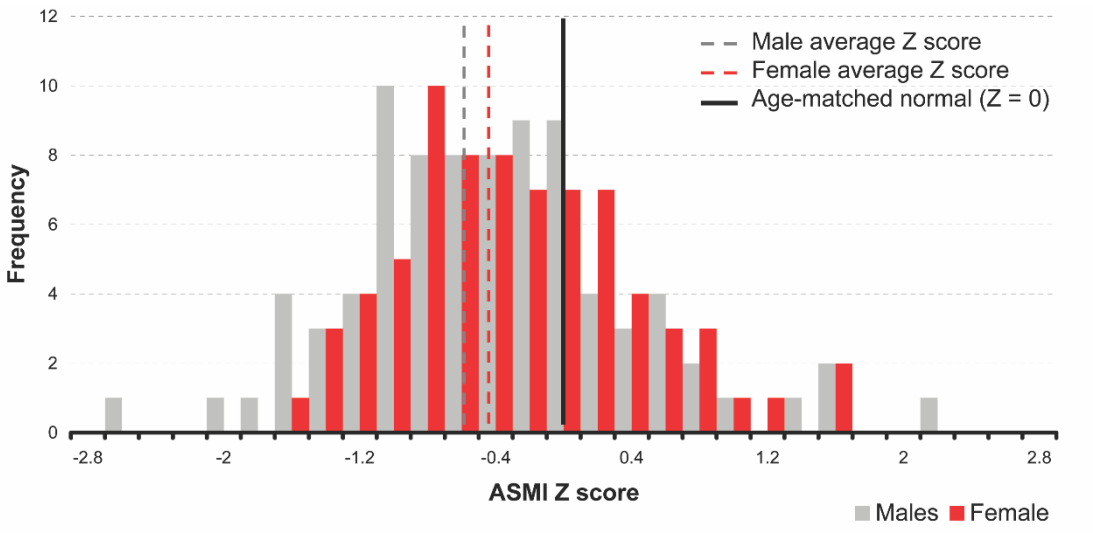


Figure 5.2. Appendicular skeletal muscle index (ASMI) z-score frequency

Legend: *ASMI z-scores calculated using standard deviation derived from population-based healthy control datasets. The figure represents a histogram of the ASMI z-score frequency amongst male and female patients with IBD. The mean z-score is significantly lower amongst IBD patients compared to healthy controls.*

Tables

Table 5.1 Inflammatory bowel disease cohort

	Crohn's disease	**Ulcerative colitis**
Demographics		
• Patients (n)	95 (69%)	42 (31%)
• Male (n, %)	51 (54%)	25 (60%)
• Age (years) (median, IQR)	31 (27–39)	30 (22–39)
• Smoking		
Current	20 (21%)	2 (5%)
Ex-smoker	27 (28%)	11 (26%)
Never smoked	45 (47%)	28 (67%)
• Alcohol use (> 20 gm ethanol per day)	5 (5%)	0 (0%)
IBD		
• Disease duration (years) (median, IQR)	8 (5–13)	6 (2–10)
• Disease extent (Montreal criteria)	A1 17% B1 41% L1 24% A2 76% B2 31% L2 30% A3 7% B3 28% L3 46%	E1 45% E2 33% E3 62%
• IBD-related surgery	No surgery 53 (56%) Small bowel resection 22 (23%) Ileo-colonic resection 15 (16%) Colectomy 2 (2%) Other 3 (3%)	No surgery 40 (95%) Colectomy 2 (5%)
IBD disease activity		
• Clinical disease score (median, IQR)	CDAI 60 (26–137)	Partial Mayo 0 (0–2)
• C-reactive protein (mg/L) (median, IQR)	2.4 (0.6–12)	1.5 (0.4-3.0)
• Faecal calprotectin (mcg/gm) (median, IQR)	83 (20–460)	60 (20–238)
• Active IBD: Composite assessment^	51 (54%)	27 (64%)
IBD medications		
• Corticosteroids# (months) (median, IQR)	12 (3–30)	6 (3.2–18)
• Current steroids	25 (26%)	15 (36%)
• Steroids ≥ 12 months	42 (44%)	13 (31%)

	Crohn's disease	**Ulcerative colitis**
• TNF antagonists	51 (54%)	4 (10%)
QoL and physical exercise • SIBDQ (QoL) • IPAQ (normal: > 600 MET-minutes/ week)	 53 (42–60) 45 (47%)	 52 (46–58.5) 20 (48%)

Legend: *Clinical characteristics of the enrolled inflammatory bowel disease (IBD) cohort (n=137). ^ Disease activity: composite measure using clinical indices (CDAI, Crohn's disease activity index; and Partial Mayo score), faecal calprotectin and CRP; # Cumulative months equivalent to prednisolone ≥10mg/day; TNF, Tumour necrosis factor alpha antagonists (current or past); SIBDQ, Short inflammatory bowel disease questionnaire (health-related quality of life); IPAQ, International Physical Activity Questionnaire (Short).*

Table 5.2 Body composition and nutritional characteristics of inflammatory bowel disease cohort

	Phenotype		**Gender**	
	Crohn's disease n = 95	**Ulcerative colitis n = 42**	**Male patients n = 76**	**Female patients n = 61**
Body mass index (kg/m2) (median, interquartile)	25.2 (22.9–30.5)	24.1 (22.0–27.4)	24.9 (23.0–29.3)	24.6 (22.1–31.0)
Appendicular skeletal muscle (ASM)				
ASMI (kg/m2) (mean ± SD)	7.6 ± 1.3	7.6 ± 1.4	8.3 ± 1.2	6.6 ± 0.8
ASMI z-score (mean ± SD)	−0.32 ± 0.45*	−0.52 ± 0.67*	−0.42 ± 0.8*	−0.33 ± 0.7*
Low ASMI (≥ 1 SD below mean)	18 (19%)	11 (26%)	19 (25%)	10 (16%)
Fat mass (FM)				
FMI (kg/m2) (±SD)	8.9 ± 5.0	7.8 ± 4.4	8.3 ± 1.2	10.3 ± 5.1
FMI z-score (mean ± SD)	0.20 ± 1.3^	0.08 ± 1.4^	0.1 ± 1.5^	0.2 ± 1.2^
Bone mineral density (BMD)				
BMD (g/cm2) (±SD)	0.97 ± 0.09	0.97 ± 0.07	1.00 ± 0.08	0.92 ± 0.06
WHO t-score (mean ± SD)	−0.3 ± 1.1*	−0.4 ± 1.1*	−0.43 ± 1.1*	−0.2 ± 1.1^
Osteopenia	37 (39%)	12 (29%)	27 (36%)	22 (36%)
Osteoporosis	2 (2%)	1 (2%)	2 (3%)	1 (1%)
Grip strength				
Grip strength (PSI) (mean ± SD)	39.5 ± 12.1	40.9 ± 12.3	46.7 ± 11.4	31.1 ± 5.9
Grip strength z-score (mean ± SD)	−0.50 ± 1.1*	−0.50 ± 1.0*	−0.63 ± 1.1*	−0.35 ± 0.9*
Low grip strength (≥ 1 SD below mean)	26 (27%)	14 (33%)	29 (38%)	11 (18%)
Sarcopenia				
ASMI AND grip strength > 1 SD below mean	11 (12%)	6 (14%)	14 (18%)	3 (5%)

	Phenotype		Gender	
	Crohn's disease n = 95	**Ulcerative colitis n = 42**	**Male patients n = 76**	**Female patients n = 61**
Serum nutritional indices				
• **Ferritin** (ng/mL) (mean ± SD)	90.4 ± 83	73.0 ± 60	89.5 ± 62	79.1 ± 91
• **Hemoglobin** (g/L) (mean ± SD)	139 ± 15	143 ± 13	146 ± 14	132 ± 10
Iron deficient	26 (27%)	13 (29%)	19 (25%)	20 (33%)
• **Serum albumin** (g/dL) (mean ± SD)	38.6 ± 6.0	40.5 ± 4.4	40.0 ± 4.4	38.2 ± 6.8
Hypoalbuminemic (< 34)	10 (11%)	3 (7%)	6 (8%)	7 (11%)
• **25 (OH) Vitamin D** (nmol/mL)(mean ± SD)	62 ± 29	77 ± 56	69 ± 46	65 ± 32
Low Vitamin D (< 50 nmol/mL)	30 (32%)	9 (21%)	21 (28%)	18 (30%)

Legend: *Body composition assessed by dual energy X-ray absorptiometry (DXA) including appendicular skeletal muscle mass (ASMI), fat mass (FM), and bone mineral densitometry (BMD). Grip strength assessed using Jamar® dynamometer. Z-scores calculated using standard deviations derived from population-based healthy control datasets. Statistical analysis using unpaired t-tests.* ******* *Significant p value < 0.05 when compared to National Health and Nutrition Examination Survey (NHANES) or grip strength normative data; PSI, Pounds per square inch; iron deficiency defined as ferritin < 30 or ferritin < 100 and CRP > 5.*

Table 5.3 Predictors of low appendicular skeletal muscle index (ASMI) in inflammatory bowel disease cohort

Variable	**Univariate analysis**			**Multivariate analysis**		
	OR	CI (95%)	p-value	OR	CI (95%)	p-value
Diagnosis: Ulcerative colitis vs. Crohn's disease	1.5	0.6–3.6	0.34			
Disease duration	0.9	0.9–1.0	0.18			
Disease activity#	1.1	0.5–2.5	0.84			
Steroids (≥ 12 months vs. < 12 months)	0.2	0.1–0.6	< 0.01*	0.2	0.1–0.9	0.04*
Faecal calprotectin (< 100 vs. ≥ 100 mcg/g)	1.5	0.6–4.1	0.38			
Iron deficiency	2.4	0.9–5.7	0.05	1.0	0.3–3.7	0.99
Serum 25-Vitamin D level (< 60 vs. ≥ 60 ng/mL)	0.9	0.3–2.1	0.82			
IPAQ[4]	0.9	0.4–2.3	0.92			
Alcohol intake	0.9	0.1–8.4	0.93			
Smoking (current/ex-smoker vs. never)	0.4	0.2–0.9	0.04*	0.3	0.1–1.1	0.07
Body mass index	0.7	0.6–0.8	< 0.01*	0.7	0.5–0.8	< 0.01*
Low grip strength (z-score ≥ 1 SD below mean)	5.7	2.4–14.8	< 0.01*	4.8	1.2–19.6	0.03*

Legend: *Analysis of disease-related, nutritional, lifestyle, and anthropometric factors as predictors of low ASMI in the studied IBD cohort. Analysis performed using univariate and multivariate logistic regression. * $p < 0.05$ statistically significant; ASMI, appendicular skeletal muscle index: appendicular skeletal muscle (kg)/height (m) squared (z-score ≥ 1 SD below mean); # Disease activity: composite measure using clinical indices (CDAI, Crohn's disease activity index; and Partial Mayo score), faecal calprotectin and CRP; iron deficiency defined as ferritin< 30 ng/mL or ferritin < 100 ng/mL if CRP > 5 mg/L); IPAQ, International Physical Activity Questionnaire (short): low vs. normal (normal: > 600 MET-minutes/ week); Alcohol intake: > 20 gm/day vs ≤ 20 gm/day; BMI analysed as a continuous variable: a 1 kg/m2 increase in BMI is associated with a 29% reduction in the odds of a low ASMI.*

Table 5.4 Predictors of osteopenia or osteoporosis in the inflammatory bowel disease cohort

Variable	**Univariate analysis**			**Multivariate analysis**		
	OR, CI (95%), p-value			OR	CI (95%)	p-value
Diagnosis: Ulcerative colitis vs. Crohn's disease	0.6	0.3–1.4	0.26			
Disease duration	1.0	1.0–1.1	< 0.01*	1.1	1.0–1.2	< 0.01*
Disease activity#	1.2	0.6–2.4	0.62			
Steroid use Cumulative use (≥ 12 months vs. < 12 months) Current steroid use	 2.0 1.1	 1.1–9.6 0.5–2.4	 0.03* 0.75	1.8	0.7–4.5	0.23
Faecal calprotectin (< 100 vs. ≥ 100 micrograms/gram)	0.8	0.4–1.8	0.64			
Serum 25 (OH)-Vitamin D level (< 60 vs. ≥ 60 ng/mL)	1.0	0.5–2.1	0.94			
IPAQ	0.6	0.3–1.3	0.21			
Alcohol intake	1.0	0.6–6.2	1.00			
Smoking (current/ex-smoker vs. never)	1.2	0.6–2.5	0.58			
Body mass index	0.9	0.9–1.0	0.14			
Fat mass index (z-score)	0.8	0.6–1.1	0.17			
Low grip strength (z-score ≥ 1 SD below mean)	2.0	1.0–4.1	0.05	1.9	0.8–4.5	0.15
Low ASMI (ASMI ≥ 1 SD below mean)[5]	2.5	1.1–5.7	0.03*	3.6	1.2–11.4	0.03*
Sarcopenia (ASMI AND Grip strength > 1 SD below mean)	3.3	1.1–59.6	0.03*	6.3	1.4–27.9	0.02*

Legend: *Analysis of disease-related, nutritional, lifestyle, and anthropometric factors as predictors of osteopenia/osteoporosis (combined endpoint) in the studied IBD cohort. Analysis performed using univariate and multivariate logistic regression. World Health Organization Definition: Osteopenia 1–2.5 standard deviations (SD), osteoporosis > 2.5 SD below mean for young adults (T score). * p < 0.05 statistically significant; # Disease activity: composite measure using clinical indices (CDAI, Crohn's disease activity index; and Partial Mayo score), faecal calprotectin and CRP; IPAQ, International Physical Activity Questionnaire (short): low vs. normal (normal: > 600 MET-minutes/ week); Alcohol intake: > 20 gm/day vs. ≤ 20 gm/day; ASMI, appendicular skeletal muscle index; Sarcopenia analysed in a separate multivariate model to ASMI and grip strength.*

REFERENCES

1. Janssen I, Baumgartner RN, Ross R, *et al*. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol. 2004;159(4):413-21.
2. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50(5):889-96.
3. Woo J, Ho SC, Sham A. Longitudinal changes in body mass index and body composition over 3 years and relationship to health outcomes in Hong Kong Chinese age 70 and older. J Am Geriatr Soc. 2001;49(6):737-46.
4. Fielding RA, Vellas B, Evans WJ, *et al*. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12(4):249-56.
5. Cooper C, Fielding R, Visser M, *et al*. Tools in the assessment of sarcopenia. Calcif Tissue Int. 2013;93(3):201-10.
6. Beenakker KG, Ling CH, Meskers CG, *et al*. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing research reviews. 2010;9(4):431-6.
7. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care. 2012;15(1):12-22.
8. Jo E, Lee SR, Park BS, *et al*. Potential mechanisms underlying the role of chronic inflammation in age-related muscle wasting. Aging Clin Exp Res. 2012;24(5):412-22.
9. Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. International journal of molecular sciences. 2010;11(4):1509-26.
10. Bryant RV, Trott MJ, Bartholomeusz FD, *et al*. Systematic review: body composition in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(3):213-25.
11. Carlsson E, Bosaeus I, Nordgren S. Body composition in patients with an ileostomy and inflammatory bowel disease: validation of bio-electric impedance spectroscopy (BIS). Eur J Clin Nutr. 2002;56(7):680-6.
12. Kim J, Wang Z, Heymsfield SB, *et al*. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr. 2002;76(2):378-83.

13. Royall D, Greenberg GR, Allard JP, B *et al*. Critical assessment of body-composition measurements in malnourished subjects with Crohn's disease: the role of bioelectric impedance analysis. Am J Clin Nutr. 1994;59(2):325-30.
14. Bakker I, Twisk JW, Van Mechelen W, *et al*. Fat-free body mass is the most important body composition determinant of 10-yr longitudinal development of lumbar bone in adult men and women. J Clin Endocrinol Metab. 2003;88(6):2607-13.
15. Wang MC, Bachrach LK, Van Loan M, *et al*. The relative contributions of lean tissue mass and fat mass to bone density in young women. Bone. 2005;37(4):474-81.
16. Lee N, Radford-Smith GL, Forwood M, *et al*. Body composition and muscle strength as predictors of bone mineral density in Crohn's disease. J Bone Miner Metab. 2009;27(4):456-63.
17. Etzel JP, Larson MF, Anawalt BD, *et al*. Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. Inflamm Bowel Dis. 2011;17(10):2122-9.
18. Goodhand JR, Kamperidis N, Nguyen H, *et al*. Application of the WHO fracture risk assessment tool (FRAX) to predict need for DEXA scanning and treatment in patients with inflammatory bowel disease at risk of osteoporosis. Aliment Pharmacol Ther. 2011;33(5):551-8.
19. Walldorf J, Krummenerl A, Engler K, *et al*. Health care for osteoporosis in inflammatory bowel disease: unmet needs in care of male patients? Journal of Crohn's & colitis. 2013;7(11):901-7.
20. Targownik LE, Bernstein CN, Leslie WD. Risk factors and management of osteoporosis in inflammatory bowel disease. Current opinion in gastroenterology. 2014; 30(2): 168-72.
21. Targownik LE, Bernstein CN, Nugent Z, *et al*. Inflammatory bowel disease and the risk of fracture after controlling for FRAX. J Bone Miner Res. 2013;28(5):1007-13.
22. Targownik LE, Bernstein CN, Nugent Z, *et al*. Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clin Gastroenterol Hepatol. 2013;11(3):278-85.
23. Bin CM, Flores C, Alvares-da-Silva MR, *et al*. Comparison between handgrip strength, subjective global assessment, anthropometry, and biochemical markers in assessing nutritional status of patients with Crohn's disease in clinical remission. Dig Dis Sci. 2010;55(1):137-44.

24. Sylvester FA, Leopold S, Lincoln M, *et al*. A two-year longitudinal study of persistent lean tissue deficits in children with Crohn's disease. Clin Gastroenterol Hepatol. 2009;7(4):452-5.
25. Wiskin AE, Wootton SA, Hunt TM, *et al*. Body composition in childhood inflammatory bowel disease. Clin Nutr. 2011;30(1):112-5.
26. Schneider SM, Al-Jaouni R, Filippi J, *et al*. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008;14(11):1562-8.
27. Valentini L, Schaper L, Buning C, *et al*. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition. 2008;24(7-8):694-702.
28. van Langenberg DR, Della Gatta P, Warmington SA, *et al*. Objectively measured muscle fatigue in Crohn's disease: Correlation with self-reported fatigue and associated factors for clinical application. Journal of Crohn's & colitis. 2014; 8(2):137-146.
29. Wiroth JB, Filippi J, Schneider SM, *et al*. Muscle performance in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2005;11(3):296-303.
30. Subramaniam K, Fallon K, Ruut T, *et al*. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015;41(5):419-28.
31. Albanese CV, Diessel E, Genant HK. Clinical applications of body composition measurements using DXA. J Clin Densitom. 2003;6(2):75-85.
32. Health AGDo. New national guidelines for alcohol consumption 2014 [27/4/2014]. Available from: http://www.alcohol.gov.au/internet/alcohol/publishing.nsf/Content/guide-adult.
33. McGuire S. U.S. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. Advances in nutrition (Bethesda, Md). 2011;2(3):293-4.
34. Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-53.
35. Best WR, Becktel JM, Singleton JW, *et al*. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439-44.

36. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-9.
37. Ainsworth BE, Macera CA, Jones DA, *et al*. Comparison of the 2001 BRFSS and the IPAQ Physical Activity Questionnaires. Med Sci Sports Exerc. 2006;38(9):1584-92.
38. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol. 1996;91(8):1571-8.
39. Practitioners TRACoG. Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men.: National Health and Medical Researcrh Council; 2010 [cited 2014 1st May 2014]. Available from: http://www.racgp.org.au/Content/NavigationMenu/ClinicalResources/RACGPGuidelines/osteoporosis1/RACGP_Osteo_guideline.pdf.
40. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One. 2009;4(9):e7038.
41. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.
42. Snow-Harter C, Bouxsein M, Lewis B, *et al*. Muscle strength as a predictor of bone mineral density in young women. J Bone Miner Res. 1990;5(6):589-95.
43. Mathiowetz V, Kashman N, Volland G, *et al*. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985;66(2):69-74.
44. Gasche C, Berstad A, Befrits R, *et al*. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis. 2007;13(12):1545-53.
45. Nowson CA, McGrath JJ, Ebeling PR, *et al*. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust. 2012;196(11):686-7.
46. Thabane L, Mbuagbaw L, Zhang S, *et al*. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol. 2013;13:92.
47. Tang K, Murano G, Wagner H, *et al*. Impaired exercise capacity and skeletal muscle function in a mouse model of pulmonary inflammation. Journal of applied physiology (Bethesda, Md : 1985). 2013;114(9):1340-50.

48. van Langenberg DR, Gatta PD, Hill B, *et al*. Delving into disability in Crohn's disease: Dysregulation of molecular pathways may explain skeletal muscle loss in Crohn's disease. Journal of Crohn's & colitis 2014;8(7):626-634.
49. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2011;24(4):313-26.
50. Haderslev KV, Jeppesen PB, Sorensen HA, *et al*. Body composition measured by dual-energy X-ray absorptiometry in patients who have undergone small-intestinal resection. Am J Clin Nutr. 2003;78(1):78-83.
51. Schneeweiss B, Lochs H, Zauner C, F *et al.* Energy and substrate metabolism in patients with active Crohn's disease. J Nutr. 1999;129(4):844-8.
52. Sousa Guerreiro C, Cravo M, Costa AR, *et al*. A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. Am J Gastroenterol. 2007;102(11):2551-6.
53. Vaisman N, Dotan I, Halack A, *et al*. Malabsorption is a major contributor to underweight in Crohn's disease patients in remission. Nutrition. 2006;22(9):855-9.
54. Valentini L, Schulzke JD. Mundane, yet challenging: the assessment of malnutrition in inflammatory bowel disease. Eur J Intern Med. 2011;22(1):13-5.
55. McKinnell IW, Rudnicki MA. Molecular mechanisms of muscle atrophy. Cell. 2004;119(7):907-10.
56. Jahnsen J, Falch JA, Mowinckel P, *et al*. Body composition in patients with inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2003;98(7):1556-62.
57. Mauro M, Armstrong D. Evaluation of densitometric bone-muscle relationships in Crohn's disease. Bone. 2007;40(6):1610-4.
58. Leslie WD, Miller N, Rogala L, *et al*. Body mass and composition affect bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. Inflamm Bowel Dis. 2009;15(1):39-46.
59. Bernstein CN. Osteoporosis in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2006;4(2):152-6.
60. Salacinski AJ, Regueiro MD, Broeder CE, *et al*. Decreased neuromuscular function in Crohn's disease patients is not associated with low serum vitamin D levels. Dig Dis Sci. 2013;58(2):526-33.

61. Van Assche G, Dignass A, Bokemeyer B, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. Journal of Crohn's & colitis. 2013;7(1):1-33.
62. Van Assche G, Dignass A, Reinisch W, *et al*. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. Journal of Crohn's & colitis. 2010;4(1):63-101.
63. Loudon CP, Corroll V, Butcher J, *et al*. The effects of physical exercise on patients with Crohn's disease. Am J Gastroenterol. 1999;94(3):697-703.
64. Ng V, Millard W, Lebrun C, *et al*. Low-intensity exercise improves quality of life in patients with Crohn's disease. Clin J Sport Med. 2007;17(5):384-8.
65. Cosnes J. Smoking, physical activity, nutrition and lifestyle: environmental factors and their impact on IBD. Dig Dis. 2010;28(3):411-7.
66. van Langenberg DR, Gibson PR. Factors associated with physical and cognitive fatigue in patients with Crohn's disease: a cross-sectional and longitudinal study. Inflamm Bowel Dis. 2014;20(1):115-25.

CHAPTER 6: BODY COMPOSITION IN PATIENTS WITH IBD OVER TIME: EMERGENCE OF OBESITY

Background

As reported in Chapter 5, abnormal body composition is common in patients with IBD, in particular low lean mass, sarcopenia, and metabolic bone disease. However, there is a paucity of prospective data evaluating the evolution of body composition over time in patients with IBD.

Obesity is a major global public health concern and parallel to the prevalence of obesity in the general population, rates in patients with IBD appear to be rising. Adipose tissue is metabolically active and could contribute toward a pro-inflammatory milieu in IBD, but data on obesity and IBD susceptibility are conflicting. Conversely, it is plausible that IBD is an independent risk factor for obesity, driven by alterations in the composition and function of the gut microbiome. However, prospective data on obesity and IBD are limited, and few studies have reported on direct measures of adiposity over time in patients with IBD.

This prospective study comprehensively evaluated body composition using DXA in adult patients with IBD over serial time points over 24 months. Changes in anthropometrics and direct measures of fat (including visceral fat), muscle, and bone were analysed over time, alongside influencing variables including IBD-related factors, lifestyle factors including habitual exercise, and nutritional indices.

Presented in this chapter is the manuscript submitted to American Journal of Clinical Nutrition, June 2018.

Specific Author Contributions

Title of Paper	Obesity in inflammatory bowel disease: gains in adiposity despite high prevalence of myopenia and osteopenia.
Publication Status	Submitted for publication
Publication Details	American Journal of Clinical Nutrition. June 2018. Impact factor: 6.77

Name of Principal Author (Candidate)	Robert Venning Bryant		
Contribution to the Paper	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21/3/2018

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Chris Schultz
Contribution to the Paper 6%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data

	sion of article		
Signature		Date	23/3/2018

Name of Co-Author	Sooi Ooi		
Contribution to the Paper 6%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	19/3/2018

Name of Co-Author	Charlotte Goess		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	19/3/2018

Name of Co-Author	Samuel Costello		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	19/3/2018

Name of Co-Author	Andrew Vincent		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	20/3/2018

Name of Co-Author	Scott Schoeman

Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	19/3/2018

Name of Co-Author	Amanda Lim		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	21/3/2018

Name of Co-Author	Francis D Bartholomeusz		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	20/3/2018

Name of Co-Author	Simon PL Travis		
Contribution to the Paper 4%	Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	21/3/2018

Name of Co-Author	Jane M Andrews		
Contribution to the Paper 10%	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	16/3/2018

[Manuscript 4] Obesity in inflammatory bowel disease: gains in adiposity despite high prevalence of myopenia and osteopenia

Short title: Obesity in IBD

Bryant RV[1,2], Schultz CG[3], Ooi S[4], Goess C[4], Costello SP[1,2], Vincent AD[5], Schoeman S[1], Lim A[1], Bartholomeusz FD[3], Travis SPL[6], Andrews JM[2,4]

[1]IBD Service, Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Woodville South, South Australia

[2]School of Medicine, Faculty of Health Sciences, University of Adelaide, Adelaide, South Australia

[3]Department of Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital, Adelaide, South Australia

[4]IBD Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, South Australia

[5]Freemasons Foundation Centre for Men's Health, School of Medicine, University of Adelaide, Adelaide, South Australia

[6]Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, Oxfordshire UK

Corresponding author

Dr Robert Bryant
IBD Service, Department of Gastroenterology and Hepatology
The Queen Elizabeth Hospital
28 Woodville Road Woodville South
South Australia 5011
Phone: +61 8 8222 6000
Email: Robert.Bryant@sa.gov.au

Acknowledgements

Royal Adelaide Hospital IBD Nurses, Rachel Grafton and Julie Hughes

Royal Adelaide Hospital, Hospital Research Foundation

Grant support and writing assistance

No funding was received for the study. No writing assistance was received for this study. RB received research support from the Royal Adelaide Hospital Research Foundation through the AR Clarkson Scholarship. JMA used personal untied research funds to purchase dynamometer and study-related faecal calprotectin measurements.

Conflicts of interest and personal interests.

The authors have no conflicts of interest to declare.

RB: Employed by CALHN/TQEH. Grant/Research support/Speaker fees (all paid to employer for research support): AbbVie, Ferring, Janssen, Shire, Takeda.

SC: Employed by CALHN/TQEH. Grant/Research support/Speaker fees (all paid to employer for research support): Pfizer, Merck Sharp & Dohme, Janssen, Shire. Consultancy with Microbiotica.

ST: Employed by Oxford University Hospitals NHS Foundation Trust and the University of Oxford. Grants/Research Support: AbbVie, IOIBD, Lilly, UCB, Vifor, and Norman Collisson Foundation. Consulting Fees: AbbVie, Allergan, Amgen, Asahi, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chemocentryx, Cosmo, Enterome, Ferring, Giuliani SpA, GSK, Genentech/Roche, Immunocore, Immunometabolism, Janssen, Lilly, MSD, Neovacs, NovoNordisk, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHsquared, Vifor, Zeria. Speaker fees: AbbVie, Amgen, Biogen, Ferring, Takeda. No stocks or share options.

JMA: Employed by CALHN/RAH. Grants/Research support/Speaker and Consultancy Fees (all paid to employer for research support): Abbot, AbbVie, Allergan, Bayer, Celgene, Ferring, Hospira, Janssen, MSD, Orphan, Pfizer, Shire, Takeda.

No other declarations were provided by co-authors.

Abstract

Background

Parallel to the general population, rising rates of obesity have been reported in patients with IBD, however prospective data are lacking.

Aims

To prospectively evaluate body composition in a routine care cohort of adults with IBD over 24 months.

Methods

Whole body dual energy X-ray absorptiometry (DXA) was performed at 0, 12, and 24 months. Bone mineral density (BMD), fat mass index (FMI (kg)/height (m^2)), appendicular skeletal muscle index (ASMI (kg)/height (m^2)), visceral adipose tissue index (VHI, VAT area (cm^3)/height (m^2)), and clinical and anthropometric assessments were performed at each time-point. Rates of obesity, sarcopenia, and osteopenia were characterised over time. Multivariable linear mixed effects regression analyses were performed.

Results

Some 154 participants were assessed at baseline (70% Crohn's disease, 55% male, median age 31 years), 129 at 12 and 110 at 24 months. BMI significantly increased over time, such that by 24 months, 62% patients were overweight or obese (annual change BMI β=0.45, 95%CI = [0.21, 0.70], p = 0.0003). Gains in BMI related to increases in both FMI and VHI (β=0.34, 95%CI = [0.15, 0.54], p = 0.0005; β=0.08, 95%CI = [0.02, 0.14], p = 0.007; respectively), whereas ASMI decreased (β=−0.06, 95%CI = [−0.11, −0.01], p = 0.02) with a concordant increase in rates of myopenia (OR = 2.6, 95%CI = [1.1, 6.2], p = 0.03). Rates of osteopenia and osteoporosis were high (37%), but unchanged over time (p = 0.23).

Conclusions

Increasing rates of obesity in patients with IBD coincide with decreases in lean muscle mass over time, while high rates of osteopenia remain stable. These previously undocumented issues warrant attention in routine care to prevent avoidable morbidity.

Key words

Body composition, obesity, visceral adipose tissue, fat, osteoporosis, osteopenia, sarcopenia, inflammatory bowel disease

Introduction

Body composition refers to proportions of bone, fat, and fat-free (lean) mass in the body and may be abnormal in many patients with inflammatory bowel disease (IBD).[1] Despite the potential negative effects of disturbances in body composition on morbidity, quality of life, cardiovascular disease, response to therapy and IBD-related outcomes, there is a paucity of prospective data on body composition in patients with IBD.[1, 2]

Rates of obesity are rising in patients with IBD, as in the general population; 15–40% of adults with IBD are obese and 20–40% are overweight.[3] IBD may be an independent risk factor for obesity, driven by dysbiosis and aberrations in intestinal microbial metabolism.[4, 5]

On the other hand, adipose tissue is metabolically active and could plausibly contribute to a pro-inflammatory susceptibility to IBD.[4, 6] However, existing data on the impact of obesity on IBD susceptibility and disease course are conflicting. This is partly due to the use of body mass index (BMI) as a blunt instrument for measuring adiposity. BMI is unable to distinguish between visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), which have distinct metabolic profiles.[3, 6-10] VAT, or mesenteric 'creeping fat', is increased in many patients with CD and has been associated with a stricturing and fistulising CD phenotype, as well as post-operative morbidity and an increased likelihood of post-operative CD recurrence.[3, 4, 6, 11-14] VAT is a strong and independent risk factor for cardio-metabolic disease, which is pertinent to an aging IBD population with a normal life expectancy. There are no longitudinal prospective data on direct measures of adiposity in patients with IBD.

There are emerging reports of high rates of both myopenia, defined as low lean mass, and sarcopenia, defined as a low lean mass coupled with loss of strength, in patients with IBD.[1, 15-17] This matters, because low lean mass has been associated with an increased need for surgery but poor surgical outcomes in IBD, as well as with osteopenia.[18-20] Lean mass deficits may be difficult to detect in clinical practice, where BMI can be falsely reassuring.[17, 18] Current data on sarcopenia in IBD are limited by small sample size and retrospective study design, as well as a lack of appropriate incorporation of a functional assessment.[1]

Deficits in bone mineral density (BMD) (osteoporosis/osteopenia) are one of the most common complications of IBD and have been reported in 20–50% of patients.[21-23] Reduced BMD is associated with an increased risk of pathological fractures and associated morbidity.[22, 24] The pathogenesis of metabolic bone disease in IBD is likely multifactorial,

with contributions from rapid weight loss, decreased mobility, corticosteroid therapy, chronic inflammation, malabsorption, and food avoidance with resulting nutritional deficiencies.[1, 25] However clinical data are lacking, and the influence of IBD-related factors beyond conventional risk factors over time remain poorly explored.[26, 27]

The aims of this study therefore were:

1. To evaluate body composition in patients with IBD prospectively, with serial measurements over time.
2. To explore the influence of clinical factors on body composition in patients with IBD.
3. To explore whether standard anthropometric testing can detect aberrations in body composition.

Materials and methods

Subjects

Consecutive patients with IBD (aged 18–50 years and pre-menopausal if female) managed by a tertiary IBD service were invited to participate in a prospective study between April 2012 and September 2013 (***Figure 6.1***). Those with significant medical or surgical comorbidity other than IBD, current pregnancy, or steroid use other than that required for IBD were excluded.

Subject data collection

Prospective data were captured at 0, 12 and 24 months. At each study time-point comprehensive case-note, IBD database and medical prescription review was undertaken by co-authors (RB, SO, CG, AL). Data capture included demographics, Montreal classification at baseline, current IBD therapy, cumulative lifetime corticosteroid use (equivalent to prednisolone ≥ 10 mg/day) and IBD-related surgery.[28]

IBD disease activity was assessed at each study time-point using clinical indices and biomarkers of inflammation. Crohn's Disease Activity Index (CDAI) was used for CD (CDAI < 150 considered clinically inactive) and the Partial Mayo Score for UC (a score ≤ 1 and no rectal bleeding considered clinically inactive). C-reactive protein (CRP) was used as a marker of systemic inflammation (CRP < 5 mg/l considered consistent with inactive disease) and faecal calprotectin (FC) as a marker of luminal inflammation using a CALPRO® ELISA

test (FC < 100µg/g considered consistent with inactive disease). IBD disease activity was dichotomised at each time-point on the basis of a composite clinical and biomarker assessment. Where there was incongruity between measures of disease activity, objective markers of disease activity took precedence over clinical indices.

Lifestyle factors were assessed at 0, 12 and 24 months. Average alcohol consumption was dichotomised into < 20 g/day vs. ≥20 g/day. Habitual physical activity was assessed using a validated self-administered Short International Physical Activity Questionnaire (IPAQ), which approximates MET-minutes per week and allows stratification into low, medium, and high activity groups.[29]

Body composition, anthropometric and nutritional assessment

Dual energy X-ray absorptiometry (DXA, General Electric Lunar Prodigy Vision bone densitometer (system DF+13727; Encore version 13.60, Madison WI, US) of the lumbar spine, total femur, and whole body was used to evaluate BMD and body composition at 0, 12 and 24 months using standard manufacturer protocols conforming to international practice guidelines.[30]

Standard calculations of fat and muscle body components were made from DEXA data. Appendicular skeletal muscle (ASM) mass was calculated as the sum of the lean mass of the arms and legs (kg). It is considered functionally relevant lean mass, given that it does not include non-fat soft tissues such as organs.[31] Analogous to the calculation of BMI, the ASM index (ASMI) is the ASM mass in kg divided by the height in metres, squared.[32] Fat mass (FM) is the sum of the body fat mass (kg). The fat mass index (FMI) is calculated as FM in kg divided by height in metres, squared.[32] VAT was measured using CoreScan® analysis software, which correlates well with CT scan measurements.[33] The software estimates VAT in the android region by determining the abdominal wall margin and subtracting subcutaneous adipose tissue (SAT) from the android fat (VAT). VAT was measured in terms of volume (centimetres^3), mass (grams), visceral adipose tissue/height index (VHI, VAT volume (cm^3)/height in metres, squared), and VAT:SAT ratio.

Usual clinical anthropometric data such as height (m) and weight (kg) were measured using standard Seca stadiometer and scale equipment at the time of DXA assessment. Waist and hip circumference were measured at the time of the DXA and the waist–hip ratio (WHR) calculated.

World Health Organization (WHO) standard categories for BMI were used: < 18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25–29.9 kg/m^2 (overweight), ≥30 kg/m^2 (obese).[34] Data from the Australian Bureau of Statistics National Health Survey 2014–2015 provided numerical comparisons with age- and sex-matched Australian population for BMI and waist circumference.[35] Population-based, age- and gender-matched normative data and standard deviation (SD) values from the National Health and Nutritional Examination Survey (NHANES) were used to calculate *z*-scores for ASMI and FMI.[17, 32] WHO population-based age- and sex-matched normative data of the lumbar spine and femur BMD were used to calculate BMD *t*-scores and *z*-scores.[36] The lowest BMD *t*-score at either site was used to stratify patients as normal (> −1), osteopenic (≤ −1 > −2.5), or osteoporotic (≤ −2.5).

Isometric hand-grip strength was measured using a Jamar® Digital Hand Dynamometer, representing a widely accepted surrogate measure of whole body strength.[31] The technique for grip strength evaluation has been described and *z*-scores were calculated from population-based age- and sex-matched normative data derived from healthy adult controls.[17]

Myopenia was defined as an ASMI ≥ 1 SD below the age- and gender-matched ASMI mean.[31] Sarcopenia was defined using combined anatomical and functional criteria, as both ASMI and grip strength > 1 SD below the age- and gender-matched means.[31]

Nutritional assessment was performed at each study time-point using clinical and laboratory criteria, including albumin, vitamin D (automated chemiluminescent assay), calcium, hemoglobin, iron studies, vitamin B12, and folate. Low vitamin D was defined as serum 25(OH) vitamin D level < 50 nmol/L. Iron deficiency was defined as a ferritin < 30 ng/ml and a transferrin saturation of < 16% if the CRP was normal (< 8 mg/L) and as a ferritin < 100 ng/ml and transferrin saturation < 16% if the CRP was elevated.

Management during prospective study period

Routine IBD care of enrolled subjects within the tertiary IBD service was consistent with international guidelines (***Figure 6.1***).[37, 38] Protocolised management of bone health and nutrition was undertaken during the study period. Oral vitamin D supplementation was recommended to those with low levels (< 50 nmol/L). All patients were advised to follow a calcium-rich diet and to engage in regular exercise. Patients found to be osteopenic (or at risk of osteopenia with current corticosteroid use) were advised to take calcium supplementation (1000 mg/day) and oral vitamin D supplementation (≥1000 IU/day). Patients found to be

osteoporotic were referred to the Endocrinology service for consideration of bisphosphonate therapy.

Ethical considerations

The study was approved by the Royal Adelaide Hospital Research Ethics Committee (#120304). Whole body DXA does not confer significant additional radiation to standard BMD assessment. Radiation safety reported that the total radiation dose per DXA study visit was 2.56μSv.

Statistical methods

Continuous outcomes are presented using means, standard deviations, medians and interquartile ranges (IQR), with categorical outcomes as counts and percentages, unless otherwise stated. The lack of existing prospective data on body composition in IBD did not allow a formal power calculation. Enrolment of 150 patients was considered sufficient to provide adequate power for multivariable analysis, allowing for a dropout rate of 30% over the 24 months.

Change in body composition change over time. Changes in anthropometric and body composition variables in individual patients over the 24-month study period were assessed using either linear or logistic mixed effects models, where appropriate. The β coefficient describes the change in the body composition variable per unit of time in the study (12 months). In all models, time since baseline assessment (years) was the linear fixed effect, with random intercepts per individual. In all models, residuals and random effect estimates were examined to ensure that model distributional assumptions appeared satisfied. As a consequence, VHI was log-transformed.

Assessment of factors associated with body composition. Linear mixed effects models were constructed to explore prospective clinical associations with serial assessments of BMI, FMI, VHI, ASMI and BMD (lumbar spine t-score) at 0, 12 and 24 months. Lumbar spine was selected for analysis a priori, given its higher trabecular bone content, which is relevant to bone fragility, sensitivity to deleterious influences and risk of fracture.[39-41] Fixed effect covariates included demographic factors, clinical factors (including biomarkers of IBD disease activity and IBD medications), body composition factors, anthropometric assessments, nutritional indices and lifestyle factors.

Initially univariable models were constructed, followed by full multivariable models, and finally backwards, stepwise variable selection was performed from the full to the final model ($p > 0.10$). We report β coefficients that describe the change in the dependent variable per unit change in a covariate. Missing data were imputed with cohort means. Significance was set at the 5% alpha level (2-sided). Analyses were performed on R software v3.4.3 using the nlme and lme4 package.

Results

Subject characteristics

Some 197 patients with IBD were assessed for eligibility during the study enrolment period (April 2012–September 2013), 43 of whom were excluded ***(Figure 6.1)***. A total of 154 patients were enrolled in the study at baseline, of whom 129 (84%) completed the 12-month and 110 (71%) the 24-month study assessment ***(Table 6.1).***

Details of the cohort at baseline have been previously published (***Supplementary Table 6.1)***.[17] In brief, 108 (70%) patients had CD and 46 (30%) ulcerative colitis (UC) (***Table 6.1***). The median age of the whole cohort was 31 years (range 18–50 years), with a median age at diagnosis of 22 years (range 5–48 years) and IBD disease duration of 7.7 years (IQR 4.5–12.3). The cohort was predominantly Caucasian (94%). Active disease, defined by composite clinical and biomarker assessment, was present in 78 patients (51%) at baseline. Some 44/108 (41%) patients with CD and 1/46 (2%) patient with UC had undergone abdominal surgery prior to enrolment. At baseline, 61 (40%) of patients were prescribed biologic therapy and 45 (29%) corticosteroid therapy. Vitamin D levels were low in 61 (40%) of patients at baseline, 59/61 (97%) of whom were prescribed replacement therapy.

Baseline body composition

A detailed cross-sectional analysis of the body composition of this cohort at baseline (n = 137, as enrolled until July 2013) has been previously published.[17] In brief, the mean BMI at baseline was 26.1 ± 5.6; with 39 (25%) classified as overweight and 33 (21%) as obese (***Table 6.2***). Myopenia was evident in 35 (23%) patients, and functional sarcopenia in 23 (15%) patients. Low BMD was prevalent at baseline, with 55 (33%) osteopenic and 5 (3%) osteoporotic (60 (36%) with either osteopenia or osteoporosis).

Changes in body composition over 24 months

Anthropometrics. BMI increased over the study period (annual change β=0.45, 95%CI = [0.21, 0.70], p = 0.0003), as did the proportion of patients categorised as overweight and obese (at 24 months, 31% overweight and 31% obese) (***Table 6.2, Figure 6.2, Supplementary Table 6.2***). Waist circumference increased over time (β=1.5, 95%CI = [0.6, 2.4], p = 0.001), although no change in WHR occurred (β=0.007, 95%CI = [−0.004, 0.018], p = 0.20). Mean BMI, waist circumference and the proportions of people characterised as overweight or obese were each numerically higher in the IBD cohort compared to the Australian population stratified by age and gender (***Supplementary Table 6.3***).

Adiposity. FMI increased significantly over the study period (β=0.34, 95%CI = [0.15, 0.54], p = 0.0005), with a concordant increase in FMI *z*-score (β=0.08, 95%CI = [0.03, 0.14], p = 0.004). (***Table 6.2, Supplementary Table 6.2, Figure 6.2, 6.3***) Similarly, VAT volume increased (β=0.08, 95%CI = [0.02, 0.14], p = 0.007), which resulted in an increase in VHI (β=0.08, 95%CI = [0.03, 0.14], p = 0.008) but not VAT:SAT (β=0.034, 95%CI = [−0.025, 0.093], p = 0.25) (***Table 6.2).***

Muscle. ASMI decreased significantly over the study period (ASMI β=−0.06, 95%CI = [−0.11, −0.01], p = 0.02; ASMI *z*-score β=−0.06, 95%CI = [−0.10, −0.02], p = 0.005) (***Table 6.2, Figure 6.4***). Whilst the overall proportion of patients with myopenia did not change in the group over time, this may be due to attrition rather than true stability of muscle mass, given that amongst the 110 individuals who had repeated measurements of ASMI, there was a significant increase in myopenia (16%, 17%, and 23% at 0, 12 and 24 months respectively; OR = 2.6, 95%CI = [1.1, 6.2], p = 0.03). However, there was no detectable change in the proportion of patients classified as sarcopenic (OR = 1.5, 95%CI = [0.9, 5.1], p = 0.09).

Bone. Femur BMD *t*-score increased significantly over the study period, but there was no change in lumbar spine BMD *t*-score (*(*β= 0.042, 95%CI = [0.017, 0.067], p = 0.001; β= 0.013, 95%CI = [−0.023, 0.048], p = 0.47, respectively). No difference in BMD *z*-scores at either site were detected over time (***Table 6.2, Figure 6.5***). Overall, there was no significant change in the proportion of patients classified with osteopenia 37/110 (34%) or osteoporosis 3/110 (3%) (p = 0.23), despite proactive management of bone health over the study period.

Clinical associations with serial BMI measurements over the study period

BMI was positively associated with older age and male gender (β=0.023, 95%CI = [0.003, 0.043], p = 0.02; β=0.5, 95%CI = [0.0, 1.0], p = 0.03, respectively), as well as alcohol intake and vitamin D level *(*β= 0.9, 95%CI = [0.1, 1.7], p = 0.02; β= 0.005, 95%CI = [0.00, 0.010], p = 0.04, respectively). FMI, ASMI, and grip strength were also positively associated with BMI over time *(*β=1.0, 95%CI = [1.0, 1.1], p < 0.0001; β=1.3, 95%CI = [1.1, 1.5], p < 0.0001; β=0.26, 95%CI = [0.008, 0.044], p = 0.005, respectively) (***Table 6.3***).

Clinical associations with serial FM and VAT measurements over the study period

Older age was positively associated with VHI (β=0.033, 95%CI = [0.021, 0.046], p < 0.0001) *(**Supplementary Tables 6.4, 6.5***). Male gender was positively associated with VHI, but negatively associated with FMI (β=0.58, 95%CI = [0.35, 0.80], p < 0.0001; β=−2.5, 95%CI = [−3.1, −1.9], p < 0.0001, respectively). Serum vitamin D was negatively associated with both VHI and FMI (β=−0.0033, 95%CI = [−0.0056, 0.0010], p = 0.02; β=−0.007, 95%CI = [−0.013, −0.001], p = 0.004).

Anthropometric measures (BMI and waist circumference) were associated with a higher FMI (β=0.54, 95%CI = [0.49, 0.60], p < 0.0001; β=0.047, 95%CI = [0.028, 0.066], p < 0.0001, respectively) and VHI (β=0.10, 95%CI = [0.08, 0.12], p < 0.0001; β=0.008, 95%CI = [0.002, 0.016], p = 0.02 respectively). In contrast, no associations were detected between WHR and either FMI or VHI. Grip strength was negatively associated with FMI (β=−0.039, 95%CI = [−0.061, −0.017], p = 0.0006).

Clinical associations with serial ASMI measurements over the study period

Male gender was associated with a higher ASMI (β=1.0, 95%CI = [0.8, 1.3], p < 0.0001) (***Supplementary Table 6.6***). FC was negatively associated with ASMI (β=−0.00039, 95%CI = [−0.00078, −0.00001], p = 0.04), whereas anthropometric measures, BMI and grip strength, were positively associated with ASMI (β=0.14, 95%CI = [0.12, 0.15], p < 0.0001*;* β=0.026, 95%CI = [0.017, 0.035], p < 0.0001, respectively).

Clinical associations with serial BMD measurements over the study period

Male gender was associated with a lower lumbar spine *t*-score (β=−0.41, 95%CI = [−0.81, −0.01], p = 0.04) (***Supplementary Table 6.7***) and habitual physical activity, assessed using

IPAQ, was positively associated with lumbar spine *t*-score (β= 0.008, 95%CI = [−0.018, 0.011], p = 0.04) as was grip strength (β=0.009, 95%CI = [0.002, 0.017], p = 0.01).[29] Neither IBD phenotype, nor therapy or vitamin D level were associated with changes in lumbar spine *t*-score.

Discussion

This prospective study has demonstrated persistent and progressive disturbances in body composition in people with IBD over a relatively short time frame. The most striking finding was a significant increase in the proportion of patients classified as overweight and obese, driven by gains in adiposity over the study period. Conversely, muscle mass decreased, with a concordant rise in rates of myopenia. Despite proactive management of bone health, rates of osteopenia remained high and unchanged. Abnormal body composition may go frequently unrecognised in clinical practice using BMI alone. This leaves patients with IBD at risk of potentially avoidable morbidity, in particular cardiovascular disease and metabolic syndrome, which are now recognised as prime causes of mortality in this young demographic.[2]

After 24 months of follow-up, 62% of patients with IBD were overweight or obese despite a median age of just 33 years, which is numerically higher than age- and gender-matched Australian population data.[35] Earlier studies of obesity in IBD have failed to take into account direct measures of adiposity.[3, 10] This study demonstrates that gains in BMI were associated with significant increases in both overall FM and VAT, which raises concerns about the long-term cardio-metabolic risk patients with IBD. VAT is a strong independent predictor of incident cardiovascular disease after adjustment for clinical risk factors, including BMI.[42, 43] Akin to other chronic inflammatory conditions, there is emerging evidence to suggest that patients with IBD are at increased risk of ischaemic heart disease, cerebrovascular disease, and mesenteric arterial thrombosis in particular.[2, 44]

How can a link between IBD and obesity be explained? In contrast to retrospective reports, we found no association between measures of adiposity and IBD phenotype, inflammatory burden, or medications over time.[3, 6-10] In keeping with findings from non-IBD populations, conventional risk factors of advancing age and gender were associated with adiposity.[45] Although habitual exercise was not statistically associated with BMI or adiposity, low levels of habitual exercise may conceivably contribute to obesity given that more than half of the cohort was classified as inactive or minimally active over the study period. Interestingly, serum vitamin D levels were negatively associated with both FMI and VAT, which may relate

to sequestration of vitamin D in adipose tissue, coupled with lifestyle factors associated with obesity (less outdoor activity).[46] It is conceivable that dysbiosis in IBD, characterised by reduced microbial diversity and an altered microbial metabolic profile, is a predisposing factor to obesity,[47-49] but this is speculation despite gut metabolomic associations with post-prandial glucose.[47-50]

While adiposity increased, muscle mass (ASMI) decreased. FC, as a measure of luminal inflammation in IBD, was negatively associated with ASMI, consistent with the known catabolic effects of chronic inflammation.[18, 20, 51] Lean mass is important in patients with IBD and has been shown to have a bearing on response to therapy, surgical outcomes, and quality of life.[15, 18, 20, 52, 53] Grip strength proved to be a simple anthropometric test that was independently and positively associated with both ASMI and BMD, while negatively associated with FMI. Neither inflammation nor IBD-related factors were associated with BMD over time, which is consistent with existing data showing minimal impact of IBD on longitudinal bone loss.[21, 23, 26, 27, 54] Likewise, vitamin D levels were not associated with BMD, consistent with other studies showing uncertain benefit of vitamin D supplementation on BMD in IBD patients.[21, 23, 26, 27, 54] Habitual exercise was, however, positively associated with BMD over time, supporting rationale for an 'exercise prescription' to patients with IBD. Nevertheless, rates of osteopenia remained high in this cohort despite not only protocolised management of bone health, but a warm climate and readily accessible dairy products.

Limitations of this study are the relatively small sample size, which may have limited power to detect associations between covariates and measures of body composition over time. There was, for instance, no association between VAT, IBD phenotype and disease activity, which may be a consequence of Type 2 error and warrants further CD-specific analysis.[11-14] The study was neither structured nor powered to evaluate the influence of body composition on hospitalisation or surgery over time. It did not account for dietary intake, nor other factors associated with cardio-metabolic risk measured (cholesterol, family history, blood pressure). The predominantly Caucasian cohort derived from a single tertiary IBD referral centre may limit the generalisability of findings. On the other hand, it is the first prospective study that has incorporated serial measures of body composition in IBD. Furthermore, DXA, in routine use for measuring BMD, is an affordable tool for monitoring body composition, adding little to the time or radiation of the test.[21, 33]

This study illustrates rising rates of obesity in patents with IBD over time, driven by gains in fat mass, while lean mass decreases and metabolic bone disease remains unchanged. Apart from raising concerns about the cardio-metabolic risk profile of patients with IBD, it is important that clinicians recognise that an increase in BMI may obscure a decrease in muscle mass (myopenia), which influences surgical outcomes. The study provides a rationale for measuring body composition, a means to do so with DXA, and supports recommendations for regular exercise in patients with IBD and the use of grip strength as a discriminatory anthropometric test in clinical practice.

Figures

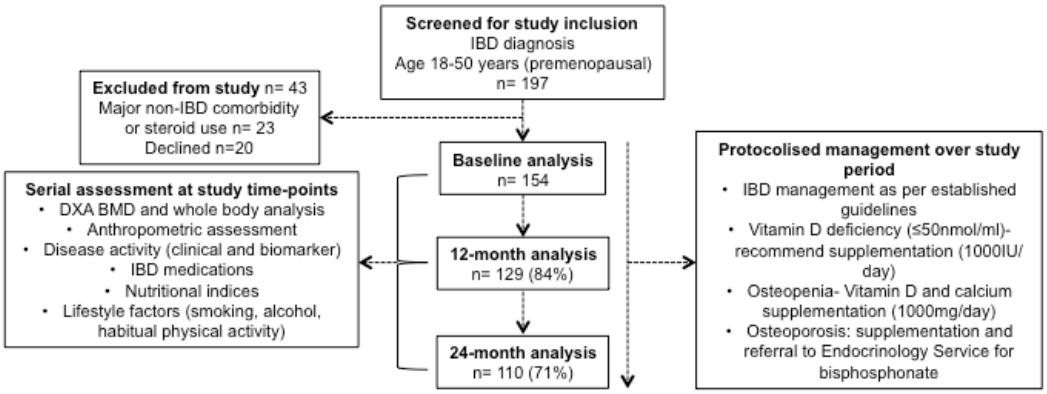


Figure 6.1 CONSORT diagram – inflammatory bowel disease (IBD) cohort

Key: *DXA, dual energy X-ray absorptiometry, BMD, bone mineral density.*

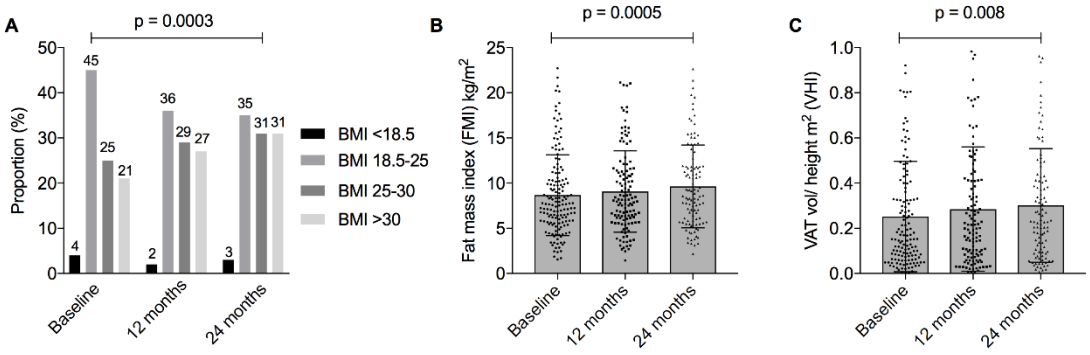


Figure 6.2 BMI and measures of adiposity in patients with IBD over 24 months

Legend: ***A.*** *Body mass index (BMI) categories according to World Health Organization criteria.* ***B.*** *Fat mass index (kg/ height m^2). Mean and standard deviation presented.* ***C.*** *Visceral adipose tissue (VAT) height index (VAT volume cm^3 / height m^2). Mean and standard deviation presented.*

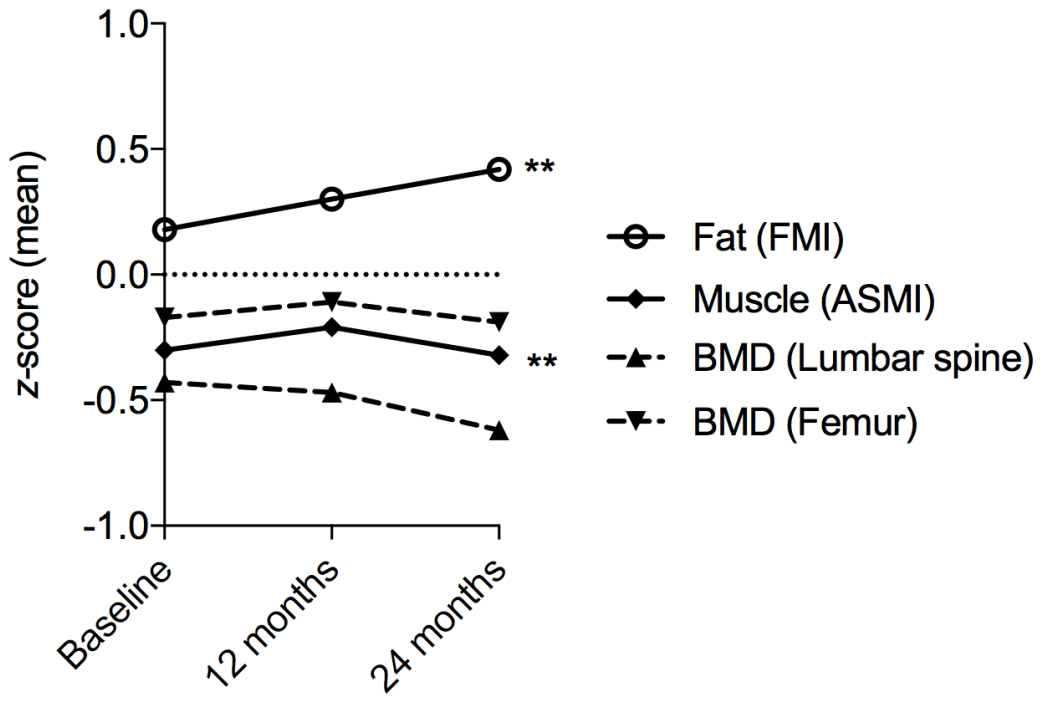


Figure 6.3 Changes in bone, muscle, and fat in patients with IBD over 24 months

Legend: *Summary of mean z-scores for fat mass index (FMI), appendicular skeletal muscle mass index (ASMI), bone mineral density (BMD) at the femur and lumbar spine.*

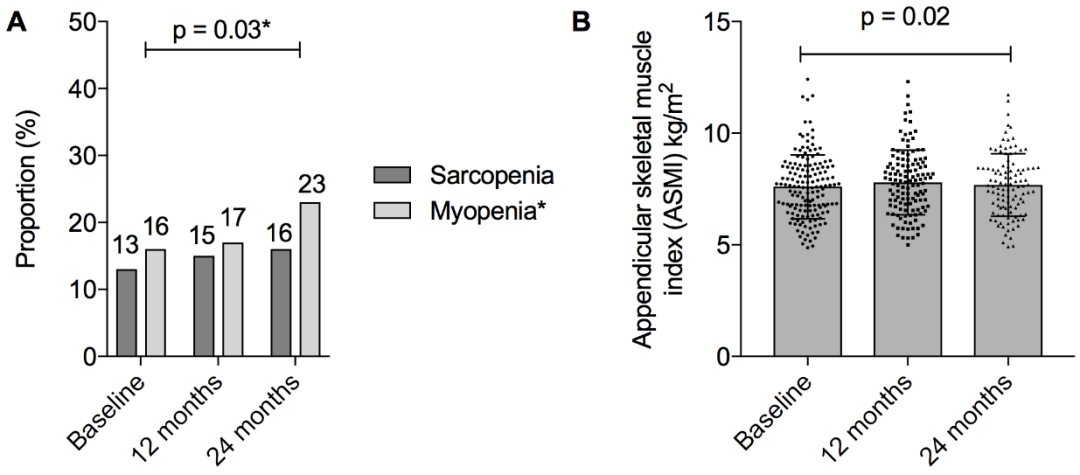


Figure 6.4 Changes in lean mass in patients with IBD over 24 months

Legend: A. *Sarcopenia defined as <u>BOTH</u> appendicular skeletal muscle index (ASMI) and grip strength < 1 standard deviation below gender- and age-matched mean. Myopenia defined as appendicular skeletal muscle index (ASMI) < 1 standard deviation below gender- and age-matched mean. Data presented from only the 110 patients with repeated measurements over 24 months* ***B.*** *ASMI kg/height m^2, mean and standard deviation presented.*

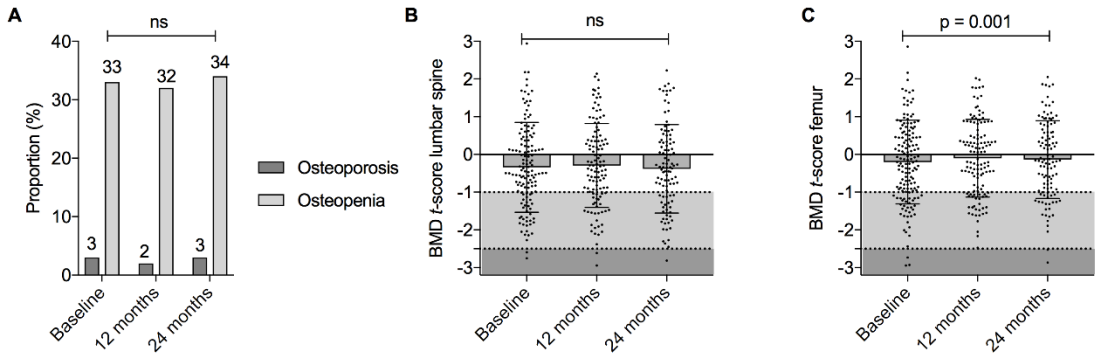


Figure 6.5 Bone mineral density in patients with IBD over 24 months

Legend: ***A.*** *Osteopenia and osteoporosis according to World Health Organization criteria. Osteopenia defined as bone mineral density (BMD) 1–2.5 standard deviations and osteoporosis as ≥ 2.5 standard deviations below the young adult mean.* ***B.*** *BMD t-score for lumbar spine.* ***C.*** *BMD t-score for femur. Mean and standard deviation presented.*

Tables

Table 6.1 Clinical and nutritional characteristics of IBD cohort over 24 months

		Baseline	**12 months**	**24 months**
Patients (n, %)		154 (100%)	129 (84%)	110 (71%)
Male (n, %)		85 (55%)	76 (59%)	62 (58%)
Age (years) (median, IQR)		31 (25–40)	32 (26–41)	33 (27–42)
IBD phenotype				
	Crohn's disease (n, %)	108 (70%)	92 (71%)	79 (72%)
	Ulcerative colitis (n, %)	46 (30%)	37 (29%)	28 (25%)
IBD-related abdominal surgery (n,%)		45 (29%)	7 (5%)	12 (11%)
IBD-related hospitalisation (n,%)		-	22 (17%)	12 (11%)
IBD clinical disease activity score				
	Crohn's Disease CDAI Mean ± SD	95 ± 98	71 ± 67	65 ± 58
	Median, IQR	68 (26–138)	62 (26–110)	49 (20–90)
	Ulcerative colitis Partial Mayo Mean ± SD	1.8 ± 2.6	1.4 ± 2.2	1.5 ± 1.9
	Median, IQR	0 (0–4)	0 (0–2)	0 (0–4)
C-reactive protein (mg/L)	Mean ± SD	8.4 ± 20	8.7 ± 21	9.3 ± 22
	Median, IQR	1.9 (0.5–8.4)	1.8 (0.5–8.3)	1.9 (0.5–8.8)
Faecal calprotectin (µg/g)	Mean ± SD	233.6 ± 269	246 ± 287	227 ± 262
	Median, IQR	135 (20–272)	110 (20–390)	105 (20–287)
Composite disease activity assessment§ (n active disease, %)		78 (51%)	70 (54%)	58 (53%)

			Baseline	12 months	24 months
Oral corticosteroids^		Current (n, %)	45 (29%)	22 (17%)	13 (12%)
		Cumulative Mean ± SD	27 ± 55	30 ± 58	30 ± 59
		Median, IQR	6 (1–24)	7 (2–24)	7.5 (2–24)
Biologic therapy		Overall (n, %)	61 (40%)	62 (48%)	58 (53%)
		Infliximab (n, %)	40 (26%)	40 (31%)	34 (31%)
		Adalimumab (n, %)	19 (12%)	19 (15%)	22 (20%)
		Vedolizumab (n, %)	2 (1%)	3 (2%)	2 (2%)
5-ASA therapy (n,%)			70 (45%)	59 (46%)	50 (45%)
Immunomodulator therapy		Overall (n,%)	86 (56%)	64 (49%)	62 (56%)
		Azathioprine (n,%)	60 (39%)	50 (39%)	41 (37%)
		Mercaptopurine (n,%)	6 (4%)	6 (5%)	5 (5%)
		Methotrexate (n,%)	3 (2%)	4 (3%)	4 (4%)
		Thiopurine/allopurinol (n,%)	17 (11%)	14 (11%)	12 (11%)
Exercise (IPAQ)¶	Continuous	Mean ± SD	4310 ± 5895	55570 ± 8952	4935 ± 6879
		Median, IQR	2160 (693–5664)	2106 (862–5745)	2445 (942–5558)
	Categorical	Inactive	64 (42%)	47 (36%)	37 (34%)
		Minimally active	38 (25%)	24 (19%)	23 (21%)
		Active	32 (21%)	41 (32%)	35 (32%)
Nutritional assessment	Albumin (g/dL)	Mean ± SD	40 ± 4.6	40 ± 3.8	40 ± 3.5
		Median, IQR	40 (37–43)	40 (37–42)	40 (38–42)

			Baseline	12 months	24 months
	Hemoglobin(g/L)	Mean ± SD	141 ± 15	141 ± 14	143 ± 13
		Median, IQR	141(131–150)	141 (130–149)	144 (136–152)
	Ferritin (ng/ml)	Mean ± SD	87 ± 82	93 ± 122	115 ± 186
		Median, IQR	63 (34–106)	63 (35– 104)	71 (42– 123)
	Calcium	Mean ± SD	2.36 ± 0.11	2.34 ± 0.1	2.34 ± 0.09
		Median, IQR	2.36 (2.29–2.43)	2.36 (2.29–2.4)	2.34 (2.30–2.4)
	Vitamin D nmol/ml#	Mean ± SD	65 ± 29	65 ± 25	70 ± 25
		Median, IQR	63 (43–84)	65 (48–80)	67 (53–85)
		Low Vitamin D level	61 (40%)	40 (31%)	38 (35%)
		Vitamin D supplementation	59 (38%)	40 (31%)	37 (34%)
		Bisphosphonate therapy	2 (1%)	4 (3%)	4 (4%)

Table Legend: *Data presented as mean ± standard deviation (SD), median (interquartile range (IQR)), counts and percentage. CDAI, Crohn's Disease Activity Index; § Composite disease activity assessment using clinical indices (CDAI or Partial Mayo) and biomarker of inflammation (faecal calprotectin and C-reactive protein). ^ Cumulative months equivalent to prednisolone ≥10mg daily. ¶International Physical Activity Questionnaire (Short). # Low Vitamin D level classified as < 50 nmol/L, vitamin D supplementation (≥1000 IU/day).*

Table 6.2 Body composition in IBD patients over 24 months

Body composition			**Baseline (n = 154)**	**Year 1 (n = 129)**	**Year 2 (n = 110)**	**p-value**
Anthropometric assessment	BMI (kg/m2)	Mean ± SD	26.1 ± 5.6	27.4 ± 5.8	27.7 ± 5.6	0.0003
		Δ ± SD	-	0.52 ± 2.53	0.84 ± 2.66	
		Median (IQR)	24.8 (22.4–29.2)	26.5 (23.2–30.7)	26.8 (23.8–30.8)	
	BMI Categorical ¶					0.0003
	Underweight < 18.5		6 (4%)	3 (2%)	3 (3%)	
	Normal 18.5- 25		70 (45%)	47 (36%)	38 (35%)	
	Overweight 25-30		39 (25%)	38 (29%)	34 (31%)	
	Class 1 Obesity 30-35		20 (13%)	19 (15%)	21 (19%)	
	Class 2 Obesity 35-40		10 (6.5%)	11 (8.5%)	10 (9%)	
	Class 3 Obese ≥ 40		3 (2%)	5 (4%)	3 (3%)	
	Overall Obese ≥ 30		33 (21%)	35 (27%)	34 (31%)	
	Waist circ. (cm)	Mean ± SD	89.7 ± 15.7	92.4 ± 14.5	94.1 ± 14.4	0.001
		Δ ± SD	-	0.73 ± 10.32	2.26 ± 9.18	
		Median (IQR)	87 (79–99)	91 (81–102)	93 (83–103)	
	Waist: Hip Ratio	Mean ± SD	0.88 ± 0.11	0.88 ± 0.10	0.89 ± 0.10	0.20
		Δ ± SD	-	0.00 ± 0.11	0.01 ± 0.12	

Body composition			**Baseline (n = 154)**	**Year 1 (n = 129)**	**Year 2 (n = 110)**	**p-value**
		Median (IQR)	0.86 (0.81–0.94)	0.87 (0.82–0.92)	0.89 (0.83–0.94)	
	Grip strength (PSI)	Mean ± SD	39.7 ± 12.2	39.5 ± 12.2	39.8 ± 12.4	0.74
		Δ ± SD	-	−0.48 ± 5.56	−0.30 ± 5.01	
		Median (IQR)	37.8 (30.0–50.0)	38.0 (29.0–49.3)	37.4 (31.1–49.1)	
	Grip strength z-score	Mean ± SD	−0.74 ± 1.45	−0.9 ± 1.49	−0.67 ± 1.23	0.70
		Δ ± SD	-	−0.27 ± 1.55	−0.01 ± 1.27	
		Median (IQR)	−0.55 (−1.33–0.15)	–0.75 (−1.41–0.12)	−0.6 (−1.32–0.15)	
Fat mass index (FMI) (kg/ height m^2)	FMI (kg/m2)	Mean ± SD	8.67 ± 4.47	9.07 ± 4.50	9.64 ± 4.59	0.0005
		Δ ± SD	-	0.26 ± 1.54	0.70 ± 2.05	
		Median (IQR)	7.67 (5.70–10.33)	8.09 (6.07– 11.32)	8.61 (5.82–11.81)	
	FMI z-score	Mean ± SD	0.18 ± 1.26	0.30 ± 1.26	0.42 ± 1.24	0.004
		Δ ± SD	-	0.06 ± 0.48	0.17 ± 0.61	
		Median (IQR)	−0.13 −0.59–0.93)	0.08 (−0.57–0.89)	0.25 (−0.47–1.15)	
Visceral adipose tissue (VAT)	VAT volume (cm^3)	Mean ± SD	797.2 ± 794.4	903.9 ± 901.6	949.9 ± 826.7	0.007
		Δ ± SD	-	67.8 ± 331.8	102.1 ± 376.6	
		Median (IQR)	493.7 (216.9, 1175.9)	600.5 (248.8, 1291)	702.1 (266.6–1354)	
	VAT (grams)^	Mean ± SD	752.1 ± 749.45	852.76 ± 850.53	896.09 ± 779.94	0.007

Body composition			**Baseline (n = 154)**	**Year 1 (n = 129)**	**Year 2 (n = 110)**	**p-value**
		Δ ± SD	-	64.0 ± 313.0	96.3 ± 355.3	
		Median (IQR)	465.74 (204.59–1109.38)	566.51 (241.63–1209.85)	662.35 (256.23–1274.44)	
	VAT:SAT^	Mean ± SD	0.63 ± 0.66	0.64 ± 0.55	0.63 ± 0.49	0.25
		Δ ± SD	-	0.05 ± 0.586	0.026 ± 0.585	
		Median (IQR)	0.45 (0.24–0.8)	0.46 (0.31–0.83)	0.49 (0.28–0.89)	
	VHI^	Mean ± SD	0.25 ± 0.24	0.28 ± 0.28	0.3 ± 0.25	0.008
		Δ ± SD	-	0.076 ± 0.53	0.127 ± 0.604	
		Median (IQR)	0.15 (0.07–0.35)	0.2 (0.08–0.41)	0.23 (0.1–0.41)	
Bone mineral density (BMD)	WHO *t*-score femur	Mean ± SD	−0.2 ± 1.11	−0.1 ± 1.03	−0.13 ± 1.03	0.001
		Δ ± SD	-	0.075 ± 0.191	0.081 ± 0.266	
		Median (IQR)	−0.21 (−0.96–0.52)	−0.20 (−0.99–0.55)	−0.17 (−0.97–0.69)	
	WHO *t*-score spine	Mean ± SD	−0.34 ± 1.19	−0.29 ± 1.11	−0.38 ± 1.17	0.47
		Δ ± SD	-	0.033 ± 0.34	0.027 ± 0.357	
		Median (IQR)	−0.48 (−1.06–0.4)	−0.37 (−1.05–0.39)	−0.36 (−1.21–0.33)	
	WHO *z*-score femur	Mean ± SD	−0.17 ± 1.16	−0.11 ± 1.03	−0.19 ± 0.93	0.83
		Δ ± SD	-	0.049 ± 0.31	0.007 ± 0.52	
		Median (IQR)	−0.24 (−0.93–0.46)	−0.14 (−0.90–0.51)	−0.12 (−0.91–0.48)	

Body composition		**Baseline (n = 154)**	**Year 1 (n = 129)**	**Year 2 (n = 110)**	**p-value**
	WHO *z*-score spine Mean ± SD	−0.43 ± 1.14	−0.47 ± 1.09	−0.62 ± 1.14	0.47
	Δ ± SD	-	0.004 ± 0.385	−0.025 ± 0.41	
	Median (IQR)	−0.52 (−1.19–0.29)	−0.52 (−1.22–0.23)	−0.58 (−1.4–0.18)	
	Bone status# Osteopenia (n, %)	55 (33%)	41 (32%)	37 (34%)	0.23
	Osteoporosis (n, %)	5 (3%)	2 (2%)	3 (3%)	
	Overall osteopenia/porosis (n, %)	60 (36%)	43 (34%)	40 (37%)	
Appendicular skeletal muscle index (ASMI) (kg/ height m^2)	ASMI (kg/m2) Mean ± SD	7.60 ± 1.43	7.80 ± 1.45	7.68 ± 1.40	0.02
	Δ ± SD	-	0.014 ± 0.486	−0.127 ± 0.546	
	Median (IQR)	7.60 (6.57–8.48)	7.84 (6.74–8.62)	7.64 (6.66–8.45)	
	ASMI z-score Mean ± SD	−0.3 ± 0.98	−0.21 ± 0.98	−0.32 ± 0.99	0.005
	Δ ± SD	-	−0.006 ± 0.392	−0.0129 ± 0.444	
	Median (IQR)	−0.31 (−0.95–0.17)	−0.3 (−0.88–0.24)	−0.45 (−0.93–0.29)	
	Myopenia (Low ASMI§)	35 (23%)	25 (19%)	25 (23%)	0.03
	Functional sarcopenia (Low ASMI AND low grip strength§)	23 (15%)	21 (16%)	17 (15%)	0.09

Table Legend: *Reported are baseline distributions and change from baseline at 12 and 24 months. Data presented as mean ± standard deviation, median (interquartile range), counts and percentage. SD, standard deviation; ^ Data log-transformed prior to analysis: ^ VAT, visceral adipose tissue; ^ VAT:SAT, visceral adipose tissue: subcutaneous adipose tissue ratio; VHI, visceral adipose tissue area (cm^3) divided*

by height (m^2); §Low ASMI and grip strength defined as ≥1 standard deviation below mean. Δ, mean difference from baseline at Year 1 and Year 2 (± standard deviation). ¶BMI categories and bone status according to World Health Organization criteria.

Table 6.3 Clinical associations with serial body mass index (BMI) measurements over 24 months

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	**P-value**	**Est. (95% CI)**	**P-value**	**Est. (95% CI)**	**P-value**
Demographics	Age at study entry	0.24 [0.15, 0.33]	< 0.0001	0.024 [0.000, 0.047]	0.04	0.023 [0.003, 0.043]	0.02
	Gender (Male vs. female)	0.8 [−1.0, 2.6]	0.37	0.48 [−0.04, 0.99]	0.06	0.5 [0.0, 1.0]	0.03
IBD-related factors	IBD phenotype (Ulcerative colitis vs. Crohn's disease)	−1.0 [−3.0, 0.9]	0.28	−0.18 [−0.57, 0.22]	0.35		
	IBD disease duration	0.014 [0.005, 0.022]	0.002	0.0001 [−0.0022, 0.0024]	0.91		
	Faecal calprotectin (µg/g)	−0.0023 [−0.0056, 0.0010]	0.16	0.00034 [−0.00032, 0.00099]	0.27		
	C- reactive protein (mg/L)	0.018 [−0.027, 0.063]	0.42	−0.002 [−0.010, 0.007]	0.69		
	Cumulative steroid use (months)	0.013 [−0.004, 0.029]	0.12	−0.0003 [−0.0036, 0.0030]	0.84		
	Biologic therapy	0.1 [−1.7, 2.0]	0.88	−0.07 [−0.43, 0.29]	0.67		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	**P-value**	**Est. (95% CI)**	**P-value**	**Est. (95% CI)**	**P-value**
	Immunomodulator therapy	0.1 [−1.8, 1.9]	0.95	−0.22 [−0.55, 0.11]	0.15		
Lifestyle and nutritional factors	Smoking status Current vs. Never Ex vs. Never	 1.0 [−1.3, 3.4] 1.7 [−0.4, 3.9]	0.26	 −0.22 [−0.70, 0.26] 0.32 [−0.10, 0.74]	0.06	 −0.15[−0.60,0.3] 0.36 [−0.03, 0.75]	0.06
	Excess alcohol intake^	1.4 [−3.2, 6.0]	0.54	0.9 [0.0, 1.8]	0.03	0.9 [0.1, 1.7]	0.02
	Vitamin D level (nmol/ml)	0.005 [−0.006, 0.016]	0.39	0.006 [0.001, 0.011]	0.02	0.005 [0.000, 0.010]	0.04
	Habitual exercise (IPAQ score, continuous)§	0.004 [−0.034, 0.043]	0.82	0.007 [−0.013, 0.026]	0.49		
	Albumin (g/dL)	0.05 [−0.03, 0.13]	0.20	0.006 [−0.038, 0.050]	0.84		
Body composition factors	Fat mass index (FMI)	1.1 [1.1, 1.2]	< 0.0001	1.0 [1.0, 1.1]	< 0.0001	1.0 [1.0, 1.1]	< 0.0001
	Appendicular skeletal muscle index (ASMI)	2.2 [1.9, 2.6]	< 0.0001	1.3 [1.1, 1.5]	< 0.0001	1.3 [1.1, 1.5]	< 0.0001
	Functional sarcopenia¶	−1.8 [−2.8, −0.8]	0.0007	0.02 [−0.45, 0.49]	0.91		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	**P-value**	**Est. (95% CI)**	**P-value**	**Est. (95% CI)**	**P-value**
	Grip strength (pounds per square inch, PSI)	0.031 [−0.015, 0.077]	0.18	0.026 [0.006, 0.045]	0.007	0.026 [0.008, 0.044]	0.005

Table legend. *^ Data log-transformed prior to analysis: ^ VAT, visceral adipose tissue; ^ VAT:SAT, visceral adipose tissue: subcutaneous adipose tissue ratio; VHI, visceral adipose tissue area (cm^3) divided by height (m^2); ¶Low ASMI and grip strength ≥1 standard deviation below mean. ^Excess alcohol use defined according to Australian healthy Drinking guidelines; § IPAQ, International Physical Active Questionnaire; FMI, fat mass index (kg/height m^2); ASMI, appendicular skeletal muscle index (kg/height m^2); Linear mixed regressions, random intercepts, backwards stepwise variable selection from full to final model (p > 0.10). Missing data imputed with cohort means.*

Supplementary Table 6.1 Baseline clinical and nutritional characteristics of IBD Cohort

		Overall	**Crohn's disease**	**Ulcerative colitis**
Patients (n)		154	108 (70%)	46 (30%)
Ethnicity	Caucasian	145 (94%)	105 (97%)	40 (87%)
	Asian	6 (4%)	2 (2%)	4 (9%)
	Black	3 (2%)	1 (1%)	2 (4%)
Male (n, %)		85 (55%)	56 (52%)	29 (63%)
Age (years) (median, IQR)		31 (25–40)	31 (27–41)	31 (23–40)
Smoking	Current	32 (21%)	29 (27%)	2 (4%)
	Ex-smoker	39 (25%)	29 (27%)	10 (22%)
	Never smoked	83 (54%)	50 (46%)	33 (72%)
Alcohol use (> 20 g ethanol/day)		6 (4%)	4 (3%)	2 (1%)
Age at IBD diagnosis (median, IQR)		22 (17–29)	21 (17–27)	24 (17–30)
Montreal criteria		A1 31 (20%)	A1 20 (19%)	A1 11 (24%)
		A2 116 (75%)	A2 82 (76%)	A2 34 (74%)
		A3 7 (5%)	A3 6 (5%)	A3 1 (2%)
IBD disease duration (months)	Mean ± SD	113 ± 88	122.2 ± 90	92 ± 79
	Median, IQR	92 (54–148)	101 (59–150)	72 (42–119)
IBD phenotype			L1 33 (31%) B1 50 (46%)	E1 2 (4%)

		Overall	Crohn's disease	Ulcerative colitis
Montreal criteria			L2 36 (33%) B2 40 (37%) L3 39 (36%) B3 18 (14%)	E2 13 (28%) E3 31 (67%)
Extra-intestinal manifestations Overall PSC Arthropathy Skin lesion Other		40 (26%) 9 (6%) 17 (11%) 8 (5%) 6 (4%)	26 (24%) 5 (5%) 12 (11%) 6 (6%) 3 (3%)	14 (30%) 4 (9%) 5 (11%) 2 (4%) 3 (7%)
IBD-related surgery			- Overall 44 (41%) - Ileal/small bowel resection 30 (28%) - Ileo-colonic resection 10 (9%) - Colectomy 4 (4%) - Multiple prior surgeries 11 (10%)	- Overall 1 (2%) Colectomy 1 (2%)
IBD Clinical disease activity score	Mean ± SD Median, IQR		CDAI 95 ± 98 68 (26-138)	Partial Mayo 1.8 ± 2.6 0 (0-4)
C-reactive protein (mg/L)	Mean ± SD Median, IQR	8.42 ± 20 1.95 (0.5–8.4)	10 ± 23 2.3 (0.5–11)	3.6 ± 6 1.0 (0.3–2.9)

		Overall	**Crohn's disease**	**Ulcerative colitis**
Faecal calprotectin (µg/g)	Mean ± SD	233.6 ± 269	240 ± 294	201 ± 288
	Median, IQR	135 (20–273)	86 (20–430)	57 (20–220)
Composite disease activity assessment§ (n, active disease (%))		78 (51%)	47 (44%)	19 (41%)
Corticosteroids^	Current (n, %)	45 (29%)	31 (29%)	14 (30%)
	Median, IQR	6 (1–24)	6 (0.6–24)	6 (2.7–18)
	Use ≥ 12 months (n, %)	64 (42%)	47 (44%)	17 (37%)
Biologic therapy (n, %)		61 (40%)	55 (51%)	6 (13%)
Overall		40 (26%)	36 (33%)	4 (9%)
Infliximab		19 (12%)	18 (17%)	1 (2%)
Adalimumab		2 (1%)	1 (1%)	1 (2%)
Vedolizumab				
5-ASA therapy (n, %)		70 (45%)	35 (32%)	35 (76%)
Immunomodulator (n, %)		86 (56%)	65 (60%)	21 (46%)
Overall		60 (39%)	45 (42%)	15 (33%)
Azathioprine		6 (4%)	5 (5%)	1 (2%)
Mercaptopurine		3 (2%)	2 (2%)	1 (2%)
Methotrexate		17 (11%)	13 (9%)	4 (9%)
Thiopurine/allopurinol				

		Overall	Crohn's disease	Ulcerative colitis
International Physical Activity Questionnaire¶				
Continuous	Mean ± SD	4310 ± 5895	4408 ± 6259	4997 ± 5194
	Median, IQR	2160 (693–5664)	1671 (816–5163)	3144 (1451–7461)
Categorical		64 (42%)	49 (45%)	15 (33%)
Low		38 (25%)	24 (22%)	14 (30%)
Medium		32 (21%)	22 (20%)	10 (22%)
High				
Albumin (g/dL)	Mean ± SD	40 ± 5	39 ± 4	40 ± 11
	Median, IQR	40 (37–43)	40 (36–43)	41 (38–44)
Hemoglobin (g/L)	Mean ±SD	140 ± 15	140 ± 16	139 ± 24
	Median, IQR	141 (131–150)	140 (129–150)	143 (133- –150)
Ferritin (ng/ml)	Mean ±SD	87 ± 82	83 ± 88	94 ± 69
	Median, IQR	63 (34–106)	56 (30–100)	85 (35–136)
	Iron deficient	17 (11%)	13 (12%)	4 (9%)
Calcium (mmol/L)	Mean ±SD	2.36 ± 0.11	2.36 ± 0.11	2.36 ± 0.10
	Median, IQR	2.36 (2.29–2.43)	2.36 (2.29–2.42)	2.37 (2.29–2.43)
Vitamin D nmol/ml	Mean ±SD	67 ± 40	64 ± 28	75 ± 57
	Median, IQR	63 (43–84)	63 (42–84)	63 (51–84)
	Vitamin D deficient# n, (%)	61 (40%)	44 (41%)	17 (37%)
	Vitamin D replacement n (%)	59 (38%)	43 (40%)	16 (36%)

		Overall	Crohn's disease	Ulcerative colitis
Quality of life (Short Inflammatory Bowel Disease Questionnaire)	Mean ± SD	50 ± 12	49 ± 13	51 ± 11
	Median, IQR	52 (43–59)	52 (41–60)	53 (46–59)

Table legend: *Data presented as mean ± standard deviation (SD), median (interquartile range (IQR)), counts and percentage. CDAI, Crohn's Disease Activity Index; § Composite disease activity assessment using clinical indices (CDAI or Partial Mayo) and biomarker of inflammation (faecal calprotectin and C-reactive protein). ^ Cumulative months equivalent to prednisolone ≥10mg daily. ¶International Physical Activity Questionnaire (Short). # Low Vitamin D level classified as < 50 nmol/L, vitamin D supplementation (≥1000 IU/day).*

Supplementary Table 6.2 Body mass index (BMI) and adiposity measures by gender over 24 months

		Baseline		12 months		24 months	
		Male	**Female**	**Male**	**Female**	**Male**	**Female**
VAT volume	Mean ± SD	1013 ± 909.1	537.2 ± 528.4	1116 ± 1029	622 ± 599.1	1122 ± 941.8	691.7 ± 527.7
	Δ	-	-	70.1 ± 388.8	64.73 ± 236.4	135.9 ± 426.8	52.17 ± 285.1
	Median IQR	685.1 (280.1, 1454)	331 (127.3, 789.9)	786.2 (330.5, 1632)	446.9 (106.7, 1053)	799.2 (374.2, 1572)	583.8 (214.3, 1078)
FMI	Mean ± SD	7.55 ± 4.02	10.06 ± 4.64	7.96 ± 3.83	10.7 ± 4.93	8.34 ± 3.84	11.61 ± 4.95
	Δ	-	-	0.35 ± 1.54	0.14 ± 1.56	0.78 ± 1.76	0.56 ± 2.45
	Median IQR	6.79 (4.78, 9.66)	8.70 (6.61, 13.20)	7.52 (5.56, 9.96)	10.21 (6.66, 14.99)	7.67 (5.49, 11.1)	10.96 (7.82, 15.43)
BMI	Mean ± SD	26.5 ± 5.35	25.7 ± 5.8	27.3 ± 5.6	27.6 ± 6.3	27.6 ± 5.3	27.9 ± 6.2
	Δ	-	-	0.74 ± 2.42	0.21 ± 2.68	1.16 ± 2.19	0.33 ± 3.24
	Median IQR	25.3 (23.0, 29.4)	24.3 (21.8, 29.3)	26.2 (23.2, 30.4)	26.8 (22.8, 32.9)	26.9 (23.8, 30.6)	26.5 (23.4, 32.5)
BMI Categorical¶	< 18.5	2 (2.4)	4 (5.8)	1 (1.3)	2 (3.8)	1 (1.6)	2 (4.2)
	18.5–25	38 (44.7)	32 46.4)	26 (34.2)	21 (39.6)	23 (37.1)	15 (31.3)
	25–30	26 (30.6)	13 (18.8)	26 (34.2)	12 (22.6)	23 (37.1)	11 (22.9)
	30–35	10 (11.8)	10 (14.5)	11 (14.5)	8 (15.1)	13 (21.0)	8 (16.7)
	35–40	5 (5.9)	5 (7.2)	5 (6.6)	6 (11.3)	4 (6.5)	6 (12.5)
	> 40	2 (2.3)	1 (1.5)	3 (3.9)	2 (3.8)	2 (3.2)	1 (2.1)

Table legend: *Reported are baseline distributions and change from baseline at 12 and 24 months. Data presented as mean ± standard deviation, median (interquartile range), counts and percentage. SD, standard deviation; VAT, visceral adipose tissue colume (cm^3); FMI, fat mass index*

(kg/height (m)2); BMI, body mass index, Δ, delta calculated as mean (± standard deviation) from baseline at Year 1 and Year 2). ¶BMI categories and bone status according to World Health Organization criteria.

Supplementary Table 6.3 Body mass index and waist circumference by age as compared to data from the Australian Bureau of Statistic National Health Survey First Results 2014–2015

	Australian Health Survey 2014–2015			IBD Cohort (24 months)			
Body mass index							
	Overall (mean)	**Obese (%)**	**Overweight/ obese (%)**	**Patient number**	**Overall (mean ± SD)**	**Obese (%)**	**Overweight/ obese (%)**
Age 18–25	25.2	17.1%	38.9%	n = 17	24.8 ± 5.5	17.6%	41.2%
Male	25.5	17.3%	43.8%	n = 10	25.9 ± 6.5	30%	50%
Female	24.8	17.3%	33.3%	n = 7	23.1 ± 3.5	0%	28.6%
Age 25–35	26.2	19.0%	52.4%	n = 38	26.7 ± 4.1	21.1%	55.3%
Male	26.9	20.8%	62.5%	n = 25	26.4 ± 3.7	20%	56%
Female	25.5	17.3%	42.5%	n = 13	27.3 ± 4.9	23.1%	53.9%
Age 35–45	27.6	28.6%	65.9%	n = 35	28.8 ± 6.5	34.3%	68.6%
Male	27.7	26.7%	74.3%	n = 19	27.5 ± 5.9	21.1%	63.2%
Female	27.6	30.7%	58.1%	n = 16	30.5 ± 7.1	50%	75%
Age 45–55	28.3	33%	70.6%	n = 20	30.3 ± 5.4	55%	80%
Male	28.6	33.2%	79.8%	n = 12	31.6 ± 4.7	58.3%	91.7%
Female	27.9	33%	61.9%	n = 8	28.3 ± 6.1	50.0%	62.5%
Waist circumference							
	Overall (mean)	**At risk waist circumference**		**Patient number**	**Overall (mean ± SD)**	**At risk waist circumference**	
Age 18–25				n = 17	88.0 ± 14.6		
Male	88	27.3%		n = 10	93.4 ± 14.9	50%	

	Australian Health Survey 2014–2015		IBD Cohort (24 months)		
Female	79.4	34.5%	n = 7	80.2 ± 11.1	42.9%
Age 25–35			n = 38	91.0 ± 11.7	
Male	92.9	41.7%	n = 25	93.3 ± 11.9	40%
Female	82.3	49.1%	n = 13	86.6 ± 10.4	69.2%
Age 35–45			n = 35	97.0 ± 15.4	
Male	96.5	55.7%	n = 19	98.1 ± 15.7	47.4%
Female	87.5	66.9%	n = 16	95.7 ± 15.5	75%
Age 45–55			n = 20	100.3 ± 14.27	
Male	100.1	69.8%	n = 12	105.7 ± 9.97	91.7%
Female	89.1	71.2%	n = 8	92.13 ± 16.45	87.5%

Table legend: *IBD cohort body composition data derived from 24-month dataset. Data presented as mean ± standard deviation, median (interquartile range), counts and percentage. SD, standard deviation. Comparative data derived from the Australian Bureau of Statistics National Health Survey 2014–2015 URL: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.001~2014-15~Main%20Features~Key%20findings~1. Overweight and obese characterisation according to WHO criteria. At risk waist circumference defined as > 80 cm for women and > 94 cm for men.*

Supplementary Table 6.4 Clinical associations with serial visceral adipose tissue (VHI)^ measurements over 24 months

Variable		**Univariable**		**Full multivariable model**		**Final multivariable model**	
		Est. (95% CI)	P-value	Est. (95% CI)	P value	Est. (95% CI)	P-value
Demographics	Age at study entry	0.059 [0.041, 0.077]	< 0.0001	0.040 [0.023, 0.056]	< 0.0001	0.033 [0.021, 0.046]	< 0.0001
	Gender (Male vs. female)	0.7 [0.4, 1.1]	< 0.0001	0.66 [0.38, 0.93]	< 0.0001	0.58 [0.35, 0.80]	< 0.0001
IBD-related factors	IBD phenotype (Ulcerative colitis vs. Crohn's disease)	−0.19 [−0.61, 0.23]	0.37	−0.18 [−0.47, 0.10]	0.18		
	IBD disease duration	0.0028 [0.0009, 0.0047]	0.003	−0.0012 [−0.0028, 0.0004]	0.14		
	Faecal calprotectin (μg/g)	−0.00009 [−0.00081, 0.00063]	0.80	0.00015 [-0.00031, 0.00061]	0.47		
	C- reactive protein (mg/L)	0.001 [−0.008, 0.011]	0.81	−0.0018 [−0.0081, 0.0045]	0.55		
	Cumulative steroid use (months)	0.0025 [−0.0010, 0.0060]	0.15	0.0006 [−0.0018, 0.0030]	0.62		
	Biologic therapy	−0.04 [−0.43,	0.84	−0.08 [−0.35,	0.50		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	P-value	Est. (95% CI)	P value	Est. (95% CI)	P-value
		0.35]		0.18]			
	Immunomodulator therapy	0.01 [−0.38, 0.39]	0.97	0.01 [−0.23, 0.25]	0.96		
Lifestyle and nutritional factors	Smoking status Current vs. Never Ex vs. Never	 0.40 [−0.09, 0.90] 0.28 [−0.18, 0.74]	0.19	 −0.13 [−0.48, 0.21] −0.15 [−0.45, 0.16]	0.54		
	Excess alcohol intake¶	0.8 [−0.2, 1.8]	0.09	0.4 [−0.3, 1.0]	0.21		
	Vitamin D level (nmol/ml)	−0.0024 [−0.0050, 0.0003]	0.07	−0.0029 [−0.0052, −0.0005]	0.01	−0.0033 [−0.0056, −0.0010]	0.004
	Habitual exercise (IPAQ score, continuous)§	0.002 [−0.007, 0.011]	0.69	−0.0007 [−0.0088, 0.0073]	0.81		
	Albumin (g/dL)	−0.002 [−0.019, 0.016]	0.84	−0.006 [−0.022, 0.011]	0.51		
Body composition factors	Body mass index (BMI)	0.12 [0.10, 0.14]	< 0.0001	0.10 [0.07, 0.12]	< 0.0001	0.10 [0.08, 0.12]	< 0.0001
	Waist circumference	0.030 [0.024, 0.036]	< 0.0001	0.009 [0.000, 0.017]	0.04	0.008 [0.002, 0.016]	0.02
	Waist:hip ratio	1.1 [0.4, 1.7]	0.0008	0.09 [−0.60, 0.78]	0.78		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	P-value	Est. (95% CI)	P value	Est. (95% CI)	P-value
	Grip strength (pounds per square inch, PSI)	0.003 [−0.007, 0.013]	0.57	−0.005 [−0.014, 0.004]	0.26		

Table legend: *^ VHI, visceral adipose tissue area (cm^3)/ height $(m)^2$, log-transformed prior to analysis; ¶Defined according to Australian Healthy Drinking guidelines; § International Physical Activity Questionnaire for assessment of habitual physical activity. Linear mixed regressions, random intercepts, backwards stepwise variable selection from full to final model (p > 0.10). Missing data imputed with cohort means.*

Supplementary Table 6.5 Clinical associations with serial fat mass index (FMI) measurements over 24 months

Variable		**Univariable**		**Full multivariable model**		**Final multivariable model**	
		Est. (95% CI)	p-value	Est. (95% CI)	p-value	Est. (95% CI)	p-value
Demographics	Age at study entry	0.17 [0.10, 0.24]	< 0.0001	0.027 [−0.008, 0.063]	0.14		
	Gender (Male vs. female)	−2.3 [−3.7, −1.0]	0.0007	−2.4 [−3.0, −1.8]	< 0.0001	−2.5 [−3.1, −1.9]	< 0.0001
IBD-related factors	IBD phenotype (Ulcerative colitis vs. Crohn's disease)	−1.1 [−2.7, 0.4]	0.14	−0.25 [−0.86, 0.36]	0.41		
	IBD disease duration	0.010 [0.003, 0.017]	0.003	−0.0019 [−0.0054, 0.0017]	0.28		
	Faecal calprotectin (μg/g)	−0.0016 [−0.0042, 0.0010]	0.20	−0.0001 [−0.0011, 0.0008]	0.79		
	C- reactive protein (mg/L)	0.025 [−0.010, 0.060]	0.15	0.008 [−0.005, 0.021]	0.21		
	Cumulative steroid use (months)	0.009 [−0.004, 0.022]	0.17	0.0040 [−0.0011, 0.0091]	0.10	0.0041 [−0.0004, 0.0085]	0.06
	Biologic therapy	0.5 [−0.9, 1.9]	0.47	−0.07 [−0.63, 0.49]	0.79		
	Immunomodulator therapy	−0.1 [−1.5, 1.3]	0.86	−0.04 [−0.55,	0.87		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	p-value	Est. (95% CI)	p-value	Est. (95% CI)	p-value
				0.47]			
Lifestyle and nutritional factors	Smoking status Current vs. Never Ex vs. Never	 0.4 [−1.4, 2.3] 0.6 [−1.1, 2.3]	0.74	 −0.5 [−1.3,0.2] −0.7 [−1.4, −0.1]	0.05		
	Excess alcohol intake^	0.4 [−3.2, 4.1]	0.81	−0.2 [−1.6, 1.2]	0.78		
	Vitamin D level (nmol/ml)	−0.0011 [−0.0092, 0.0070]	0.79	−0.007 [−0.013, −0.001]	0.02	−0.007 [−0.013, −0.001]	0.02
	Habitual exercise (IPAQ score, continuous)§	−0.010 [−0.039, 0.019]	0.49	−0.015 [−0.038, 0.008]	0.16		
	Albumin (g/dL)	0.024 [−0.031, 0.080]	0.39	−0.013 [−0.058, 0.032]	0.54		
Body composition factors	Body mass index (BMI)	0.56 [0.51, 0.61]	< 0.0001	0.52 [0.46, 0.58]	< 0.0001	0.54 [0.49, 0.60]	< 0.0001
	Waist circumference	0.11 [0.09, 0.12]	< 0.0001	0.055 [0.031, 0.079]	< 0.0001	0.047 [0.028, 0.066]	< 0.0001
	Waist:hip ratio (WHR)	2.7 [0.8, 4.6]	0.005	−1.4 [−3.4, 0.5]	0.12		
	Grip strength (pounds per square inch, PSI)	−0.033 [−0.067, 0.001]	0.05	-0.037 [−0.059, −0.014]	0.0007	−0.039 [−0.061, −0.017]	0.0006

Table legend. *^ Excess alcohol use defined according to Australian Healthy Drinking guidelines; § IPAQ, International Physical Active Questionnaire; FMI, fat mass index (kg/ height m^2); ASMI, appendicular skeletal muscle index (kg/ height m^2); linear mixed regressions, random intercepts, backwards stepwise variable selection from full to final model ($p > 0.10$). Missing data imputed with cohort means.*

Supplementary Table 6.6 Clinical associations with serial appendicular skeletal muscle index (ASMI) measurements over 24 months

Variable		**Univariable**		**Full multivariable model**		**Final multivariable model**	
		Est. (95% CI)	P-value	Est. (95% CI)	P-value	Est. (95% CI)	P-value
Demographics	Age at study entry	0.016 [−0.006, 0.037]	0.16	0.004 [−0.011, 0.019]	0.58		
	Gender (Male vs. female)	1.5 [1.1, 1.9]	< 0.0001	1.1 [0.8, 1.3]	< 0.0001	1.0 [0.8, 1.3]	< 0.0001
IBD-related factors	IBD phenotype (Ulcerative colitis vs. Crohn's disease)	−0.02 [−0.52, 0.49]	0.95	−0.10 [−0.37, 0.16]	0.42		
	IBD disease duration	−0.0003 [−0.0025, 0.0018]	0.77	−0.0013 [−0.0028, 0.0002]	0.10	−0.0011 [−0.0024, 0.0001]	0.08
	Faecal calprotectin (μg/g)	−0.0005 [−0.0014, 0.0003]	0.23	−0.00042 [−0.00084, 0.00000]	0.04	−0.00039 [−0.00078, −0.00001]	0.04
	C- reactive protein (mg/L)	−0.004 [−0.015, 0.007]	0.48	−0.0018 [−0.0075, 0.0039]	0.47		
	Cumulative steroid use (months)	0.0033 [−0.0009, 0.0075]	0.11	0.0019 [−0.0003, 0.0041]	0.08	0.0019 [−0.0002, 0.0040]	0.06
	Biologic therapy	−0.12 [−0.59, 0.35]	0.60	0.01 [−0.23, 0.25]	0.91		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	P-value	Est. (95% CI)	P-value	Est. (95% CI)	P-value
	Immunomodulator therapy	0.00 [−0.46, 0.47]	0.98	0.02 [−0.20, 0.24]	0.83		
Lifestyle and nutritional factors	Smoking status Current vs. Never Ex vs. Never	 0.02 [−0.57, 0.62] 0.42 [−0.13, 0.97]	0.28	 −0.11 [−0.42, 0.21] 0.19 [−0.08, 0.47]	0.16		
	Excess alcohol intake^	0.0 [−1.2, 1.2]	0.97	−0.20 [−0.80, 0.39]	0.43		
	Vitamin D level (nmol/ml)	−0.0006 [−0.0029, 0.0018]	0.63	−0.0002 [−0.0026, 0.0021]	0.93		
	Habitual exercise (IPAQ score, continuous)§	0.004 [−0.005, 0.012]	0.37	0.002 [−0.006, 0.011]	0.57		
	Albumin (g/dL)	0.016 [−0.001, 0.032]	0.06	0.003 [−0.014, 0.019]	0.77		
Body composition factors	Body mass index (BMI)	0.10 [0.08, 0.12]	< 0.0001	0.13 [0.12, 0.15]	< 0.0001	0.14 [0.12, 0.15]	< 0.0001
	Grip strength (pounds per square inch, PSI)	0.023 [0.013, 0.033]	< 0.0001	0.024 [0.015, 0.033]	< 0.0001	0.026 [0.017, 0.035]	< 0.0001

Table legend: *^ Excess alcohol use defined according to Australian Healthy Drinking guidelines; § IPAQ, International Physical Active Questionnaire; FMI, fat mass index (kg/height m^2); ASMI, appendicular skeletal muscle index (kg/height m^2); linear mixed regressions, random intercepts, backwards stepwise variable selection from full to final model ($p > 0.10$). Missing data imputed with cohort means.*

Supplementary Table 6.7 Clinical associations with serial bone mineral density measurements (lumbar spine t-score) over 24 months

Variable		**Univariable**		**Full multivariable model**		**Final multivariable model**	
		Est. (95% CI)	P-value	Est. (95% CI)	P-value	Est. (95% CI)	P-value
Demographics	Age at study entry	−0.003 [−0.021, 0.016]	0.75	0.011 [−0.016, 0.038]	0.41		
	Gender (Male vs. female)	−0.28 [−0.68, 0.11]	0.15	−0.43 [−0.88, 0.02]	0.05	−0.41 [−0.81, −0.01]	0.04
IBD-related factors	IBD phenotype (ulcerative colitis vs. Crohn's disease)	−0.05 [−0.49, 0.39]	0.81	−0.27 [−0.76, 0.22]	0.25		
	IBD disease duration	−0.0011 [−0.0028, 0.0007]	0.22	−0.0013 [−0.0038, 0.0013]	0.28		
	Faecal calprotectin (μg/g)	0.00014 [−0.00059, 0.00088]	0.40	0.0003 [−0.0004, 0.0011]	0.40		
	C- reactive protein (mg/L)	−0.004 [−0.014, 0.006]	0.40	−0.005 [−0.015, 0.005]	0.30		
IBD therapy	Cumulative steroid use (months)	−0.0021 [−0.0057, 0.0015]	0.23	−0.0021 [−0.0059, 0.0018]	0.27		
	Biologic therapy	−0.03 [−0.43, 0.38]	0.89	−0.06 [−0.50, 0.38]	0.78		
	Immunomodulator therapy	−0.34 [−0.73, 0.06]	0.09	−0.42 [−0.82, −0.02]	0.03	−0.32 [−0.70, 0.07]	0.10
Lifestyle and nutritional factors	Smoking status Current vs. Never	−0.28 [−0.79, 0.24]	0.27	−0.36 [−0.94, 0.21]	0.36		

Variable		Univariable		Full multivariable model		Final multivariable model	
		Est. (95% CI)	P-value	Est. (95% CI)	P-value	Est. (95% CI)	P-value
	Ex vs. Never	0.19 [−0.28, 0.66]		0.01 [−0.48, 0.50]			
	Excess alcohol intake^	−0.8 [−1.8, 0.2]	0.09	−0.6 [−1.6, 0.5]	0.25	−0.8 [−1.8, 0.1]	0.08
	Vitamin D level (nmol/ml)	−0.0007 [−0.0023, 0.0010]	0.42	−0.0002 [−0.0019, 0.0015]	0.80		
	Habitual exercise (IPAQ score, continuous)§	0.006 [0.000, 0.011]	0.05	0.006 [0.000, 0.011]	0.04	0.008 [−0.018, 0.011]	0.04
	Calcium	−0.23 [−0.66, 0.20]	0.29	−0.24 [−0.74, 0.25]	0.31		
	Albumin (g/dL)	0.002 [−0.009, 0.013]	0.74	0.004 [−0.009, 0.017]	0.52		
Body composition factors	Body mass index (BMI)	−0.002 [−0.017, 0.014]	0.83	−0.006 [−0.029, 0.016]	0.58		
	Grip strength (pounds per square inch, PSI)	0.007 [0.000, 0.014]	0.04	0.008 [0.001, 0.016]	0.03	0.009 [0.002, 0.017]	0.01
	Fat mass index (FMI)	0.003 [−0.019, 0.025]	0.79	0.005 [−0.028, 0.037]	0.74		
	Appendicular skeletal muscle index (ASMI)	0.03 [−0.05, 0.11]	0.44	0.05 [−0.05, 0.14]	0.29		
	Functional sarcopenia¶	−0.03 [−0.18, 0.13]	0.72	0.01 [−0.15, 0.17]	0.94		

***Table legend**: ^ Excess alcohol use defined according to Australian Healthy Drinking guidelines; § IPAQ, International Physical Active Questionnaire; FMI, fat mass index (kg/height m^2); ASMI, appendicular skeletal muscle index (kg/height m^2); ¶functional sarcopenia, low ASMI and grip strength ≥1 standard deviation below mean. * Significant P value (< 0.05) linear mixed regressions, random intercepts, backwards stepwise variable selection from full to final.*

REFERENCES

1. Bryant RV, Trott MJ, Bartholomeusz FD, *et al*. Systematic review: body composition in adults with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Aug;38(3):213-25.
2. Kirchgesner J, Beaugerie L, Carrat F, *et al*. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. Gut. 2018; 67(7):1261-68.
3. Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, *et al*. Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nature reviews Gastroenterology & hepatology. 2017 Feb;14(2):110-21.
4. Winer DA, Luck H, Tsai S, *et al*. The Intestinal Immune System in Obesity and Insulin Resistance. Cell metabolism. 2016 Mar 8;23(3):413-26.
5. Karmiris K, Koutroubakis IE, Xidakis C, *et al*. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflammatory bowel diseases. 2006 Feb;12(2):100-5.
6. Fink C, Karagiannides I, Bakirtzi K, *et al*. Adipose tissue and inflammatory bowel disease pathogenesis. Inflammatory bowel diseases. 2012 Aug;18(8):1550-7.
7. Flores A, Burstein E, Cipher DJ, *et al*. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. Digestive diseases and sciences. 2015 Aug;60(8):2436-45.
8. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, *et al*. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. Inflammatory bowel diseases. 2015 Dec;21(12):2857-63.
9. Hass DJ, Brensinger CM, Lewis JD, *et al*. The impact of increased body mass index on the clinical course of Crohn's disease. Clinical gastroenterology and hepatology. 2006 Apr;4(4):482-8.
10. Chan SS, Luben R, Olsen A, *et al*. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). The American journal of gastroenterology. 2013 Apr;108(4):575-82.
11. Buning C, von Kraft C, Hermsdorf M, *et al*. Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. Inflammatory bowel diseases. 2015 Nov;21(11):2590-7.

12. Erhayiem B, Dhingsa R, Hawkey CJ, *et al*. Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. Clinical gastroenterology and hepatology. 2011 Aug;9(8):684-7.
13. Holt DQ, Moore GT, Strauss BJ, *et al*. Visceral adiposity predicts post-operative Crohn's disease recurrence. Alimentary pharmacology & therapeutics. 2017 May;45(9):1255-64.
14. Liu G, Wu X, Li Y, *et al*. Postoperative excessive gain in visceral adipose tissue as well as body mass index are associated with adverse outcomes of an ileal pouch. Gastroenterology report. 2016 Sep (epub ahead of print).
15. van Langenberg DR, Gatta PD, Hill B, *et al*. Delving into disability in Crohn's disease: Dysregulation of molecular pathways may explain skeletal muscle loss in Crohn's disease. Journal of Crohn's & colitis. 2014;8(7):626-34.
16. Schneider SM, Al-Jaouni R, Filippi J, *et al*. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008;14(11):1562-8.
17. Bryant RV, Ooi S, Schultz CG, *et al*. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2015 May;41(9):895-906.
18. Adams DW, Gurwara S, Silver HJ, *et al*. Sarcopenia Is Common in Overweight Patients with Inflammatory Bowel Disease and May Predict Need for Surgery. Inflammatory bowel diseases. 2017 Jul;23(7):1182-6.
19. Pedersen M, Cromwell J, Nau P. Sarcopenia is a Predictor of Surgical Morbidity in Inflammatory Bowel Disease. Inflammatory bowel diseases. 2017 Oct;23(10):1867-72.
20. Bamba S, Sasaki M, Takaoka A, *et al*. Sarcopenia is a predictive factor for intestinal resection in admitted patients with Crohn's disease. PloS one. 2017;12(6):e0180036.
21. Harbord M, Annese V, Vavricka SR, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2016 Mar;10(3):239-54.
22. Targownik LE, Bernstein CN, Nugent Z, *et al*. Inflammatory bowel disease and the risk of fracture after controlling for FRAX. J Bone Miner Res. 2013 May;28(5):1007-13.
23. Targownik LE, Bernstein CN, Nugent Z, *et al*. Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clinical gastroenterology and hepatology. 2013 Mar;11(3):278-85.

24. Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Annals of internal medicine. 2000 Nov 21;133(10):795-9.
25. Valentini L, Schulzke JD. Mundane, yet challenging: the assessment of malnutrition in inflammatory bowel disease. European journal of internal medicine. 2011 Feb;22(1):13-5.
26. Casals-Seoane F, Chaparro M, Mate J, *et al*. Clinical Course of Bone Metabolism Disorders in Patients with Inflammatory Bowel Disease: A 5-Year Prospective Study. Inflammatory bowel diseases. 2016 Aug;22(8):1929-36.
27. Targownik LE, Leslie WD, Carr R, *et al*. Longitudinal change in bone mineral density in a population-based cohort of patients with inflammatory bowel disease. Calcified tissue international. 2012 Nov;91(5):356-63.
28. Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749-53.
29. Ainsworth BE, Macera CA, Jones DA, *et al*. Comparison of the 2001 BRFSS and the IPAQ Physical Activity Questionnaires. Medicine and science in sports and exercise. 2006 Sep;38(9):1584-92.
30. Hans DB, Shepherd JA, Schwartz EN, *et al*. Peripheral dual-energy X-ray absorptiometry in the management of osteoporosis: the 2007 ISCD Official Positions. Journal of clinical densitometry. 2008 Jan-Mar;11(1):188-206.
31. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, *et al*. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010 Jul;39(4):412-23.
32. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. PloS one. 2009;4(9):e7038.
33. Kaul S, Rothney MP, Peters DM, *et al*. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring, Md). 2012 Jun;20(6):1313-8.
34. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. The American journal of clinical nutrition. 1998 Oct;68(4):899-917.
35. National Health Survey: First Results, 2014-2015 [database on the Internet]2015 [cited 10/01/2018]. Available from:

http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by Subject/4364.0.55.001~2014-15~Main Features~Overweight and obesity~22

36. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.
37. Dignass A, Lindsay JO, Sturm A, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's & colitis. 2012 Dec;6(10):991-1030.
38. Dignass A, Van Assche G, Lindsay JO, *et al*. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. Journal of Crohn's & colitis. 2010 Feb;4(1):28-62.
39. Ananthakrishnan AN, McGinley EL, Binion DG, *et al*. Fracture-associated hospitalizations in patients with inflammatory bowel disease. Digestive diseases and sciences. 2011 Jan;56(1):176-82.
40. Vazquez MA, Lopez E, Montoya MJ, *et al*. Vertebral fractures in patients with inflammatory bowel disease compared with a healthy population: a prospective case-control study. BMC gastroenterology. 2012 May 14;12:47.
41. Weiss RJ, Wick MC, Ackermann PW, *et al*. Increased fracture risk in patients with rheumatic disorders and other inflammatory diseases -- a case-control study with 53,108 patients with fracture. The Journal of rheumatology. 2010 Nov;37(11):2247-50.
42. Britton KA, Massaro JM, Murabito JM, *et al*. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. Journal of the American College of Cardiology. 2013 Sep 3;62(10):921-5.
43. Preis SR, Massaro JM, Robins SJ, *et al*. Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study. Obesity (Silver Spring, Md). 2010 Nov;18(11):2191-8.
44. Singh S, Singh H, Loftus EV, Jr., *et al*. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clinical gastroenterology and hepatology. 2014 Mar;12(3):382-93.e1.
45. Seidell JC, Oosterlee A, Deurenberg P, *et al*. Abdominal fat depots measured with computed tomography: effects of degree of obesity, sex, and age. European journal of clinical nutrition. 1988 Sep;42(9):805-15.

46. Cheng S, Massaro JM, Fox CS, *et al*. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. Diabetes. 2010 Jan;59(1):242-8.
47. Pedersen HK, Gudmundsdottir V, Nielsen HB, *et al*. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016 Jul 21;535(7612):376-81.
48. Qin J, Li Y, Cai Z, *et al*. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012 Oct 4;490(7418):55-60.
49. Le Chatelier E, Nielsen T, Qin J, *et al*. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013 Aug 29;500(7464):541-6.
50. Zeevi D, Korem T, Zmora N, *et al*. Personalized Nutrition by Prediction of Glycemic Responses. Cell. 2015 Nov 19;163(5):1079-94.
51. Subramaniam K, Fallon K, Ruut T, *et al*. Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015 Mar;41(5):419-28.
52. Ding NS, Malietzis G, Lung PFC, *et al*. The body composition profile is associated with response to anti-TNF therapy in Crohn's disease and may offer an alternative dosing paradigm. Alimentary pharmacology & therapeutics. 2017 Nov;46(9):883-91.
53. Holt DQ, Varma P, Strauss BJG, *et al*. Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis. European journal of clinical nutrition. 2017 Jun;71(6):773-7.
54. Krajcovicova A, Hlavaty T, Killinger Z, *et al*. Combination therapy with an immunomodulator and anti-TNFalpha agent improves bone mineral density in IBD patients. Journal of Crohn's & colitis. 2014 Dec;8(12):1693-701.

CHAPTER 7: VISCERAL ADIPOSE TISSUE IN CROHN'S DISEASE: PHENOTYPE, DISEASE ACTIVITY AND QUALITY OF LIFE

Background

Rising rates of obesity in patients with IBD reported in the previous chapter of this thesis were driven by gains in overall adiposity as well as VAT. However, in contrast to previous reports, there was no association observed between overall adiposity or VAT and IBD phenotype, disease activity, or medications.

VAT is a potent source of pro-inflammatory cytokines and is purported to play a role in the pathogenesis of CD, where intestinal 'fat wrapping' is a common and disease-specific feature in surgical resections. There are clinical data to suggest that VAT may be a biomarker for disease severity and outcomes in CD; however, data are limited by small sample sizes and retrospective design.

To further investigate the potential for VAT to influence phenotype, disease activity, and outcomes in CD, this prospective analysis of serial VAT measurements over 24 months was undertaken. VAT was measured using DXA, alongside anthropometric assessments, IBD-related factors, lifestyle factors including exercise, and nutritional indices.

Presented in this chapter is the manuscript under revision for publication in Inflammatory Bowel Diseases Journal, June 2018.

Specific Author Contributions

Title of Paper	Obesity in inflammatory bowel disease: gains in adiposity despite high prevalence of myopenia and osteopenia.
Publication Status	Under revision for publication
Publication Details	Inflammatory Bowel Diseases. June 2018. Impact factor: 4.5

Name of Principal Author (Candidate)	Robert Venning Bryant		
Contribution to the Paper	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Overall percentage (%)	50%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	4/3/2018

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Chris Schultz		
Contribution to the Paper 6%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data D vision of article		
Signature		Date	27/2/2018

Name of Co-Author	Sooi Ooi		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	27/2/2018

Name of Co-Author	Charlotte Goess		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	1/3/2018

Name of Co-Author	Samuel Costello		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	5/3/2018

Name of Co-Author	Andrew Vincent		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	1/3/2018

Name of Co-Author	Scott Schoeman		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	3/3/2018

Name of Co-Author	Amanda Lim		
Contribution to the Paper 4%	Data acquisition and management Drafting and revision of article		
Signature		Date	27/2/2018

Name of Co-Author	Francis D Bartholomeusz		
Contribution to the Paper 4%	Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	1/3/2018

Name of Co-Author	Simon PL Travis		
Contribution to the Paper 6%	Concept and design of project Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	27/2/2018

Name of Co-Author	Jane M Andrews		
Contribution to the Paper 10%	Concept and design of project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	1/3/2018

[Manuscript 5] Visceral adipose tissue is associated with stricturing Crohn's disease behaviour, faecal calprotectin and quality of life

Short title: VAT in Crohn's disease

Bryant RV[1,2], Schultz CG[3], Ooi S[4], Goess C[4], Costello SP[1,2], Vincent AD[5], Schoeman S[1], Lim A[1], Bartholomeusz FD[3], Travis SPL[6], Andrews JM[2,4]

[1]IBD Service, Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital, Woodville South, South Australia

[2]School of Medicine, Faculty of Health Sciences, University of Adelaide, Adelaide, South Australia

[3]Department of Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital, Adelaide, South Australia

[4]IBD Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, South Australia

[5]Freemasons Foundation Centre for Men's Health, School of Medicine, University of Adelaide, Adelaide, South Australia

[6]Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, Oxfordshire UK

Corresponding author

Dr Robert Bryant
IBD Service, Department of Gastroenterology and Hepatology
The Queen Elizabeth Hospital
28 Woodville Road Woodville South
South Australia 5011
Phone: +61 8 8222 6000
Email: Robert.Bryant@sa.gov.au

Acknowledgements

Royal Adelaide Hospital IBD Nurses, Rachel Grafton and Julie Hughes

Royal Adelaide Hospital, Hospital Research Foundation

Grant support and writing assistance

No funding was received for the study. No writing assistance was received for this study. RB received research support from the Royal Adelaide Hospital Research Foundation through the AR Clarkson Scholarship. JMA used personal untied research funds to purchase dynamometer and study-related faecal calprotectin measurements. No writing assistance was received for this study.

Conflicts of interest and personal interests

There are no conflicts of interest to declare for any of the authors.

RB: Employed by CALHN/TQEH. Grant/Research support/Speaker fees (all paid to employer for research support): AbbVie, Ferring, Janssen, Shire, Takeda.

SC: Employed by CALHN/TQEH. Grant/Research support/Speaker fees (all paid to employer for research support): Pfizer, Merck Sharp & Dohme, Janssen, Shire. Consultancy with Microbiotica.

ST: Employed by Oxford University Hospitals NHS Foundation Trust and the University of Oxford. Grants/Research Support: AbbVie, IOIBD, Lilly, UCB, Vifor, and Norman Collisson Foundation. Consulting Fees: AbbVie, Allergan, Amgen, Asahi, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chemocentryx, Cosmo, Enterome, Ferring, Giuliani SpA, GSK, Genentech/Roche, Immunocore, Immunometabolism, Janssen, Lilly, MSD, Neovacs, NovoNordisk, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHsquared, Vifor, Zeria. Speaker fees: AbbVie, Amgen, Biogen, Ferring, Takeda. No stocks or share options.

JMA: Employed by CALHN/RAH. Grants/Research support/Speaker and Consultancy Fees (all paid to employer for research support): Abbot, AbbVie, Allergan, Bayer, Celgene, Ferring, Hospira, Janssen, MSD, Orphan, Pfizer, Shire, Takeda.

Abstract

Background and aims

Visceral adipose tissue (VAT) has been proposed to play a pathogenic role in Crohn's disease (CD), however prospective clinical data are lacking. The aim was to evaluate whether VAT is associated with CD behaviour, disease activity, quality of life (QoL) or outcomes.

Methods

Body composition data, clinical, anthropometric, disease activity (C-reactive protein (CRP) and faecal calprotectin (FC)) and QoL scores were gathered prospectively on adults with CD at 0, 12 and 24 months. VAT metrics including VAT: subcutaneous adipose tissue (SAT) ratio were calculated. IBD-related surgery and hospitalisation were recorded over extended follow-up (median 51 months). Multivariable linear mixed effects and logistic regression analyses were performed.

Results

Ninety-seven participants were assessed at baseline (55% male, median age 31 years), 84 at 12 and 72 at 24 months. Serial VAT:SAT measurements over 24 months were higher in those with stricturing CD behaviour at enrolment (β=0.83, 95%CI = [0.04,0.71], p = 0.03). Higher serial VAT:SAT was also associated with elevated FC in patients with ileo-colonic disease (β=0.83, 95%CI = [0.27,1.4], p = 0.004) and lower QoL in those with ileal disease (β=−4.5, 95%CI = [−9.1, 0.09], p = 0.05). However, no prospective associations were observed between serial VAT measurements and time to surgery or hospitalisation. No correlations were found between body mass index and disease behaviour, activity, or QoL.

Conclusions

VAT, rather than total body fat, is associated with stricturing CD behaviour, as well as elevated FC and reduced QoL in a disease distribution-dependent manner. Further studies are required to determine whether strategies to reduce VAT might influence outcomes in CD.

Key words

Visceral adipose tissue, obesity, Crohn's disease

Introduction

Intestinal mesenteric fat wrapping or 'creeping fat' was first described by Burrill Crohn and colleagues as a disease-specific feature of 'regional ileitis'.[1] Mesenteric fat accumulation occurs early in the course of CD and is evident in most small bowel resection specimens.[2, 3] More than an innocent bystander, mesenteric adipocytes are a source of pro-inflammatory cytokines in CD, including tumour necrosis factor-alpha (TNF-α), peroxisome proliferator-activating receptor-gamma, and interleukin-6.[2-5] However, despite the plausible role of visceral adipose tissue (VAT) in the pathogenesis of CD, data are lacking and debate persists as to whether VAT is a clinically relevant biomarker in CD.[4]

Human adipose tissue is anatomically distributed in two main compartments with distinct biochemical and metabolic characteristics; VAT and subcutaneous adipose tissue (SAT).[6, 7] In patients with CD, increased VAT compared to healthy controls is well described, yet is not able to be reliably detected by crude, non-specific anthropometric measures such as body mass index (BMI).[3, 8] Rather, cross-sectional imaging techniques such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), have been used to quantify VAT in patients with CD.[9-12] Although accurate in measuring VAT, cross-sectional imaging techniques are limited by radiation, expense and availability.[6] Dual energy X-ray absorptiometry (DXA) is performed routinely in patients with CD to assess bone mineral density (BMD). Whole body DXA is an accurate means of assessing VAT, yet has not previously been studied in patients with CD.

The clinical significance of VAT as a biomarker for disease severity or outcomes has been evaluated in a number of studies, albeit with conflicting results.[2, 3, 8-11, 13] An increase in VAT has been associated with a complex CD phenotype (stricturing and/or fistulising disease), an increased likelihood of post-operative CD recurrence, increased post-operative morbidity and adverse pouch outcomes.[8-11, 13, 14] However, these studies are limited by small sample sizes and retrospective study design. Moreover, heterogeneity in the techniques used to evaluate VAT, as well as the VAT metric reported, limit meaningful interpretation of results.[3, 8-11, 13, 14]

Therefore, to clarify the possible role of VAT in CD and make sense of the conflicting data published to date, we gathered prospective data using an affordable technique (DXA) during routine care. In addition, we examined the degree of correlation between various VAT metrics

and their relationship to other established anthropometric measures. Thus, the aims of this study were to:

1. Evaluate whether VAT measured by DXA is associated with stricturing and/or fistulising disease, hospitalisation or surgery in CD.
2. To prospectively examine whether VAT is associated with disease activity and/or quality of life (QoL) in CD.
3. Explore the correlation between various VAT metrics and other anthropometric assessments.

Material and methods

Subjects

Consecutive patients with CD (aged 18–50 years and pre-menopausal if female) managed by a tertiary IBD service were invited to participate in a prospective study between April 2012 and September 2013 (***Figure 7.1***). Those with medical or surgical comorbidities other than IBD, current pregnancy, or steroid use other than for IBD were excluded. Patients were reviewed at 12 and 24 months after their baseline assessment.

Subject data collection

Prospective data were captured by interview and questionnaire at 0, 12 and 24 months. A comprehensive case-note, IBD database, endoscopy, histopathology and prescription review was undertaken by co-authors. Data capture included demographics, Montreal classification (baseline only), current IBD therapy, current and cumulative lifetime duration of corticosteroid use (equivalent to prednisolone ≥ 10 mg/day) and IBD-related surgery.[15]

C-reactive protein (CRP) was used as a marker of systemic inflammation at each study time-point (CRP < 5 mg/L considered inactive disease). Faecal calprotectin (FC) was assessed as a marker of luminal inflammation using the CALPRO® ELISA (FC < 100µg/g considered inactive disease).

Lifestyle factors were also assessed at 0, 12 and 24 months. Alcohol consumption was dichotomised into < 20 g/day vs. ≥20 g/day. Habitual physical activity was assessed using the validated, self-administered Short International Physical Activity Questionnaire (IPAQ),

which estimates metabolic equivalent (MET)-minutes per week.[16] QoL was assessed by the validated Short Inflammatory Bowel Disease Questionnaire.[17]

Extended prospective follow-up of specific IBD-related outcomes (corticosteroid use, hospitalisation, and surgery) was undertaken until July 2017, a median of 51 months from enrolment (IQR 48–54 months).

VAT and anthropometric assessment

At 0, 12 and 24 months, whole body DXA (General Electric Lunar Prodigy Vision bone densitometer, system DF+13727; Encore 14.20, Madison WI, US) was performed to evaluate body composition, using standard manufacturer protocols conforming to international guidelines.[18]

VAT was measured using CoreScan® analysis software, which is documented to correlate well with CT scan measurements.[19, 20] The software estimates VAT in the android region by determining the abdominal wall margin and subtracting the subcutaneous adipose tissue (SAT) from android fat (VAT) (***Supplementary Figure 7.1***). Multiple VAT metrics were then calculated including VAT area (centimetres^3), mass (grams), visceral adipose tissue/height index (VHI, VAT area (cm^3)/height in metres, squared), and VAT:SAT ratio.

Participants' height (m) and weight (kg) were measured with standard stadiometer and scale equipment at the time of DXA assessment. World Health Organization (WHO) standard categories for BMI were used; < 18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25–29.9 kg/m^2 (overweight), ≥ 30 kg/m^2 (obesity).[21] Waist and hip circumference (cm) were also measured at the time of DXA for calculation of waist:hip circumference ratio (WHR).

Ethical considerations

The study was approved by the Royal Adelaide Hospital Human Research Ethics Committee (#120304). Whole body DXA does not confer significant additional radiation to standard BMD assessment. Radiation safety reported the radiation dose per DXA as 2.56μSv.

Statistical methods

Continuous outcomes were presented as means, standard deviations, medians and interquartile ranges (IQR), with categorical outcomes as counts and percentages, unless otherwise stated.

Measures of VAT and anthropometrics were compared using Pearson correlations. Comparisons in adiposity measures between CD phenotypes were performed using unpaired non-parametric Mann-Whitney U tests. The lack of existing prospective data on VAT and disease outcomes in CD did not allow a formal power calculation to be performed. However, enrolment of 100 patients at baseline was assumed to provide adequate power for clinically relevant effect sizes and multivariable analysis, allowing for dropout over the study period. The line of enquiry within the study and associated statistical associations are described below.

Is VAT correlated with CD behaviour at baseline? Logistic binomial regressions were constructed to assess factors associated with Montreal CD disease behaviour classifications (B1 vs. B2 or B3) as assessed at study enrolment. Cross-sectional factors included age, gender, VHI, VAT:SAT, BMI, IBD disease duration, prior CD resection, FC and CRP.

What factors are associated with serial VAT measurements over time? Linear mixed effects models were constructed for serial VHI and VAT:SAT ratio measurements performed at 0, 12 and 24 months. Log-transformations were applied to the outcome variables, and random intercepts included per individual. Fixed effects covariates included Montreal phenotype as assessed at study enrolment, age, gender, IBD therapy (immunomodulator therapy, biologic therapy, cumulative duration of oral corticosteroid therapy), habitual physical activity (IPAQ), FC, CRP, alcohol intake, and prior CD-related resection.

Does VAT influence disease activity and/or QoL over time? Linear mixed effects models were constructed to assess prospective associations between serial QoL, FC, and CRP levels performed at 0, 12 and 24 months. The latter two measures were log-transformed. Random intercepts were included per individual; the primary predictors of interest were VHI and VAT:SAT ratio (both log-transformed) and their pairwise interactions with the Montreal disease behaviour classification as assessed at study enrolment (both L and B criteria). Analyses were adjusted for covariates listed for the prior analysis as well as BMI, with these factors being included as fixed effects.

In all models, residuals and, where appropriate, random effect estimates, were examined to ensure that model distributional assumptions were not violated. Log-likelihood ratio (LLR) tests of nested models assessed differences across factors with multiple levels. A limited list of factors believed associated with each outcome was determined a priori. These factors,

along with associated factors identified in the full models, were included in a final, reduced model for each outcome. As reported in regression analyses, β coefficient describes the change in the dependent variable for each unit change in the fixed effect covariate.

Does VAT predict time to surgery and/or hospitalisation over extended follow-up? Possible predictors for time to hospitalisation and time to IBD-related surgery over the extended prospective follow-up period were evaluated with Cox regression analyses. Follow-up was calculated as time-to-last contact or death using Kaplan-Meier methodology with deaths censored. The primary predictors of interest were VAT metrics (included in the model as the average of repeated measures over time) and Montreal CD behaviour as assessed at study enrolment. Adjustment for other covariates was not performed due to a limited number of events. Survival curves were constructed using the Kaplan-Meier method.

All tests were 2-tailed and assessed at the 5% alpha level. Analyses were performed on R software (v3.4.3).

Results

Baseline subject characteristics

One hundred and thirty-five patients with CD were assessed for eligibility during the enrolment period (April 2012–September 2013), 38 of whom were excluded (***Figure 7.1***). Some 97 patients were enrolled at baseline, of whom 84 (87%) completed a 12-month and 72 (74%) completed a 24-month follow-up. Median duration of extended follow-up for surgical and hospitalisation events was 51 months (95%CI 48–54).

Median age was 31 years (range 18–49), median age of diagnosis 21 years (range 9–48) and disease duration 8.1 years (IQR 4.7–12.5 years) (***Table 7.1***). CD distribution was ileal (L1) in 28 (29%) patients, colonic (L2) in 32 (33%) and ileo-colonic (L3) in 37 (38%). At baseline, disease behaviour was classified as inflammatory (non-stricturing, non-penetrating, B1) in 43 (44%) patients, stricturing (B2) in 38 (39%) and penetrating (B3) in 16 (16%). 40 (41%) patients had undergone abdominal surgery for CD prior to enrolment: 36 (37%) ileal/ileocolic resection, 4 (4%) colectomy and 6 (6%) multiple operations. 27 (28%) patients were on oral corticosteroid therapy at baseline and 47 (48%) on biologic therapy.

The cohort was predominantly Caucasian (98%). Some 25 (26%) patients were current smokers and 4 (4%) self-reported consumption of > 20 g alcohol per day. Habitual physical

activity measured in MET-minutes/week was low in 44 (45%), medium in 22 (23%) and high in 19 (20%) patients.[16] Mean SIBDQ score was 50/70 (SD = 12.6). QoL was severely reduced (SIBDQ < 45/70) in 23 patients (24%), moderately reduced (SIBDQ 45–60/70) in 38 (39%), and normal (SIBDQ > 60/70) in only 21 (22%).[17] Mean BMI was 26.5 kg/m^2 (SD = 5.4), with 5 (5%) classified as underweight, 24 (25%) overweight and 25 (26%) obese.[21]

Baseline VAT and CD behaviour

VAT:SAT was positively associated with stricturing (B2), but not fistulising (B3) CD behaviour at baseline in multivariable logistic regression analysis (B2 log(OR)= 1.6, 95%CI = [0.33, 3], p = 0.01; B3 log(OR)= 0.94, 95%CI = [−0.68, 2.6], p = 0.25) (***Table 7.2 and Supplementary Table 7.1***). This was in contrast to BMI, which did not significantly associate with CD behaviour. Female gender was also associated with B2 disease at baseline (female vs. male log(OR) = 1.7, 95%CI = [0.29, 3.2], p = 0.02) (***Table 7.2***).

Associations with serial VAT measurements over study period

Serial VAT:SAT measurements at 0, 12, and 24 months were higher in patients with B2 disease in linear mixed effects analyses (β=0.38, 95%CI = [0.04, 0.71], p = 0.03) (***Table 7.3***). VAT:SAT was positively associated with age (β=0.037, 95%CI = [0.022, 0.052], p < 0.001) and male gender (β=1.0, 95%CI = [0.7, 1.3], p < 0.001). However, when the analysis was restricted to only the patients who had not undergone prior surgery (n = 57), the association between VAT:SAT and stricturing (B2) disease remained significant (β= 0.42, 95%CI = [0.014, 0.82], p = 0.04) (***Supplementary Table 7.2***). Similar results were observed for VHI (***Supplementary Table 7.3***).

VAT associations with disease activity over study period

A positive association between serial VAT:SAT and FC measurements at 0, 12, and 24 months was observed in patients with ileo-colonic (L3) disease distribution in linear mixed effects analyses (β=0.83, 95%CI = [0.27, 1.4], p = 0.004, ***Figure 7.2, Supplementary Table 7.4***). In contrast, a negative association was observed between VHI and FC levels (β=−0.38, 95%CI = [−0.68, −0.09], p = 0.01). No associations between VAT:SAT or VHI and CRP levels over the study period were observed (***Supplementary Table 7.5***). BMI was not associated with either FC or CRP.

Predictors of IBD-related hospitalisation or surgery over extended follow-up

Over the extended follow-up period (median 51 months), 45 patients (46%) were hospitalised and 18 (18%) underwent IBD-related surgery. The event rates were higher in those patients classified as B2/3 as compared to B1 at enrolment (***Supplementary Figure 7.2***).

No associations with VAT metrics were detected with either time to hospitalisation or surgery after adjusting for baseline disease phenotype (distribution and behaviour) (***Supplementary Table 7.6***). Only B2 CD behaviour was associated with time to surgery (β=1.4, 95%CI = [0.05, 2.7], p = 0.04), whilst there was a trend for fistulising phenotype to increase risk of surgery (β=1.3, 95%CI = [−0.2, 2.9], p = 0.08).

VAT associations with QoL over study period

A negative association between serial VAT:SAT and QoL measurements at 0, 12, and 24 months was observed in patients with ileal CD (L1) and to a lesser extent in those with ileo-colonic disease compared to patients with colonic disease in linear mixed effects analyses (interaction p = 0.03, 2 degrees of freedom) (***Supplementary Table 7.7 and Supplementary Figure 7.3***). QoL was also positively associated with male gender (β=5.8, 95%CI = [0.7, 11], p = 0.03).

Correlations between VAT, overall adiposity and anthropometric assessments

Because VAT is reported variably in previous studies, correlations amongst different VAT metrics were analysed (**Figure 7.3**). VHI correlated almost perfectly with VAT mass (g) and strongly with both overall fat mass (g) and VAT:SAT. In contrast, VAT:SAT correlated strongly with VAT mass (g) but poorly with overall fat mass (g).

Further correlation analyses explored the relationship between visceral adiposity and other clinical anthropometric assessments (**Supplementary Figure 7.4**). Waist circumference and BMI both strongly correlated with VHI, whereas WHR only moderately correlated with VHI. Correlations with VAT:SAT ratio were much lower. A very weak correlation was observed between VAT:SAT and BMI and only weak correlations between VAT:SAT and waist circumference and WHR .

Discussion

In a prospective well-characterised cohort of patients with CD, VAT was associated with stricturing disease behaviour at baseline and independently associated with both FC and QoL in a disease distribution-dependent manner when measured serially over 24 months. In contrast, there was no association between overall adiposity, as measured using BMI, and CD phenotype, disease activity or QoL, suggesting a specific role for VAT as previously proposed.

That VAT is associated with CD behaviour is supported by early surgical descriptions and retrospective or cross-sectional studies.[2, 10, 12, 13] Several studies have reported that VAT is associated with higher rates of surgery, raised inflammatory markers, increased surgical morbidity, or higher rates of post-operative CD recurrence.[8, 9, 11, 12, 14, 22] An association between VAT and disease behaviour in CD is plausible given that visceral adipocytes are a source of cytokine production in CD (including TNF-alpha and IL-6) and are likely to play a role in innate immunity.[3-5] Bacterial translocation may lead to immune infiltration of mesenteric fat, perpetuating the inflammatory response with resultant mesenteric fat hypertrophy.[23] In contrast, overall adiposity as measured using BMI is not associated with CD behaviour or activity in this or other studies.[24] This highlights the different metabolic profiles between VAT and SAT compartments and the lack of discriminatory capacity of BMI as a tool to measure adiposity.[25]

We report a positive association between VAT and FC measurements in patients with ileo-colonic disease over 24 months. This is the first study to examine serial measures of both inflammation and VAT concurrently. Small studies have reported conflicting findings on the relationship between VAT and clinical disease activity.[3, 13, 22] It is notable that fat wrapping in CD is more often a feature of ileal than colonic disease, although elevated FC associates with colonic inflammation, and may be normal even in the presence of large ileal ulcers.[2, 3, 26] To account for the association between VAT:SAT and FC in ileo-colonic disease, it is possible that this reflects ileal fat wrapping and colonic inflammation is detected by FC. However, given that VHI, an alternative measure of VAT, was inversely associated with FC, the association needs substantiation. The lack of observed association between VAT and CRP may reflect the known modest correlation between CRP and luminal inflammation in CD, although VAT is a potent source of IL-6.[22, 27] Higher serial VAT, but not BMI measurements, were also associated with reduced QoL in patients with ileal CD. This is the

first reported association between VAT and QoL in CD. Impaired QoL in IBD has been previously associated with active disease (for which VAT may be a surrogate marker), psychological comorbidity, disability, or nutritional deficiency.[28]

Limitations to this study must be acknowledged before proclaiming VAT measurements as clinically useful in CD. First, VAT was independently associated with previous surgery, gender and advanced age, meaning that any predictive index needs to account for these variables. The influence of gender was confounding since female gender was associated with stricturing CD behaviour, yet male gender correlated with higher VAT, in keeping with non-IBD populations.[29] Prior abdominal surgery was associated with a classification of complicated disease behaviour at enrolment, yet independently associated with lower serial VAT measurements during follow-up, as well as a trend toward lower FC over time. It is conceivable that mesocolic excision of visceral fat reduced the risk of post-operative recurrence and subsequent improved disease control.[30] Second, without published IBD-specific VAT risk 'cut-offs', clinical interpretation of VAT measurements is limited. Third, there was no observed association between VAT and hospitalisation or surgery over more than 4 years of follow-up. Although other studies have reported an association between VAT and outcomes in CD, they have been limited by retrospective or post-hoc design and lacked analysis of confounding variables.[8-11, 13] Although prospective, the number of events at time of analysis in this study suggests that the multivariable analysis for surgery and hospitalisation was underpowered for small–moderate effect sizes. Classification of CD behaviour at study enrolment without adjustment over time was another potential limitation, although hospitalisation and surgery acted as surrogate makers of disease behaviour. Furthermore, this patient cohort was predominantly Caucasian, which may limit generalisability.

This study illustrates that VAT metrics differ from one another and are associated with unique risk profiles in CD. VHI was shown to correlate only moderately with VAT:SAT ratio. Similar disparity between VAT metrics has been reported in other studies; VHI but not VAT:SAT ratio was shown to be a significant predictor of post-operative CD recurrence.[11] The distinction between VAT metrics in imparting cardio-metabolic risk has been well reported, yet most existing IBD studies only report a single VAT metric.[25] Our data emphasise the importance of incorporating multiple VAT metrics into future studies in CD. This may be achieved by using whole body DXA, which is accurate, relatively inexpensive,

associated with minimal associated ionising radiation, and in routine use for measuring BMD in IBD.[19, 20]

In summary, VAT is associated with stricturing CD behaviour, as well as prospective disease activity and QoL. The challenge remains to determine the influence of VAT on CD outcomes from diagnosis and whether interventions to reduce VAT can modify disease course in CD. Until such data are available, VAT as a biomarker in CD holds promise, but is not yet ready for prime time.

Figures

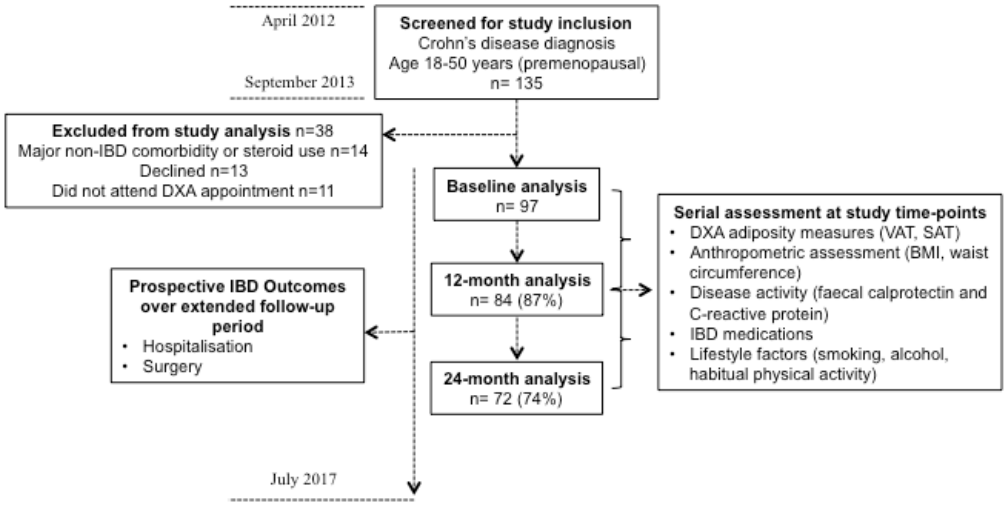


Figure 7.1 Study design CONSORT diagram

***Legend**: DXA, dual energy X-ray absorptiometry; IBD, inflammatory bowel disease; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index.*

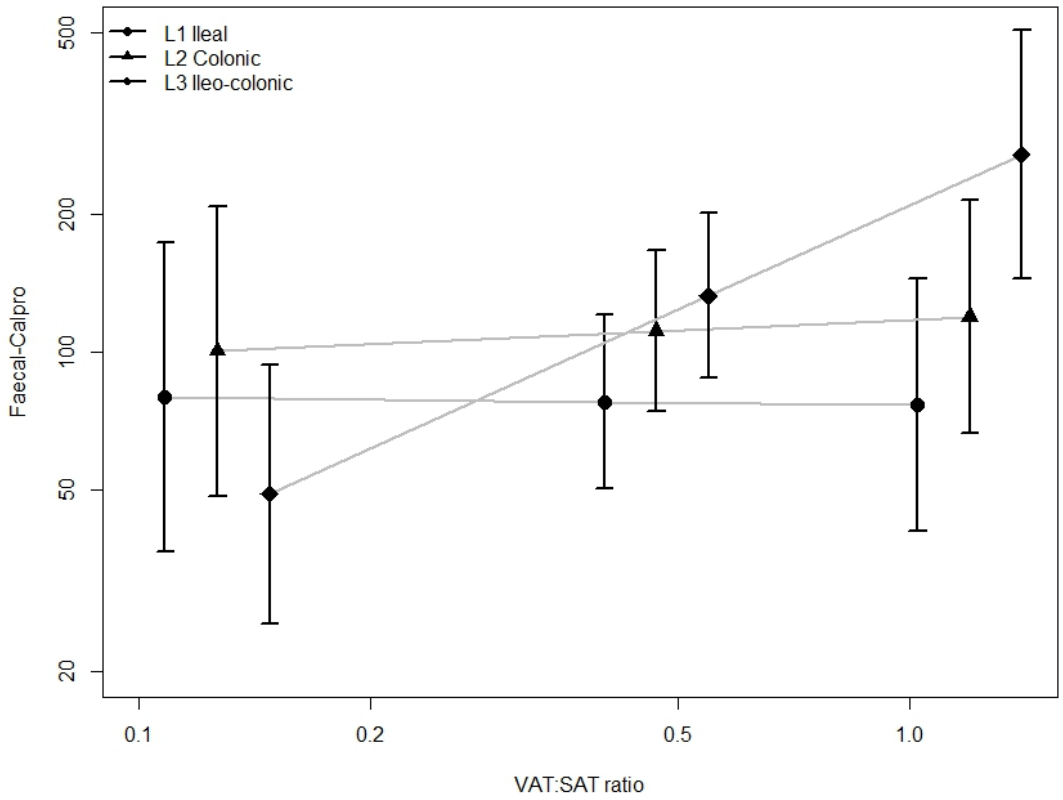


Figure 7.2 Association between serial VAT:SAT and faecal calprotectin measurements over 24 months in Crohn's disease

***Legend**: Both visceral adipose tissue: subcutaneous adipose tissue ratio (VAT:SAT) and faecal calprotectin (µg/g) measured at baseline and at 1 and 2 years of follow-up. IBD disease distribution classified according to the Montreal criteria. Statistical analysis performed using multivariable linear mixed effects models.*

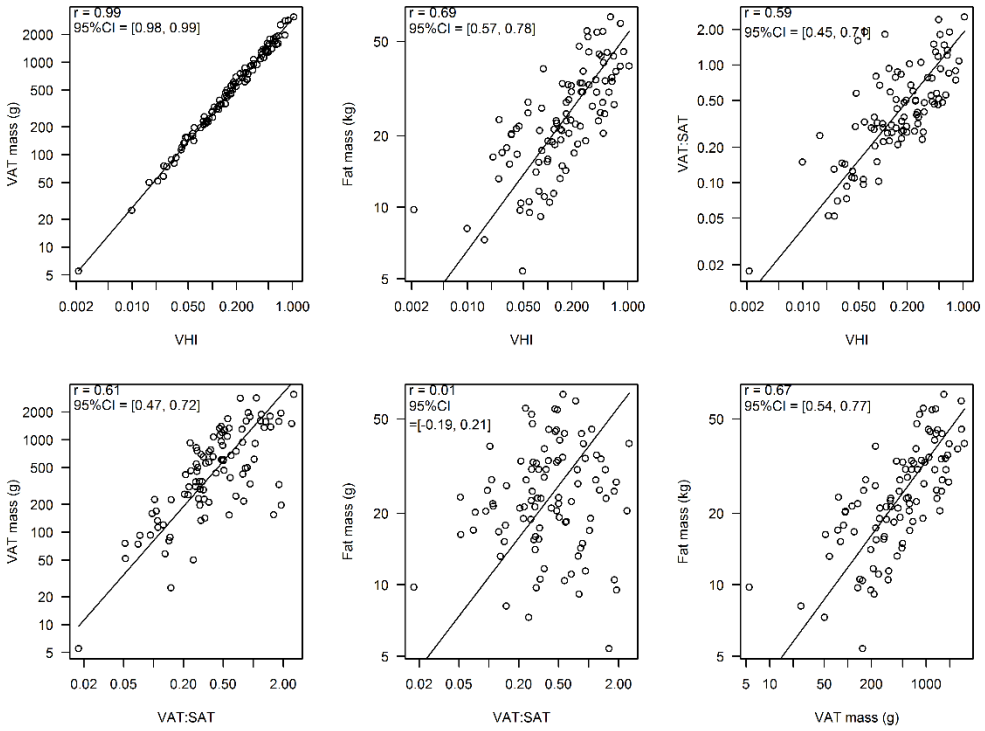
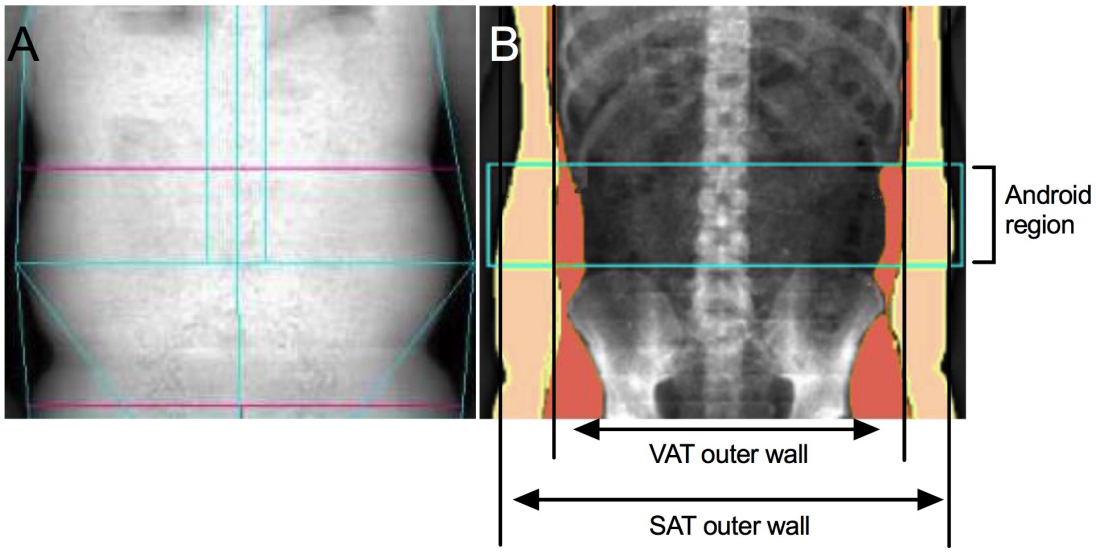


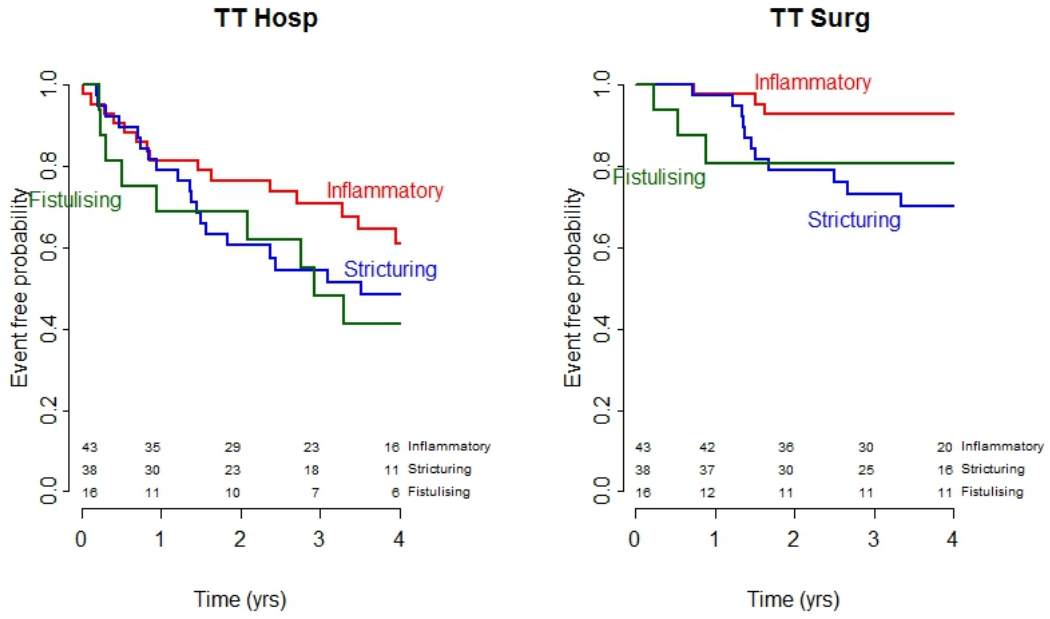
Figure 7.3 Correlation analysis between visceral adipose tissue metrics in Crohn's disease

***Legend**: VAT, visceral adipose tissue; VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; VAT:SAT, visceral adipose tissue: subcutaneous adipose tissue ratio. Statistical analysis performed using Pearson correlation coefficients.*



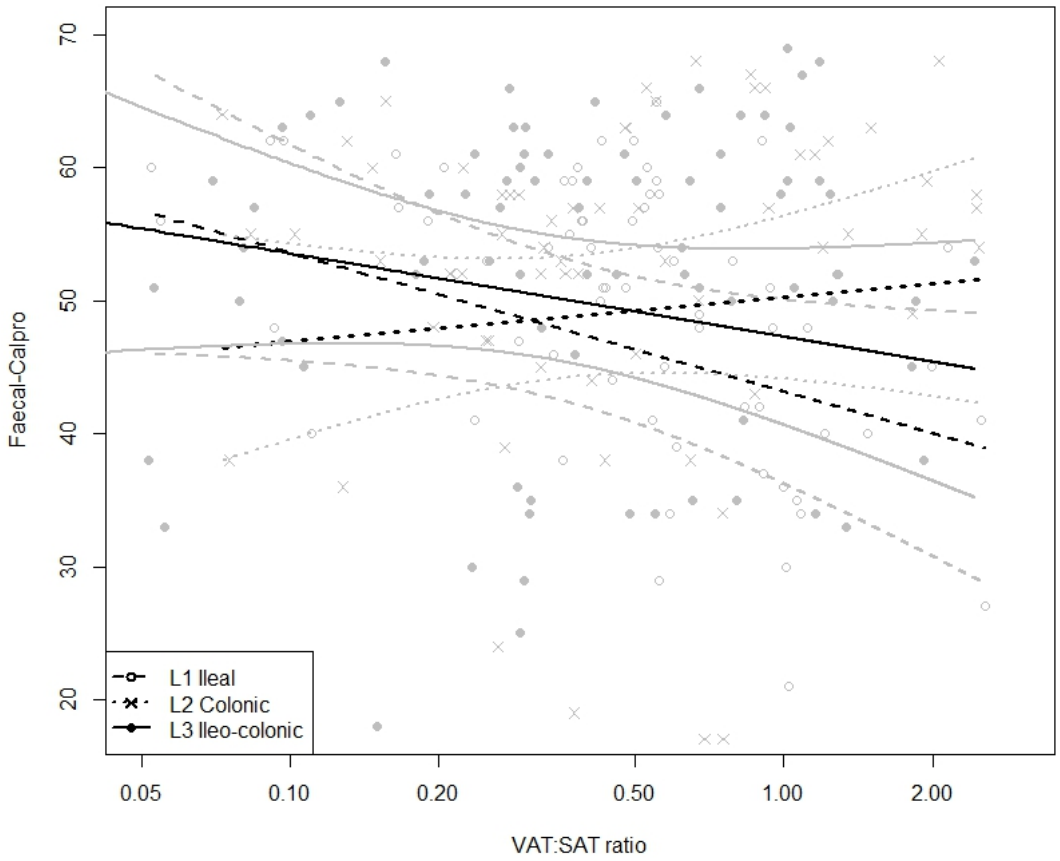
Supplementary Figure 7.1 Dual energy X-ray absorptiometry (DXA) visceral adipose tissue analysis method

***Legend**. A. DXA whole body image of the android region. DXA allows differentiation between fat, lean tissue, and bone. B. DXA image interpreted using General Electric CoreScan® software, allowing calculation of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in the android region. Images adapted from Del Rio et al., presented at 15th ECO, April 2007, Budapest, Hungary (without permission).*



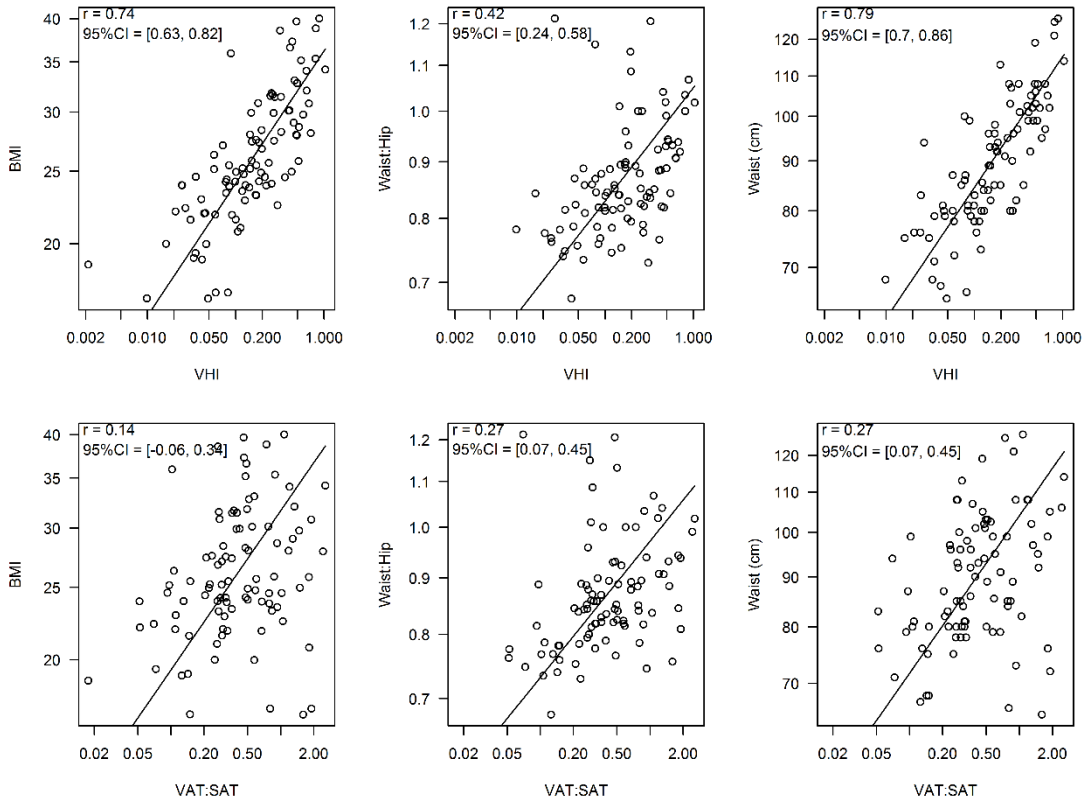
Supplementary Figure 7.2 Time to hospitalisation and surgery according to Crohn's disease behaviour phenotype over 4-year follow-up period

Legend. *Crohn's disease phenotype classified according to the Montreal criteria. Data on IBD-related hospitalisation and IBD-related abdominal surgery collected over prospective follow-up period.*



Supplementary Figure 7.3 Association between serial VAT:SAT and quality of life measurements over 24 months in Crohn's disease

Legend. *Both visceral adipose tissue: subcutaneous adipose tissue ratio (VAT:SAT) and Short Inflammatory Bowel Disease Questionnaire measured at baseline and at 1 and 2 years of follow-up. IBD disease distribution classified according to the Montreal criteria. Statistical analysis performed using multivariable linear mixed effects models.*



Supplementary Figure 7.4 Correlation between anthropometric assessments and visceral adipose tissue metrics in Crohn's disease

Legend. *BMI, body mass index; VAT, visceral adipose tissue; VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; VAT:SAT, visceral adipose tissue: subcutaneous adipose tissue ratio. Statistical analysis performed using Pearson correlation coefficients.*

Tables

Table 7.1 Baseline clinical characteristics of inflammatory bowel disease cohort

		Crohn's disease
Patients (n)		97
Ethnicity	Caucasian Asian	95 (98%) 2 (2%)
Male (n, %)		49 (51%)
Age at baseline (years) (median, range)		31 (18–-49)
Smoking	Current	25 (26%)
	Ex-smoker	26 (27%)
	Never smoked	46 (47%)
Alcohol use (> 20 g ethanol/day, n, %)`		4 (3%)
Age at diagnosis (median, range) Montreal criteria^		21 (9–-48) A1 16 (17%) A2 75 (77%) A3 6 (6%)
Disease duration (months)	Mean ± SD Median, IQR	118.4 ± 90 97 (56–-150)
Disease phenotype (n, %) Montreal criteria^		L1 28 (29%) B1 43 (44%) L2 32 (33%) B2 38 (39%) L3 37 (38%) B3 16 (17%) p 37 (38%) L4 2 (2%)
Extra-intestinal manifestations (n, %)	Overall Primary sclerosing cholangitis Arthropathy Skin lesion Other	26 (27%) 2 (2%) 15 (16%) 6 (6%) 3 (3%)
IBD-related surgery (n, %)		40 (41%)
Clinical disease activity score	Mean ± SD Median, IQR	CDAI 95 ± 101 60 (26–144)
C-reactive protein (mg/L)	Mean ± SD Median, IQR	9 ± 19 2.4 (0.6–12)
Faecal calprotectin (µg/g)	Mean ± SD Median, IQR	252 ± 297 95 (20–475)
Composite disease activity assessment (n active disease, %)		43 (44%)
Corticosteroids	Current (n, %) Median, IQR Use ≥ 12 months (n, %)	27 (28%) 6 (0.6–24) 41 (42%)
Biologic therapy (n, %)	Overall Infliximab	47 (48%) 30 (33%)

			Crohn's disease
		Adalimumab	16 (17%)
		Vedolizumab	1 (1%)
5-aminosalicylic acid (5-ASA) therapy (n, %)			33 (33%)
Immunomodulator (n, %)		Overall	58 (60%)
		Azathioprine	39 (40%)
		Mercaptopurine	4 (4%)
		Methotrexate	2 (2%)
		Thiopurine/allopurinol	13 (13%)
Exercise (IPAQ~)	Continuous	Mean ± SD	4345 ± 6215
		Median, IQR	1671 (841–4650)
	Categorical	Low	44 (45%)
		Medium	22 (23%)
		High	19 (20%)
Health-related quality of life (SIBDQ*)		Mean ± SD	50 ± 12.6
		Median, IQR	53 (42- 60)
Body mass index (BMI)		Mean ± SD	26.5 ± 5.4
		Median, IQR	25.3 (22.9–30.4)
Body mass index categories (n, %)		BMI < 18.5	5 (5%)
		BMI 18.5–24.9	41 (42%)
		BMI 25–29.9	24 (25%)
		BMI 30–34.9	17 (18%)
		BMI 35–39.9	6 (6%)
		BMI ≥ 40	2 (2%)

Table legend: *Data presented as mean ± standard deviation (SD), median (interquartile range (IQR)), counts and percentage. IBD, inflammatory bowel disease; ^ Montreal Criteria for classification of IBD; * SIBDQ, Short Inflammatory Bowel Disease Questionnaire; ~ IPAQ, International Physical Active Questionnaire (data for 87 patients available); `Excess alcohol use defined according to Australian Healthy Drinking guidelines. Composite disease activity assessment using clinical indices (CDAI or Partial Mayo) and biomarker of inflammation (faecal calprotectin and C-reactive protein).*

*Table 7.2: Associations with stricturing (B2) Crohn's disease behaviour at baseline^*

Covariates	Unadjusted		Multiple adjusted		Reduced model	
	log(OR) [95% CI]	p-value	log(OR) [95% CI]	p-value	log(OR) [95% CI]	p-value
Gender (male v female)	**−0.25 [−1.1, 0.65]**	**0.58**	**−1.8 [−3.3, −0.27]**	**0.02**	**−1.7 [−3.2, −0.29]**	**0.02**
Age at IBD diagnosis	−0.009 [−0.016, −0.002]	0.01	−0.091 [−0.19, 0.0028]	0.05	−0.085 [−0.17, 0.0031]	0.05
VHI	0.49 [−1.4, 2.4]	0.6	−0.08 [−3.9, 3.8]	0.97		
VAT:SAT	**0.32 [−0.53, 1.2]**	**0.45**	**1.6 [−0.047, 3.2]**	**0.05**	**1.6 [0.33, 3]**	**0.01**
Body mass index (BMI)	0.034 [−0.052, 0.12	0.43	0.013 [−0.15, 0.17]	0.87		
IBD disease duration	0.0086 [0.0024, 0.015]	0.01	−0.088 [−0.18, 0.0035]	0.05	−0.082 [−0.17, 0.0043]	0.06
Prior IBD abdominal surgery (baseline)	**2.5 [1.4, 3.6]**	**< 0.0001**	**3.1 [1.5, 4.7]**	**0.0001**	**3.1 [1.5, 4.7]**	**< 0.0001**
Faecal calprotectin (μg/g)	−0.0011 [−0.0028, 0.00061]	0.2	−0.00013 [−0.0023, 0.002]	0.9		
C−reactive protein (mg/L)	−0.019 [−0.058, 0.02]	0.33	−0.024 [−0.091, 0.042]	0.47		

Table legend: *VHI, visceral adipose tissue/height^2 index; VAT:SAT, visceral adipose tissue: subcutaneous adipose tissue ratio measured at baseline. ^ Montreal criteria for classification of IBD. log(OR) = log odds ratio. Statistical analysis using logistic regression multivariable analysis, with comparison between structuring (B2) and non-stricturing/non-penetrating disease (B1) performed.*

Table 7.3 Associations with serial VAT:SAT measurements in Crohn's disease over 24-months.

Covariates	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	p-value	Est. [95% CI]	p-value	Est. [95% CI]	p-value
Age	**0.028 [0.010, 0.047]**	**0.002**	**0.030 [0.012, 0.048]**	**0.001**	**0.037 [0.022, 0.052]**	**< 0.0001**
Gender (male v female)	**0.93 [0.63, 1.2]**	**< 0.0001**	**0.98 [0.69, 1.3]**	**< 0.0001**	**1.0 [0.7, 1.3]**	**< 0.0001**
Montreal B criteria^ (vs. B1)						
Stricturing (B2)	**0.07 [−0.32, 0.46]**	**0.71**	**0.34 [−0.02, 0.69]**	**0.06**	**0.38 [0.04, 0.71]**	**0.03**
Fistulising (B3)	−0.14 [−0.65, 0.38]	0.59	0.08 [−0.36, 0.53]	0.72	0.08 [−0.34, 0.49]	0.72
Montreal L criteria^ (vs. L1)						
Colonic (L3)	−0.12 [−0.57, 0.33]	0.59	−0.04 [−0.42, 0.33]	0.82		
Ileo-colonic (L2)	−0.29 [−0.72, 0.15]	0.19	−0.14 [−0.51, 0.22]	0.44		
IBD disease duration	0.0015 [−0.0003, 0.0033]	0.10	0.0010 [−0.0011, 0.0031]	0.33		
Biologic therapy	−0.37 [−0.72, −0.02]	0.04	−0.18 [−0.48, 0.12]	0.23	−0.18 [−0.45, 0.10]	0.20
Immunomodulator therapy	0.23 [−0.13, 0.59]	0.20	0.28 [−0.01, 0.58]	0.06	0.26 [−0.02, 0.54]	0.06
Cumulative duration of oral corticosteroid use (months)	0.0012 [−0.0020, 0.0044]	0.46	0.0005 [−0.0024, 0.0034]	0.74		
IBD abdominal surgery prior to enrolment	**−0.04 [−0.40, 0.32]**	**0.82**	**−0.44 [−0.80, −0.09]**	**0.01**	**−0.41 [−0.73, −0.09]**	**0.01**
Faecal calprotectin (μg/g)	−0.00001 [−0.00066,	0.97	0.00010 [−0.00045,	0.72		

Covariates	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	p-value	Est. [95% CI]	p-value	Est. [95% CI]	p-value
	0.00064]		0.00066]			
C-reactive protein (mg/L)	−0.008 [−0.017, 0.001]	0.07	−0.003 [−0.011, 0.004]	0.38		
Alcohol intake (> 20 g/day)~	0.80 [−0.08, 1.7]	0.07	0.36 [−0.37, 1.1]	0.33		
Habitual exercise (IPAQ)”	0.009 [−0.022, 0.039]	0.57	−0.010 [−0.035, 0.015]	0.41	−0.007 [−0.030, 0.017]	0.58

Table legend: *VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue (VAT:SAT) ratio assessed at baseline, 12 months, and 24 months; IBD, inflammatory bowel disease; ^ Crohn’s disease phenotype defined according Montreal classification at study enrolment. Statistical analysis using linear mixed effects model multivariable analysis. ~Defined according to Australian Healthy Drinking guidelines; International Physical Activity Questionnaire for assessment of habitual physical activity (per 1000). Age, IBD disease duration, cumulative corticosteroid use, faecal calprotectin, C-reactive protein, and habitual exercise assessed as continuous variables.*

Supplementary Table 7.1: Associations with fistulizing (B3) Crohn's disease behaviour at baseline^

Covariates	Unadjusted		Multiple adjusted		Reduced model	
	log(OR) [95% CI]	p-value	log(OR) [95% CI]	p-value	log(OR) [95% CI]	p-value
Gender (male v female)	−0.14 [−1.3, 1]	0.81	−0.79 [−2.7, 1.1]	0.39	−1 [−2.7, 0.66]	0.22
Age at IBD diagnosis	−0.0071 [−0.014, −0.00023]	0.04	−0.032 [−0.14, 0.076]	0.55	−0.025 [−0.11, 0.066]	0.59
VHI	0.59 [−1.9, 3]	0.63	−1.4 [−7.7, 4.8]	0.65		
VAT:SAT	0.34 [−0.78, 1.4]	0.55	1.2 [−0.9, 3.3]	0.25	0.94 [−0.68, 2.6]	0.25
Body mass index (BMI)	0.036 [−0.076, 0.15]	0.52	0.028 [−0.21, 0.27]	0.82		
IBD disease duration	0.0069 [0.00026, 0.013]	0.04	−0.027 [−0.13, 0.079]	0.61	−0.02 [−0.11, 0.067]	0.65
Prior IBD abdominal surgery (baseline)	2.1 [0.73, 3.4]	**0.002**	1.9 [0.34, 3.6]	**0.02**	2.1 [0.59, 3.6]	**0.01**
Faecal calprotectin (μg/g)	−0.0024 [−0.0053, 0.00056]	0.11	−0.0026 [−0.0062, 0.0011]	0.16		
C-reactive protein (mg/L)	0.0059 [−0.017, 0.028]	0.6	0.019 [−0.0089, 0.048]	0.17		

Table legend: *VHI, visceral adipose tissue/height^2 index; VAT:SAT, visceral adipose tissue: subcutaneous adipose tissue ratio measured at baseline. ^ Montreal criteria for classification of IBD. log(OR) = log odds ratio. Statistical analysis using logistic regression multivariable analysis, with comparison between fistulising (B3) and non-stricturing/non-penetrating disease (B1) performed.*

Supplementary Table 7.2: Associations with serial VAT:SAT measurements in Crohn's disease over 24 months in patients without prior Crohn's disease-related surgery.

Covariates	Unadjusted		Multiple adjusted		Reduced	
	Est. [95% CI]	**p-value**	**Est. [95% CI]**	**p-value**	**Est. [95% CI]**	**p-value**
Age	**0.028 [0.0099, 0.047]**	**0.002**	**0.029 [0.0083, 0.049]**	**0.01**	**0.034 [0.017, 0.052]**	**0.0002**
Gender (male v female)	**0.93 [0.63, 1.2]**	**< 0.0001**	**0.95 [0.57, 1.3]**	**< 0.0001**	**1 [0.7, 1.4]**	**< 0.0001**
Montreal B criteria^ (vs. B1)						
Stricturing (B2)	**0.074 [−0.32, 0.46]**	**0.71**	**0.37 [−0.052, 0.8]**	**0.09**	**0.42 [0.014, 0.82]**	**0.04**
Fistulising (B3)	−0.14 [−0.65, 0.38]	0.59	−0.038 [−0.69, 0.61]	0.91	0.088 [−0.41, 0.59]	0.73
Montreal L criteria^ (vs. L1)						
Colonic (L3)	−0.12 [−0.57, 0.33]	0.59	−0.028 [−0.54, 0.49]	0.91		
Ileo-colonic (L2)	−0.29 [−0.72, 0.15]	0.19	−0.064 [−0.61, 0.48]	0.82		
IBD disease duration	0.0015 [−0.00033, 0.0033]	0.1	0.0021 [−0.0017, 0.006]	0.28		
Biologic therapy	−0.37 [−0.72, −0.023]	0.04	−0.2 [−0.6, 0.19]	0.31	−0.18 [−0.51, 0.16]	0.3
Immunomodulator therapy	0.23 [−0.13, 0.59]	0.2	0.22 [−0.18, 0.62]	0.28	0.17 [−0.16, 0.5]	0.3
Cumulative duration of oral corticosteroid use (months)	0.0012 [−0.002, 0.0044]	0.46	−0.00044 [−0.005, 0.0042]	0.85		
Faecal calprotectin (μg/g)	−0.000012 [−0.00066, 0.00064]	0.97	−0.00000054 [−0.00063, 0.00063]	1		

Covariates	Unadjusted		Multiple adjusted		Reduced	
	Est. [95% CI]	p-value	Est. [95% CI]	p-value	Est. [95% CI]	p-value
C-reactive protein (mg/L)	−0.008 [−0.017, 0.00086]	0.07	−0.00018 [−0.0082, 0.0078]	0.96		
Alcohol intake (> 20 g/day)~	0.8 [−0.078, 1.7]	0.07	0.58 [−0.22, 1.4]	0.15		
Habitual exercise (IPAQ)”	0.0087 [−0.022, 0.039]	0.57	−0.027 [−0.066, 0.013]	0.19	−0.026 [−0.062, 0.01]	0.16

Table legend: *VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue (VAT:SAT) ratio assessed at baseline, 12 months, and 24 months; IBD, inflammatory bowel disease; ^ Crohn’s disease phenotype defined according Montreal classification at study enrolment. Statistical analysis using linear mixed effects model multivariable analysis. ~ Defined according to Australian Healthy Drinking guidelines; International Physical Activity Questionnaire for assessment of habitual physical activity (per 1000). Age, IBD disease duration, cumulative corticosteroid use, faecal calprotectin, C-reactive protein, and habitual exercise assessed as continuous variables. 57 patients without prior Crohn’s disease-related surgery included in analysis.*

Supplementary Table 7.3: Associations with serial Visceral adipose tissue /height squared, VHI) in Crohn's disease

	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	**p-value**	**Est. [95% CI]**	**p-value**	**Est. [95% CI]**	**p-value**
Age	**0.045 [0.024, 0.067]**	**< 0.0001**	**0.048 [0.021, 0.074]**	**0.0004**	**0.053 [0.032, 0.074]**	**< 0.0001**
Gender (male v female)	**0.37 [−0.07, 0.80]**	**0.1**	**0.50 [0.07, 0.93]**	**0.02**	**0.51 [0.10, 0.92]**	**0.01**
Montreal B criteria^ (vs. B1)						
Stricturing (B2)	**0.17 [−0.32, 0.65]**	**0.49**	**0.48 [−0.05, 1.00]**	**0.07**	**0.55 [0.05, 1.10]**	**0.03**
Fistulising (B3)	−0.073 [−0.71, 0.56]	0.82	0.16 [−0.51, 0.82]	0.64	0.23 [−0.39, 0.85]	0.46
Montreal L criteria^ (vs. L1)						
Colonic (L3)	−0.24 [−0.81, 0.32]	0.39	−0.19 [−0.75, 0.37]	0.49		
Ileo-colonic (L2)	−0.15 [−0.7, 0.39]	0.58	0.03 [−0.51, 0.58]	0.91		
IBD disease duration	0.0022 [−0.0000079, 0.0043]	0.05	0.0006 [−0.0024, 0.0036]	0.69		
Biologic therapy	−0.38 [−0.81, 0.055]	0.08	−0.33 [−0.77, 0.11]	0.14	−0.31 [−0.72, 0.1]	0.14
Immunomodulator therapy	0.22 [−0.23, 0.67]	0.33	0.34 [−0.10, 0.78]	0.12	0.26 [−0.15, 0.68]	0.20
Cumulative duration of oral corticosteroid use (months)	0.003 [−0.002, 0.007]	0.22	0.002 [−0.002, 0.006]	0.30		

	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	**p-value**	**Est. [95% CI]**	**p-value**	**Est. [95% CI]**	**p-value**
Prior abdominal surgery (baseline)	**−0.15 [−0.60, 0.29]**	**0.50**	**−0.67 [−1.2, −0.15]**	**0.01**	**−0.58 [−1.1, −0.10]**	**0.02**
Faecal calprotectin (µg/g)	−0.0002 [−0.001, 0.0006]	0.55	−0.0002 [−0.001, 0.0007]	0.68		
C-reactive protein (mg/L)	−0.005 [−0.016, 0.006]	0.38	−0.001 [−0.012, 0.01]	0.87		
Alcohol intake (> 20 g/day)~	0.68 [−0.42, 1.8]	0.22	0.10 [−0.98, 1.2]	0.85		
Habitual exercise (IPAQ)”	−0.02 [−0.05, 0.02]	0.42	−0.03 [−0.07, 0.01]	0.11	−0.025 [−0.06, 0.011]	0.17

***Table legend**: VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; ~ Defined according to Australian Healthy Drinking guidelines; International Physical Activity Questionnaire for assessment of habitual physical activity (per 1000). ^ Crohn’s disease phenotype defined according Montreal classification. Statistical analysis using linear mixed effects model multivariable analysis.*

Supplementary Table 7.4: Associations with serial faecal calprotectin measurements in Crohn's disease over 24-months

Covariates	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	p-value	Est. [95% CI]	p-value	Est. [95% CI]	p-value
Age	−0.020 [−0.046, 0.006]	0.13	−0.001 [−0.034, 0.032]	0.95		
Gender (male v female)	0.17 [−0.31, 0.65]	0.48	0.14 [−0.45, 0.73]	0.63		
Montreal B criteria^ (vs. B1)						
Stricturing (B2)	−0.49 [−1.0, 0.03]	0.06	−0.11 [−0.74, 0.52]	0.73	−0.17 [−0.75, 0.41]	0.55
Fistulising (B3)	−0.59 [−1.3, 0.08]	0.08	−0.16 [−0.90, 0.58]	0.67	−0.25 [−0.94, 0.43]	0.46
Montreal L criteria^ (vs. L1)						
Colonic (L3)	0.51 [−0.09, 1.1]	0.09	0.28 [−0.35, 0.92]	0.38	0.27 [−0.31, 0.85]	0.35
Ileo-colonic (L2)	0.36 [−0.21, 0.94]	0.21	0.46 [−0.14, 1.1]	0.13	0.43 [−0.11, 0.97]	0.11
IBD disease duration	−0.0015 [−0.0041, 0.0010]	0.23	0.0002 [−0.0034, 0.0037]	0.91		
Immunomodulator therapy.	0.11 [−0.38, 0.61]	0.65	0.11 [−0.40, 0.62]	0.66		
Cumulative duration of oral corticosteroid use (months).	−0.0035 [−0.0077, 0.0007]	0.10	−0.0019 [−0.0068, 0.0029]	0.43		
Biologic therapy	−0.21 [−0.70, 0.27]	0.37	−0.11 [−0.61, 0.38]	0.65		
Prior abdominal surgery (baseline)	−0.63 [−1.1, −0.16]	0.01	−0.52 [−1.1, 0.11]	0.10	−0.49 [−1.0, 0.04]	0.07
Visceral adipose tissue (VAT)						
VAT: SAT (log)	−0.04 [−0.28, 0.21]	0.76	−0.11 [−0.73, 0.51]	0.72	−0.07 [−0.57, 0.43]	0.77
VHI (log)	**−0.21 [−0.42, 0.01]**	**0.05**	**−0.37 [−0.90, 0.16]**	**0.16**	**−0.38 [−0.68,**	**0.01**

Covariates	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	p-value	Est. [95% CI]	p-value	Est. [95% CI]	p-value
					−0.09]	
VAT vs. Montreal (L1)^						
VAT:SAT (log):Colonic			0.11 [−0.51, 0.74]	0.72	0.16 [−0.42, 0.74]	0.59
VAT:SAT (log):Ileo-colonic			**0.81 [0.21, 1.4]**	**0.01**	**0.83 [0.27, 1.4]**	**0.004**
Body mass index (BMI)	−0.045 [−0.086, −0.004]	0.03	0.003 [−0.066, 0.071]	0.94		
Alcohol intake (> 20 g/day)~	0.33 [−0.81, 1.5]	0.56	0.03 [−1.2, 1.2]	0.96		

***Table legend**: VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; ^ Crohn's disease phenotype defined according Montreal classification at study enrolment. Statistical analysis using linear mixed effects model multivariable analysis; ~ Defined according to Australian Healthy Drinking guidelines.*

Supplementary Table 7.5: Associations with serial C-reactive protein measurements over 24-months in Crohn's disease

	Unadjusted		Multiple adjusted	
	Est. [95% CI]	**p-value**	**Est. [95% CI]**	**p-value**
Age	−0.008 [−0.041, 0.025]	0.65	−0.001 [−0.043, 0.042]	0.98
Gender (male v female)	−0.59 [−1.2, −0.004]	0.05	−0.29 [−1.0, 0.45]	0.44
Montreal B criteria^ (vs. B1)				
Stricturing (B2)	0.15 [−0.52, 0.81]	0.66	0.46 [−0.35, 1.3]	0.26
Fistulising (B3)	−0.05 [−0.91, 0.80]	0.90	0.10 [−0.85, 1.1]	0.83
Montreal L criteria^ (vs. L1)				
Colonic (L3)	0.31 [−0.45, 1.1]	0.42	0.15 [−0.69, 1.0]	0.72
Ileo-colonic (L2)	0.41 [−0.32, 1.1]	0.27	0.28 [−0.51, 1.1]	0.48
IBD disease duration	−0.001 [−0.004, 0.002]	0.62	0.0004 [−0.0042, 0.0051]	0.85
Immunomodulator therapy.	−0.06 [−0.68, 0.55]	0.84	0.04 [−0.63, 0.71]	0.91
Cumulative duration of oral corticosteroid use (months).	−0.0023 [−0.0076, 0.0030]	0.38	−0.0031 [−0.0094, 0.0032]	0.33
Biologic therapy	0.38 [−0.21, 0.98]	0.20	0.38 [−0.27, 1.0]	0.24
Prior abdominal surgery (baseline)	−0.4 [−1.0, 0.2]	0.18	−0.6 [−1.4, 0.2]	0.14
Visceral adipose tissue (VAT)				
VAT: SAT (log)	−0.18 [−0.45, 0.09]	0.18	0.01 [−0.53, 0.56]	0.97
VHI (log)	−0.04 [−0.28, 0.20]	0.77	−0.22 [−0.80, 0.37]	0.46
Body mass index (BMI)	0.03 [−0.02, 0.08]	0.18	0.06[−0.02, 0.14]	0.15
Alcohol intake (> 20 g/day)~	0.02 [−1.5, 1.5]	0.97	0.1 [−1.5, 1.7]	0.92

Table legend: *VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; ^ Crohn's disease phenotype defined according Montreal classification. ~ Defined according to Australian Healthy Drinking guidelines.*

Supplementary Table 7.6: Mutivariable Cox regression analysis of time to IBD-related hospitalisation and surgery over 4 years of follow-up.

Time to hospitalisation					
Variable	**VHI – Multiple adjusted**			**VAT:SAT – Multiple adjusted**	
	Est. [95% CI]	**p-value**		**Est. [95% CI]**	**p-value**
VHI	−0.0011 [−0.0026, 0.0004]	0.13	VAT:SAT	−0.27 [−0.94, 0.40]	0.42
Stricturing	0.46 [−0.25, 1.2]	0.19	Stricturing	0.42 [−0.28, 1.1]	0.23
Fistulising	0.81 [−0.04, 1.7]	0.06	Fistulising	0.70 [−0.15, 1.5]	0.10
Colonic	−0.11 [−1.0, 0.78]	0.81	Colonic	−0.13 [−1.0, 0.76]	0.78
Ileo-colonic	0.43 [−0.32, 1.2]	0.25	Ileo-colonic	0.45 [−0.28, 1.2]	0.22
Time to surgery					
	VHI – Multiple adjusted			**VAT:SAT – Multiple adjusted**	
	Est. [95% CI]	**p-value**		**Est. [95% CI]**	**p-value**
VHI	−0.0011 [−0.0034, 0.0012]	0.33	VAT:SAT	−0.27 [−1.2, 0.65]	0.55
Stricturing	**1.4 [0.05, 2.7]**	**0.04**	**Stricturing**	**1.4 [0.057, 2.7]**	**0.04**
Fistulising	1.3 [−0.2, 2.9]	0.08	Fistulising	1.3 [−0.2, 2.9]	0.09
Colonic	−1.0 [−2.7, 0.7]	0.25	Colonic	−0.8 [−2.5, 0.9]	0.34
Ileo-colonic	0.45 [−0.64, 1.5]	0.41	Ileo-colonic	0.58 [−0.52, 1.7]	0.29

***Table legend**: VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue (VAT:SAT ratio); VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; Crohn's disease phenotype defined according Montreal classification at study enrolment. Statistical analysis using linear mixed effects model multivariable analysis.*

Supplementary Table 7.7: Associations with serial measurements of quality of life over 24-months in Crohn's disease

	Unadjusted		**Multiple adjusted**		**Reduced model**	
	Est. [95% CI]	**p-value**	**Est. [95% CI]**	**p-value**	**Est. [95% CI]**	**p-value**
Age	−0.05 [−0.30, 0.20]	0.70	0.10 [−0.24, 0.44]	0.56		
Gender (male v female)	**3.5 [−0.86, 7.9]**	**0.11**	**6.8 [1.2, 12]**	**0.02**	**5.8 [0.7, 11]**	**0.03**
Montreal B criteria^ (vs. B1)						
Stricturing (B2)	−0.8 [−5.7, 4.1]	0.75	2.4 [−3.7, 8.4]	0.43		
Fistulising (B3)	1.0 [−5.5, 7.4]	0.77	1.7 [−5.4, 8.8]	0.63		
Montreal L criteria^ (vs. L1)						
Colonic (L3)	2.0 [−3.7, 7.7]	0.48	1.7 [−4.6, 8.0]	0.59	2.1 [−3.6, 7.8]	0.46
Ileo-colonic (L2)	2.5 [−2.9, 8.0]	0.35	2.1 [−3.9, 8.0]	0.49	2.6 [−2.7, 7.9]	0.33
IBD disease duration	0.013 [−0.011, 0.037]	0.27	0.028 [−0.007, 0.062]	0.11		
Immunomodulator therapy.	−0.9 [−5.4, 3.7]	0.70	1.1 [−3.8, 6.1]	0.65		
Cumulative duration of oral corticosteroid use (months).	0.004 [−0.035, 0.043]	0.83	−0.007 [−0.054, 0.040]	0.77		
Biologic therapy	−0.5 [−4.9, 4.0]	0.83	−0.7 [−5.6, 4.2]	0.77		
Prior abdominal surgery (baseline)	−1.7 [−6.2, 2.8]	0.45	−6.1 [−12, 0.05]	0.05	−2.2 [−6.7, 2.3]	0.33
Visceral adipose tissue (VAT)						
VAT: SAT (log)	−1.0 [−3.0, 1.0]	0.30	−4.5 [−9.5, 0.5]	0.08	−4.5 [−9.1, 0.09]	0.05
VHI (log)	−1.2 [−3.1, 0.6]	0.17	−1.2 [−5.6, 3.2]	0.58	−0.3 [−3.0, 2.5]	0.83
VAT vs. Montreal (L1)						
VAT:SAT (log):Colonic			**6.2 [0.9, 12]**	**0.02**	**6.0 [0.8, 11]**	**0.02**
VAT:SAT (log):Ileo-colonic			1.2 [−4.0, 6.3]	0.64	1.8 [−3.1, 6.8]	0.46

	Unadjusted		Multiple adjusted		Reduced model	
	Est. [95% CI]	**p-value**	**Est. [95% CI]**	**p-value**	**Est. [95% CI]**	**p-value**
Body mass index (BMI)	−0.12 [−0.49, 0.25]	0.52	0.09 [−0.51, 0.68]	0.78		
Alcohol intake (> 20 g/day)~	1.4 [−9.4, 12]	0.80	−1.8 [−13, 10]	0.76		

***Table legend**: VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VHI, visceral adipose tissue volume (cm^3)/height (m^2) index; ~ Defined according to Australian Healthy Drinking guidelines; ^ Crohn's disease phenotype defined according Montreal classification.*

REFERENCES

1. Crohn BB, Ginzburg L, Oppenheimer GD. Landmark article Oct 15, 1932. Regional ileitis. A pathological and clinical entity. By Burril B. Crohn, Leon Ginzburg, and Gordon D. Oppenheimer. Jama. 1984 Jan 06;251(1):73-9.
2. Sheehan AL, Warren BF, Gear MW*, et al.* Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. The British journal of surgery. 1992 Sep;79(9):955-8.
3. Desreumaux P, Ernst O, Geboes K*, et al.* Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. Gastroenterology. 1999 Jul;117(1):73-81.
4. Schaffler A, Herfarth H. Creeping fat in Crohn's disease: travelling in a creeper lane of research? Gut. 2005 Jun;54(6):742-4.
5. Fink C, Karagiannides I, Bakirtzi K*, et al.* Adipose tissue and inflammatory bowel disease pathogenesis. Inflammatory bowel diseases. 2012 Aug;18(8):1550-7.
6. Shuster A, Patlas M, Pinthus JH*, et al.* The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. The British journal of radiology. 2012 Jan;85(1009):1-10.
7. Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. Biochimica et biophysica acta. 2000 Jan 03;1500(1):88-96.
8. Ding Z, Wu XR, Remer EM*, et al.* Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. Colorectal disease. 2016 Feb;18(2):163-72.
9. Connelly TM, Juza RM, Sangster W*, et al.* Volumetric fat ratio and not body mass index is predictive of ileocolectomy outcomes in Crohn's disease patients. Digestive surgery. 2014;31(3):219-24.
10. Erhayiem B, Dhingsa R, Hawkey CJ*, et al.* Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. Clinical gastroenterology and hepatology. 2011 Aug;9(8):684-7.
11. Holt DQ, Moore GT, Strauss BJ*, et al.* Visceral adiposity predicts post-operative Crohn's disease recurrence. Alimentary pharmacology & therapeutics. 2017 May;45(9):1255-64.

12. Van Der Sloot KW, Joshi AD, Bellavance DR*, et al.* Visceral Adiposity, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. Inflammatory bowel diseases. 2017 Jan;23(1):82-8.
13. Buning C, von Kraft C, Hermsdorf M*, et al.* Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. Inflammatory bowel diseases. 2015 Nov;21(11):2590-7.
14. Liu G, Wu X, Li Y*, et al.* Postoperative excessive gain in visceral adipose tissue as well as body mass index are associated with adverse outcomes of an ileal pouch. Gastroenterology report. 2016 (epub ahead of print).
15. Satsangi J, Silverberg MS, Vermeire S*, et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749-53.
16. Ainsworth BE, Macera CA, Jones DA*, et al.* Comparison of the 2001 BRFSS and the IPAQ Physical Activity Questionnaires. Medicine and science in sports and exercise. 2006 Sep;38(9):1584-92.
17. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. The American journal of gastroenterology. 1996 Aug;91(8):1571-8.
18. Hans DB, Shepherd JA, Schwartz EN*, et al.* Peripheral dual-energy X-ray absorptiometry in the management of osteoporosis: the 2007 ISCD Official Positions. Journal of clinical densitometry. 2008 Jan-Mar;11(1):188-206.
19. Direk K, Cecelja M, Astle W*, et al.* The relationship between DXA-based and anthropometric measures of visceral fat and morbidity in women. BMC cardiovascular disorders. 2013 Apr 03;13:25.
20. Kaul S, Rothney MP, Peters DM*, et al.* Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring, Md). 2012 Jun;20(6):1313-8.
21. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series. 2000;894:i-xii, 1-253.
22. Colombel JF, Solem CA, Sandborn WJ*, et al.* Quantitative measurement and visual assessment of ileal Crohn's disease activity by computed tomography enterography: correlation with endoscopic severity and C reactive protein. Gut. 2006 Nov;55(11):1561-7.

23. Peyrin-Biroulet L, Gonzalez F, Dubuquoy L*, et al.* Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. Gut. 2012 Jan;61(1):78-85.
24. Singh S, Dulai PS, Zarrinpar A*, et al.* Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nature reviews Gastroenterology & hepatology. 2017 Feb;14(2):110-21.
25. Kaess BM, Pedley A, Massaro JM*, et al.* The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. Diabetologia. 2012 Oct;55(10):2622-30.
26. Gecse KB, Brandse JF, van Wilpe S*, et al.* Impact of disease location on fecal calprotectin levels in Crohn's disease. Scandinavian journal of gastroenterology. 2015 Jul;50(7):841-7.
27. Mosli MH, Zou G, Garg SK*, et al.* C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. The American journal of gastroenterology. 2015 Jun;110(6):802-19.
28. Irvine EJ. Quality of life issues in patients with inflammatory bowel disease. The American journal of gastroenterology. 1997 Dec;92(12 Suppl):18s-24s.
29. Rothney MP, Catapano AL, Xia J*, et al.* Abdominal visceral fat measurement using dual-energy X-ray: association with cardiometabolic risk factors. Obesity (Silver Spring, Md). 2013 Sep;21(9):1798-802.
30. Coffey JC, O'Leary DP, Kiernan MG*, et al.* The mesentery in Crohn's disease: friend or foe? Current opinion in gastroenterology. 2016 Jul;32(4):267-73.

CHAPTER 8: DISCUSSION

The body of research presented in this thesis explores treatment targets and body composition in IBD; disparate but important aspects of quality care for people with IBD (***Figure 8.1***).

Treatment directed at objective inflammation is the cornerstone of modern IBD management. However, implementation of a 'treat to target' approach in IBD in routine practice is challenged by the complexity of current disease activity indices, lack of clarity as to optimal treatment targets, proof that it benefits patients and clinician uptake of this approach.

Abnormal body composition is common in patients with IBD, including sarcopenia, metabolic bone disease, and obesity. Body composition may influence morbidity and outcomes in patients with IBD; VAT was shown to be associated with disease behaviour, activity and quality of life in CD.

The work performed in this thesis illustrates that management of IBD requires a multifaceted approach, addressing both disease activity and its corollaries, so as to improve quality of care in IBD.

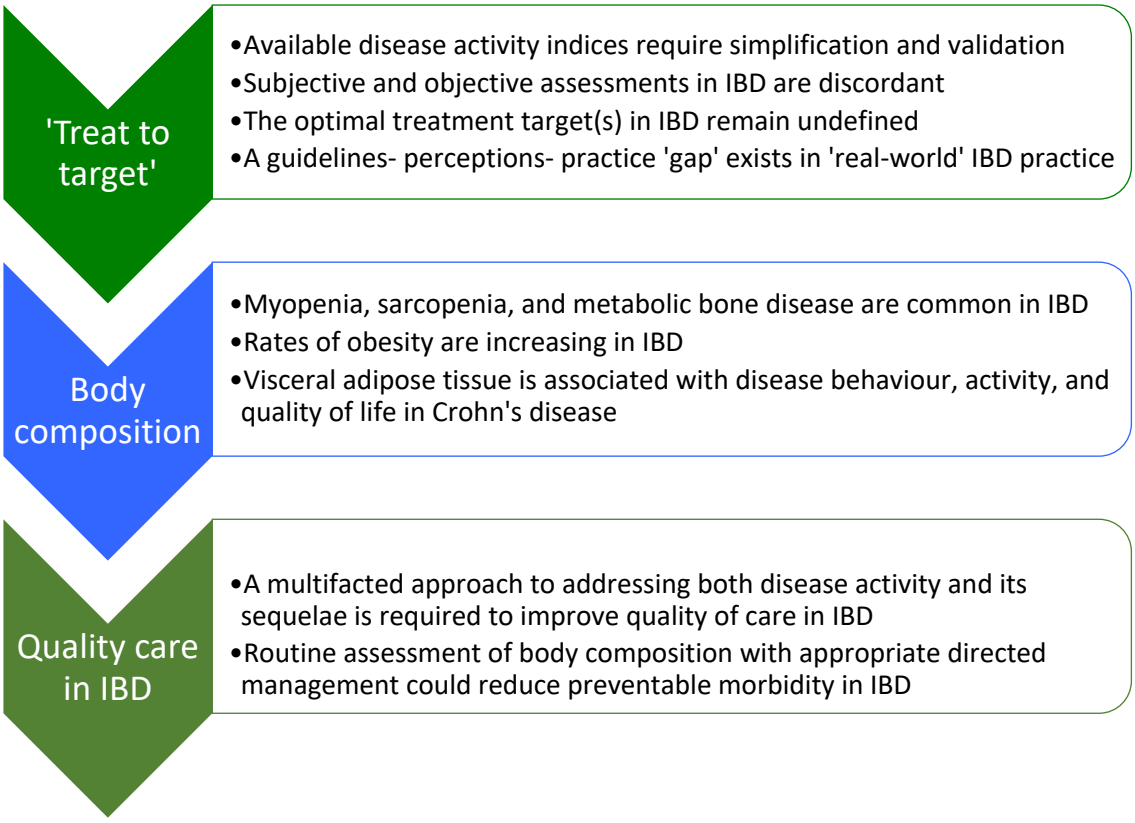


Figure 8.1 Key outcomes of thesis

Key outcomes, significance and limitations

Conventional treatment targets in IBD

A 'treat to target' approach in IBD advocates striving beyond resolution of symptoms toward objective resolution of disease activity. Regular objective assessment of inflammation is therefore required to inform treatment decisions, with the aim of therapy a composite endpoint of *both* clinical and endoscopic remission. Although the guiding principles are sound, work performed in this thesis has identified issues that need to be addressed to allow translation of a 'treat to target' approach into routine IBD care.

a. Current disease activity indices in IBD are complex and inadequate. Indices for disease activity assessment in IBD are important metrics of care in that they provide a standardised approach and 'common language' amongst clinicians for therapeutic decision-making. However, IBD is a heterogeneous disease entity and there are multiple domains of disease activity assessment. Systematic review performed as a part of this thesis illustrates that within each domain there are a vast array of indices, most of which are unvalidated, complex, and better suited to research than clinical practice. Few current indices are developed using appropriate predictive modelling.[1] Further confusing the matter, many indices incorporate both subjective and objective domains, confounding formal assessment of each. As a consequence, there are no 'gold-standard(s)' of disease activity assessment in IBD.

b. Disease activity measures in IBD are distinct and discordant. It is becoming increasingly recognised that subjective and objective measures of disease in IBD are disparate; however, there has been limited evaluation of concordance between indices. Systematic appraisal performed as a part of this thesis revealed modest concordance between clinical, endoscopic, and histological indices overall. The greatest disparity was observed between clinical and objective assessment, which is consistent with Truelove's early observations and a conceptual challenge to clinicians trained to treat symptoms alone.[2] This is hardly surprising given that symptoms in patients with IBD are not only a result of inflammation; concurrent irritable bowel syndrome affects more than 40% of patients, not to mention the effects of medications, prior surgery, and infection.[3, 4]

A significant finding was the distinction between endoscopic mucosal healing and histological healing in UC. Microscopic inflammation was observed to persist in 25% of patients with endoscopic mucosal healing, highlighting that inflammatory cell infiltration is

not seen using conventional endoscopy.[5-7] This finding is consistent with prior studies, although the large range (16–90%) reflects different indices and definitions of remission for endoscopy and histopathology.[8-15]

Limitations of the study performed in this thesis included the use of unvalidated indices to measure endoscopic and histological inflammation, along with the small sample size studied. Simple indices were selected for practicality (Baron score for endoscopy and Truelove and Richards's index for histology), since selection predated the development of validated indices (such as the UCEIS or Nancy Index).

c. Histological remission imparts prognostic benefit beyond endoscopic remission in UC. The STRIDE guidelines propose that endoscopic remission is the optimal target for objective resolution of inflammation in IBD.[16] However, given the observed disparity between endoscopic and histological remission, work performed in this thesis evaluated the prognostic benefit of histological remission as a marker of 'complete remission' in UC.[11, 17]

Over an extended follow-up period, histological remission, but not endoscopic mucosal healing, predicted lower rates of steroid usage and lower rates of acute severe UC requiring hospitalisation. The long duration of follow-up and prospective design of this study represent a substantial contribution to existing literature showing that persistent histological inflammation is associated with an increased risk of relapse, hospitalisation, and colectomy, as well as an increased risk of colorectal neoplasia in patients with UC.[9, 10, 14, 18-23]

The study was limited by its use of an unvalidated histopathology index (Truelove and Richards' index), which does not provide a summative scale, nor take into account features such as basal plasmacytosis shown to predict patient outcomes.[2, 10, 24]

d. Uptake of 'treat to target' in clinical practice is modest. Guidelines are impotent and do not affect patient outcomes if they are cannot be integrated into clinical practice. In a multicentre 'real-world' study of patients with UC, only one-third of patients attained both clinical *and* endoscopic remission, and an even smaller proportion the 'optimal' target of Mayo 0 endoscopic remission (17%). IBD-related factors did not predict the attainment of the composite remission endpoint, but rather therapeutic factors and the hospital at which IBD care was delivered. The most common barrier to implementation of a 'treatment to target' strategy were clinician-dependent practice behaviours; in particular, failure to assess for

endoscopic remission. Rather, clinicians relied upon CRP to evaluate disease activity in UC, despite the modest correlation between CRP and endoscopy outside of acute severe UC.[25-27]

Clinician perceptions were a prevailing factor behind the observed discord between guidelines and clinical practice. Survey data capturing most Gastroenterologists in South Australia revealed that only two-thirds of clinicians were familiar with the concept of 'treat to target'. Familiarity was associated with perceived relevance and only two-thirds of clinicians felt that a 'treat to target' approach was relevant to their current practice. Estimates of care outcomes were also overly optimistic, with broad disparity between clinician reporting of targets achieved and their own 'real-world' outcomes.

Body composition in IBD: an un-promoted area of care

With clinician focus on ameliorating inflammation in IBD, comorbid factors are often overlooked. The work performed in this thesis illustrates that abnormal body composition is common in patients with IBD, associated with morbidity, and represents an un-promoted area of quality care.

a. Myopenia and sarcopenia are common in IBD. Low lean muscle mass (myopenia) and sarcopenia were found to be prevalent in patients with IBD (21% and 12% respectively). Moreover, lean muscle declined over time, despite gains in BMI and adiposity. FC was negatively associated with lean mass, consistent with catabolic effects of chronic inflammation.[28-30] The aetiology of 'accelerated' sarcopenia in patients with IBD is postulated to be multifactorial, contributed to by malnutrition, malabsorption, a pro-inflammatory cytokine milieu (NF-κβ, tumour necrosis factor, and interleukin-6), immobility, and surgery.[31-33] Sarcopenia may thus be a surrogate marker for poorly controlled IBD. There is evidence to suggest an association between myopenia and higher rates of surgery, fatigue and poor QoL, and primary non-response to biologic therapy in IBD.[28, 29, 34-37] Sarcopenia was also demonstrated to be the strongest predictor of metabolic bone disease in patients with IBD.

The methodological quality of the studies performed advances current understanding of sarcopenia in IBD. Measurement of functional muscle, appendicular skeletal muscle, was performed using DXA, which is considered an accurate tool for assessment.[38-40] The correct definition of sarcopenia was used, with normative data derived from age- and sex-matched population-based controls, alongside analysis of lifestyle and IBD-related factors.[38, 41]

Relatively small patient numbers limited power for analysis of sarcopenia and IBD-related outcomes such as surgery and hospitalisation. No correlation between sarcopenia and reduced QoL was evident, which is in contrast to previous studies and may also reflect a lack of power to detect an association.[36, 37]

b. High rates of metabolic bone disease in patients with IBD. More than one-third of patients met criteria for osteopenia or osteoporosis, which is in keeping with existing literature.[42-47] Despite protocolised management of bone health over 24 months, rates of osteopenia and osteoporosis remained unchanged (43% overall at 24 months). These data raise concerns as to the high burden of metabolic bone disease and associated morbidity likely to affect an aging IBD cohort.

Habitual physical activity was found to positively correlate with BMD over time, which informs the rationale for an 'exercise prescription' for patients with IBD. On the other hand, neither IBD-related factors nor serum vitamin D were found to correlate with BMD. Previous studies have also shown minimal impact of IBD phenotype or disease activity on bone loss, and there is conflicting data as to longitudinal benefit of vitamin D and calcium supplementation on BMD in IBD.[43, 46, 48-50]

The study was limited by lack of assessment of adherence to vitamin D supplementation and lack of data on bone fractures. There are conflicting studies of the risk of pathological fractures in patients with IBD, and further data are required to substantiate the risk.[45, 51, 52]

c. Emerging obesity in patients with IBD. Work in this thesis exposed a rising prevalence of obesity in patients with IBD over time; 62% of patients with IBD were overweight or obese after 2 years of follow-up, which was numerically higher than the age- and gender-matched Australian population.[53] Prior cross-sectional studies report that 15–40% of adult patients with IBD are obese and 20–40% are overweight according to BMI criteria, however direct measures of adiposity have been previously lacking.[54-59] This study showed that observed gains in BMI are driven by significant gains in both fat mass and VAT.

The study findings prompt speculation of a link between IBD and obesity. Such a link could not be explained by IBD-related clinical factors, which were not associated with gains in adiposity over time. Rather, dysbiosis of the gut microbiome could be a common factor between IBD and obesity.[60-63] An individual's gut microbiome has been shown to predict postprandial blood glucose and risk of metabolic disease.[64] Faecal transplantation from lean

donors to individuals with metabolic syndrome significantly increased their insulin sensitivity.[65] Therefore, in patients with IBD, dysbiosis and altered gut microbial metabolism could conceivably contribute to development of obesity, through hormonal signalling, satiety-related peptides, and bile acids.[60-62, 66, 67]

d. VAT is associated with disease behaviour in CD. VAT was shown to associate with a stricturing CD phenotype as well as FC and QoL in a disease distribution-dependent manner. These data support the hypothesis that VAT has a pathogenic role in CD. The association is plausible given that VAT is a potent source of pro-inflammatory adipokines and is likely to play a role in innate immunity.[68-71] In contrast, obesity, as measured using BMI, did not show any association with CD phenotype, which is in keeping with existing literature.[54-56, 72] This data serves to highlight the different metabolic profiles between VAT and SAT compartments.[73, 74]

Although the association between VAT and CD phenotype is enticing, existing data do not yet support VAT as a useful biomarker in practice. VAT was also independently associated with gender, advanced age, and prior surgery. The lack of published VAT 'cut-offs' limits clinical interpretation of VAT measurements. Beyond established disease phenotype, there was no observed association between VAT and hospitalisation or surgery over follow-up. This may have reflected a lack of power to detect an association, as prior studies, albeit limited by retrospective or post-hoc design as well as a lack of analysis of confounding variables, have shown an association between VAT and CD outcomes.[68, 69, 75-77]

e. Clinical assessment of body composition in IBD: BMI alone is not enough. BMI is a poor surrogate measure of body composition in patients with IBD, correlating more closely with fat mass than lean mass. Grip strength testing on the other hand, was shown to positively correlate with lean mass and BMD, whilst negatively correlating with fat mass, making it a useful discriminatory test in patients with IBD.

Serum vitamin D levels were shown to be another useful discriminatory test for body composition in patients with IBD. Serum vitamin D levels negatively correlated with fat mass, yet positively with lean muscle mass. Prior studies have shown serum vitamin D to be associated with muscle function at a molecular level in patients with IBD.[37]

Implications for clinical practice

The body of research presented in this thesis illustrates that both treatment targets and body composition are important aspects of quality of care in IBD. Based on current data and the body of research presented in this thesis, recommendations for clinical practice are presented below and summarised in ***Figure 8.2***.

1. Treatment decisions should incorporate both symptoms and objective measures of inflammation. The discordance between symptoms and inflammation identified in this thesis is relevant to IBD clinical practice, informing the rationale for seeking objective measures of inflammation to guide treatment decisions.[16] A 'treat to target' strategy is accepted practice within other chronic inflammatory diseases such as rheumatoid arthritis and has led to improved outcomes for patients.[78, 79] Traditional management of IBD directed toward symptoms alone may be misguided and deleterious, given that many factors aside from inflammation can contribute to symptoms in IBD. That said, although inflammation is important to clinicians, it is symptoms and QoL that matter to patients, and clinicians should also address symptoms arising from concurrent factors such as IBS.[80] Non-invasive biomarkers are useful alternatives to endoscopy to guide therapy in IBD. FC correlates with endoscopic inflammation, response to therapy, and risk of relapse in IBD.[81-85] Gastrointestinal ultrasound (GIUS) has also been shown to correlate closely with endoscopy and cross-sectional imaging.[86, 87]

2. Incorporate disease activity indices into routine care. Disease activity indices provide a standardised approach to assessment of IBD in routine care. Many Gastroenterologists do not document disease activity, let alone use an index to assist with clinical decision-making. This may relate in part to confusion due to the multiplicity and complexity of current indices in IBD.

Systematic review identified several indices useful for clinical practice: Ulcerative Colitis Endoscopic Index of Severity (UCEIS), The Nancy Index for Histopathology, and the IBD-Control questionnaire for QoL.[88-91] PROM's also represent a simple tool to measure clinical symptoms from the patient perspective.[92-94] Given that the FDA advocates for use of PROM's as clinical trial endpoints, they are useful for both trials and practice.[92, 94] Beyond disease activity, patient outcomes should be measured in practice, which is now achievable using a standard set of patient-centred outcomes for IBD defined by ICHOM.[93]

3. Histology is a useful and sensitive measure of inflammation in UC. Data from this thesis add substance to the value of mucosal biopsy and histological assessment in UC. Although further research is required to establish histological healing as a treatment target in IBD, assessment of histology can assist in clinical decision-making. Persistent microscopic inflammation would imply that UC maintenance therapy should not be decreased or stopped.[11]

4. Undertake regular audit of IBD practice and outcomes. Audit of practice should be routinely implemented, both for individual clinicians as well as services caring for patients with IBD. Work performed in this thesis illustrated a 'gap' between guidelines, perceptions, and practice. Clinicians were prone to over-estimation of targets of remission achieved in practice, and used objective measures of inflammation to guide management decisions less often than reported. Audit of practice is therefore key to understanding practice behaviours and outcomes. The Crohn's Colitis Australia IBD Audit was a national example of this process, and provided key insights into the disparity in organisation and provision of IBD care within Australia.[95]

5. Incorporate grip strength testing into routine IBD practice. Clinicians measuring BMI alone will be falsely reassured as to the nutritional status of IBD patients. Beyond BMI, grip strength was shown to be a useful discriminatory test, positively correlating with muscle mass and negatively with fat mass. Grip strength testing is cheap, quick, and feasible within the clinic setting.

6. Incorporate whole body DXA into routine practice. DXA scanning is routine to evaluate BMD in patients with IBD.[43] Whole body DXA adds little to the time taken or radiation exposure of a BMD scan, yet is accurate in identifying sarcopenia and fat distribution profiles (VAT and SAT).[96, 97] The high rates of aberrant body composition in patients with IBD identified in this thesis support the clinical utility of whole body DXA in routine IBD practice.

7. 'Manage the manageable': obesity, metabolic bone disease and exercise in IBD. Although easily overlooked in the clinical setting, obesity, metabolic bone disease, and lack of habitual exercise are important factors contributing to future risk of morbidity, particularly as patients with IBD age.

IBD clinicians are trained to screen for malnutrition, however to date there has been little recognition of burgeoning rates of obesity within the IBD cohort. Identification of obesity coupled with proactive management of the long-term cardio-metabolic implications should be part of quality care in IBD.

Osteopenia and osteoporosis are highly prevalent in patients with IBD. Identification and management of metabolic bone disease is imperative to reduce the risk of pathological fracture and associated morbidity in patients with IBD. This will become more imperative as patients with IBD age. Routine BMD DXA is therefore an important part of quality care in IBD and is supported by professional groups.[43, 98]

The importance of regular exercise for bone health was illustrated in this thesis. Beyond BMD, prior studies have described an association between regular exercise and QoL, clinical disease activity, and fatigue in patients with IBD.[99-101] Although habitual exercise is frequently overlooked in the busy clinic setting, these data expound the benefits of a regular exercise 'prescription' for patients with IBD.

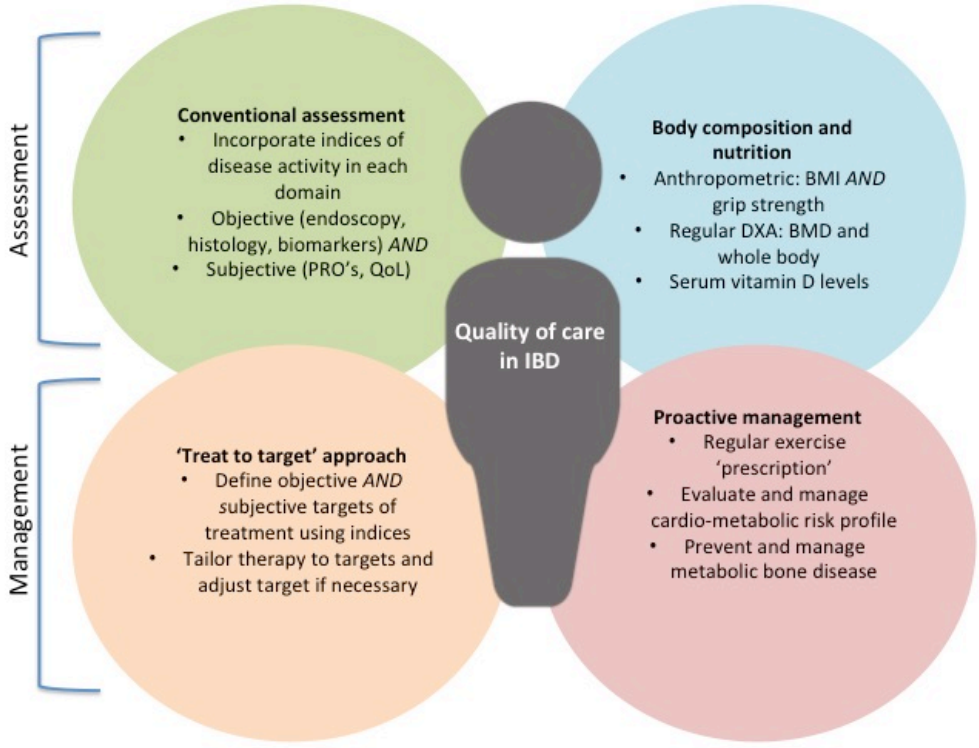


Figure 8.2 Clinical implications of thesis: improving quality of care in IBD

Future research directions

Based on the work performed in this thesis, future research directions to improve quality of care for patients with IBD are presented below.

1. Validate and simplify indices for disease activity assessment in IBD. For application in practice, an index of disease activity must be validated, so that the metrics of responsiveness, reproducibility, reliability, and inter-observer variability are understood. The index also needs to be simple enough to apply within the constraints of practice (***Figure 8.3***).

There is a need for international collaborative efforts to develop and validate simple disease activity indices for use in clinical trials and practice. Domains of disease activity assessment in IBD are distinct; patient-centred domains (symptoms and QoL) are not synonymous with objective measures of inflammation and should be viewed separately. Development of validated indices of disease activity in each domain of assessment should be prioritised above development of 'composite' indices, which are appealing as a unifying tool for practice, but are limited by confounding factors.

2. Define the optimal treatment target in IBD. Although histology is recognised as a sensitive measure of inflammation, current guidelines do not advocate striving for histological healing in UC.[16] A sceptical view is that histological healing is akin to 'backing a winner', and is a marker of good prognosis rather than an actual target of therapy. There is a quantum leap between observational associations and sequential escalation of therapy until 'complete' histological remission is achieved. Any treatment strategy aiming for histological healing needs to account for risks of therapy, patient desires, and healthcare costs.[11] The same can also be said for endoscopic mucosal healing in IBD, where evidence is lacking for sequential escalation until the target is reached. Randomised trials using validated metrics are required to evaluate whether such 'treat to target' strategies modify the course of disease in IBD. The feasibility of 'treat to target' in 'real-world' clinical practice needs to be examined thereafter, taking into account healthcare resource utilisation and patient preferences. Until such time, the 'optimal' treatment target in IBD remains elusive.

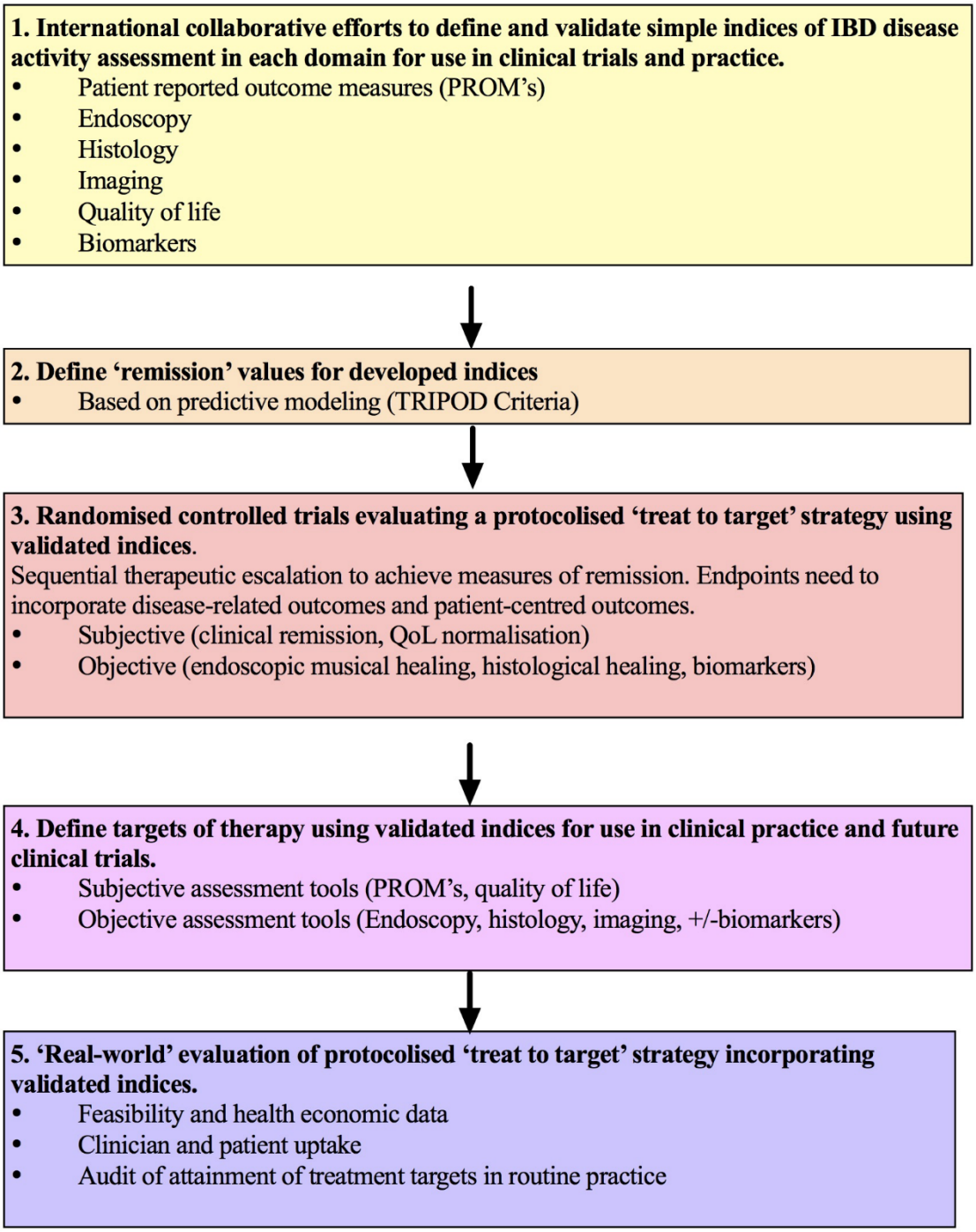


Figure 8.3 Future research to define a 'treat to target' approach in IBD

3. Sarcopenia in IBD: impact and management. Further data are required to understand the impact of sarcopenia on IBD-related outcomes, including response to therapy and surgical morbidity. This will require prospective capture of both disease-related and lifestyle factors (including diet) in large IBD cohorts, preferably from inception. Moreover, the challenge remains to define management strategies for sarcopenia and to assess whether addressing lean muscle deficits can improve outcomes for patients with IBD.

4. Prevention and management of metabolic bone disease in IBD. Further studies are required to better understand how best to prevent and manage metabolic bone disease in patients with IBD. The role of habitual exercise needs to be evaluated in large prospective studies. The role of vitamin D and calcium supplementation in IBD also needs to be better defined, incorporating assessment of patient adherence to supplementation. The influence of IBD-related factors on bone health needs to be better studied to inform appropriate screening guidelines for the IBD cohort.[43]

5. Aetiology and cardio-metabolic impact of obesity in IBD. Observed gains in adiposity and VAT raise concerns as to cardio-metabolic risk profiles in patients with IBD. VAT is more metabolically active than SAT and imparts independent risk for incipient cardiovascular disease, even after adjustment for BMI and clinical factors.[102-104] Patients with IBD are at increased risk of ischaemic heart disease, cerebrovascular disease and thromboembolic disease.[105-107] Further studies are required to elucidate mechanisms of obesity and cardio-metabolic risk in patients with IBD, incorporating analysis of the microbiome, metabolome, and adipocytokine production. Data are also needed to determine whether proactive strategies can modulate cardio-metabolic risk in patients with IBD.

6. The role of VAT as a biomarker in CD. Further research is required to determine the influence of VAT on outcomes in CD and whether it can be used as a biomarker in clinical practice. This will require large, prospective studies of well-phenotyped CD cohorts, optimally with evaluation of VAT metrics from diagnosis. The challenge remains to determine whether interventions to reduce VAT can modify disease course in CD.

Conclusion

Treatment targets and body composition are different aspects of the same challenge: to improve quality of care for patients with IBD.

Therapy directed at objective inflammation has the potential to improve outcomes for patients with IBD. However, most current indices of disease activity assessment in IBD are complex and unvalidated and the optimal target of treatment remains unclear. Attainment of treatment targets in real-world practice is modest and there exists a guidelines-perceptions-practice ‘gap’ amongst clinicians.

Abnormal body composition is common in patients with IBD, including sarcopenia, metabolic bone disease, obesity, and increased VAT. Conventional assessment of IBD disease activity fails to capture abnormal body composition, identification and management of which has the propensity to improve quality of care delivery for patients with IBD.

The work performed in this thesis has identified opportunities for improving quality of care for patients with IBD via:

a) Development of simple and validated indices of disease activity for routine clinical assessment in IBD.

b) Integration of both subjective and objective indices of assessment into routine practice to inform clinical decision-making.

c) Definition of the optimal treatment target(s) in IBD that is feasible and safe for clinical practice.

d) Routine assessment of body composition in clinical practice using grip strength assessment as well as whole body DXA.

e) Proactive management of lean muscle mass deficits, metabolic bone disease, obesity and cardio-metabolic risk in patients with IBD, which may be aided by a regular exercise ‘prescription’.

f) Further research into the role of VAT in the pathogenesis of CD and whether VAT is a useful biomarker in clinical practice.

REFERENCES

1. Collins GS, Reitsma JB, Altman DG*, et al.* Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD Statement. The British journal of surgery. 2015 Feb;102(3):148-58.
2. Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. British medical journal. 1956 Jun 9;1(4979):1315-8.
3. Bryant RV, van Langenberg DR, Holtmann GJ*, et al.* Functional gastrointestinal disorders in inflammatory bowel disease: impact on quality of life and psychological status. Journal of gastroenterology and hepatology. 2011 May;26(5):916-23.
4. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. The American journal of gastroenterology. 2012 Oct;107(10):1474-82.
5. Kiesslich R, Fritsch J, Holtmann M*, et al.* Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003 Apr;124(4):880-8.
6. Tontini GE, Vecchi M, Neurath MF*, et al.* Review article: newer optical and digital chromoendoscopy techniques vs. dye-based chromoendoscopy for diagnosis and surveillance in inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Nov;38(10):1198-208.
7. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012 Nov;61(11):1619-35.
8. Baars JE, Nuij VJ, Oldenburg B*, et al.* Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflammatory bowel diseases. 2012 Sep;18(9):1634-40.
9. Bessissow T, Lemmens B, Ferrante M*, et al.* Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. The American journal of gastroenterology. 2012 Nov;107(11):1684-92.
10. Bitton A, Peppercorn MA, Antonioli DA*, et al.* Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001 Jan;120(1):13-20.
11. Bryant RV, Winer S, Travis SP*, et al.* Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's & colitis. 2014 Dec 1;8(12):1582-97.

12. Gomes P, du Boulay C, Smith CL*, et al.* Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986 Jan;27(1):92-5.
13. Lemmens B, Arijs I, Van Assche G*, et al.* Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. Inflammatory bowel diseases. 2013 May;19(6):1194-201.
14. Riley SA, Mani V, Goodman MJ*, et al.* Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991 Feb;32(2):174-8.
15. Rosenberg L, Nanda KS, Zenlea T*, et al.* Histologic markers of inflammation in patients with ulcerative colitis in clinical remission. Clinical gastroenterology and hepatology. 2013 Aug;11(8):991-6.
16. Peyrin-Biroulet L, Sandborn W, Sands BE*, et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Sep;110(9):1324-38.
17. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic Remission: The Ultimate Therapeutic Goal in Ulcerative Colitis? Clinical gastroenterology and hepatology. 2014;12(6):929-34.
18. Azad S, Sood N, Sood A. Biological and histological parameters as predictors of relapse in ulcerative colitis: a prospective study. Saudi journal of gastroenterology. 2011 May-Jun;17(3):194-8.
19. Gupta RB, Harpaz N, Itzkowitz S*, et al.* Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007 Oct;133(4):1099-105.
20. Hefti MM, Chessin DB, Harpaz NH*, et al.* Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Diseases of the colon and rectum. 2009 Feb;52(2):193-7.
21. Rubin DT HD, Hetzel JT et al Increased degree of histological inflammation predicts colectomy and hospitalisation in patients with ulcerative colitis. Gut. 2007;132 (Suppl. 1):A-19 (Abstract 103).
22. Rutter M, Saunders B, Wilkinson K*, et al.* Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004 Feb;126(2):451-9.
23. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. The American journal of digestive diseases. 1966 Nov;11(11):847-57.

24. Geboes K, Riddell R, Ost A*, et al.* A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000 Sep;47(3):404-9.
25. Travis SP, Farrant JM, Ricketts C*, et al.* Predicting outcome in severe ulcerative colitis. Gut. 1996 Jun;38(6):905-10.
26. Yoon JY, Park SJ, Hong SP*, et al.* Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. Digestive diseases and sciences. 2014 Apr;59(4):829-37.
27. Peyrin-Biroulet L, Sandborn W, Sands BE*, et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Aug 25;110(9):1324-38.
28. Adams DW, Gurwara S, Silver HJ*, et al.* Sarcopenia Is Common in Overweight Patients with Inflammatory Bowel Disease and May Predict Need for Surgery. Inflammatory bowel diseases. 2017 Jul;23(7):1182-6.
29. Bamba S, Sasaki M, Takaoka A*, et al.* Sarcopenia is a predictive factor for intestinal resection in admitted patients with Crohn's disease. PloS one. 2017;12(6):e0180036.
30. Subramaniam K, Fallon K, Ruut T*, et al.* Infliximab reverses inflammatory muscle wasting (sarcopenia) in Crohn's disease. Aliment Pharmacol Ther. 2015 Mar;41(5):419-28.
31. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. Journal of human nutrition and dietetics. 2011 Aug;24(4):313-26.
32. Sousa Guerreiro C, Cravo M, Costa AR*, et al.* A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. Am J Gastroenterol. 2007;102(11):2551-6.
33. Valentini L, Schulzke JD. Mundane, yet challenging: the assessment of malnutrition in inflammatory bowel disease. European journal of internal medicine. 2011 Feb; 22(1): 13-5.
34. Ding NS, Malietzis G, Lung PFC*, et al.* The body composition profile is associated with response to anti-TNF therapy in Crohn's disease and may offer an alternative dosing paradigm. Alimentary pharmacology & therapeutics. 2017 Nov;46(9):883-91.
35. Holt DQ, Varma P, Strauss BJG*, et al.* Low muscle mass at initiation of anti-TNF therapy for inflammatory bowel disease is associated with early treatment failure: a retrospective analysis. European journal of clinical nutrition. 2017 Jun;71(6):773-7.

36. van Langenberg DR, Della Gatta P, Warmington SA*, et al.* Objectively measured muscle fatigue in Crohn's disease: Correlation with self-reported fatigue and associated factors for clinical application. Journal of Crohn's & colitis. 2014; 8(2):137-46.
37. van Langenberg DR, Gatta PD, Hill B*, et al.* Delving into disability in Crohn's disease: Dysregulation of molecular pathways may explain skeletal muscle loss in Crohn's disease. Journal of Crohn's & colitis. 2014; 8(7):626-34.
38. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. PloS one. 2009;4(9):e7038.
39. Kim J, Wang Z, Heymsfield SB*, et al.* Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr. 2002;76(2):378-83.
40. Schneider SM, Al-Jaouni R, Filippi J*, et al.* Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008;14(11):1562-8.
41. Cruz-Jentoft AJ, Baeyens JP, Bauer JM*, et al.* Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010 Jul;39(4):412-23.
42. Siffledeen JS, Fedorak RN, Siminoski K*, et al.* Bones and Crohn's: risk factors associated with low bone mineral density in patients with Crohn's disease. Inflammatory bowel diseases. 2004 May;10(3):220-8.
43. Harbord M, Annese V, Vavricka SR*, et al.* The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2016 Mar;10(3):239-54.
44. Goodhand JR, Kamperidis N, Nguyen H*, et al.* Application of the WHO fracture risk assessment tool (FRAX) to predict need for DEXA scanning and treatment in patients with inflammatory bowel disease at risk of osteoporosis. Aliment Pharmacol Ther. 2011 Mar;33(5):551-8.
45. Targownik LE, Bernstein CN, Nugent Z*, et al.* Inflammatory bowel disease and the risk of fracture after controlling for FRAX. J Bone Miner Res. 2013 May;28(5):1007-13.
46. Targownik LE, Bernstein CN, Nugent Z*, et al.* Inflammatory bowel disease has a small effect on bone mineral density and risk for osteoporosis. Clinical gastroenterology and hepatology. 2013 Mar;11(3):278-85.

47. Wada Y, Hisamatsu T, Naganuma M, *et al.* Risk factors for decreased bone mineral density in inflammatory bowel disease: A cross-sectional study. Clinical nutrition (Edinburgh, Scotland). 2015 Dec;34(6):1202-9.
48. Casals-Seoane F, Chaparro M, Mate J, *et al.* Clinical Course of Bone Metabolism Disorders in Patients with Inflammatory Bowel Disease: A 5-Year Prospective Study. Inflammatory bowel diseases. 2016 Aug;22(8):1929-36.
49. Krajcovicova A, Hlavaty T, Killinger Z, *et al.* Combination therapy with an immunomodulator and anti-TNFalpha agent improves bone mineral density in IBD patients. Journal of Crohn's & colitis. 2014 Dec;8(12):1693-701.
50. Targownik LE, Leslie WD, Carr R, *et al.* Longitudinal change in bone mineral density in a population-based cohort of patients with inflammatory bowel disease. Calcified tissue international. 2012 Nov;91(5):356-63.
51. Bernstein CN. Osteoporosis in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2006;4(2):152-6.
52. Bernstein CN, Blanchard JF, Leslie W, *et al.* The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Annals of internal medicine. 2000 Nov 21;133(10):795-9.
53. National Health Survey: First Results, 2014-2015 [database on the Internet]2015 [cited 10/01/2018]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by Subject/4364.0.55.001~2014-15~Main Features~Overweight and obesity~22
54. Flores A, Burstein E, Cipher DJ, *et al.* Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. Digestive diseases and sciences. 2015 Aug;60(8):2436-45.
55. Pringle PL, Stewart KO, Peloquin JM, *et al.* Body Mass Index, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. Inflammatory bowel diseases. 2015 Oct;21(10):2304-10.
56. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, *et al.* Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. Inflammatory bowel diseases. 2015 Dec;21(12):2857-63.
57. Nic Suibhne T, Raftery TC, McMahon O, *et al.* High prevalence of overweight and obesity in adults with Crohn's disease: Associations with disease and lifestyle factors. Journal of Crohn's & colitis. 2013; 7(7):e241-8.

58. Mendall MA, Gunasekera AV, John BJ*, et al.* Is obesity a risk factor for Crohn's disease? Digestive diseases and sciences. 2011 Mar;56(3):837-44.
59. Stabroth-Akil D, Leifeld L, Pfutzer R*, et al.* The effect of body weight on the severity and clinical course of ulcerative colitis. International journal of colorectal disease. 2015 Feb;30(2):237-42.
60. Pedersen HK, Gudmundsdottir V, Nielsen HB*, et al.* Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016 Jul 21;535(7612):376-81.
61. Qin J, Li Y, Cai Z*, et al.* A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012 Oct 4;490(7418):55-60.
62. Le Chatelier E, Nielsen T, Qin J*, et al.* Richness of human gut microbiome correlates with metabolic markers. Nature. 2013 Aug 29;500(7464):541-6.
63. Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. Gut. 2013 Oct;62(10):1505-10.
64. Zeevi D, Korem T, Zmora N*, et al.* Personalized Nutrition by Prediction of Glycemic Responses. Cell. 2015 Nov 19;163(5):1079-94.
65. Vrieze A, Van Nood E, Holleman F*, et al.* Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012 Oct;143(4):913-16.
66. Karmiris K, Koutroubakis IE, Xidakis C*, et al.* Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflammatory bowel diseases. 2006 Feb;12(2):100-5.
67. Singh S, Dulai PS, Zarrinpar A*, et al.* Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nature reviews Gastroenterology & hepatology. 2017 Feb;14(2):110-21.
68. Buning C, von Kraft C, Hermsdorf M*, et al.* Visceral Adipose Tissue in Patients with Crohn's Disease Correlates with Disease Activity, Inflammatory Markers, and Outcome. Inflammatory bowel diseases. 2015 Nov;21(11):2590-7.
69. Erhayiem B, Dhingsa R, Hawkey CJ*, et al.* Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. Clinical gastroenterology and hepatology. 2011 Aug;9(8):684-7.
70. Van Der Sloot KW, Joshi AD, Bellavance DR*, et al.* Visceral Adiposity, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. Inflammatory bowel diseases. 2017 Jan;23(1):82-8.

71. Fink C, Karagiannides I, Bakirtzi K*, et al.* Adipose tissue and inflammatory bowel disease pathogenesis. Inflammatory bowel diseases. 2012 Aug;18(8):1550-7.
72. Hass DJ, Brensinger CM, Lewis JD*, et al.* The impact of increased body mass index on the clinical course of Crohn's disease. Clinical gastroenterology and hepatology. 2006 Apr;4(4):482-8.
73. Kaess BM, Pedley A, Massaro JM*, et al.* The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. Diabetologia. 2012 Oct;55(10):2622-30.
74. Fontana L, Eagon JC, Trujillo ME*, et al.* Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes. 2007 Apr;56(4):1010-3.
75. Connelly TM, Juza RM, Sangster W*, et al.* Volumetric fat ratio and not body mass index is predictive of ileocolectomy outcomes in Crohn's disease patients. Digestive surgery. 2014;31(3):219-24.
76. Ding Z, Wu XR, Remer EM*, et al.* Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. Colorectal disease. 2016 Feb;18(2):163-72.
77. Holt DQ, Moore GT, Strauss BJ*, et al.* Visceral adiposity predicts post-operative Crohn's disease recurrence. Alimentary pharmacology & therapeutics. 2017 May;45(9):1255-64.
78. Smolen JS, Aletaha D, Bijlsma JW*, et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the rheumatic diseases. 2010 Apr;69(4):631-7.
79. Vermeer M, Kuper HH, Bernelot Moens HJ*, et al.* Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. Arthritis research & therapy. 2012 Nov 23;14(6):R254.
80. Burgell R, Asthana A, Gibson PR. Irritable bowel syndrome in patients with quiescent inflammatory bowel disease. A review. Minerva gastroenterologica e dietologica. 2015; 61(4):201-213.
81. De Vos M, Louis EJ, Jahnsen J*, et al.* Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. Inflammatory bowel diseases. 2013 Sep;19(10):2111-7.
82. Gisbert JP, Bermejo F, Perez-Calle JL*, et al.* Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflammatory bowel diseases. 2009 Aug;15(8):1190-8.

83. Molander P, af Bjorkesten CG, Mustonen H*, et al.* Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFalpha blocking agents. Inflammatory bowel diseases. 2012 Nov;18(11):2011-7.
84. Theede K, Holck S, Ibsen P*, et al.* Level of Fecal Calprotectin Correlates With Endoscopic and Histologic Inflammation and Identifies Patients With Mucosal Healing in Ulcerative Colitis. Clinical gastroenterology and hepatology. 2015 Nov;13(11):1929-36.e1.
85. Yamamoto T, Shiraki M, Bamba T*, et al.* Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy. International journal of colorectal disease. 2014 Apr;29(4):485-91.
86. Bryant RV, Friedman A, Wright EK*, et al.* Gastrointestinal ultrasound in inflammatory bowel disease: an underused resource with potential paradigm-changing application. Gut. 2018; 67(5):973-985.
87. Kucharzik T, Wittig BM, Helwig U*, et al.* Use of Intestinal Ultrasound to Monitor Crohn's Disease Activity. Clinical gastroenterology and hepatology. 2017 Apr;15(4):535-42.e2.
88. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C*, et al.* Development and validation of the Nancy histological index for UC. Gut. 2017; 66(1):43-49.
89. Travis SP, Schnell D, Krzeski P*, et al.* Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012 Apr;61(4):535-42.
90. Travis SP, Schnell D, Krzeski P*, et al.* Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013 Nov;145(5):987-95.
91. Bodger K, Ormerod C, Shackcloth D*, et al.* Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. Gut. 2014 Jul;63(7):1092-102.
92. Jairath V, Khanna R, Zou GY*, et al.* Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. Alimentary pharmacology & therapeutics. 2015 Nov;42(10):1200-10.
93. Kim AH, Roberts C, Feagan BG*, et al.* Developing a Standard Set of Patient-Centred Outcomes for Inflammatory Bowel Disease - an International, Cross-disciplinary Consensus. Journal of Crohn's & colitis. 2017; 12(4):408-418.

94. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. Clinical gastroenterology and hepatology. 2014 Aug;12(8):1246-56 e6.
95. Australia CsaC. Crohn's and Colitis Australia IBD Audit Report. 2017 [cited 2018 12.4.2018]. Available from: https://www.crohnsandcolitis.com.au/ibdqoc/ibd-audit-report/
96. Bryant RV, Trott MJ, Bartholomeusz FD, *et al.* Systematic review: body composition in adults with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Aug;38(3):213-25.
97. Schule S, Rossel JB, Frey D, *et al.* Widely differing screening and treatment practice for osteoporosis in patients with inflammatory bowel diseases in the Swiss IBD cohort study. Medicine. 2017 Jun;96(22):e6788.
98. Nguyen GC, Devlin SM, Afif W, *et al.* Defining quality indicators for best-practice management of inflammatory bowel disease in Canada. Canadian journal of gastroenterology & hepatology. 2014 May;28(5):275-85.
99. Loudon CP, Corroll V, Butcher J, *et al.* The effects of physical exercise on patients with Crohn's disease. Am J Gastroenterol. 1999 Mar;94(3):697-703.
100. Ng V, Millard W, Lebrun C, *et al.* Low-intensity exercise improves quality of life in patients with Crohn's disease. Clinical journal of sport medicine. 2007 Sep;17(5):384-8.
101. van Langenberg DR, Della Gatta P, Warmington SA, *et al.* Objectively measured muscle fatigue in Crohn's disease: correlation with self-reported fatigue and associated factors for clinical application. Journal of Crohn's & colitis. 2014 Feb;8(2):137-46.
102. Flegal KM, Kit BK, Orpana H, *et al.* Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Jama. 2013 Jan 02;309(1):71-82.
103. Britton KA, Massaro JM, Murabito JM, *et al.* Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. Journal of the American College of Cardiology. 2013 Sep 3;62(10):921-5.
104. Preis SR, Massaro JM, Robins SJ, *et al.* Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study. Obesity (Silver Spring, Md). 2010 Nov;18(11):2191-8.

105. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clinical gastroenterology and hepatology. 2008 Jan;6(1):41-5.
106. Hansen PR. Chronic inflammatory diseases and atherosclerotic cardiovascular disease: Innocent bystanders or partners in crime? Current pharmaceutical design. 2018; 24(3):281-290.
107. Singh S, Singh H, Loftus EV, Jr.*, et al.* Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clinical gastroenterology and hepatology. 2014 Mar;12(3):382-93.

APPENDIX: CONVENTIONAL DISEASE ACTIVITY ASSESSMENT IN IBD

Background

There are multiple domains of disease activity assessment in IBD, each of which has its merits and none of which is perfect. IBD disease activity can be measured using clinical, endoscopic, histological, or radiological assessment tools, as well as biomarkers and QoL. To further complicate matters, within each domain, there are multiple indices, many of which are confounded by lack of validation, confusing terminology, and composite use of symptoms with objective measures of inflammation.

Nonetheless, indices of disease activity assessment in IBD are important metrics in quality care, in that they are repeatable and responsive to change. Use of disease activity indices in routine IBD practice better allows interpretation of therapeutic efficacy, in keeping with a 'treat to target' approach.

This systematic review set out to evaluate all available measures of disease activity in both UC and CD. A subjective appraisal of the best indices for use in clinical practice is provided, based on index validation, responsiveness and experience in clinical trials, international specialist opinion, and practicality and suitability for use in clinical practice.

Presented in this chapter is the manuscript published in Nature Reviews Gastroenterology and Hepatology 2016; 42 (12): 567-79.

Specific author contributions

Title of Paper	Current best practice for disease activity assessment in IBD
Publication Status	Published
Publication Details	Nature Reviews Gastroenterology and Hepatology. 2016; 42 (12): 567-79. Impact factor: 13.7

APPENDIX 1

Name of Principal Author (Candidate)	Robert Venning Bryant		
Contribution to the Paper	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Overall percentage (%)	45% *(Joint first author)		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	12/02/2018

Name of Co-Author	Alissa Walsh		
Contribution to the Paper 45% *	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	11/02/2018

Name of Co-Author	Simon PL Travis (Corresponding author)		
Contribution to the Paper 10%	Conception and design of the project Data acquisition and management Analysis and interpretation of research data Drafting and revision of article		
Signature		Date	10/02/2018

[Manuscript 6] Current best practice for disease activity assessment in IBD

Robert V. Bryant*[2,3], Alissa J. Walsh*[1] and Simon P. L. Travis[1]

*Joint first authors

[1]Translational Gastroenterology Unit, Experimental Medicine Division, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, United Kingdom

[2]Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, 5000, Australia

[3]School of Medicine, University of Adelaide, Adelaide, South Australia, 5005, Australia.

Correspondence to AJW

alissa.walsh@linacre.ox.ac.uk

Acknowledgements

None

Grant support and writing assistance

No funding was received for the study. No writing assistance was received for this study. RB received research support from the Royal Adelaide Hospital Research Foundation through the AR Clarkson Scholarship.

Conflicts of interest and personal interests

There are no conflicts of interest to declare for any of the co-authors.

AJW has served as an advisory board member for AbbVie, Ferring, Janssen-Cilag, Hospira and Takeda. She has received honoraria for speaking from AbbVie, Ferring, Janssen-Cilag and Shire, and has received grants for support of research from AbbVie, Ferring, Janssen-Cilag and Shire.

RVB has received conference attendance support from Ferring, Janssen, and Takeda, and honoraria for speaking from Shire, Janssen-Cilag, and AbbVie.

SPLT has received grants for research support from AbbVie, Lilly, Norman Collison Foundation, UCB and Vifor. He has received consulting and/or speaker fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cosmo, Ferring, Giuliani SpA, GlaxoSmithKline, Lilly, MSD, Neovacs, Novartis, Norman Collison Foundation, Novo Nordisk, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, TopiVert, UCB, VHsquared, Vifor, and Warner Chilcott.

Abstract

Therapeutic advances in the management of IBD have led to a paradigm shift in the assessment of IBD disease activity. Beyond clinical remission, objective assessment of inflammation is now critical to guiding subsequent therapy as part of a 'treat to target' strategy. Multiple domains of disease activity assessment in IBD exist, each of which has its merits, although none are perfect. The aim of this review is to comprehensively evaluate measures of disease activity in both ulcerative colitis and Crohn's disease, including clinical, endoscopic, histological and radiological assessment tools, as well as the use of biomarkers and quality of life (QoL) evaluation. A subjective appraisal of the best indices for use in clinical practice is provided, based on index validation, responsiveness and experience in clinical trials, international specialist opinion, and practicality and suitability for use in clinical practice. The aim of this review is to enable the reader to gain confidence in IBD disease activity assessment and to give ready access to the necessary tools.

Summary

- Objective assessment of disease activity assessment in IBD is important to guiding subsequent therapy as a part of a 'treat to target' strategy.
- There are multiple domains of disease activity assessment in IBD, within each remission targets should be recognised by clinicians and healthcare providers as goals for therapy.

The following disease assessment indices are recommended for ulcerative colitis:

1. Clinical Activity Assessment: Simple Colitis Clinical Activity Index (SCCAI), Partial Mayo Clinic Index, Paediatric Ulcerative Colitis Activity Index (PUCAI). For acute severe ulcerative colitis use the Truelove and Witts' Index.
2. Endoscopic Assessment: Mayo clinic index: endoscopic subscore and Ulcerative Colitis Endoscopic Index of Severity (UCEIS).
3. Histologic Assessment: Nancy Histological Index and Robarts Histopathology Index.
4. Radiologic Assessment: MRI assessment is preferred using either magnetic resonance colonography simplified index (MRC-S) or segmental magnetic resonance score (MR-score-S), ultrasound assessment using the Bowel Ultrasound Severity index. Avoid CT scan if possible due to radiation risk. For acute severe colitis, plain abdominal X-ray is recommended.

5. Biomarker assessment: C-reactive protein and faecal calprotectin.
6. Quality of Life Assessment: IBD-Control, Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and Crohn's Ulcerative Colitis Questionnaire-8 (CUCQ-8).

The following disease assessment indices are recommended for Crohn's disease:

1. Clinical activity assessment: Crohn's Disease Activity Index (CDAI), Harvey-Bradshaw Index (HBI). For perianal disease use the Perianal Crohn's Disease Activity index (PDAI).
2. Endoscopic assessment: Simple Endoscopic Score for Crohn's Disease (SES-CD) or detailed documentation of the presence or absence of ulcers. For surveillance following ileocolic resection, use the Rutgeerts' Post-operative Index.
3. Histologic assessment: currently no index of choice. Any histologic activity should caution against de-escalation of therapy.
4. Radiologic assessment: Magnetic Resonance Index of Severity (MaRIA), Limberg scoring system for bowel ultrasound. For perianal Crohn' s disease, use the MRI-based Score for Severity of Perianal Crohn's Disease.
5. Biomarker assessment: C-reactive protein and faecal calprotectin.
6. Quality of Life Assessment: IBD-Control, Short Inflammatory Bowel Disease Questionnaire (SIBDQ) or Crohn's Ulcerative Colitis Questionnaire-8 (CUCQ-8)

Introduction

Management of IBD is guided by the anatomical distribution of disease, symptom severity, response to medical therapy and the ability of the patient to accept and tolerate treatment.[1, 2] Disease severity indices help to guide clinical decisions and are particularly helpful for patients who fail to show adequate response to therapy as they clearly show (in a numerical manner) that they have not met the desired target (Table A1, A2). Advances such as increased availability and use of biologic agents for the treatment of IBD have led to a paradigm shift in the assessment of disease activity and we are now better able to achieve remission targets. Beyond clinical remission, ongoing treatment strategies require guidance from objective assessment of disease activity. IBD disease activity comprises multiple domains that can be assessed; each of these domains has its merits, although none are perfect.

The aim of this review is to evaluate measures of disease activity assessment in both ulcerative colitis and Crohn's disease. Formal evaluation of disease activity in IBD is associated with many challenges, including confusing terminology, different names or abbreviations for the same index, and the tendency to use composite indices that combine symptom assessment with objective measures of inflammation or quality of life (QoL).

To make this summary clinically useful, we have divided the paper into sections on ulcerative colitis and Crohn's disease, and in each we will discuss clinical, endoscopic, histological and radiological assessment, as well as biomarkers and QoL. A subjective evaluation of the best disease activity indices for use in clinical practice is provided. Remission thresholds for disease activity indices are also provided when possible. The indices were selected after several considerations: extent of validation, responsiveness and experience in clinical trials, international expert opinion,[3] active comparison between all indices in clinical practice,[4] and ease of use in clinical practice. Although to some extent the choice of indices was that of the authors, the selection is informed by our extensive involvement in index development, evaluation, formal guideline development, clinical trials and clinical practice.[3-9] This review aims to give the reader ready access to appropriate assessment tools, and enable the reader to gain confidence in IBD disease activity assessment. A comprehensive list of relevant disease activity indices is provided as a supplementary table for both ulcerative colitis and Crohn's disease (see Supplementary information S1 (Tables 1 and 2, respectively)). A good case can be made (and one that we advocate) for separating the components of disease activity assessment, using distinct and independently validated symptom, endoscopic, histological,

quality of life and clinical indices. We recognise that this may as yet represent a minority view, but we believe it will gain ground, particularly as quality of life becomes an important outcome measure for care.

Ulcerative colitis

Clinical assessment of disease activity.

There are 17 ulcerative colitis indices that evaluate symptoms, eight of which do so independently of endoscopic scoring or biochemical markers (see Supplementary information S1 (table 1) online). For assessment of mild to moderate ulcerative colitis, we recommend the Simple Colitis Clinical Activity Index (SCCAI),[10] Partial Mayo Clinic Index[11, 12] and the Paediatric Ulcerative Colitis Activity Index (PUCAI).[13] For severe disease, we recommend Truelove and Witts' criteria.[14]

The SCCAI (see Supplementary information S1 (table 3) online) is one of the 8 indices that excludes endoscopic assessment and biochemical markers. Importantly, it includes nocturnal bowel movements and urgency of defecation.[10] These symptoms are of vital importance to patients due to their effect on QoL, but are neglected by other indices. Scores in this index range from 0–19 points. The SCCAI has been compared prospectively with the multiple other ulcerative colitis indices and, along with the PUCAI, performed best of all non-invasive indices for validity, reliability, responsiveness (ability to measure the change in disease activity) and feasibility. It was sufficiently able to discriminate remission from active disease.[15] As the SCCAI does not include a Physician's Global Assessment (the opinion of the treating physician as to how severe they feel that the patient's symptoms are), it can readily be completed by patients. The remission target is a SCCAI total score of < 1.[3]

The Partial Mayo Clinic Index (see Supplementary information S1 (table 4)) is currently the most widely used index in trial design.[11][12] The full Mayo Clinic Index (Partial Mayo Clinic Index plus endoscopic subscore) has become the standard for assessing disease activity in adult clinical trials where endoscopic assessment is mandated by the Food and Drug Administration in the United States.[16] Rectal bleeding and frequency of bowel motions are the only two symptoms assessed. Although readily criticised because it is an unvalidated derivation of an unvalidated index, when the Partial Mayo Index was compared with other non-invasive indices, it performed well for discriminating remission from active disease, and showed responsiveness and good construct validity.[15] A Global Physician assessment is

necessary for the Partial Mayo Index and therefore makes it less feasible. The remission target is a Partial Mayo total score of ≤1.[3]

The PUCAI (see Supplementary information S1 (table 5)) was devised by paediatric Gastroenterologists as a non-invasive instrument to assess disease activity in children; repeated endoscopy in this setting is less tolerable to both patients and parents.[13] This index comprises 6 descriptors, each with different levels, creating a total score ranging from 0–85: abdominal pain, degree of rectal bleeding, average stool consistency, number of stools in 24 h, presence of nocturnal stools and patient activity level are assessed. The PUCAI was rigorously developed and validated in children,[13] and has also been shown to be valid, reliable and responsive in adults.[15] This index permits less frequent endoscopic assessment for all patients with ulcerative colitis both in clinical practice and clinical trials [15] The remission target is a PUCAI total score of < 10.[3]

For severe disease assessment and management, we encourage the use of the Truelove and Witts' criteria (see Supplementary information S1 (table 6)).[14] This index provides objective criteria to identify acute severe colitis, and has been widely used to define the need for hospital admission and intravenous steroids.[17] The criteria for acute severe colitis are ≥6 stools per day, with frequent blood in the stool, with at least one of the following features: body temperature > 37.8°C; heart rate > 90 bpm, hemoglobin levels < 10.5 g/dl and erythrocyte sedimentation rate > 30 mm/h. Patients with more of these criteria present at admission have a greater chance of needing a colectomy on that admission.[18]

Endoscopic assessment of disease activity

Mucosal healing is the remission target when assessing IBD disease activity endoscopically. Simply stated, mucosal healing should imply the absence of ulceration and erosions. Nevertheless, there is currently no validated definition of mucosal healing in IBD.[16, 19, 20]

Mucosal healing should be recognised as the ultimate therapeutic goal for ulcerative colitis, as the disease is limited to the mucosa.[19] As we are now striving to achieve mucosal healing, endoscopic assessment of patients with ulcerative colitis is increasingly used in clinical practice to guide treatment decision-making. Mucosal healing in ulcerative colitis has been associated with decreased need for corticosteroids,[21] decreased hospitalisation rates,[22-24]

sustained clinical remission,[25] decreased colectomy[21, 22, 24, 25] and decreased risk of colorectal cancer.[26]

Many different endoscopic indices for ulcerative colitis have been used in clinical trials (see Supplementary information S1 (table 1)). This review focuses on the endoscopic indices that we, the authors, feel are best used in clinical practice: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[8, 9] and Mayo Clinic endoscopy subscore.[11]

The UCEIS is the only validated endoscopic index in ulcerative colitis (see Supplementary information S1 (table 7)),[8, 9] and was developed because of wide inter-observer variation in endoscopic assessment of disease activity when using previously published endoscopic indices.[4] The UCEIS is simple to use in clinical practice as all it requires is the endoscopist to grade vascular pattern, bleeding and erosions/ulceration that then allows a total score of 0–8 to be calculated. Use of the UCEIS has been shown to reduce inter-observer variation.[8][27] The UCEIS is being used in clinical trials of ulcerative colitis currently in progress, which will define its responsiveness.[28] We encourage its use in clinical practice so that there is a uniform language for describing disease activity. The remission target is a UCEIS total score of ≤1.[3]

The Mayo Clinic endoscopy subscore has not been formally validated; however, it has been the standard for assessing disease activity in adult clinical trials where endoscopic assessment is mandated by the Food and Drug Administration in the United States.[16] The subscore has four components, each with a maximum score of 3 (see Supplementary information S1 (table 8)).[2] Overlap in the features of the different levels contributes to inter-observer variation. The value of using the Mayo Clinic Score in clinical practice simply reflects familiarity amongst practitioners. The remission target is a Mayo Clinic endoscopy subscore of ≤1, because this has been used as the outcome measure in clinical trials, has been associated with a lower colectomy rate during follow-up and recommended by a group of international specialists.[3]

Histological assessment of disease activity

Substantial disparity exists between histological and endoscopic disease activity assessment in ulcerative colitis.[5] Microscopic inflammation can persist despite the appearance of endoscopically healed colonic mucosa, representing a harbinger of residual active disease.[29, 30] Accordingly, observational studies have shown that persistent histological inflammation in ulcerative colitis is associated with an increased risk of clinical relapse, hospitalisation,

colectomy and colorectal neoplasia.[30-33] Histological remission is not yet recommended as a target of treatment in either clinical trials or practice;[3] however, the FDA are considering documentation of patient histological disease activity at trial inclusion and as an outcome measure in clinical trials.[5] Histological healing represents 'complete' remission in UC, and given its association with improved patient outcomes and reduced disease-related complications, is likely to be a future therapeutic target in clinical practice.[5]

There are 26 histological activity indices in ulcerative colitis, only 2 of which are validated (see Supplementary information S1 (table 1)).[6, 34] As a consequence, no gold-standard exists for assessing histological disease activity, nor for defining histological remission, in patients with ulcerative colitis. The operating characteristics of any histological scoring system in ulcerative colitis depend on the number, quality and distribution of colonic biopsy samples taken, as well as the histological features incorporated.[5, 35, 36] Histological features with the highest intra-observer and inter-observer agreement are erosion or ulceration, and the presence and density of lamina propria neutrophil infiltrate.[36, 37] Basal plasmacytosis has been associated with increased risk of ulcerative colitis relapse,[30] but concordance between reporting histopathologists of reporting is poor.[36, 37]

Until 2015, the Riley Score (see Supplementary information S1 (table 9)),[38] and the Geboes Score (see Supplementary information S1 (table 10)) were the most useful histological indices in patients with ulcerative colitis.[39] These scoring systems are widely used, and each has been shown to predict clinical relapse in patients with endoscopically quiescent disease.[30, 38, 40] However, the operating characteristics of the scores in assessing the intended histological parameters are only partially validated and each includes histological features, such as crypt destruction, crypt architectural changes, and lamina propria eosinophils, that lack reproducibility.[36, 37] Two new, validated indices have been developed for use in patients with ulcerative colitis: the Nancy Index (see Supplementary information S1 (table 11)),[6] and the Robarts Histopathology Index (RHI; see Supplementary information S1 (table 12)).[34] Of these indices, the Nancy Index is our recommendation for use in clinical practice, because of its simplicity, reproducibility and ease of use, whereas the RHI will probably be preferred for clinical trials, owing to well-defined responsiveness.

The Nancy Index and the RHI are validated, reproducible and responsive.[6, 34] The Nancy Index has three histological descriptors (the presence of ulceration, the severity of acute inflammatory infiltrate and the severity of chronic inflammatory infiltrate) defining 5 grades

of activity (grade 0, least severe disease, to grade 4, most severe disease) in a weighted scoring algorithm (presence of ulceration defines the most severe disease).[6] The RHI incorporates 4 histological descriptors (severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium and the severity of erosions or ulceration), each of which is objectively graded between 0 and 3. Using data from a phase II trial of vedolizumab, this index has been shown to be responsive to disease activity change, and is probably a useful tool for clinical trials.[41]

Radiological assessment of disease activity

Imaging techniques are adjunctive to endoscopic assessment of disease activity in ulcerative colitis, and resolution of radiologic abnormalities in UC is not considered a treatment target in clinical practice.[3, 42]

Abdominal radiography is indicated in patients with severe ulcerative colitis to assess the extent of faecal residue, colonic dilatation or mucosal islands (areas of preserved colonic mucosa amidst denuded ulcerated mucosa).[42] Features on plain abdominal X-ray, in particular toxic megacolon (colonic dilatation > 5.5 cm), assist with prognostication of patients with severe colitis, and can direct management toward colectomy.[42, 43] Plain abdominal X-ray has no role in ulcerative colitis disease activity assessment outside of the acute setting, since it lacks sensitivity in evaluating mild–moderate grades of disease severity, but might identify proximal constipation as a cause of refractory distal disease.[42, 44]

Cross-sectional imaging in ulcerative colitis is predominantly performed to assess complications of disease, to exclude small bowel inflammation and Crohn's disease as a differential diagnosis and to assess colonic disease when stenosis or severe comorbidities limit the utility of colonoscopy.[17, 42] CT is associated with radiation exposure and has little role in assessing disease activity in ulcerative colitis; inflammation as assessed by CT correlates only moderately with endoscopic colonic inflammation (sensitivity 74%),[45] and use of CT infrequently leads to a change in clinical management.[46]

MRI and bowel ultrasonography demonstrate good sensitivity for evaluating disease activity and extent in ulcerative colitis without associated ionising radiation, and represent the most useful techniques for assessing luminal disease activity in ulcerative colitis where patient or disease-related factors render endoscopic examination infeasible (see Supplementary information S1 (table 1)).[42] Two scoring systems have been described for the assessment of

colonic inflammation in ulcerative colitis with MRI, one with and one without bowel preparation.[47, 48] A simplified magnetic resonance colonography index (MRC-S), based on 4 radiological features (gadolinium contrast uptake, presence of oedema, lymphadenopathy, and presence of the comb sign (hypervascularity of the mesentery)), correlates significantly with endoscopy as a reference standard ($r = 0.81$, $p < 0.001$) (see Supplementary information S1 (table 13)).[47] The presence of one of these features (MRC-S ≥ 1) has high sensitivity and specificity for active disease (87% and 88% respectively). Using MRI and diffusion-weighted imaging (technique used to evaluate cellular movement within a tissue voxel) without bowel preparation, a segmental MRI score (MR-score-S) of > 1, demonstrated a sensitivity and specificity of 89% and 86% for active disease (see Supplementary information S1 (table 14)).[48] The MR-score-S is calculated from 6 radiological features, including the presence of intestinal ulceration, parietal oedema, and differentiation between bowel wall layers. The MRC-S may be simpler score to use in clinical practice as it includes fewer variables, however the MR-score-S is benefited by lack of requirement for bowel preparation,

Disease assessment by bowel ultrasonography has been shown to correlate with colonic inflammation in ulcerative colitis, although performance is operator-dependent and might not be generalisable.[42] An ultrasonography scoring system proposed by Parente *et al* is useful in clinical practice and incorporates measurement of colonic wall thickness with the degree of intramural blood flow (Supplementary table 15).[49, 50] This score is concordant with the severity of endoscopically assessed inflammation in moderate to severe ulcerative colitis (weighted kappa 0.76–0.90), and is responsive to disease activity change after steroid therapy, predicting disease outcomes at 15 months.[49] Bowel ultrasound is a helpful adjunct to endoscopy in UC, as it is a cheap, non-invasive, and non-irradiating means of monitoring disease activity and extent, and is convenient to patients given that it may be readily performed in the clinical setting.[51] However, expertise in bowel ultrasound may be limited in many centres, and MRI may be the preferred imaging modality.

Biomarkers to assess disease activity.

Biomarkers are a useful adjunct to endoscopy for assessing disease activity in ulcerative colitis,[3] in that they are non-invasive and yet provide objective evidence of inflammation beyond clinical assessment alone. The most useful biomarkers in UC are plasma levels of C-reactive protein (CRP) and faecal calprotectin.

CRP is a useful marker in clinical practice for predicting disease outcomes at the time of diagnosis of ulcerative colitis, and in patients with severe ulcerative colitis. Plasma CRP levels have been shown to predict the risk of colectomy in patients with ulcerative colitis.[52-57] The Oxford criteria (more than 8 stools per day or 3–8 stools per day and plasma CRP concentration > 45 mg/l (> 428.6 nmol/l) predicts an 85% risk of colectomy during the period that hospital admission after 3 days of intravenous corticosteroid therapy for acute severe colitis (Supplementary table 16).[55] These criteria provide an indication of the need for medical rescue therapy, such as cyclosporine or infliximab.[1] A scoring system involving plasma CRP levels, extent of disease, and serum hemoglobin levels at the time of diagnosis of UC, has been shown to predict the risk of acute severe colitis within 3 years.[58, 59] Although a reduction in plasma CRP level has been shown to correlate with treatment response, CRP concentration is less useful in quiescent, mild, or moderately active ulcerative colitis, as it correlates weakly with endoscopic disease activity.[60]

Faecal calprotectin level is a useful non-invasive tool for monitoring disease activity over time. This biomarker has been shown to predict persistent inflammation[61-63] and risk of relapse[64-68] in patients with ulcerative colitis, and is responsive to up-titration of therapy.[69] However, a single faecal calprotectin cut-off value to predict endoscopically assessed disease remission is not credible, because a broad range of cut-off values have been described (ranging from < 50 μg/g to < 250 μg/g), mostly with only moderate sensitivity and specificity for disease activity.[70, 71] Faecal calprotectin level varies widely between stools on a daily basis in patients with active ulcerative colitis,[72] and readings can be influenced by variability inherent in the assay.[73] The clinical utility of faecal calprotectin levels for an individual patient lies in monitoring the change of this biomarker over time (Δfaecal calprotectin); rising faecal calprotectin levels prompt endoscopic evaluation and guide therapy. No useful disease activity scoring system based upon faecal calprotectin levels exists.

QOL in ulcerative colitis

Measurement of QoL is important in the assessment of IBD because it evaluates the patient's social and emotional wellbeing, behaviours and attitudes, and (to some extent) physical disease-related symptoms. QoL assessments are now an important component of medical decision-making in that QoL is now increasingly considered an important patient-related outcome measures, since improving QoL is the ultimate goal of therapy and value-based health. An international working group is developing a standard set of measures in IBD

(www.ichom.org), due to report in late 2016. Nevertheless, most disease-specific QoL indices (such as the IBDQ for IBD) are lengthy and time-consuming and this often precludes their use in clinical settings. The challenge is to find a measure of QoL that is fast to complete, valid, internally reliable, reproducible, responsive and acceptable to patients.

The questionnaire that we recommend for use in clinical practice is the IBD-Control (Supplementary information S1 (table 17)).[74] IBD-Control is the first patient-related outcome measure to capture disease control from the patient's perspective using a simple set of generic terms applicable to both ulcerative colitis and Crohn's disease. Summary scores have shown strong validity versus more complex QoL questionnaires, disease activity scores and Global Physician assessment.[74] This questionnaire is applicable to routine care, is free to use and (unlike the Short Inflammatory Bowel Disease Questionnaire) not subject to license. Its simplicity, the fact that it is completed by patients and that it has been adopted by international groups (ICHOM and the UK IBD Registry) are other advantages.

Other QoL questionnaires used in clinical practice include the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)[75] (see Supplementary information S1 (table 18)) and the Crohn's Ulcerative Colitis Questionnaire-8 (CUCQ-8)[76] (see Supplementary information S1 (table 19)). These short questionnaires (the SIBDQ has 10 questions and the CUCQ-8 has 8 questions) explain > 95% of the variance of their respective 32 question versions (the IBDQ and the CUCQ-32).

The SIBDQ gives results similar to the full 32-item IBDQ,[77] is widely accepted and has been validated in different populations.[75] Scores generated by this index range from 10 to70, which correspond to poor to good QoL, respectively. This questionnaire is reproducible and responsive to changes in disease severity,[78] but there is a licensing fee attached to its use.

The CUCQ-8, developed from the CUCQ-32, was designed for use in clinical practice, both for patients with stable disease as well as those with acute IBD. Scores range from 0–8, which correspond to good to poor QoL, notably the opposite way round to the SIBDQ, where a high score represents a good QoL. The CUCQ-8 requires no licensing fee for its use and is the only QoL index that has been used as a primary endpoint in a randomised clinical trial (CONSTRUCT) in ulcerative colitis.[79]

Crohn's disease

Clinical assessment of disease activity

The Crohn's Disease Activity Index (CDAI, see Supplementary information S1 (table 20)) is the most commonly used tool for assessing disease response to treatment in Crohn's disease clinical trials.[80] However, calculation of the CDAI is complex and involves 8 items, including haematocrit, physical examination (abdominal examination and weight measurement) and a 7-day patient diary (to record number of soft tools, abdominal pain and general wellbeing), so it is rarely used in clinical practice. Inter-observer variability between CDAI scores is high, even amongst experienced physicians.[81] The remission target is a CDAI < 150.[3]

The Harvey-Bradshaw Index (HBI)[82] (see Supplementary information S1 (table 21) online) is simpler to use than the CDAI and this makes data collection easier.[83] Moreover, scores from this index have been shown to correlate closely with CDAI scores.[83] The HBI has 5 variables (including general wellbeing, severity of abdominal pain, number of liquid stools, presence of abdominal mass and presence of complications) and items are scored based upon the previous day, so it does not require prospective 7-day data collection. The remission target for this index is an HBI score ≤4.[3]

The CDAI is not an accurate instrument to assess the activity of perianal Crohn's disease or Crohn's disease with other fistulae. This is because the presence of perianal disease or other fistulae (which can be terribly disabling for the patient) only accounts for a small proportion of the total score. The perianal Crohn's disease activity index (PDAI)[84] is currently the gold-standard for evaluating the severity of perianal disease (see Supplementary information S1 (table 22)). This index comprises 5 items: discharge, pain, restriction of sexual activity, type of perianal disease and degree of induration. Discharge, pain and degree of induration seem to be more commonly used in clinical practice.

Endoscopic assessment of disease activity

In contrast to ulcerative colitis, mucosal healing in Crohn's disease might reasonably be considered a minimal (rather than the ultimate) therapeutic goal, because Crohn's disease is transmural. The benefits of achieving mucosal healing include decreased need for

corticosteroids, decreased hospitalisation, sustained clinical remission and decreased need for surgery.[21, 23, 24]

Complete resolution of all endoscopically visible ulcers is a simple definition of mucosal healing for clinical practice and has been recommended by international consensus bodies.[85] Nevertheless, the binomial definition (presence or absence of ulcers) is currently unvalidated, difficult to achieve and crude, because it does not allow quantification of improvement of mucosal inflammation.[86]

Validated endoscopic indices have been developed for the assessment of Crohn's disease activity (see Supplementary information S1 (table 2) online). The Crohn's Disease Activity Index of Severity (CDEIS)[87] is the most commonly used tool in clinical trials, whereas the Simple Endoscopic Score for Crohn's Disease (SES-CD)[88] is a slightly simplified version of the same index. Rutgeerts' Post-operative Endoscopic Index[89] is used for estimating the risk of disease recurrence after ileocolic resection for Crohn's disease.

The CDEIS examines 4 endoscopic variables (the presence of deep ulceration, superficial ulceration, the length of ulcerated mucosa and the length of diseased mucosa) in each of the following locations: rectum, sigmoid and left colon, transverse colon, right colon and ileum (see Supplementary information S1 (table 23)). Although the CDEIS is a reproducible and validated index, it is complex, requiring over 30 entries to reach the final score.[87] As with all indices, implementation requires both training and experience, but the complexity of the CDEIS makes it cumbersome to use in clinical practice. The remission target is a total CDEIS score of < 3.[3]

The SES-CD (see Supplementary information S1 (table 24)) correlates well with the CDEIS, but is only slightly less complex, requiring over 20 entries to complete the total score.[88] Endoscopic features (ulcer size, extent of ulcerated surfaces, extent of surfaces with any other lesions and stenosis) are scored from 0 to 3 depending on severity or extent in each of the 5 colorectal locations assessed by the CDEIS. An SES-CD score of 0 equates to absence of ulcers.

Rutgeerts' Post-operative Endoscopic Index (see Supplementary information S1 (table 25)) determines the severity of endoscopic disease recurrence at the anastomosis and in the neo-terminal ileum after ileocolic resection.[89, 90] This index consists of 5 grades of increasing disease recurrence severity, between i0 and i4, as assessed by the number and nature of ulcers

in the distal ileum. The Post-operative Endoscopic Index has gained popularity because its assessment of disease recurrence predicts symptom recurrence but questions have been raised about its discriminative ability, especially the i2 domain as there is high inter-observer variability. The remission target is a grade < i2.[3]

For endoscopic reporting of Crohn's disease activity in clinical practice, we recommend using the SES-CD, or at the very least reporting, for each bowel section, the presence or absence of ulcers, stenosis and the proportion of surface area affected. For post-operative assessment of disease recurrence following ileocolic resection, we recommend Rutgeerts' score.

Histological assessment of disease activity

Histological disease activity assessment in Crohn's disease is difficult because inflammation is discontinuous, transmural and can exist beyond the reach of the endoscope.[5, 35] Targeted mucosal biopsies can be used in an attempt to limit sampling error, but transmural inflammation can only be assessed in specimens obtained during surgical resection. Thus, histological scoring systems for mucosal biopsy samples are challenging both to develop and to use in practice.[91] Nevertheless, microscopic inflammation can persist in biopsy samples from tissue that appears quiescent when observed endoscopically,[29, 92, 93] and some limited evidence suggests that presence of microscopic inflammation is associated with increased rates of clinical relapse, stricture formation and surgery.[29]

Several histological scoring systems have been proposed for assessing Crohn's disease activity (see Supplementary information S1 (table 2)), the best known of which are the Colonic and Ileal Global Histologic Disease Activity Scores (CGHAS and IGHAS) (see Supplementary information S1 (table 26)).[91, 94, 95] Due to the complexity of these scoring systems and lack of evidence correlating histological disease activity with disease outcomes in Crohn's disease, we do not recommend routine use of such scoring in clinical practice. Rather, the presence of histological inflammation in endoscopically quiescent disease should caution against de-escalation of therapy.[5]

Radiological assessment of disease activity

Given that transmural inflammation in Crohn's disease can extend beyond the reach of endoscopy, imaging has an important role in assessing disease activity.[42] Imaging also enables evaluation of the complications of Crohn's disease, including stricturing disease,

fistulae and abscesses.[96] MRI is the preferred modality for assessing extraluminal complications of Crohn's disease and the presence and severity of perianal fistulae in particular. MRI and ultrasonography are the preferred modalities for assessing luminal disease activity and strictures in Crohn's disease.[42]

Although the overall accuracy of CT, ultrasonography and MRI for assessing luminal disease activity in Crohn's disease is similar,[42, 96] radiation exposure limits the use of CT, which is particularly relevant to younger patients who might be exposed to a substantial cumulative radiation dose over their disease course. CT is therefore not the first-choice imaging technique for assessing disease activity in Crohn's disease; when MRI and ultrasonography are unavailable, low-dose CT can be an alternative.[97] Plain film radiography and barium contrast studies now have little role in Crohn's disease, due to their limited sensitivity for assessing activity in comparison to MRI, CT and ultrasonography.[42]

Intestinal MRI requires rapid image acquisition and luminal distension for accurate assessment of disease distribution and activity, which can be achieved with a neutral contrast agent delivered via enterography or enteroclysis.[98] Amongst the available scoring systems (see Supplementary information S1 (table 2)), the Magnetic Resonance Index of Activity (MaRIA) is for assessment of disease activity in CD and we recommend its use in clinical practice (see Supplementary information S1 (table 27)).[99, 100] The MaRIA correlates well with CDEIS scores assessed by ileocolonoscopy ($r = 0.83$, $p < 0.001$),[99] and has been shown to be reliable in assessing disease response to therapy in Crohn's disease (90% accuracy for detecting ulcer healing and 83% accuracy for detecting endoscopic remission as assessed using CDEIS).[101] Although MRI is expensive in comparison to other imaging modalities, the technique is cost-effective compared with CT in patients younger than 50 years old, based on quality-adjusted life-year data factoring in radiation exposure.[102]

MRI is a widely used and accurate tool to assess the presence and severity of perianal fistulising disease.[42] The Van Assche MRI-based score for assessing the severity of perianal Crohn's disease,[103] based on the classification of perianal fistula developed at St. Mark's Hospital, Harrow, UK,[104] is useful for formal assessment of response of fistulising disease to therapy (see Supplementary information S1 (table 28)). The score incorporates criteria relating to the local extension of fistulae, as well as active inflammation, and it demonstrates good inter-observer agreement and responsiveness following anti-TNF therapy.[103] The score is useful for clinical trials, but has less utility in clinical practice due to its relative complexity.

Doppler ultrasonography is helpful in assessing disease activity, based on intestinal wall thickness and intensity of flow.[105-107] Although there are several scoring systems for ultrasonographic assessment of disease activity (see Supplementary information S1 (table 2)), the most widely used of which is the Limberg Score (see Supplementary information S1 (table 29)),[108] none of these indices have been validated. Small studies (n = 24–110) have shown that ultrasonography is responsive to improvements in disease activity following therapy,[109-112] and might be useful for disease monitoring after surgical resection.[113, 114] Point-of-care ultrasonography has also been shown to influence clinical decision-making, particularly when patients are asymptomatic but ultrasound reveals evidence of active disease.[115] Despite promising data, the use of ultrasonography remains limited by the availability of an experienced bowel sonographer. Outside of Europe, ultrasound has been less commonly used, and has traditionally been trumped by cross-sectional imaging (CT and MRI), favoured for its reproducible protocols and capacity for archival of images. However, as clinician awareness of the imperative for close monitoring of IBD disease activity as a part of a 'treat to target' management strategy grows, ultrasound is becoming increasingly appealing as a cheap and non-invasive tool, and its use is burgeoning in countries such as Australia.[51]

Biomarkers to assess disease activity

Biomarkers are a non-invasive adjunct to endoscopy and cross-sectional imaging for monitoring disease activity in Crohn's disease.[3] Plasma levels of CRP and faecal calprotectin are the most useful biomarkers in clinical practice.

An improvement in plasma CRP levels (that is, a reduced plasma concentration of CRP) has been shown to correlate with a clinical therapeutic response in Crohn's disease.[116-122] An elevated plasma CRP level predicts clinical relapse in Crohn's disease,[123, 124] in both asymptomatic patients,[125] as well as following withdrawal of therapy.[126-128] Higher plasma CRP levels prior to treatment have been shown to predict a better likelihood of maintenance of remission following anti-TNF therapy.[129] However, CRP level correlates only modestly with endoscopic disease activity in Crohn's disease,[70, 71, 130-133] and a normal plasma CRP concentration has been reported in patients with active disease, particularly those with predominantly ileal rather than predominantly colonic pathology.[134-136] The converse is also true, as an elevated CRP level does not always correlate with active disease.[130] Plasma CRP

concentration is therefore not a target of therapy, but rather a tool to monitor inflammation to guide the necessity of radiological or endoscopic activity assessment.

Faecal calprotectin level has been shown to correlate with endoscopic and MRI-based assessment of disease activity in Crohn's disease,[131, 137-139] and to predict disease relapse.[65, 68, 140, 141] Levels of faecal calprotectin are also useful in monitoring disease activity following initiation of therapy,[122] as well as in the post-operative Crohn's disease setting.[136, 142] However, faecal calprotectin concentration is less accurate for ileal than colonic disease, and can be normal even in the presence of large ulcers.[143] Faecal calprotectin level cut-off values for predicting remission vary widely between studies (from < 50 μg/g to < 250 μg/g) and are only moderately predictive for individual patients,[71] unless a stringent cut-off value is used (such as < 50 μg/g), which comes at the expense of sensitivity or unnecessary investigations. Thus, as for ulcerative colitis, it seems that the change in faecal calprotectin level, rather than the absolute level in an individual patient, is best used in clinical practice to aid treatment decision-making.

QoL

The 3 QoL questionnaires that we recommend for use in clinical practice are the same as those used in ulcerative colitis: IBD-Control, the SIBDQ[75] (see Supplementary information (table 17)) or the CUCQ-8[76] (see Supplementary information (table 18)).

Conclusions

The overarching goal of therapy in IBD is to modify the disease course to improve QoL and avoid disability, whilst balancing the risks associated with therapy.[144, 145] To reach this goal, therapy must be directed to achieve resolution of both objective inflammation and clinical symptoms, as well as normalisation of QoL. This 'treat to target' approach requires a clinician to look beyond clinical symptoms and to assess disease activity as objectively as possible. This method enables a composite appraisal of the measurable burden of inflammation, the burden of disease on the patient and the cumulative complications of disease over its course.[145]

Despite the disparity between clinical and objective measures of inflammation in IBD, both are important when assessing disease activity. The objective burden of inflammation denotes risk of negative disease outcomes in IBD, whilst clinicians realise that symptoms and QoL are most important to patients. Amongst the confusing myriad of disease activity indices within

each domain of assessment, this review has collected and appraised the most practical and relevant indices for clinical practice, augmented by supplementary tables to provide a comprehensive overview. Current indices need to be validated according to well-established statistical criteria. The metrics will help with clinical decision-making and encourage physicians to strive for appropriate treatment targets that can be expected to improve outcomes for people with IBD.

Figure

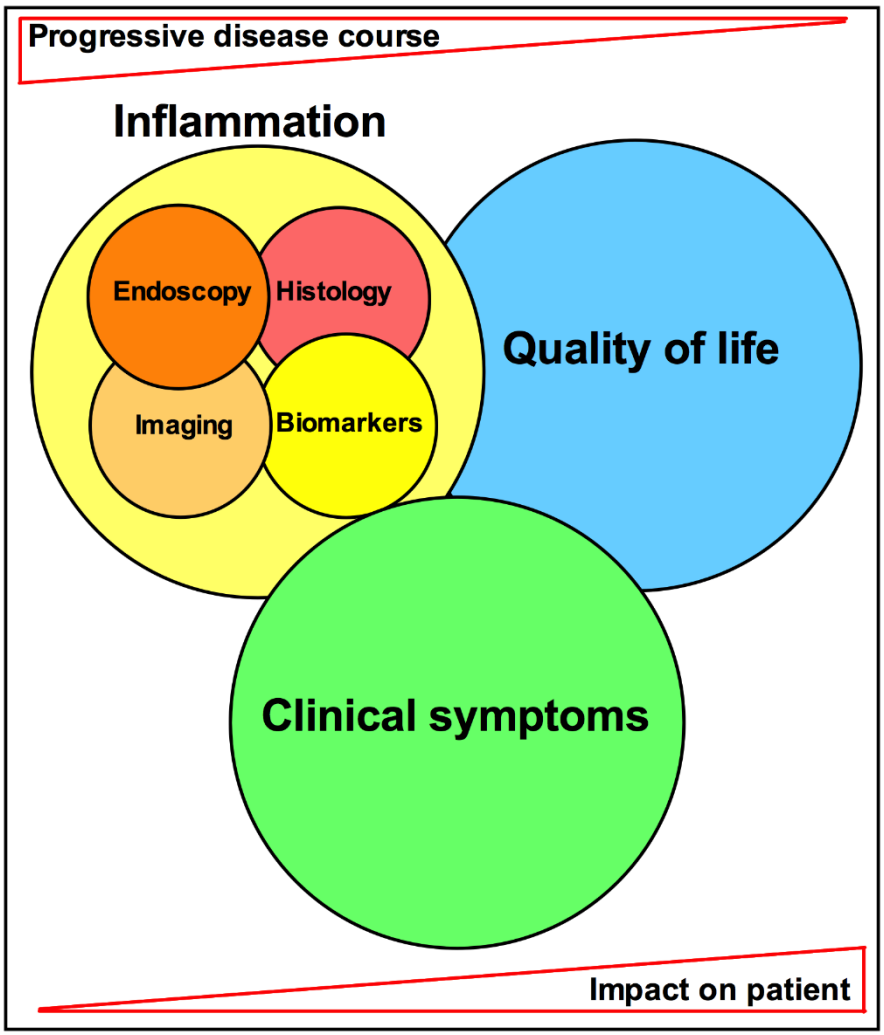


Figure A1. Domains of disease activity assessment in IBD

Legend. *The overlapping domains of disease activity assessment in IBD: inflammation, clinical symptoms, and quality of life. Inflammation can be assessed by endoscopy, histology, imaging, and/or biomarkers.*

Tables

Table A1: Ulcerative colitis disease activity assessment indices in clinical practice

Domain	Index name	Abbreviation	Range and remission threshold	Strengths	Weaknesses
Clinical	Simple Clinical Colitis Activity Index[1]	SCCAI	0–19 Remission: ≤2	-Able to be completed by patient -Includes important factors such as urgency, incontinence and nocturnal bowel movements -Reliable, valid, responsive and feasible	Not validated
	Partial Mayo Index[2, 3]	NA	0–9 Remission: ≤ 1	-Most widely used -Discriminates remission from active disease	-Not validated -Relies on subjective Physician Global assessment
	Paediatric Ulcerative Colitis Activity Index[4]	PUCAI	0–85 Remission: < 10	-Validated -Reliable and responsive in adults -Might permit less frequent endoscopic assessment	-Has not been widely adopted in the adult population

Domain	Index name	Abbreviation	Range and remission threshold	Strengths	Weaknesses
	Truelove and Witts' Severity Index[5]	TWC		-Objective criteria for acute severe colitis -Useful for prognosis	-Not validated, although widely used
Endoscopic	Mayo Clinic Index: endoscopic subscore[3]		0–3 Remission: ≤1	Easy to use Commonly used in clinical trials	-Overlap of the different levels results in inter-observer variation -No validated definition of mucosal healing -Subjective terms (minimal or slight friability) reduce concordance - Does not consider disease extent
	Ulcerative Colitis Endoscopic Index of Severity[6, 7]	UCEIS	0–8 Remission: ≤1	-Validated index -Easy to use -Accounts for 88% of variation between observers -Now used in clinical trials	-No validated definition of mucosal healing or response -Does not consider disease extent -No thresholds for mild, moderate or severe disease
Histology	Riley Score[8]	NA	0–18	-Widely used, simple, predictive value in	-Partially validated, includes items with poor reproducibility

Domain	Index name	Abbreviation	Range and remission threshold	Strengths	Weaknesses
				outcomes in ulcerative colitis	
	Geboes Score[9]	NA	0.0–5.4 Remission: < 3.1	Widely used, predicts value in outcomes in ulcerative colitis	-Partially validated, includes items with poor reproducibility
	Nancy Histological Index[10]	NA	0–4 Remission: 0	-Validated, responsive, good intra- and inter-observer agreement -Reliable, simple, and easy to use	-Lacks data on predictive value on outcomes in ulcerative colitis
	Robarts histopathological index[11]	RHI	0–12 Remission: ≤ 6	-Validated and responsive (compared with endoscopic and QoL indices)	-Lack data on predictive value on outcomes in ulcerative colitis
Radiology	Magnetic resonance colonography simplified index[12]	MRC-S	0–4 Remission: 0	-Simple and correlates well with endoscopic disease activity	-Not validated -Cost and availability of MRI and requirement for bowel preparation
	Segmental magnetic	MR-score-S	0–6	-Good reproducibility and inter-observer agreement,	-Not validated.

Domain	Index name	Abbreviation	Range and remission threshold	Strengths	Weaknesses
	resonance score[13]		Remission: 0	correlates well with endoscopic features -No need for bowel preparation	-Cost and availability of MRI
	Bowel Ultrasound Severity Score[14]	NA	0–3 Remission: 0	-High concordance between US score and endoscopic disease activity -Bowel US score predictive of outcomes in ulcerative colitis	-Not validated. -Dependent on expert and experienced sonographer
Biomarkers	C-reactive protein	CRP	0 to > 200 mg/l (1904 nmol/l) Remission: ≤3 to < 19 mg/l	-Predictive of outcomes in acute severe colitis (Oxford criteria*) -Widely available	-Less useful in mild disease -Poor correlation with endoscopic disease activity
	Faecal calprotectin	FC	0 to > 1000µg/g Remission: < 50 to < 250 µg/g	-Useful for monitoring disease activity in ulcerative colitis (using ΔFC)	-Wide range of cut-off values for determining active vs inactive disease -Lacks sensitivity and specificity for endoscopy disease activity

Domain	Index name	Abbreviation	Range and remission threshold	Strengths	Weaknesses
QoL	Short Inflammatory Bowel Disease Questionnaire[15]	SIBDQ	10–70	-Easy to use -Results correlate to the longer 32-item IBDQ -Widely accepted -Validated -Reproducible and responsive	-Licensing fee required for use
	Crohn's Ulcerative Colitis Questionnaire-8[16]	CUCQ-8	0–8	-Easy to use -Results correlate with longer 32-item questionnaire -Validated -No licensing fee	-Calculating total score requires each question to be translated into a subscore out of 1

*For a full list of identified indices, please see Supplementary information S1 (table 1). *Oxford criteria defined as more than 8 stools per day or 3–8 stools per day and plasma CRP concentration > 45 mg/l. FC, faecal calprotectin; NA, not applicable; QOL, quality of life; US, ultrasonography.*

Table A2: Crohn's disease activity assessment indices in clinical practice

Domain	Index name	Abbreviation	Range (remission threshold)	Strengths	Weaknesses
Clinical	Crohn's Disease Activity Index[17]	CDAI	0–600 Remission: < 150	-Widely used	-Complex calculation involving a 7-day diary -High variability
	Harvey-Bradshaw Index[18]	HBI	0–50 Remission: ≤ 4	-Simpler, less cumbersome -Does not require a 7-day diary	-Low contribution to total score for perianal disease
	Perianal Crohn's Disease Activity Index[19]	PDAI	0–19	-Easy to use	-Does not allow documentation of fistula severity
Endoscopic	Crohn's Disease Endoscopic Index of Severity[20]	CDEIS	0–44 Remission: < 3	-Current gold-standard -Reproducible and validated	-Complex -Cumbersome to use in clinical practice -Needs experience and training -No validated definition of mucosal healing
	Simple	SES-CD	0–12	-Simplified version of the CDEIS.	-Only slightly less complex than CDEIS

Domain	Index name	Abbreviation	Range (remission threshold)	Strengths	Weaknesses
	Endoscopic Score for Crohn's Disease[21]			-Performance correlates well with CDEIS	-Validated against CDEIS in only one study -No validated definition of mucosal healing
	Rutgeerts' Post-operative Endoscopic Index[22, 23]	NA	i0 to i4 Remission: < i2	-Standard for evaluating post-operative recurrence -Validated levels for predicting relapse -Widely used	-Discriminative ability unclear, especially of the i2 domain -Only for use after ileocolic resection
Histology	Colonic and Ileal Global Histologic Disease Activity Score[24, 25]	CGHAS IGHAS	0–16	-Takes into account patchy disease activity	-Not validated -No data on reproducibility -Inherit issues with histological scoring in Crohn's disease
Radiology	Magnetic Resonance Index of Activity[26-28]	MaRIA	Segmental mucosal healing < 7 Segmental ulcer	-Validated -Good intra-observer and inter-observer concordance, correlates well with endoscopy	-May be best used in clinical trials rather than clinical practice

Domain	Index name	Abbreviation	Range (remission threshold)	Strengths	Weaknesses
			healing < 11	-Responsive index	
	Van Assche MRI-based Score for Severity of Perianal Crohn's Disease[29]	NA	0–24	-Validated -Good inter-observer concordance	-Utility in clinical practice might be limited due to complexity
	Limberg scoring system for bowel ultrasound[30]	Limberg Score	0–4	-Widely used	-Not validated
Biomarkers	C-reactive protein	CRP	0 to > 200 mg/l Remission: ≤5 to < 8 mg/l	-Useful for monitoring disease activity in Crohn's disease -Predictive of relapse whilst on therapy and following withdrawal	-Modest correlation with endoscopic disease activity (especially ileal disease)
	Faecal calprotectin	FC	0 to > 1000µg/g	-Useful for monitoring disease activity in Crohn's disease (using	-Wide range of cut-off values for determining active vs inactive disease

Domain	Index name	Abbreviation	Range (remission threshold)	Strengths	Weaknesses
			Remission: < 50 to < 250 µg/g	ΔFC)	-Lacks sensitivity and specificity for endoscopy disease activity
QoL	Short Inflammatory Bowel Disease Questionnaire[15]	SIBDQ	NA	-Easy to use -Results correlate to the longer 32-item IBDQ -Widely accepted -Validated -Reproducible and responsive	-Licensing fee required for use
	Crohn's Ulcerative Colitis Questionnaire-8[16]	CUCQ-8	NA	-Easy to use Results correlate with longer 32-item questionnaire -Validated for both stable patients as well as those with acute disease -No licensing fee	-Calculating total score requires each question to be translated into a subscore out of 1

For a full list of identified indices, please see Supplementary table A1, A2. FC, faecal calprotectin

REFERENCES

1. Dignass A, Lindsay JO, Sturm A, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's & colitis. 2012 Dec;6(10):991-1030.
2. Dignass A, Van Assche G, Lindsay JO, *et al*. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. Journal of Crohn's & colitis. 2010 Feb;4(1):28-62.
3. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al*. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015 Sep;110(9):1324-38.
4. Walsh AJ, Ghosh A, Brain AO, *et al*. Comparing disease activity indices in ulcerative colitis. Journal of Crohn's & colitis. 2014 Apr 1;8(4):318-25.
5. Bryant RV, Winer S, Travis SP, *et al*. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. Journal of Crohn's & colitis. 2014 Dec 1;8(12):1582-97.
6. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, *et al*. Development and validation of the Nancy histological index for UC. Gut. 2017; 66(1):43-49.
7. Travis SP, Danese S, Kupcinskas L, *et al*. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut. 2014 Mar;63(3):433-41.
8. Travis SP, Schnell D, Krzeski P, *et al*. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012 Apr;61(4):535-42.
9. Travis SP, Schnell D, Krzeski P, *et al*. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013 Nov;145(5):987-95.
10. Walmsley RS, Ayres RC, Pounder RE, *et al*. A simple clinical colitis activity index. Gut. 1998 Jul;43(1):29-32.
11. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. The New England journal of medicine. 1987 Dec 24;317(26):1625-9.
12. Sandborn WJ, Sands BE, Wolf DC, *et al*. Repifermin (keratinocyte growth factor-2) for the treatment of active ulcerative colitis: a randomized, double-blind, placebo-

controlled, dose-escalation trial. Alimentary pharmacology & therapeutics. 2003 Jun 1;17(11):1355-64.

13. Turner D, Otley AR, Mack D, *et al*. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007 Aug;133(2):423-32.
14. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. British medical journal. 1955 Oct 29;2(4947):1041-8.
15. Turner D, Seow CH, Greenberg GR, *et al*. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. Clinical gastroenterology and hepatology. 2009 Oct;7(10):1081-8.
16. D'Haens G, Sandborn WJ, Feagan BG, *et al*. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007 Feb;132(2):763-86.
17. Dignass A, Eliakim R, Magro F, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. Journal of Crohn's & colitis. 2012 Dec;6(10):965-90.
18. Dinesen LC, Walsh AJ, Protic MN, *et al*. The pattern and outcome of acute severe colitis. Journal of Crohn's & colitis. 2010 Oct;4(4):431-7.
19. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012 Nov;61(11):1619-35.
20. Sandborn WJ, Feagan BG, Hanauer SB, *et al*. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology. 2002 Feb;122(2):512-30.
21. Froslie KF, Jahnsen J, Moum BA, *et al*. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007 Aug;133(2):412-22.
22. Ardizzone S, Maconi G, Russo A, *et al*. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006 Jan;55(1):47-53.
23. Rutgeerts P, Diamond RH, Bala M, *et al*. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointestinal endoscopy. 2006 Mar;63(3):433-42.

24. Schnitzler F, Fidder H, Ferrante M, *et al*. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflammatory bowel diseases. 2009 Sep;15(9):1295-301.
25. Colombel JF, Rutgeerts P, Reinisch W, *et al*. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011 Oct;141(4):1194-201.
26. Rutter M, Saunders B, Wilkinson K, *et al*. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004 Feb;126(2):451-9.
27. Corte CJ, Fernandopulle A, Catuneanu A, *et al*. Association between the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and outcomes in acute severe ulcerative colitis. Journal of Crohn's & colitis. 2015; 9(5): 376-81.
28. Ikeya K, Hanai H, Sugimoto K, *et al*. The Ulcerative Colitis Endoscopic Index of Severity More Accurately Reflects Clinical Outcomes and Long-term Prognosis than the Mayo Endoscopic Score. Journal of Crohn's & colitis. 2016; 10(3): 286-95.
29. Baars JE, Nuij VJ, Oldenburg B, *et al*. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflammatory bowel diseases. 2012 Sep;18(9):1634-40.
30. Bessissow T, Lemmens B, Ferrante M, *et al*. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. The American journal of gastroenterology. 2012 Nov;107(11):1684-92.
31. Bitton A, Peppercorn MA, Antonioli DA, *et al*. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001 Jan;120(1):13-20.
32. Bryant RV, Burger DC, Delo J, *et al*. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut. 2016; 65(3): 408-14.
33. Gupta RB, Harpaz N, Itzkowitz S, *et al*. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007 Oct;133(4):1099-105.
34. Mosli MH, Feagan BG, Zou G, *et al*. Development and validation of a histological index for UC. Gut. 2017; 66(1): 50-58.
35. Magro F, Langner C, Driessen A, *et al*. European consensus on the histopathology of inflammatory bowel disease. Journal of Crohn's & colitis. 2013 Nov;7(10):827-51.

36. Mosli MH, Feagan BG, Zou G, *et al*. Reproducibility of histological assessments of disease activity in UC. Gut. 2015 Nov;64(11):1765-73.
37. Bressenot A, Salleron J, Bastien C, *et al*. Comparing histological activity indexes in UC. Gut. 2015; 64(9): 1412-18.
38. Riley SA, Mani V, Goodman MJ, *et al*. Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991 Feb;32(2):174-8.
39. Geboes K, Riddell R, Ost A, *et al*. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000 Sep;47(3):404-9.
40. Azad S, Sood N, Sood A. Biological and histological parameters as predictors of relapse in ulcerative colitis: a prospective study. Saudi journal of gastroenterology. 2011 May-Jun;17(3):194-8.
41. Feagan BG, Greenberg GR, Wild G, *et al*. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. The New England journal of medicine. 2005 Jun 16;352(24):2499-507.
42. Panes J, Bouhnik Y, Reinisch W, *et al*. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. Journal of Crohn's & colitis. 2013 Aug;7(7):556-85.
43. Benchimol EI, Turner D, Mann EH, *et al*. Toxic megacolon in children with inflammatory bowel disease: clinical and radiographic characteristics. The American journal of gastroenterology. 2008 Jun;103(6):1524-31.
44. Allison MC, Vallance R. Prevalence of proximal faecal stasis in active ulcerative colitis. Gut. 1991 Feb;32(2):179-82.
45. Fletcher JG, Fidler JL, Bruining DH, *et al*. New concepts in intestinal imaging for inflammatory bowel diseases. Gastroenterology. 2011 May;140(6):1795-806.
46. Yarur AJ, Mandalia AB, Dauer RM, *et al*. Predictive factors for clinically actionable computed tomography findings in inflammatory bowel disease patients seen in the emergency department with acute gastrointestinal symptoms. Journal of Crohn's & colitis. 2014 Jun;8(6):504-12.
47. Ordas I, Rimola J, Garcia-Bosch O, Rodriguez S, *et al*. Diagnostic accuracy of magnetic resonance colonography for the evaluation of disease activity and severity in ulcerative colitis: a prospective study. Gut. 2013 Nov;62(11):1566-72.
48. Oussalah A, Laurent V, Bruot O, *et al*. Diffusion-weighted magnetic resonance without bowel preparation for detecting colonic inflammation in inflammatory bowel disease. Gut. 2010 Aug;59(8):1056-65.

49. Parente F, Molteni M, Marino B, *et al*. Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis?: a prospective study. The American journal of gastroenterology. 2010 May;105(5):1150-7.
50. Parente FA, Greco, S. *et al*. Response to high-dose steroids of severe attacks of ulcerative colitis may rely on bowel ultrasound instead of colonoscopy. A preliminary study . Gut. 2006;55 ((Suppl V)):A118.
51. Asthana AK, Friedman AB, Maconi G, *et al*. Failure of gastroenterologists to apply intestinal ultrasound in inflammatory bowel disease in the Asia-Pacific: a need for action. Journal of gastroenterology and hepatology. 2015 Mar;30(3):446-52.
52. Solem CA, Loftus EV, Jr., Tremaine WJ, *et al*. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflammatory bowel diseases. 2005 Aug;11(8):707-12.
53. Osada T, Ohkusa T, Okayasu I, Y *et al*. Correlations among total colonoscopic findings, clinical symptoms, and laboratory markers in ulcerative colitis. Journal of gastroenterology and hepatology. 2008 Dec;23 Suppl 2:S262-7.
54. Turner D, Mack D, Leleiko N, *et al*. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology. 2010 Jun;138(7):2282-91.
55. Travis SP, Farrant JM, Ricketts C, *et al*. Predicting outcome in severe ulcerative colitis. Gut. 1996 Jun;38(6):905-10.
56. Kumar S, Ghoshal UC, Aggarwal R, *et al*. Severe ulcerative colitis: prospective study of parameters determining outcome. Journal of gastroenterology and hepatology. 2004 Nov;19(11):1247-52.
57. Aceituno M, Garcia-Planella E, Heredia C, *et al*. Steroid-refractory ulcerative colitis: predictive factors of response to cyclosporine and validation in an independent cohort. Inflammatory bowel diseases. 2008 Mar;14(3):347-52.
58. Cesarini MC, G.; Ronnblom, A.; Santos, A.; *et al*. P079. Predicting the risk of acute severe colitis (ASC) at diagnosis of Ulcerative Colitis (UC): external validation. Journal of Crohn's & colitis. 2015 Feb;9 Suppl 1:S117-8.
59. Henriksen M, Jahnsen J, Lygren I, *et al*. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut. 2008 Nov;57(11):1518-23.

60. Yoon JY, Park SJ, Hong SP, *et al*. Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. Digestive diseases and sciences. 2014 Apr;59(4):829-37.
61. Guardiola J, Lobaton T, Rodriguez-Alonso L, *et al*. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. Clinical gastroenterology and hepatology. 2014 Nov;12(11):1865-70.
62. Yamaguchi S, Takeuchi Y, Arai K, *et al*. Fecal calprotectin is a clinically relevant biomarker of mucosal healing in patients with quiescent ulcerative colitis. Journal of gastroenterology and hepatology. 2016; 31(1): 93-98.
63. Theede K, Holck S, Ibsen P, *et al*. Level of Fecal Calprotectin Correlates With Endoscopic and Histologic Inflammation and Identifies Patients With Mucosal Healing in Ulcerative Colitis. Clinical gastroenterology and hepatology. 2015 Nov;13(11):1929-36.e1.
64. Yamamoto T, Shiraki M, Bamba T, *et al*. Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy. International journal of colorectal disease. 2014 Apr;29(4):485-91.
65. Gisbert JP, Bermejo F, Perez-Calle JL, *et al*. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflammatory bowel diseases. 2009 Aug;15(8):1190-8.
66. De Vos M, Louis EJ, Jahnsen J, *et al*. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. Inflammatory bowel diseases. 2013 Sep;19(10):2111-7.
67. Molander P, af Bjorkesten CG, Mustonen H, *et al*. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFalpha blocking agents. Inflammatory bowel diseases. 2012 Nov;18(11):2011-7.
68. Molander P, Farkkila M, Ristimaki A, *et al*. Does fecal calprotectin predict short-term relapse after stopping TNFalpha-blocking agents in inflammatory bowel disease patients in deep remission? Journal of Crohn's & colitis. 2015 Jan;9(1):33-40.
69. Osterman MT, Aberra FN, Cross R, *et al*. Mesalamine dose escalation reduces fecal calprotectin in patients with quiescent ulcerative colitis. Clinical gastroenterology and hepatology. 2014 Nov;12(11):1887-93.

70. Falvey JD, Hoskin T, Meijer B, *et al*. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. Inflammatory bowel diseases. 2015 Apr;21(4):824-31.
71. Mosli MH, Zou G, Garg SK, *et al*. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. The American journal of gastroenterology. 2015 Jun;110(6):802-19.
72. Calafat M, Cabre E, Manosa M, *et al*. High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what is the best timing for stool sampling? Inflammatory bowel diseases. 2015 May;21(5):1072-6.
73. Kristensen V, Klepp P, Cvancarova M, *et al*. Prediction of endoscopic disease activity in ulcerative colitis by two different assays for fecal calprotectin. Journal of Crohn's & colitis. 2015 Feb;9(2):164-9.
74. Bodger K, Ormerod C, Shackcloth D, *et al*. Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. Gut. 2014 Jul;63(7):1092-102.
75. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. The American journal of gastroenterology. 1996 Aug;91(8):1571-8.
76. Alrubaiy L, Cheung WY, Dodds P, *et al*. Development of a short questionnaire to assess the quality of life in Crohn's disease and ulcerative colitis. Journal of Crohn's & colitis. 2015 Jan;9(1):66-76.
77. Guyatt G, Mitchell A, Irvine EJ, *et al*. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar;96(3):804-10.
78. Jowett SL, Seal CJ, Barton JR, *et al*. The short inflammatory bowel disease questionnaire is reliable and responsive to clinically important change in ulcerative colitis. The American journal of gastroenterology. 2001 Oct;96(10):2921-8.
79. Seagrove AC, Alam MF, Alrubaiy L, *et al*. Randomised controlled trial. Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: Trial design and protocol (CONSTRUCT). BMJ open. 2014;4(4):e005091.
80. Best WR, Becktel JM, Singleton JW, *et al*. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976 Mar;70(3):439-44.

81. Sands BE, Ooi CJ. A survey of methodological variation in the Crohn's disease activity index. Inflammatory bowel diseases. 2005 Feb;11(2):133-8.
82. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980 Mar 8;1(8167):514.
83. Vermeire S, Schreiber S, Sandborn WJ, *et al*. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clinical gastroenterology and hepatology. 2010 Apr;8(4):357-63.
84. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. Journal of clinical gastroenterology. 1995 Jan;20(1):27-32.
85. D'Haens GR, Fedorak R, Lemann M, *et al*. Endpoints for clinical trials evaluating disease modification and structural damage in adults with Crohn's disease. Inflammatory bowel diseases. 2009 Oct;15(10):1599-604.
86. De Cruz P, Kamm MA, Prideaux L, *et al*. Mucosal healing in Crohn's disease: a systematic review. Inflammatory bowel diseases. 2013 Feb;19(2):429-44.
87. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989 Jul;30(7):983-9.
88. Daperno M, D'Haens G, Van Assche G, *et al*. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointestinal endoscopy. 2004 Oct;60(4):505-12.
89. Rutgeerts P, Geboes K, Vantrappen G, *et al*. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990 Oct;99(4):956-63.
90. Rutgeerts P, Geboes K, Vantrappen G, *et al*. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut. 1984 Jun;25(6):665-72.
91. D'Haens GR, Geboes K, Peeters M, *et al*. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998 Feb;114(2):262-7.
92. Korelitz BI, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. Journal of clinical gastroenterology. 1984 Apr;6(2):123-7.

93. Molander P, Sipponen T, Kemppainen H, *et al*. Achievement of deep remission during scheduled maintenance therapy with TNFalpha-blocking agents in IBD. Journal of Crohn's & colitis. 2013 Oct;7(9):730-5.
94. D'Haens G, Van Deventer S, Van Hogezand R, *et al*. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology. 1999 May;116(5):1029-34.
95. Geboes K, Rutgeerts P, Opdenakker G, *et al*. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. Current medical research and opinion. 2005 Nov;21(11):1741-54.
96. Panes J, Bouzas R, Chaparro M, *et al*. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Alimentary pharmacology & therapeutics. 2011 Jul;34(2):125-45.
97. Craig O, O'Neill S, O'Neill F, McLaughlin P, *et al*. Diagnostic accuracy of computed tomography using lower doses of radiation for patients with Crohn's disease. Clinical gastroenterology and hepatology. 2012 Aug;10(8):886-92.
98. Kuehle CA, Ajaj W, Ladd SC, *et al*. Hydro-MRI of the small bowel: effect of contrast volume, timing of contrast administration, and data acquisition on bowel distention. AJR American journal of roentgenology. 2006 Oct;187(4):W375-85.
99. Rimola J, Ordas I, Rodriguez S, *et al*. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. Inflammatory bowel diseases. 2011 Aug;17(8):1759-68.
100. Rimola J, Rodriguez S, Garcia-Bosch O, *et al*. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut. 2009 Aug;58(8):1113-20.
101. Ordas I, Rimola J, Rodriguez S, P *et al*. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology. 2014 Feb;146(2):374-82.e1.
102. Cipriano LE, Levesque BG, Zaric GS, *et al*. Cost-effectiveness of imaging strategies to reduce radiation-induced cancer risk in Crohn's disease. Inflammatory bowel diseases. 2012 Jul;18(7):1240-8.

103. Van Assche G, Vanbeckevoort D, Bielen D, *et al*. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. The American journal of gastroenterology. 2003 Feb;98(2):332-9.
104. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. The British journal of surgery. 1976 Jan;63(1):1-12.
105. Martinez MJ, Ripolles T, Paredes JM, *et al*. Assessment of the extension and the inflammatory activity in Crohn's disease: comparison of ultrasound and MRI. Abdominal imaging. 2009 Mar-Apr;34(2):141-8.
106. Migaleddu V, Scanu AM, Quaia E, *et al*. Contrast-enhanced ultrasonographic evaluation of inflammatory activity in Crohn's disease. Gastroenterology. 2009 Jul;137(1):43-52.
107. Neye H, Voderholzer W, Rickes S, *et al*. Evaluation of criteria for the activity of Crohn's disease by power Doppler sonography. Digestive diseases (Basel, Switzerland). 2004;22(1):67-72.
108. Limberg B. [Diagnosis of chronic inflammatory bowel disease by ultrasonography]. Zeitschrift fur Gastroenterologie. 1999 Jun;37(6):495-508.
109. Paredes JM, Ripolles T, Cortes X, *et al*. Abdominal sonographic changes after antibody to tumor necrosis factor (anti-TNF) alpha therapy in Crohn's Disease. Digestive diseases and sciences. 2010 Feb;55(2):404-10.
110. Calabrese E, Zorzi F, Zuzzi S, *et al*. Development of a numerical index quantitating small bowel damage as detected by ultrasonography in Crohn's disease. Journal of Crohn's & colitis. 2012 Sep;6(8):852-60.
111. Moreno N, Ripolles T, Paredes JM, *et al*. Usefulness of abdominal ultrasonography in the analysis of endoscopic activity in patients with Crohn's disease: changes following treatment with immunomodulators and/or anti-TNF antibodies. Journal of Crohn's & colitis. 2014 Sep;8(9):1079-87.
112. Zorzi F, Stasi E, Bevivino G, Scarozza P, *et al*. A sonographic lesion index for Crohn's disease helps monitor changes in transmural bowel damage during therapy. Clinical gastroenterology and hepatology. 2014 Dec;12(12):2071-7.
113. Calabrese E, Zorzi F, Onali S, *et al*. Accuracy of small-intestine contrast ultrasonography, compared with computed tomography enteroclysis, in characterizing lesions in patients with Crohn's disease. Clinical gastroenterology and hepatology. 2013 Aug;11(8):950-5.

114. Castiglione F, Bucci L, Pesce G, *et al*. Oral contrast-enhanced sonography for the diagnosis and grading of postsurgical recurrence of Crohn's disease. Inflammatory bowel diseases. 2008 Sep;14(9):1240-5.
115. Novak K, Tanyingoh D, Petersen F, *et al*. Clinic-based Point of Care Transabdominal Ultrasound for Monitoring Crohn's Disease: Impact on Clinical Decision Making. Journal of Crohn's & colitis. 2015 Sep;9(9):795-801.
116. Kiss LS, Szamosi T, Molnar T, *et al*. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. Alimentary pharmacology & therapeutics. 2011 Oct;34(8):911-22.
117. Hanauer SB, Sandborn WJ, Rutgeerts P, F *et al*. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006 Feb;130(2):323-33.
118. Lamireau T, Cezard JP, Dabadie A, *et al*. Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. Inflammatory bowel diseases. 2004 Nov;10(6):745-50.
119. Rutgeerts P, D'Haens G, Targan S, *et al*. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology. 1999 Oct;117(4):761-9.
120. Targan SR, Hanauer SB, van Deventer SJ, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. The New England journal of medicine. 1997 Oct 9;337(15):1029-35.
121. Reinisch W, Colombel JF, Sandborn WJ, *et al*. Factors associated with short- and long-term outcomes of therapy for Crohn's disease. Clinical gastroenterology and hepatology. 2015 Mar;13(3):539-47.e2.
122. Sipponen T, Bjorkesten CG, Farkkila M, *et al*. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scandinavian journal of gastroenterology. 2010 Mar;45(3):325-31.
123. Kiss LS, Papp M, Lovasz BD, *et al*. High-sensitivity C-reactive protein for identification of disease phenotype, active disease, and clinical relapses in Crohn's disease: a marker for patient classification? Inflammatory bowel diseases. 2012 Sep;18(9):1647-54.

124. Henderson P, Kennedy NA, Van Limbergen JE, *et al*. Serum C-reactive protein and CRP genotype in pediatric inflammatory bowel disease: influence on phenotype, natural history, and response to therapy. Inflammatory bowel diseases. 2015 Mar;21(3):596-605.
125. Click B, Vargas EJ, Anderson AM, P *et al*. Silent Crohn's Disease: Asymptomatic Patients with Elevated C-reactive Protein Are at Risk for Subsequent Hospitalization. Inflammatory bowel diseases. 2015 Oct;21(10):2254-61.
126. Kennedy NA, Kalla R, Warner B, *et al*. Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: relapse and recapture rates, with predictive factors in 237 patients. Alimentary pharmacology & therapeutics. 2014 Dec;40(11-12):1313-23.
127. Louis E, Mary JY, Vernier-Massouille G, *et al*. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012 Jan;142(1):63-70 e5.
128. Treton X, Bouhnik Y, Mary JY, *et al*. Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. Clinical gastroenterology and hepatology. 2009 Jan;7(1):80-5.
129. Reinisch W, Wang Y, Oddens BJ, *et al*. C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. Alimentary pharmacology & therapeutics. 2012 Mar;35(5):568-76.
130. Jones J, Loftus EV, Jr., Panaccione R, *et al*. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. Clinical gastroenterology and hepatology. 2008 Nov;6(11):1218-24.
131. Zubin G, Peter L. Predicting Endoscopic Crohn's Disease Activity Before and After Induction Therapy in Children: A Comprehensive Assessment of PCDAI, CRP, and Fecal Calprotectin. Inflammatory bowel diseases. 2015 Jun;21(6):1386-91.
132. Chamouard P, Richert Z, Meyer N, *et al*. Diagnostic value of C-reactive protein for predicting activity level of Crohn's disease. Clinical gastroenterology and hepatology. 2006 Jul;4(7):882-7.
133. Karoui S, Ouerdiane S, Serghini M, *et al*. Correlation between levels of C-reactive protein and clinical activity in Crohn's disease. Digestive and liver disease. 2007 Nov;39(11):1006-10.

134. Florin TH, Paterson EW, Fowler EV, *et al*. Clinically active Crohn's disease in the presence of a low C-reactive protein. Scandinavian journal of gastroenterology. 2006 Mar;41(3):306-11.
135. Yang DH, Yang SK, Park SH, *et al*. Usefulness of C-reactive protein as a disease activity marker in Crohn's disease according to the location of disease. Gut and liver. 2015 Jan;9(1):80-6.
136. Wright EK, Kamm MA, De Cruz P, *et al*. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology. 2015 May;148(5):938-47 e1.
137. Cerrillo E, Beltran B, Pous S, *et al*. Fecal Calprotectin in Ileal Crohn's Disease: Relationship with Magnetic Resonance Enterography and a Pathology Score. Inflammatory bowel diseases. 2015 Jul;21(7):1572-9.
138. Schoepfer AM, Beglinger C, Straumann A, *et al*. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflammatory bowel diseases. 2013 Feb;19(2):332-41.
139. D'Haens G, Ferrante M, Vermeire S, *et al*. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflammatory bowel diseases. 2012 Dec;18(12):2218-24.
140. Ferreiro-Iglesias R, Barreiro-de Acosta M, Otero Santiago M, *et al*. Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. Journal of clinical gastroenterology. 2016; 50(2):147-151.
141. Mooiweer E, Severs M, Schipper ME, *et al*. Low fecal calprotectin predicts sustained clinical remission in inflammatory bowel disease patients: a plea for deep remission. Journal of Crohn's & colitis. 2015 Jan;9(1):50-5.
142. De Cruz P, Bernardi MP, Kamm MA, *et al*. Postoperative recurrence of Crohn's disease: impact of endoscopic monitoring and treatment step-up. Colorectal disease. 2013 Feb;15(2):187-97.
143. Gecse KB, Brandse JF, van Wilpe S, *et al*. Impact of disease location on fecal calprotectin levels in Crohn's disease. Scandinavian journal of gastroenterology. 2015 Jul;50(7):841-7.
144. Allen PB, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. Current opinion in gastroenterology. 2013 Jul;29(4):397-404.

145. Peyrin-Biroulet L, Panes J, Sandborn WJ, *et al*. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clinical gastroenterology and hepatology. 2016; 14(3):348-54.

Supplementary information

Review criteria

A literature search was performed to evaluate available disease activity assessment indices within each of the prescribed domains; clinical, endoscopic, histologic, and radiologic assessment, biomarkers and quality of life.

Supplementary Table A1: List of disease activity indices for ulcerative colitis

Type of index	Index main name	Abbreviation; As known as (AKA)	Reference
Symptoms	Partial Mayo Score (2003)		(1, 2)
	Simple Clinical Colitis Activity Index (1998)	SCCAI	(3)
	Modified Truelove & Witts' index (1990)	MTWSI; Lichtiger score	(4)
	Ulcerative Colitis Clinical Score (2005)	UCCS	(5)
	Physician Global assessment (1993)	PGA	(6)
	Investigators Global Evaluation (1998)		(7)
	Paediatric Ulcerative Colitis Activity Index (2007)	PUCAI	(8)
	Beattie Paediatric Ulcerative Colitis Index (1996)		(9)
Symptoms and endoscopy	Mayo Clinic Score (1987)	DAI; Disease Activity Index; Mayo Score	(2)
	Sutherland index (1987)	UCDAI; Ulcerative colitis Disease Activity Index	(10)
	Powell-Tuck Index (1982)	PTI; St Mark's score	**(11)**
	Improvement based on individual symptom scores (2002)		(12)
	Rachmilewitz index (1989)	CAI; Clinical Activity Index	(13)

APPENDIX 1

Type of index	Index main name	Abbreviation; As known as (AKA)	Reference
Symptoms and biomarkers	Seo index (1992)	Seo; Activity Index	(14)
	Ho index	Edinburgh Index	(15)
	Truelove & Witts' index (1955)	T&W	(16)
	Montreal Classification (2006)		(17)
Endoscopy	Baron score (1964)	Baron	**(18)**
	Truelove and Witts' endoscopy index (1955)		(16)
	Powell-Tuck sigmoidoscopic index (1982)		(11)
	Sutherland Endoscopic Index (1987)		(10)
	Modified Baron Index (2005)		(5)
	Mayo Clinic Index: Endoscopic subscore (1987)	Mayo Endoscopy score	(2)
	Rachmilewitz endoscopic index (1989)		(13)
	Endoscopy Activity Index (2010)	EAI	(19)
	Matts index (1961)		(20)
	Ulcerative Colitis Endoscopic Index of Severity (2012)	UCEIS	(21, 22)
	Truelove and Richards Index (1956)		(23)
	Matts Score (1961)		(20)
	Watts Score (1966)		(24)
	Korelitz Index (1976)		(25)
	Powell-Tuck Score (1982)		(11)
	Keren Score (1984)		(26)
	Friedman Index (1986)		(27)
	Gomes Score(1986)		(28)
	Saverymutti Index (1986)		(29)
	Floren Index(1987)		(30)

Type of index	Index main name	Abbreviation; As known as (AKA)	Reference
	Initial Riley Score (1988)		(31)
	Riley Score (1991)		(32)
	Scheppach Score (1991)		(33)
	Hanauer Score (1993)		(6)
	Odze Score (1993)		(34)
	Sandborn Score (1993)		(35)
	Geboes Score (2000)		(36)
	Harpaz Score (2003)		(37)
	Rutter Score (2004)		(38)
	Modified Riley Score (2005)		(5)
	The Chicago Score (2007)		(39)
	Gupta Index (2007)		(40)
	Gramlich Index (2007)		(41)
	Baars Score (2012)		(42)
	The Nancy Histological Index (2015)	Nancy Index	(43)
	Robarts Histopathology Index (2015)	RHI	(44)
Imaging	US scoring system for ulcerative colitis (2010)		(45, 46)
	Tsuga colorectal ultrasound criteria (2005)		(47)
	Limberg Score (1999)		(48, 49)
	Segmental simplified magnetic resonance colonography index (2013)	MRC-S	(50)
	Segmental Magnetic Resonance Score (2010)	MR-score-S	(51)
Biomarkers	Oxford criteria in acute severe colitis (1996)	Oxford Criteria	(52)
Quality of life	Inflammatory Bowel Disease	IBDQ	(53)

Type of index	Index main name	Abbreviation; As known as (AKA)	Reference
	Questionnaire (1989)		
	Short Inflammatory Bowel Disease Questionnaire 1996)	SIBQD	(54)
	Crohn's Ulcerative Colitis Quality-8 (2015)	CUCQ-8	(55)
	Rating Form of IBD Patient Concerns (1991)		(56)
	UK Inflammatory Bowel Disease Questionnaire (2000)	UKIBDQ	(57)
	SF-36 (1992)		(58)

Supplementary Table A2: List of disease activity indices for Crohn's disease

Type of index	Index main name	Abbreviation As known as (AKA)	Reference
Symptoms	Crohn's Disease Activity Index (1976)	CDAI	(59)
	Harvey-Bradshaw Index (1980)	HBI	(60)
	Paediatric Crohn's Disease Activity Index (2007)	PCDAI	(8)
	Perianal Disease Activity Index (2005)	PDAI	(61)
	Fistula Drainage Assessment		(62)
	Organization Mondiale de Gastroenterologie (OMGE) index (1984)		(63)
	Van Hees Index (1980)	Dutch Index	(64)
	Cape Town Index (1985)		(65)
Endoscopy	Crohn's Disease Endoscopic Index of Severity (1989)	CDEIS	(66)
	Short Endoscopic Score for Crohn's disease (2004)	SES-CD	(67)
	Rutgeerts Post-operative (1984, 1990)		(68, 69)
Histopathology	Colonic and ileal Global Histologic Disease Activity Score (1999, 2005)	C/I GHAS	(70) (71)
	Nicholls Histological Score (1994)		(72)

Type of index	Index main name	Abbreviation As known as (AKA)	Reference
	Breese Histological Score (1995)		(73)
	Baars Histological Score (2012)		(42)
Imaging	Sonographic Lesion Index for Crohn's Disease (US) (2012)	SLIC	(74)
	Limberg Score (US) (1999)	Limberg	(48, 49)
	Magnetic Resonance Index of Severity (MRI) (2011)	MaRIA	(75, 76)
	Segmental Magnetic Resonance Score (2010)	MR-score-S	(51)
	MRI scoring system for Crohn's disease of the terminal ileum (2008)		(77)
	MRI scoring system for Crohn's disease of the terminal ileum (2011)		(78)
	MRI scoring system for Crohn's disease of the terminal ileum (2008)		(79-81)
Quality of Life	Inflammatory Bowel Disease Questionnaire (1989)	IBDQ	(53)
	Short Inflammatory Bowel Disease Questionnaire (1996)	SIBDQ	(54)
	Crohn's Ulcerative Colitis Quality-8 (2015)	CUCQ-8	(55)
	Rating Form of IBD Patient Concerns (1991)		(56)
	UK Inflammatory Bowel Disease Questionnaire (2000)	UKIBDQ	(57)
	SF-36 (1992)		(58)

REFERENCES

1. Sandborn WJ, Sands BE, Wolf DC, *et al*. Repifermin (keratinocyte growth factor-2) for the treatment of active ulcerative colitis: a randomized, double-blind, placebo-controlled, dose-escalation trial. Alimentary pharmacology & therapeutics. 2003 Jun 1;17(11):1355-64.
2. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. The New England journal of medicine. 1987 Dec 24;317(26):1625-9.
3. Walmsley RS, Ayres RC, Pounder RE, *et al*. A simple clinical colitis activity index. Gut. 1998 Jul;43(1):29-32.
4. Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. Lancet. 1990 Jul 7;336(8706):16-9.
5. Feagan BG, Greenberg GR, Wild G, *et al*. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. The New England journal of medicine. 2005 Jun 16;352(24):2499-507.
6. Hanauer S, Schwartz J, Robinson M, R *et al*. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. The American journal of gastroenterology. 1993 Aug;88(8):1188-97.
7. Hanauer SB, Robinson M, Pruitt R, *et al*. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. Gastroenterology. 1998 Sep;115(3):525-32.
8. Turner D, Otley AR, Mack D, *et al*. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007 Aug;133(2):423-32.
9. Beattie RM, Nicholls SW, Domizio P, *et al*. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. Journal of pediatric gastroenterology and nutrition. 1996 May;22(4):373-9.
10. Sutherland LR, Martin F, Greer S, *et al*. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987 Jun;92(6):1894-8.
11. Powell-Tuck J, Day DW, Buckell NA, *et al*. Correlations between defined sigmoidoscopic appearances and other measures of disease activity in ulcerative colitis. Digestive diseases and sciences. 1982 Jun;27(6):533-7.

12. Levine DS, Riff DS, Pruitt R, *et al*. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. The American journal of gastroenterology. 2002 Jun;97(6):1398-407.
13. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ (Clinical research ed). 1989 Jan 14;298(6666):82-6.
14. Seo M, Okada M, Yao T, *et al*. An index of disease activity in patients with ulcerative colitis. The American journal of gastroenterology. 1992 Aug;87(8):971-6.
15. Ho GT, Mowat C, Goddard CJ, *et al*. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. Alimentary pharmacology & therapeutics. 2004 May 15;19(10):1079-87.
16. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. British medical journal. 1955 Oct 29;2(4947):1041-8.
17. Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749-53.
18. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. British medical journal. 1964 Jan 11;1(5375):89-92.
19. Naganuma M, Ichikawa H, Inoue N, *et al*. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. Journal of gastroenterology. 2010 Sep;45(9):936-43.
20. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. The Quarterly journal of medicine. 1961 Oct;30:393-407.
21. Travis SP, Schnell D, Krzeski P, *et al*. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012 Apr;61(4):535-42.
22. Travis SP, Schnell D, Krzeski P, *et al*. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013 Nov;145(5):987-95.
23. Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. British medical journal. 1956 Jun 9;1(4979):1315-8.

24. Watts JM, Thompson H, Goligher JC. Sigmoidoscopy and cytology in the detection of microscopic disease of the rectal mucosa in ulcerative colitis. Gut. 1966 Jun;7(3):288-94.
25. Korelitz BI, Sommers SC. Responses to drug therapy in ulcerative colitis. Evaluation by rectal biopsy and mucosal cell counts. The American journal of digestive diseases. 1976 Jun;21(6):441-7.
26. Keren DF, Appelman HD, Dobbins WO, 3rd, *et al*. Correlation of histopathologic evidence of disease activity with the presence of immunoglobulin-containing cells in the colons of patients with inflammatory bowel disease. Human pathology. 1984 Aug;15(8):757-63.
27. Friedman LS, Richter JM, Kirkham SE, *et al*. 5-Aminosalicylic acid enemas in refractory distal ulcerative colitis: a randomized, controlled trial. The American journal of gastroenterology. 1986 Jun;81(6):412-8.
28. Gomes P, du Boulay C, Smith CL, *et al*. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986 Jan;27(1):92-5.
29. Saverymuttu SH, Camilleri M, Rees H, *et al*. Indium 111-granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease. A comparison with colonoscopy, histology, and fecal indium 111-granulocyte excretion. Gastroenterology. 1986 May;90(5 Pt 1):1121-8.
30. Floren CH, Benoni C, Willen R. Histologic and colonoscopic assessment of disease extension in ulcerative colitis. Scandinavian journal of gastroenterology. 1987 May;22(4):459-62.
31. Riley SA, Mani V, Goodman MJ, *et al*. Comparison of delayed-release 5-aminosalicylic acid (mesalazine) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. Gastroenterology. 1988 Jun;94(6):1383-9.
32. Riley SA, Mani V, Goodman MJ, *et al*. Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991 Feb;32(2):174-8.
33. Scheppach W, Sommer H, Kirchner T, *et al*. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology. 1992 Jul;103(1):51-6.
34. Odze R, Antonioli D, Peppercorn M, *et al*. Effect of topical 5-aminosalicylic acid (5-ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. The American journal of surgical pathology. 1993 Sep;17(9):869-75.

35. Sandborn WJ, Tremaine WJ, Schroeder KW, S *et al*. Cyclosporine enemas for treatment-resistant, mildly to moderately active, left-sided ulcerative colitis. The American journal of gastroenterology. 1993 May;88(5):640-5.
36. Geboes K, Riddell R, Ost A, *et al*. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000 Sep;47(3):404-9.
37. Fiel MQL SAea. Histologic grading of disease activity in chronic IBD: inter- and intra-observer variation amongst pathologists with different levels of experience. . Modern Pathology. 2003;16:118A.
38. Rutter M, Saunders B, Wilkinson K, *et al*. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004 Feb;126(2):451-9.
39. Rubin DT HJ, et al. Increased degree of histological inflammation predicts colectomy and hospitalization in patients with ulcerative colitis. Gut. 2007;132(Supplementary 1):A19.
40. Gupta RB, Harpaz N, Itzkowitz S, *et al*. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007 Oct;133(4):1099-105.
41. Gramlich T, Petras RE. Pathology of inflammatory bowel disease. Seminars in pediatric surgery. 2007 Aug;16(3):154-63.
42. Baars JE, Nuij VJ, Oldenburg B, *et al*. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflammatory bowel diseases. 2012 Sep;18(9):1634-40.
43. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, *et al*. Development and validation of the Nancy histological index for UC. Gut. 2017; 66(1): 43-49.
44. Mosli MH, Feagan BG, Zou G, *et al*. Development and validation of a histological index for UC. Gut. 2017; 66(1): 50-58.
45. Parente F, Molteni M, Marino B, *et al*. Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis?: a prospective study. The American journal of gastroenterology. 2010 May;105(5):1150-7.
46. Parente FA, Greco, S, et al. Response to high-dose steroids of severe attacks of ulcerative colitis may rely on bowel ultrasound instead of colonoscopy. A preliminary study . Gut. 2006;55 ((Suppl V)):A118.
47. Hurlstone DP, Sanders DS, Lobo AJ, *et al*. Prospective evaluation of high-frequency mini-probe ultrasound colonoscopic imaging in ulcerative colitis: a valid tool for

predicting clinical severity. European journal of gastroenterology & hepatology. 2005 Dec;17(12):1325-31.

48. Drews BH, Barth TF, Hanle MM, *et al*. Comparison of sonographically measured bowel wall vascularity, histology, and disease activity in Crohn's disease. European radiology. 2009 Jun;19(6):1379-86.
49. Limberg B. [Diagnosis of chronic inflammatory bowel disease by ultrasonography]. Zeitschrift fur Gastroenterologie. 1999 Jun;37(6):495-508.
50. Ordas I, Rimola J, Garcia-Bosch O, *et al*. Diagnostic accuracy of magnetic resonance colonography for the evaluation of disease activity and severity in ulcerative colitis: a prospective study. Gut. 2013 Nov;62(11):1566-72.
51. Oussalah A, Laurent V, Bruot O, *et al*. Diffusion-weighted magnetic resonance without bowel preparation for detecting colonic inflammation in inflammatory bowel disease. Gut. 2010 Aug;59(8):1056-65.
52. Travis SP, Farrant JM, Ricketts C, *et al*. Predicting outcome in severe ulcerative colitis. Gut. 1996 Jun;38(6):905-10.
53. Guyatt G, Mitchell A, Irvine EJ, *et al*. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar;96(3):804-10.
54. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. The American journal of gastroenterology. 1996 Aug;91(8):1571-8.
55. Alrubaiy L, Cheung WY, Dodds P, *et al*. Development of a short questionnaire to assess the quality of life in Crohn's disease and ulcerative colitis. Journal of Crohn's & colitis. 2015 Jan;9(1):66-76.
56. Drossman DA, Leserman J, Li ZM, *et al*. The rating form of IBD patient concerns: a new measure of health status. Psychosomatic medicine. 1991 Nov-Dec;53(6):701-12.
57. Cheung WY, Garratt AM, Russell IT, *et al*. The UK IBDQ-a British version of the inflammatory bowel disease questionnaire. development and validation. Journal of clinical epidemiology. 2000 Mar 1;53(3):297-306.
58. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992 Jun;30(6):473-83.
59. Best WR, Becktel JM, Singleton JW, *et al.* Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976 Mar;70(3):439-44.

60. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980 Mar 8;1(8167):514.
61. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. Journal of clinical gastroenterology. 1995 Jan;20(1):27-32.
62. Present DH, Rutgeerts P, Targan S, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. The New England journal of medicine. 1999 May 6;340(18):1398-405.
63. Myren J, Bouchier IA, Watkinson G, *et al*. The O.M.G.E. Multinational Inflammatory Bowel Disease Survey 1976-1982. A further report on 2,657 cases. Scandinavian journal of gastroenterology Supplement. 1984;95:1-27.
64. van Hees PA, van Elteren PH, van Lier HJ, *et al*. An index of inflammatory activity in patients with Crohn's disease. Gut. 1980 Apr;21(4):279-86.
65. Wright JP, Marks IN, Parfitt A. A simple clinical index of Crohn's disease activity--the Cape Town index. South African medical journal. 1985 Sep 28;68(7):502-3.
66. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989 Jul;30(7):983-9.
67. Daperno M, D'Haens G, Van Assche G, *et al*. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointestinal endoscopy. 2004 Oct;60(4):505-12.
68. Rutgeerts P, Geboes K, Vantrappen G, *et al*. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990 Oct;99(4):956-63.
69. Rutgeerts P, Geboes K, Vantrappen G, *et al*. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut. 1984 Jun;25(6):665-72.
70. D'Haens G, Van Deventer S, Van Hogezand R, *et al*. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology. 1999 May;116(5):1029-34.
71. Geboes K, Rutgeerts P, Opdenakker G, *et al*. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. Current medical research and opinion. 2005 Nov;21(11):1741-54.

72. Nicholls S, Domizio P, Williams CB, *et al*. Cyclosporin as initial treatment for Crohn's disease. Archives of disease in childhood. 1994 Sep;71(3):243-7.
73. Breese EJ, Michie CA, Nicholls SW, *et al*. The effect of treatment on lymphokine-secreting cells in the intestinal mucosa of children with Crohn's disease. Alimentary pharmacology & therapeutics. 1995 Oct;9(5):547-52.
74. Calabrese E, Zorzi F, Zuzzi S, *et al*. Development of a numerical index quantitating small bowel damage as detected by ultrasonography in Crohn's disease. Journal of Crohn's & colitis. 2012 Sep;6(8):852-60.
75. Rimola J, Ordas I, Rodriguez S, *et al*. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. Inflammatory bowel diseases. 2011 Aug;17(8):1759-68.
76. Rimola J, Rodriguez S, Garcia-Bosch O, *et al*. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut. 2009 Aug;58(8):1113-20.
77. Girometti R, Zuiani C, Toso F, *et al*. MRI scoring system including dynamic motility evaluation in assessing the activity of Crohn's disease of the terminal ileum. Academic radiology. 2008 Feb;15(2):153-64.
78. Gallego JC, Echarri AI, Porta A, *et al*. Ileal Crohn's disease: MRI with endoscopic correlation. European journal of radiology. 2011 Nov;80(2):e8-12.
79. Van Assche G, Herrmann KA, Louis E, *et al*. Effects of infliximab therapy on transmural lesions as assessed by magnetic resonance enteroclysis in patients with ileal Crohn's disease. Journal of Crohn's & colitis. 2013 Dec;7(12):950-7.
80. Sailer J, Peloschek P, Reinisch W, *et al*. Anastomotic recurrence of Crohn's disease after ileocolic resection: comparison of MR enteroclysis with endoscopy. European radiology. 2008 Nov;18(11):2512-21.
81. Koilakou S, Sailer J, Peloschek P, *et al*. Endoscopy and MR enteroclysis: equivalent tools in predicting clinical recurrence in patients with Crohn's disease after ileocolic resection. Inflammatory bowel diseases. 2010 Feb;16(2):198-203.