Bile Reflux Post-Bariatric Surgery

by

Thomas Andrew Eldredge

A thesis submitted for the degree of

Doctor of Philosophy

Discipline of Surgery, School of Medicine
Faculty of Health & Medical Sciences
The University of Adelaide

February 2022

Table of Contents

Thesis Abstract

Introduction

Metabolic and obesity surgery (MOS) is proven to be our most effective treatment for obesity, resulting in profound and sustained metabolic improvements. The one-anastomosis gastric bypass (OAGB) is a burgeoning procedure with equivalent, if not superior, outcomes to the two most-commonly performed procedures: sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). However, utilisation of the procedure has been marred by contention surrounding oesophageal bile reflux and the associated long-term carcinogenic potential. Bile reflux is difficult to diagnose with no gold-standard investigation. The few studies investigating bile reflux post-MOS use diverse diagnostic methods, and as such, data on the incidence and severity of oesophageal bile reflux is limited, with comparative studies lacking.

Objectives:

1. To review existing diagnostic techniques for bile reflux diagnosis and develop a specifically tailored diagnostic protocol, optimised for use in a post-MOS cohort.
2. To use this tailored diagnostic protocol to investigate the incidence, severity, and sequelae of gastric and oesophageal bile reflux after OAGB, SG and RYGB.

Methods

A systematised review of PubMed and EMBASE databases was undertaken to identify and compare available techniques for detection of bile reflux. The findings were considered in the context of the anatomical and physiological changes incurred by MOS, with specific issues identified and solutions implemented to develop an optimal diagnostic approach in this cohort. Utilising this study protocol, a non-randomised prospective study was undertaken involving fifty-eight participants who underwent OAGB (20), SG (15) or RYGB (23) between November

2018 - July 2020. Pre-operative reflux symptom assessment, acid-suppression therapy usage and gastroscopy (+ biopsies and gastric fluid bilirubin analysis) were performed and repeated post-operatively at 6-months along with modified biliary scintigraphy.

Results

Gastric reflux of bile was identified by biliary scintigraphy in 14 OAGB (70%), one RYGB (5%) and four SG participants (31%), with a mean of 2.9% (SD 1.5) reflux (% of total radioactivity). Only one participant (OAGB) demonstrated oesophageal bile reflux. *De novo* macro- or microscopic gastroesophagitis occurred in 11 OAGB (58%), 8 SG (57%), and 7 RYGB (30%) participants. Of note, complete resolution of macroscopic oesophagitis occurred in 100% (n=4) of OAGB participants, with no *de novo* development of macroscopic findings. Improved post-operative reflux scores were observed in 21 participants (OAGB – 10; SG – 3; RYGB – 8), whereas worsened scored were observed in 13 participants (OAGB – 4; SG – 7; RYGB – 2). OAGB was the only procedure with a statistically significant improvement in reflux symptom score. Positive scintigraphic bile reflux bore no statistical association with *de novo* gastroesophagitis, or worsened reflux symptoms.

Conclusions

Despite high incidence of gastric bile reflux post-OAGB, oesophageal bile reflux is rare. With scarce literature of tumour development post-OAGB, frequent low volume gastric bile reflux likely bears little clinical consequence, however longer-term studies are needed to fully elucidate risk of prolonged gastric bile exposure.

Thesis 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.

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

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Thomas Andrew Eldredge

Date: 27/2/2022

Published works

Below are the published works contained within this dissertation, as well as a list of scientific meetings at which the research has been presented. I acknowledge the copyright of the works listed below belongs to the copyright holder of those works.

Scientific publications

Eldredge T A, Myers J C, Kiroff G K, Shenfine J. *Detecting Bile Reflux – The Enigma of Bariatric Surgery.* Obesity Surgery. 2018 Feb;28(2):559-566. DOI: 10.1007/s11695-017-3026-6.

Eldredge T A, Myers J C, Kiroff G K, Shenfine J. *Response to Letter to the Editor: Detecting Bile Reflux – The Enigma of Bariatric Surgery.* Obesity Surgery. 2018 Jul;28(7):2052. DOI: 10.1007/s11695-018-3277-x

Eldredge T A, Bills M, Myers J C, Bartholomeusz D, Kiroff G K, Shenfine J. *HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery.* Obesity Surgery. 2020 May;30(5):2038-2045. DOI: 10.1007/s11695-020-04510-7

Eldredge T A, Bills M, Ting Y Y, Dimitri M, Watson M W, Harris M C, Myers J C, Bartholomeusz D, Kiroff G K, Shenfine J. *Once in a Bile – The Incidence of Bile Reflux Post-Bariatric Surgery.* Obesity Surgery. 2022 Feb (published online 28/2/22). DOI: 10.1007/s11695-022-05977-2

> *Obesity Surgery* is Published by Springer Nature Switzerland AG for the *International Federation for the Surgery of Obesity & Metabolic Disorders.* (Print ISSN 0960-8923; Online ISSN 1708-0428). Text of above publications presented within thesis reproduced with permission.

Conference presentations

Oral presentations

Eldredge T A. "Detecting Bile Reflux – The Enigma of Bariatric Surgery" SA Training Committee Registrar's Paper Day, General Surgeons Australia, 4 August 2018, Adelaide Pavilion, Adelaide.

Eldredge T A. "Objective Investigation of Patients with Problematic Reflux Symptoms Post-Bariatric Surgery" Annual Conference, Australian & New Zealand Metabolic and Obesity Surgery Society, 6-7 September 2018, Pullman Albert Park, Melbourne.

Eldredge T A. "Challenges of Medical Imaging for Bile Reflux after Obesity Surgery." Basil Hetzel Institute Research Expo, 10-11 October 2019, Basil Hetzel Institute, Adelaide.

Eldredge T A. "Biliary Scintigraphy provides accurate data on the incidence and extent of bile reflux post-bariatric surgery." Annual Scientific Meeting, Australia and New Zealand Society of Nuclear Medicine, Virtual platform, 21-23 May 2021.

Eldredge T A. "Bile Reflux After One Anastomosis Gastric Bypass - A Wolf in Sheep's Clothing or Just a Sheep?" Annual Conference, Australian & New Zealand Metabolic and Obesity Surgery Society, 27-29 October 2021, Cairns, Australia (online conference).

Eldredge T A. "Bile Reflux After One Anastomosis Gastric Bypass - A Wolf in Sheep's Clothing or Just a Sheep?" International Federation for the Surgery of Obesity and Metabolic Disorders 25th World Congress, 19-23 October 2021, Miami, Florida, USA. **Conference delayed due to COVID-19 restrictions, after pre-recorded oral presentation already submitted. Rescheduled for 23-27 August 2022.*

Poster presentations

Eldredge T A. “Bile Reflux - The Storm in the Weight Loss Surgery Teacup.” University of Adelaide 15th Annual Florey Postgraduate Research Conference, 22 September 2021, Adelaide, Australia. **Accepted for poster presentation; withdrawn post acceptance due to COVID-19 cross border restrictions preventing presentation.*

Eldredge T A. “Bile Reflux - The Storm in the Weight Loss Surgery Teacup.” Royal Australasian College of Surgeons Annual Academic Surgery Conference 2021, 4 November 2021, Adelaide, Australia.

Acknowledgements

It is only fitting that I thank my amazing supervisors first and foremost. From what started as a casual conversation about a small potential research project, your belief in me led to a full-time PhD – a trajectory I never anticipated!

Jon- you are the surgeon I aspire to be. Seeing the love and respect you receive from your patients and colleagues is testament to the brilliant surgeon and human being you are. You have been such an inspirational mentor and I am very grateful for all the support and guidance you have given me.

George – your vast knowledge and pragmatism have truly guided me through the unknown waters involved in undertaking a PhD. You have been unwavering in your support of not only this project, but my life and career at large, despite the personal hurdles you have faced. I would certainly not be where I am today without your foresight and encouragement.

Jenny – I would have been absolutely lost without your eye for detail and 'lived experience'. Thank you for the myriad phone calls and emails answering all my queries, no matter how trivial. You truly formed a crucial part of my supervisory team with your fine-toothed comb and red marker.

Thank you to my collaborators - Dylan Bartholomeusz, Madi Bills and Mikayla Dimitri. You are an incredible group of people, and it has been an absolute pleasure to work with you. Your enthusiasm, vision and support made our ideas possible and led us to completion of a fantastic project. This extends to Ying Yang Ting, Matt Watson and Mark Harris for helping with data collection and patient follow-up when I wasn't able. You are absolute legends and I know good things are coming for all of you. Thank you also to Martin Bruening for being so willing to perform endoscopies and sample collection for our trial participants.

I am very grateful to The Royal Australasian College of Surgeons, who made it possible for me to solely focus on my research by honouring me with the RP Jepson Research Scholarship. I hope I made Professor Jepson proud. The lovely research team at The Queen Elizabeth Hospital also deserve a shout-out. Jess Reid and Jessie Clarke – I loved sharing an office with you two and won't forget the good times and banter we had.

Clinical trials rely on the kindness of strangers. Without my amazing participants kindly donating their time and bodies, there would have been no research at all, let alone a thesis to write. Words cannot express my appreciation to these kind-hearted individuals and their selflessness; I am forever indebted to you. This appreciation extends to the surgeons who supported me in this project and were willing to allow me to invite their patients to participate: Philip Game, Lilian Kow, Jacob Chisholm, Markus Trochsler, Harsh Kanhere and Shalvin Prasad.

I am forever grateful to my parents - thank you for being my biggest fans and for not only letting me fly the coop all those years ago to try my hand at becoming a doctor but also your loving support ever since. I would also like to thank my second family - Ali, Eamonn, Pat and Phoebe. I couldn't have asked for a more caring, inclusive, and supportive family-in-law, with a touch of craziness to keep things interesting. Thank you for treating me like family from day 1.

Lastly, I would like to thank my amazing wife, Jess. You, along with Frankie, have been an unwavering support for me throughout the highs and lows of this degree. We have conquered living apart for months on end and living almost on top of each other for what seemed like an eternity during Melbourne lockdowns. Throughout all this, your endless patience and support has enabled our love to grow only stronger. I can't wait to see what the next chapter (of life, not thesis) holds for us.

Abbreviations

AUD	Australian dollars
BMI	Body mass index
BO	Barrett's oesophagus
BP	Biliopancreatic
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion with duodenal switch
CCK	Cholecystokinin
CHO	Carbohydrate
CT	Computed tomography
DGOR / DGER	Duodeno-gastro-(o)esophageal reflux
DGR	Duodenogastric reflux
DIS	Dilated intercellular space
DNA	Deoxyribonucleic acid
EGD	Esophagogastroduodenoscopy
EWL	Excess weight loss
Fr.	French size (external diameter) of the French gauge system
FXR	Farnesoid X receptor
GB	Gastric bypass
GIT	Gastrointestinal tract
GORD / GERD	Gastro-(o)esophageal reflux disease
GP	General practitioner
HIDA	Hepatobiliary iminodiacetic acid
HRIM	High resolution impedance manometry

IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders
IV	Intravenous
JIB	Jejuno-ileal bypass
LA	Los Angeles
LOS	Lower oesophageal sphincter
MII-pH	Multi-channel intraluminal impedance-pH
MOS	Metabolic and obesity surgery
MRI	Magnetic resonance imaging
mSv	Millisieverts
NAFLD	Non-alcoholic fatty liver disease
NF-kB	Nuclear factor-kappa B
NPY	Neuropeptide Y
OAGB	One-anastomosis gastric bypass
PPI	Proton pump inhibitor
PYY	Peptide YY; Peptide tyrosine-tyrosine
ROC	Receiver operating characteristic
ROI	Region of interest
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
SPECT	Single photon emission computed tomography
Tc-99m	Technitium-99m
TGR5	Takeda G protein-coupled receptor 5
UGIE	Upper gastrointestinal endoscopy

Thesis Overview

Metabolic and obesity surgery (MOS) is the most effective intervention available to combat the obesity epidemic. The one anastomosis gastric bypass (OAGB) is a procedure growing in popularity due to excellent metabolic improvement and technical advantages over other MOS procedures. Significant concern exists regarding bile reflux (the movement of bile from the small intestine into the stomach and oesophagus) after OAGB, which may damage gastric and oesophageal tissue irreversibly, including risk of carcinogenesis. Bile reflux is challenging to diagnose however, with the few published studies evaluating bile reflux after MOS utilising heterogenous diagnostic protocols, due to the absence of a 'gold standard' investigation. The aim of the presented body of research is to develop a tailored diagnostic protocol for optimal diagnosis of post-operative bile reflux, enabling evaluation of the incidence and severity after OAGB, with comparison to the two most-commonly performed MOS procedures: sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). Elucidating the incidence and severity of bile reflux will further our understanding of the safety of these procedures in the context of potential lifelong oesophageal mucosal exposure to bile.

Firstly, the best method for diagnosing bile reflux must be determined, particularly considering the anatomical and physiological changes that occur after MOS. Study 1 (Chapter 3) is a systematised review evaluating all available methods for bile reflux diagnosis based on: sensitivity and specificity; patient tolerability; infrastructure and skill requirements; and cost. This review demonstrated a combination of biliary scintigraphy and upper gastrointestinal endoscopy to be optimal. Study 2 (Chapter 4) demonstrates the efficacy and reproducibility of the modified biliary scintigraphy protocol I developed for a post-MOS cohort, incorporating 3 changes to address the anatomical and physiological alterations secondary to surgery: 1) inclusion of a single positron emission / computed tomography (SPECT-CT) scan for improved anatomical localisation of bile reflux; 2) ingestion of a 'fatty meal' to improve impaired gallbladder emptying following gastric bypass procedures; and 3) longer scan duration (75-90min), to allow adequate gallbladder filling/emptying and for bile to pass beyond the gastro-jejunal anastomosis.

The substantive component of this thesis is a non-randomised, prospective, multi-centre, multi-arm clinical trial investigating the incidence and severity of post-operative bile reflux after SG, RYGB and OAGB (Study 3 – Chapter 5). The key findings of the trial illustrate high incidence of duodenogastric reflux post-OAGB (70%), compared with SG (31%) and RYGB (5%), but more importantly, the incidence of oesophageal bile reflux is rare, occurring in only one patient, post-OAGB. Interestingly, the study also demonstrated indistinguishable incidence of *de novo* gastro-oesophagitis between OAGB and SG; 58% and 57% respectively, despite a large disparity in duodenogastric reflux incidence. Further, OAGB was the only procedure with a statistically significant improvement in overall reflux symptom score; OAGB had the greatest number of patients with improved symptoms, and SG had the greatest number with worsened symptoms.

The findings of these investigations show that low volume bile reflux occurs frequently after OAGB, and to a lesser extent, SG and RYGB, but no association exists between positive bile reflux and worsened reflux symptoms and/or development of *de novo* gastro-oesophagitis. Oesophageal bile reflux, which is of greater clinical concern, occurs rarely, dispelling a major concern and criticism of the procedure. With only two case reports of cancer development post-OAGB with improbable causation, despite a 20-year time frame from inception, the occurrence of duodenogastric reflux post-operatively appears clinically insignificant. This research contributes to the growing body of evidence demonstrating the safety and efficacy of the OAGB, supporting increased future utilisation of the procedure, translating to improved patient outcomes.

CHAPTER 1:

Introduction

1.1. Obesity and Bariatric Surgery in Australia

The World Health Organisation defines being overweight and obese as having a body mass index (BMI) ≥25kg/m² and ≥30kg/m² respectively (World Health Organisation 2017) (Figure 1.1.1). Obesity is a major health issue, and in Australia the prevalence of individuals being overweight and obese is increasing at a concerning rate. Most alarmingly, the rate of severe obesity (BMI ≥35kg/m²) more than doubled between 1995 and 2017/18 from 4.9% to 11% (Australian Institute of Health and Welfare 2019). In 2017/18, 67% of Australian adults (aged 18 and over) were overweight or obese with a preponderance for men (75%; 60% for females), indigenous people (69%; 67% for non-indigenous), low socio-economic status (72%; 62% for those in highest group) and regional/remote populations (70%; 65% for those in major cities) (Australian Institute of Health and Welfare 2019). Drivers of obesity are multi-factorial, including convenience of access to cheap, highly processed and high caloric foods, and increasingly sedentary lifestyles (Allender *et al.* 2012).

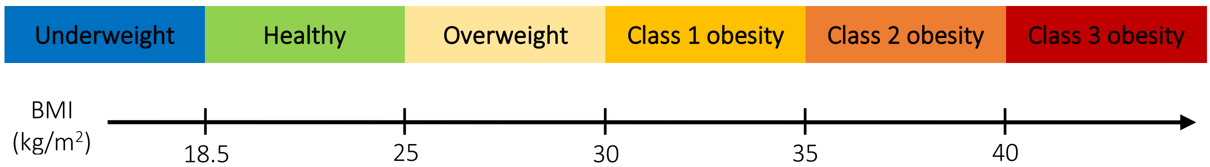


Figure 1.1.1: Weight classes, categorised based on body mass index (BMI) (National Health and Medical Research Council 2013)

At the individual level, obesity is a risk factor for the development of many other chronic diseases. Obesity-related comorbidities include type 2 diabetes mellitus, dyslipidaemia, sleep apnoea, hypertension, and osteoarthritis (Nguyen *et al.* 2008). Obesity also increases the risk of developing cardiovascular disease, stroke, non-alcoholic fatty liver disease (NAFLD) and numerous cancers (Bogers *et al.* 2007; Milic, Lulic & Stimac 2014; Renehan *et al.* 2008). Medical conditions unrelated to obesity are more difficult to treat in the obese population, translating to longer hospital admissions and, if requiring surgery, increased risk of adverse outcomes from both anaesthetic and surgical viewpoints (American Society of Anesthesiologists 2014; Ri, Aikou & Seto 2018).

Obesity has numerous health and financial implications for Australians individually and as a nation. The burden of obesity on the Australian economy was estimated to be $8.6 billion Australian dollars (AUD) in 2011-12, including direct ($3.8b) and indirect ($4.8b) costs (PricewaterhouseCoopers 2015). Applying these cost assumptions to the 2017/2018 population estimates of people with obesity, which still underestimates current day figures, the cost of obesity increases to an estimated $11.8 billion AUD; $5.4b direct and $6.4b indirect costs (The Obesity Collective 2019). In 2014/15 more than 124,600 procedures relating to weight-loss surgery were billed to Medicare at a cost of $25.7m, and a further $37.1m paid by patients and/or health insurance providers (Australian Institute of Health and Welfare 2017b). Alarmingly, current trends imply the prevalence and associated costs of obesity will continue to increase unless there are major population-level changes.

Multi-disciplinary input from dieticians, exercise physiologists / physiotherapists, psychologists, nurses, and medical practitioners forms the optimal approach for successful weight loss. Intervention strategies to induce weight loss include lifestyle modification, pharmacological and surgical approaches. Unfortunately, medical therapies alone continue to disappoint, compared to surgical interventions where effective and sustained weight loss is more consistently achieved. Compared with medical therapy alone, the addition of metabolic and obesity surgery (MOS) is more effective in reducing obesity-related mortality (Pontiroli & Morabito 2011), cardiovascular events (Kwok *et al.* 2014), type 2 diabetes (Mingrone *et al.* 2015; Schauer *et al.* 2017) and NAFLD (Fakhry *et al.* 2019). Economic models in the USA and UK have shown cost-effectiveness of metabolic and obesity surgery with decreased healthcare expenditure over a patient's lifetime when compared with no surgery (Alsumali *et al.* 2018; Borisenko, Lukyanov & Ahmed 2018). Maximal cost-effectiveness was seen in diabetic patients and those with higher BMI. In patients with BMI 35-43, sleeve gastrectomy was the most cost-effective procedure, with Roux-en-Y gastric bypass more cost-effective in patients with BMI greater than 43 (Alsumali *et al.* 2018). Surgery is only considered however, if patients meet certain eligibility criteria stipulated by the National Health and Medical Research Council (Figure 1.1.2) (National Health and Medical Research Council 2013).

Eligibility criteria for metabolic and obesity surgery:

- BMI >40kg/m^2 **OR** BMI >35kg/m^2 PLUS ≥1 obesity-related complications*
- Documented previous attempts at weight loss
- Positive attitude to permanent lifestyle modification

*Complications include type 2 diabetes, hypertension, dyslipidaemia, obstructive sleep apnoea, non-alcoholic fatty liver disease, debilitating arthritis, or considerably impaired quality of life.

Figure 1.1.2: Eligibility criteria for weight-loss surgery (National Health and Medical Research Council 2013)

The rate of paediatric patients meeting the eligibility criteria for, and undergoing, MOS is increasing. This concerning trend warrants a clear understanding of the long-term post-operative risks, such as potential lifelong exposure to bile reflux, the substantive topic of this thesis. Adolescent obesity confers an increased risk of developing numerous comorbidities in adulthood, regardless of adult BMI (Inge *et al.* 2013). The cumulative effect of obesity from adolescence into adulthood also places this cohort at an increased risk of death (Inge *et al.* 2013). The evidence base for MOS in adolescents is now well established, supported by data from three large international studies: The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) trial, the Adolescent Morbid Obesity Surgery (AMOS) Trial, and the Follow-up of Adolescent

Bariatric Surgery study (FABS 5+) (Inge *et al.* 2019; Inge *et al.* 2017; Olbers *et al.* 2017). The optimal timing of surgery in this cohort is yet to be determined, however. Beamish and Olbers are currently leading the AMOS-2 Trial to investigate the benefit of surgery at time of recruitment (age 13-16) compared with a 2-year intensive medical therapy program prior to surgery (Beamish & Olbers 2019). Participants (n=50) are randomised to either Roux-en-Y gastric bypass or intensive medical therapy and followed up 2, 7, 12 and 17 years after treatment commencement to assess weight change/ BMI, metabolic control, and quality of life among other outcomes. Undergoing MOS in adolescence exposes this cohort of patients to lifelong post-operative sequelae that may have long-term ramifications. Chronic malabsorption may require ongoing supplementation of macro- and micronutrients (see Chapter 1.3.2). Exposure to post-operative bile reflux, the substantive topic of this thesis, has the potential for development of pre-malignant and malignant lesions of the oesophagus (see Chapter 1.4.3). Investigating the long-term safety and efficacy of MOS in adolescents is vital; exposure to these potential sequelae from adolescence demands a clear understanding of the risks to be considered alongside the potential benefits in this cohort.

Current trends in population obesity will continue to place financial stress on the economy and more specifically the healthcare system. The health and economic benefit of bariatric surgery in adult and paediatric populations is established, but further work is needed to further understand the safety and efficacy of surgical interventions.

1.2. Metabolic & Obesity Surgery and Gastro-intestinal Anatomy

In current practice, metabolic and obesity surgery produces safe and sustainable weight loss with significant improvements in obesity-related comorbidities. The history of surgical weight loss, however, is littered with failures and catastrophes.

1.2.1. Evolution of Bariatric Surgery

The mechanisms of post-operative weight loss are complex, multifactorial processes incorporating many organ systems, however in the early development of metabolic and obesity surgery, two basic concepts predominate:

1. Malabsorption - Surgery which limits calories by bypassing a portion of the normal absorbing gastrointestinal tract (GIT).
2. Restriction – Surgery which limits calories by simply reducing how much food can be taken in, usually through reduction in gastric capacity

10th Century AD

The earliest report of 'weight loss surgery' dates back to the 10th century Spain (Hopkins & Lehmann 1995). The Ruler of Leon, King Sancho I ('Sancho the fat'), was usurped on the grounds of being unfit to rule due to his obesity. His grandmother took him to see a learned physician in Cordoba, who sutured his mouth shut and fed him a liquid-only diet containing *teriaca*: a mixture of herbs containing opium. He successfully lost half his weight, returned to Leon, and reclaimed his throne! This is the earliest description of *restrictive* weight loss surgery.

The need for surgical weight loss had been established, however it took centuries for knowledge to advance and enable more effective, but invasive, procedures on the gastrointestinal tract.

1950s

Through decades of observation, clinicians identified a link between intestinal resection and weight loss. Increasing knowledge of the deleterious effects of obesity prompted the consideration of bowel resection to treat morbid obesity, utilising the *malabsorptive* concept of weight loss.

The earliest report of 'modern' metabolic and obesity surgery is attributed to the Swedish surgeon, Dr Viktor Henrikson, in 1952 (Henrikson 1994). He resected 105cm of small intestine in a 32-year-old female with severe obesity (actual weight not reported), with the aim of inducing weight loss and improving intestinal function. Fourteen months post-operatively her weight had increased by 2kg, however she reported significant improvement in bowel function and general health. This novel case report heralded several similarly innovative, albeit ultimately unsuccessful, weight loss procedures, many of which lack detail in the biometric data recorded, surgical technique, location of resected bowel and amount of remaining bowel.

However, shortly thereafter, a prototype procedure for weight loss was described, the *jejunoileal bypass (JIB)*. Pioneered in 1954 by Dr. Arnold Kremen from Mount Sinai Hospital in Minneapolis, based on canine experimental work, the procedure involved bypassing two-thirds of the small intestine, from proximal jejunum (35cm from *ligament of Treitz*[1]) to terminal ileum (Kremen, Linner & Nelson 1954) (Figure 1.2.1). Their first patient, a woman weighing 130kg and measuring

1 *Ligament of Treitz* – a thin suspensory muscle connecting the duodenum and jejunum posteriorly to connective tissue. It marks the formal demarcation between the duodenum and jejunum.

162cm in height (BMI 49.5kg/m^2), lost 30kg initially and with re-operation to further shorten small bowel length, reached a nadir weight of 77kg (BMI 29.3kg/m^2). Using this technique, a larger study of 70 patients affirmed the procedure's weight loss success; averaging 3.7kg per month weight loss for the first year and 2.1kg and 1kg per month for the second and third years respectively (Payne & DeWind 1969).

Building on the knowledge from the JIB procedure, Payne *et al*. published in 1963, a case series of ten women incorporating a modification affecting small & large bowel; bypassing from the proximal jejunum (35cm from ligament of Treitz) to the transverse colon (*jejunocolic bypass/shunt*) (Figure 1.2.1) (Payne, Dewind & Commons 1963). The study design was to reverse the bypass once the ideal body weight had been achieved (definition not reported). The study found good initial weight loss but had an unacceptable rate of complications and significant weight re-gain post-reversal: one patient died from a pulmonary embolism prior to reversal, two patients required premature reversal due to serious metabolic disturbances, four patients returned to their pre-operative weight, and five had significant electrolyte abnormalities.

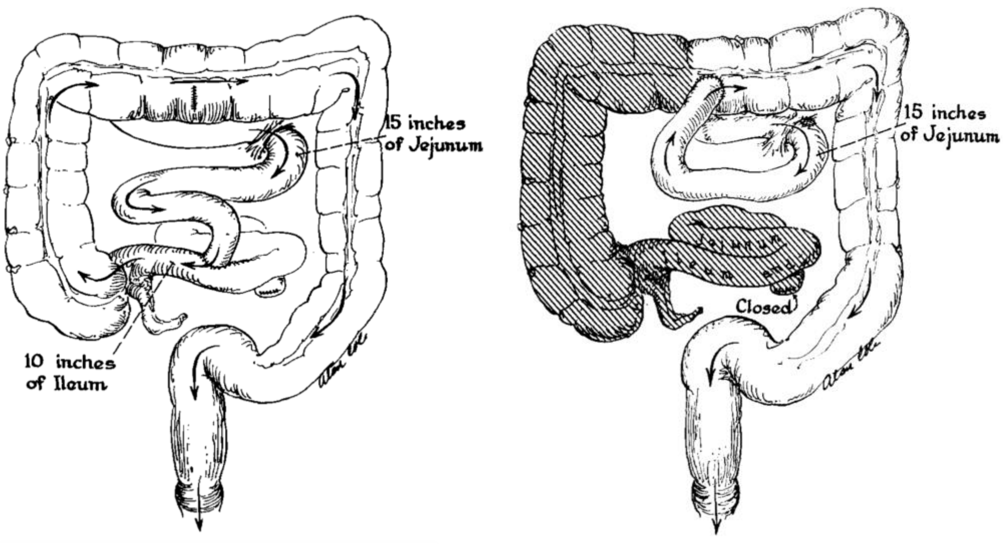


Figure 1.2.1: Left – Jejunoileal bypass procedure; Right – Jejunocolic bypass/shunt procedure. *Reproduced from Payne et al. Am J Surg 1963, with permission from Elsevier©; Amsterdam, Netherlands (Payne, Dewind & Commons 1963).*

1960s – 1970s

Over time, *jejuno-colic bypass* was abandoned due to the associated risks of intractable diarrhoea, electrolyte derangement and liver dysfunction (Payne & DeWind 1969). Whereas an adapted JIB was widely adopted, using an end-to-end jejunoileal anastomosis, with drainage of the closed jejunum loop into the colon. The adaptation was recommended after a trial of 4 different JIB configurations reported 100% (11/11) of patients with an end-to-side anastomosis had either unsatisfactory weight loss, metabolic deficits or troublesome diarrhoea (Scott *et al.* 1976). Numerous studies evaluated *jejunoileal bypass* surgery with differing lengths of remaining jejunum and ileum and the location of the jejuno-colonic drainage; however, no configuration proved superior (Buchwald & Varco 1971; Salmon 1971; Scott *et al.* 1977). Although all these techniques demonstrated acceptable weight loss, the morbidity rate was high, with up to 58% of patients having major complications including liver failure or fibrosis, recurrent kidney stones and gallstones (Halverson *et al.* 1978). Further, up to one fifth of patients required surgical reversal for liver failure or unmanageable electrolyte derangements.

Around the same time, American surgeon Dr. Edward Mason, widely touted as the father of bariatric surgery, began utilising both 'restrictive' and 'mixed restrictive/ malabsorptive' methods of surgical weight loss.

Ed Mason as he was known, along with Japanese surgeon Chekashi Ito, developed the first *gastric bypass* (GB) procedure adopting a 'mixed restrictive/malabsorptive' mechanism of weight loss (Mason & Ito 1967). The procedure involved horizontal transection of the upper stomach to create a small pouch (restrictive component) followed by a loop gastrojejunostomy (malabsorptive component) (Figure 1.2.2). In 1977, Alden reported a simple modification to *Mason's GB* by stapling, but not dividing, the upper stomach. Although not explicitly stated, the impetus for modification was presumably to reduce the risk of staple line leaks and bleeding

(Alden 1977). In a study comparing *GB* with *JIB*, Griffen observed bilious vomiting in a number of *GB* patients, modifying his bypass technique to a *Roux-en-Y*[2], rather than loop, gastrojejunostomy to prevent bile reflux into the proximal stomach (Griffen, Young & Stevenson 1977) (Figure 1.2.2). Although nausea persisted for some patients, bilious vomiting improved significantly. *Gastric bypass* superseded *JIB* as the predominant weight loss operation after the comparative studies by Alden and Griffen demonstrated significantly fewer long-term complications.

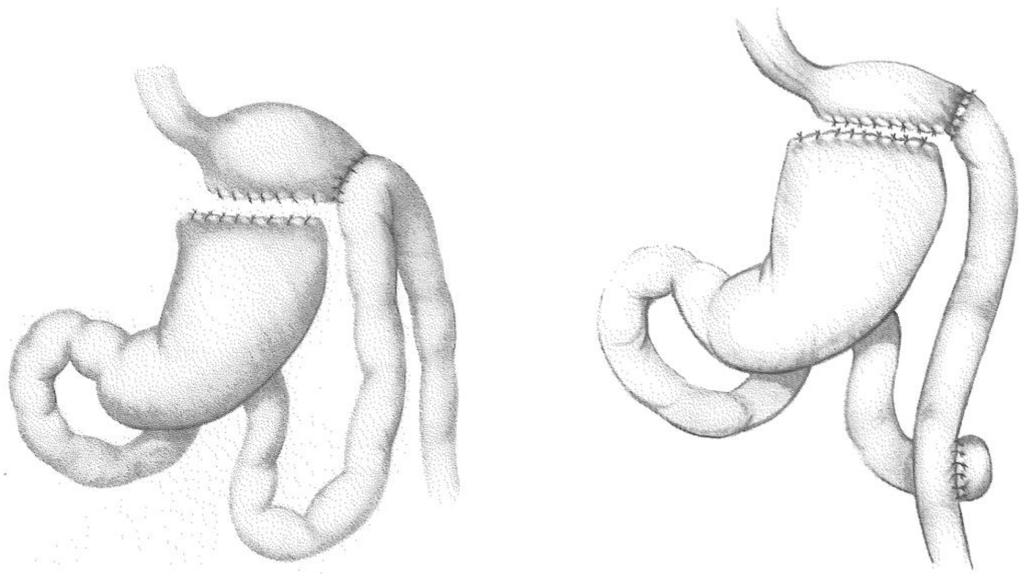


Figure 1.2.2: Left: Mason gastric bypass. Right: Griffen gastric bypass. Images adapted from Linner *et al.* (Linner 1987) with permission from Elsevier ©, Amsterdam, Netherlands.

Mason also described the *horizontal gastroplasty* in 1971, fashioning a small upper gastric pouch with a connection to the remainder of the stomach via an opening near the greater curvature (Figure 1.2.3) (Printen & Mason 1973). Inadequate weight loss in comparison to *gastric bypass* was observed, with median weight loss of 53lbs (24kg) at 12 months, compared with 100lbs

---

2 The R*oux-en-Y* procedure is named after the Swiss surgeon César Roux (1857-1934), after he described a method of bypassing a gastric outlet obstruction (Hutchison & Hutchison 2010). The 'Y' comes from the vague similarity of the procedure diagrammatically resembling the letter. The procedure is described later in this chapter.

(45kg); attributable to dilation of the proximal stomach and widening of the greater curvature channel.

1980s

Despite numerous technique modifications of the *horizontal gastroplasty*, inadequate weight loss persisted. This prompted change to a *vertical gastroplasty* to exclude the distensible gastric fundus, while retaining secretory and digestive functions (Figure 1.2.3). The *vertical banded gastroplasty* of 1982 (Mason 1982) initially gained popularity for favourable short-term weight loss, however weight regain and high rates of surgical revision and conversion operations (>20%) saw popularity wane (Marsk *et al.* 2009).

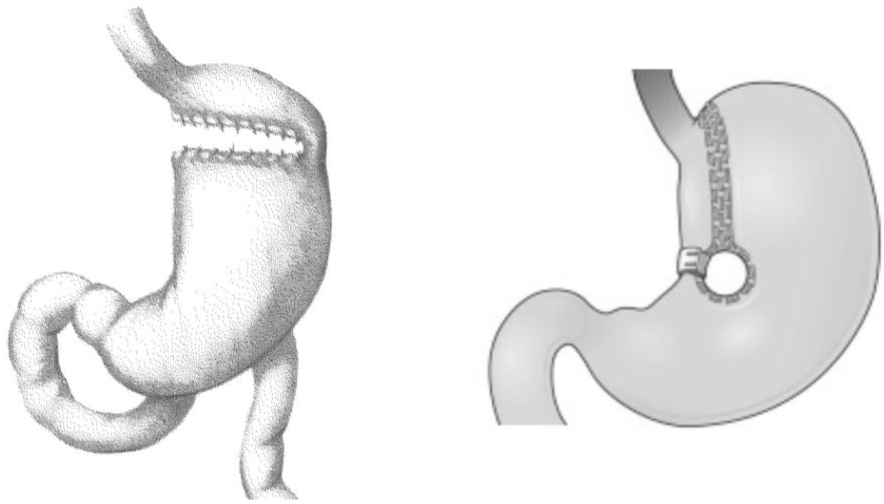


Figure 1.2.3: Left: Horizontal gastroplasty. Image adapted from Linner *et al.* (Linner 1987) Right: Vertical banded gastroplasty. *Image adapted from Jonnalagadda et al. (Jonnalagadda & Likhitsup 2019). Both images reproduced with permission from Elsevier ©, Amsterdam, Netherlands.*

Following the concept of reducing the stomach inlet volume, *gastric banding* was conceived as a minimally invasive alternative option (Figure 1.2.4) (Wilkinson & Peloso 1981). In the mid-1980s, non-adjustable bands were quickly superseded by adjustable versions, allowing tailored stoma size for individual patients (Hallberg & Forsell 1985; Kuzmak 1986). The technical ease of band placement, along with the advent of minimally invasive laparoscopic surgery (Broadbent, Tracey & Harrington 1993), led to widespread use of gastric bands for weight loss, accounting for up to 42% of weight-loss procedures by 2008 (Buchwald & Oien 2013). In modern practice, however, use of gastric bands has drastically diminished to <4% of global procedures (IFSO 2021), due to unacceptable level of complications. Irreversible oesophageal dysfunction, found in 13% of patients (Naef *et al.* 2011); band migration, and; erosion through gastric tissue has resulted in up to 1-in-4 patients requiring revisional surgery (Altieri *et al.* 2018). Complete band removal now outnumbers band placement more than 3-to-1 (Backman *et al.* 2020).

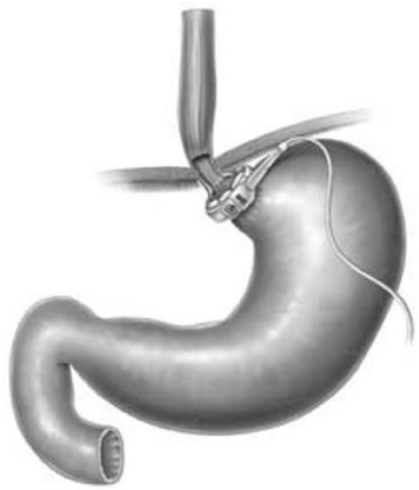


Figure 1.2.4: Adjustable gastric banding. Image reproduced from Burton and Brown (Burton & Brown 2011) with permission from Springer Nature ©, Basingstoke, United Kingdom.

After being widely adopted, multiple modifications to Griffen's Roux-en-Y gastric bypass (RYGB) were evaluated. In their study of 300 patients, Torres *et al.* described a vertical, rather than horizontal, gastric pouch based along the lesser curvature (Figure 1.2.5) (Torres, Oca & Garrison 1983). Reported advantages of this technique include; reduced splenic injury from 10% to 0% (Griffen, Young & Stevenson 1977); easier use of stapling devices and more favourable anatomic reconstruction for gastric emptying. Although not a comparative study, the large case series demonstrated a safe, improved technique, which is still utilised in modern practice. The 'banded gastric bypass', involving placement of a silastic ring around the vertical gastric pouch (Figure 1.2.5), was devised by Fobi *et al.* as a way of controlling the outflow of the gastric pouch and reducing pouch dilation (Fobi & Lee 1994). Despite non-inferior metabolic improvements compared with non-banded RYGB, the addition of a gastric band goes hand in hand with band-related complications; gastric outlet stenosis, band erosion, and band slippage occurring in 2.8%, 2.3%, and 1.5 % of patients, respectively (Buchwald, Buchwald & McGlennon 2014). As such, banded gastric bypass procedures are uncommon in modern practice.

Figure 1.2.5: Left: Torres gastric bypass; Right: banded gastric bypass. Images adapted from Saber *et al.* Obes Surg 2008 (Saber, Elgamal & McLeod 2008) with permission from Elsevier ©, Amsterdam, Netherlands.

In a kind of evolutionary sidestep, the *biliopancreatic diversion (BPD)* was developed in the 1980s (Figure 1.2.6), building on experience from the jejunoileal bypass (Scopinaro *et al.* 1979). Although achieving weight loss nearing 20% of initial weight at 6 months post-operatively, 15% of patients suffered from peptic ulcers and 6% from early dumping syndrome (Michielson, Van Hee & Hendrickx 1996); abdominal pain, dizziness and diaphoresis due to rapid delivery of high sugar load into the small intestine. To combat this, the original procedure was modified to preserve the pyloric sphincter, known as the *BPD with duodenal switch (BPD-DS)* (Hess & Hess 1998*)*. This is achieved by performing a vertical (sleeve-shaped), rather than horizontal, gastrectomy with post-pyloric duodeno-enterostomy (Figure 1.2.6). Due to the technical difficulty of BPD-DS, especially in patients with extreme obesity (BMI >60), in whom up to 38%

have major complications (Ren, Patterson & Gagner 2000), a two-stage procedure was proposed; first a vertical 'sleeve' gastrectomy to induce restrictive weight loss, followed by the remainder of the BPD-DS at a separate operation (Chu, Gagner & Quinn 2002). Gagner *et al*. reported mean BMI reduction of 15kg/m^2 at 18 months post-operatively, and complication rate of 16%, with only 27/85 patients ultimately proceeding to the second stage to attain further weight loss. For patients with extreme obesity, the staged procedure offers a lower-risk alternative. The BPD-DS is still performed today, but has largely been superseded by less technically challenging procedures, and now only represent <0.5% of global weight loss procedures (IFSO 2021).

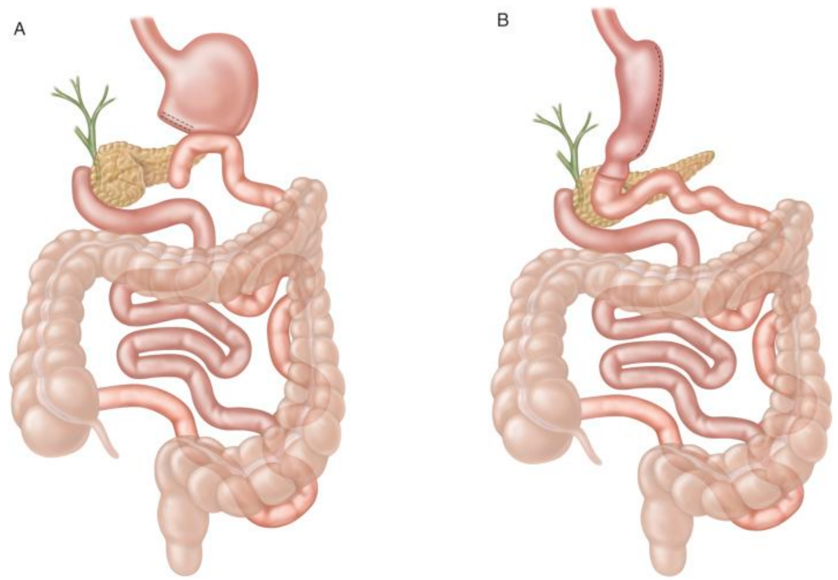


Figure 1.2.6: A) Biliopancreatic diversion; B) Biliopancreatic diversion with duodenal switch. Reproduced from 'ERCP in Surgically Altered Anatomy' (Lo 2019) with permission from Elsevier ©, Amsterdam, Netherlands.

1990s and 2000s

The failures of the *vertical banded gastroplasty* gave rise to the *Magenstrasse and Mill (M&M)* procedure, conceived by David Johnston (Johnston *et al.* 2003). The procedure draws on the concept of the vertical gastroplasty but avoids leaving foreign material in the abdomen. A long, vertical, transected gastroplasty is performed along the lesser curvature, calibrated by a transoral bougie, from a circular stapled defect created in the gastric antrum to the angle of His[3] (Figure 1.2.7). Despite 72% of patients achieving >50% excess weight loss, and only 4% encountering major complications, the M&M was quickly superseded by the sleeve gastrectomy. The success of weight loss from staged vertical gastrectomy in BPD procedures, as well as the success seen with the M&M, prompted surgeons to explore sleeve gastrectomy as a stand-alone weight loss procedure (Gumbs *et al.* 2007).

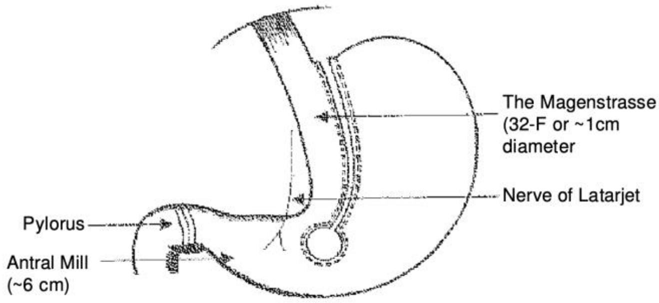


Figure 1.2.7: The Magenstrasse and Mill procedure. Reproduced from Johnston *et al.* (Johnston *et al.* 2003) with permission from Springer Nature ©, Basingstoke, United Kingdom.

The technical difficulty of the RYGB, and risk of anastomotic leak at 2 sites, prompted development of the *one-anastomosis gastric bypass (OABG;* also termed the *mini gastric bypass* or *omega-loop gastric bypass)* by Robert Rutledge (Rutledge 2001). Rather than transecting the jejunum to create an end-to-end gastrojejunostomy with a small gastric pouch (as with RYGB), a loop of jejunum is used to form a loop end-to-side gastrojejunostomy (Figure 1.2.11). This procedure presents numerous technical advantages over the RYGB: shorter operative time and thus shorter anaesthetic (Lee *et al.* 2005); shorter learning curve to reach proficiency (Wang *et al.* 2005); fewer anastomoses to develop ulceration, bleeding or leaks, and; no resultant mesenteric defect through which an internal hernia could occur. Further, large systematic reviews and meta-analyses demonstrate equivalent, if not superior, weight loss and remission of

[3] Angle of His – the acute angle between the oesophagus and the cardia portion of the stomach.

diabetes mellitus compared with RYGB and sleeve gastrectomy (Jia *et al.* 2020; Wang *et al.* 2017). Today, the OAGB is the third most performed weight loss procedure globally, behind sleeve gastrectomy and RYGB (IFSO 2021).

1.2.2. Current Operative Techniques

Illustrated by the evolution of metabolic and obesity surgery, no single procedure is superior to all others. Rather, multiple procedures form the armamentarium currently used for surgical weight loss. Sleeve gastrectomy (SG), RYGB and OAGB are the most performed procedures globally, accounting for 50%, 37% and 8% of all weight loss operations respectively (IFSO 2021). At present, Australian surgeons show lower preference for RYGB, opting more commonly for SG and OAGB, compared with international figures (Figure 1.2.8). Australian trends for the past 6 years show rapid growth of SG procedures, gradual increase in OAGB procedures, stable number of RYGB procedures and marked decrease in use of gastric bands (Figure 1.2.8). Cumulatively, weight loss procedures in Australia now exceed the number of cholecystectomies, the previously most performed gastrointestinal operation, illustrating the significant population impact of any associated morbidity (Services Australia 2021). Surgical techniques for sleeve gastrectomy, Roux-en-Y gastric bypass and one-anastomosis gastric bypass form the focus of the research work of this thesis.

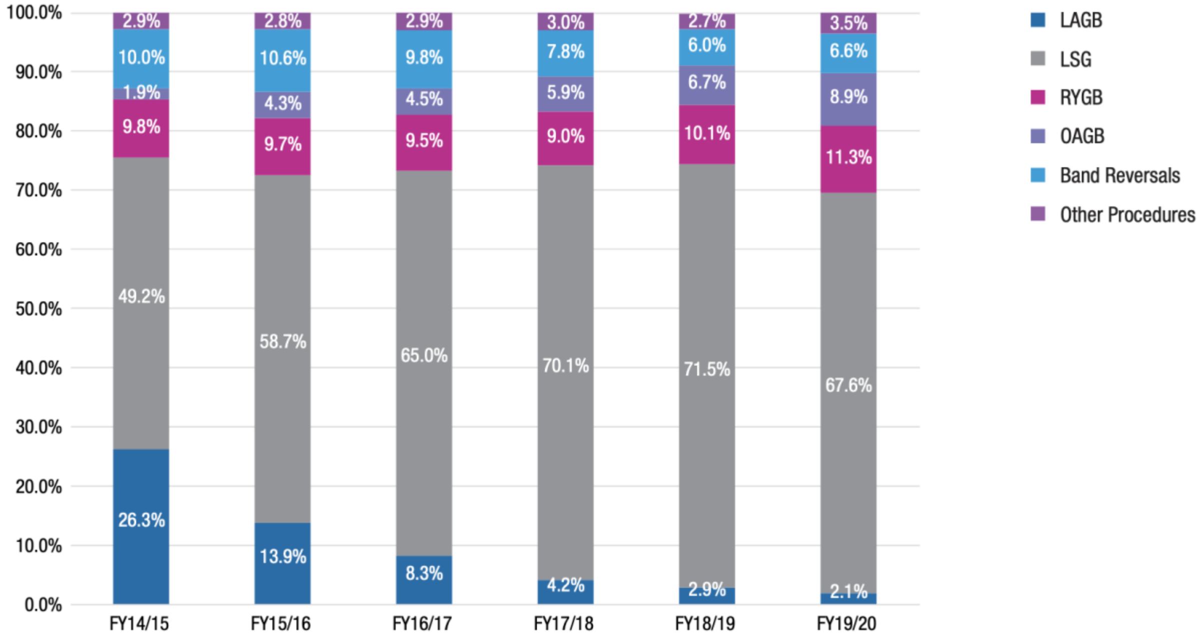


Figure 1.2.8: Proportions of primary weight loss operations performed in Australia as captured by the *Bariatric Surgery Registry*. Image reproduced with permission from the Bariatric Surgery Registry 8th Annual Report 2019/2020 (Backman *et al.* 2020).

Sleeve Gastrectomy

Sleeve gastrectomy is primarily a restrictive procedure; however, it also impacts nutrient absorption through alterations in gastric secretion and GIT neuro-hormonal changes (see Chapter 1.3) (Demerdash, Sabry & Arida 2018; Dimitriadis *et al.* 2013). The operation is predominantly performed laparoscopically, with standard trocar placements as pictured in Figure 1.2.9. Once all ports are inserted, the liver is retracted, and the patient is placed in a reverse Trendelenburg position (lying supine on a 15-30° incline with the head elevated above the level of the feet).

First, the stomach is mobilised along the greater curvature, by dividing the greater curve tributaries of the gastro-epiploic arcade together with the short gastric arteries. Transection of the stomach commences distally, approximately 5 cm proximal to the pylorus. After placement of a transoral bougie, the stomach is transected along the lesser curvature using an endoscopic stapler, with the lumen size of the gastric sleeve determined by the size of the bougie in place. Optimal bougie size is 32-40 Fr. (i.e. 10.7-13.3 mm), with studies showing superior weight loss and a similar complication rate when compared to larger or smaller size bougies (Rosenthal *et al.* 2012; Wang *et al.* 2018). The dissection concludes proximally on the fundus, at approximately 1 cm lateral to the angle of His, the acute angle between the oesophagus and fundus, to avoid oesophageal injury and preserve the function of the lower oesophageal sphincter: a barrier to gastroesophageal reflux. Reinforcement of the staple line with a buttress or oversewing may be performed to reduce the risk of bleeding, dehiscence, and leaks (Wang *et al.* 2016). The latter is not routine practice though, with a recent survey revealing almost one-third of surgeons prefer no staple line reinforcement (Gagner, Hutchinson & Rosenthal 2016). An intra-operative 'leak test' can be performed to check and rectify any technical leakage, and possibly reduce the probability of post-operative leaks. The 'leak test' sensitivity is poor however, with one recent study showing up to 91% of patients with post-operative leaks had a negative intra-operative leak test (Bingham *et al.* 2017).

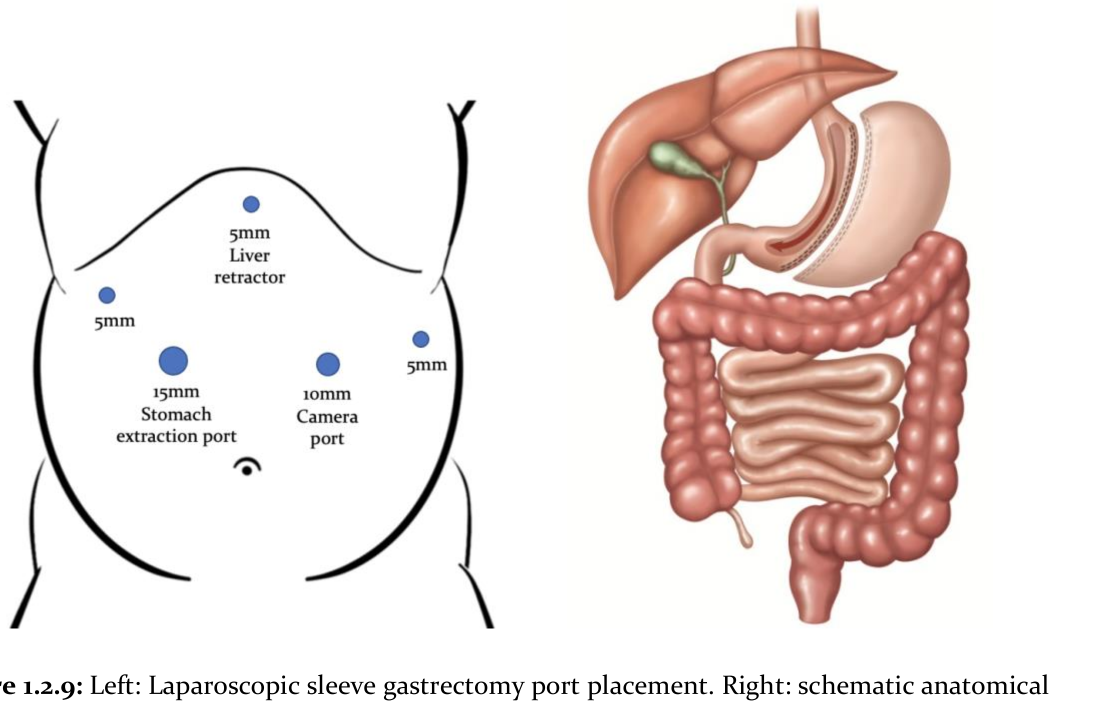


Figure 1.2.9: Left: Laparoscopic sleeve gastrectomy port placement. Right: schematic anatomical changes, reproduced with permission from Ethicon©, Raritan, USA.

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass achieves weight loss predominantly through malabsorptive means and is restrictive to a lesser degree. The procedure is now largely performed laparoscopically. Trocar placement is shown in Figure 1.2.10 and patient positioning on the operative table is the same as for sleeve gastrectomy (described above). Creation of a small gastric pouch of approximately 30 mL in volume, along the lesser curvature of the stomach, is achieved by dividing a section of the gastro-hepatic ligament to enable endoscopic stapling. The remainder of the stomach remains *in situ*, in continuity with the duodenum. The jejunum is divided at a distance 30-50 cm distal to the ligament of Treitz. The distal end is anastomosed to the gastric pouch (efferent limb) and the proximal limb is anastomosed to the jejunum (afferent limb) at 100-150 cm distal to the gastrojejunostomy. Various limb lengths have been examined, with consensus that 100-200cm combined length of afferent and efferent limbs achieves optimal weight loss (Mahawar *et al.* 2016). Minor changes in the afferent-to-efferent limb length ratio do not alter outcomes if the total bypassed length remains constant. Closure of mesenteric defects is recommended to avoid internal herniation of bowel, a surgical emergency. Two recent meta-analyses both concluded that mesenteric defect closure results in 70-75% risk reduction for internal hernia (odds ratios 0.28 & 0.25, both $p<0.0001$) and re-operation for small bowel obstruction (odds ratios 0.30 & 0.28, both $p<0.001$) (Hajibandeh *et al.* 2020; Magouliotis *et al.* 2020).

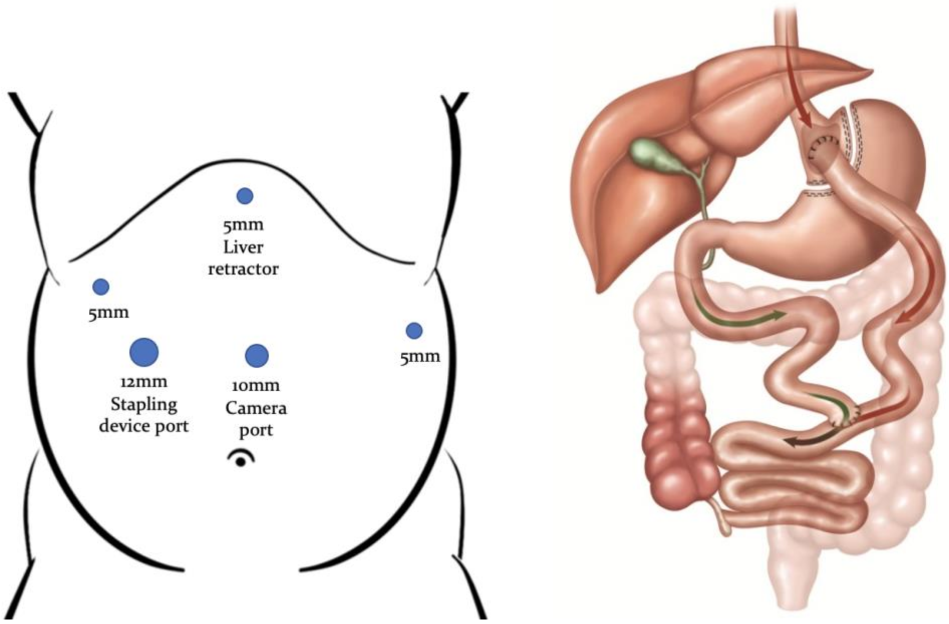


Figure 1.2.10: Laparoscopic Roux-en-Y gastric bypass port placement (A), and schematic anatomical changes (B). Picture B reproduced with permission from Ethicon©, Raritan, USA.

One-Anastomosis Gastric Bypass

Like RYGB, the one-anastomosis gastric bypass is primarily a malabsorptive procedure, with a small restrictive component. The procedure is also predominantly performed laparoscopically. Trocar placement is shown in Figure 1.2.11 and patient positioning is the same as for sleeve gastrectomy. Firstly, a small, vertical gastric pouch is created in similar fashion to a RYGB. The pouch is longer than in RYGB, commencing near the *incisura angularis* of the stomach (junction of antrum and body of the stomach), and continuing vertically along the lesser curvature. The remainder of the stomach remains *in situ*, in continuity with the duodenum. A transoral bougie is used to calibrate the pouch (Bougie size 36/38Fr.). A loop of jejunum, 150-200cm from the ligament of Treitz, is brought up to the gastric pouch and a gastrojejunostomy is performed (Rutledge, Kular & Manchanda 2019). A slight technique modification, described by Carbajo in 2004, is to perform a lateral rather than anterior gastrojejunostomy (García-Caballero & Carbajo 2004) (Figure 1.2.11). This modification addresses concerns about bile reflux into the gastric pouch, aiming to encourage gravity-assisted movement of biliopancreatic secretions past the anastomosis. No mesenteric defects are created with either technique, essentially eliminating the risk of internal bowel herniation.

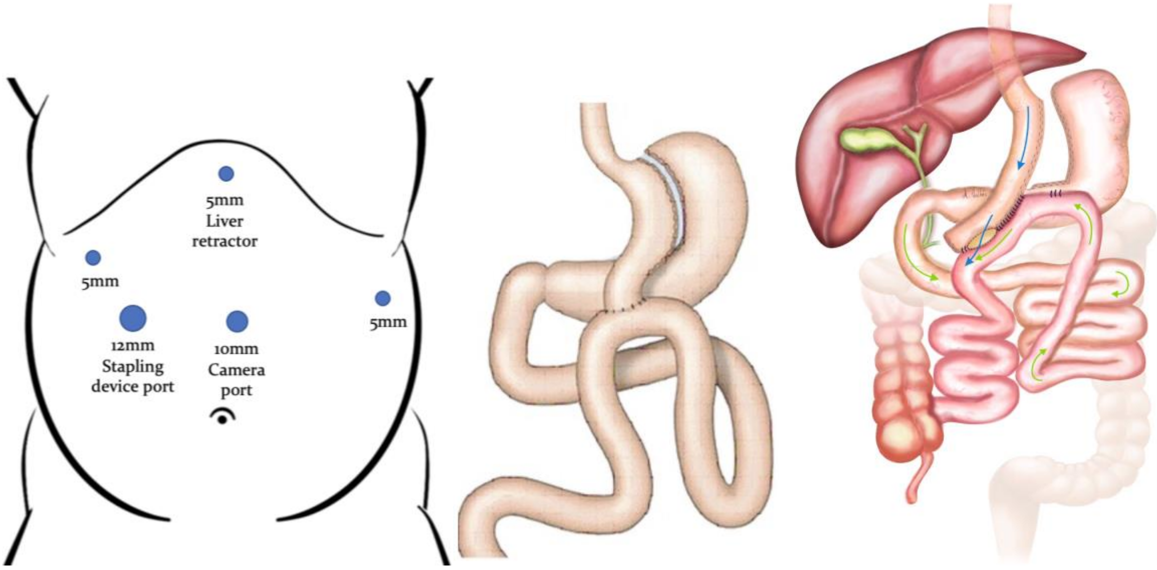


Figure 1.2.11: Left: Laparoscopic one-anastomosis gastric bypass port placement; Middle: schematic anatomical changes, and; Right: modification with lateral gastrojejunostomy. Middle and right images reproduced from 'Essentials of Mini-One Anastomosis Gastric Bypass' (Deitel 2018), with permission from Springer Nature©, Basingstoke, United Kingdom.

The myriad of techniques for surgical weight loss investigated over the past five decades reveal some successes built on many failures; change often driven by adverse outcomes and long-term risks. It is likely that no single procedure will reign supreme, rather an armamentarium will be available for individualised care. Metabolic and obesity surgery techniques will continue to evolve as knowledge of the complex physiological impact of MOS is further elucidated.

1.3. Physiological impact of bariatric surgery

Surgical alteration of the stomach and small intestine in metabolic and obesity surgery has numerous physiological sequelae, some intentional and others unavoidable. The underlying mechanism of weight loss from MOS is not simply restriction of food intake or absorption, as previously thought. Rather there is a complex interplay of altered appetite and satiety modulation, nutrient digestion and absorption, and glycaemic control and insulin sensitivity (Cornejo-Pareja, Clemente-Postigo & Tinahones 2019; Holst *et al.* 2018; Lin & Qu 2020). Multiple organ systems are impacted – gut, brain, adipose tissue, pancreas, muscles, liver – and act together to result in desired metabolic changes.

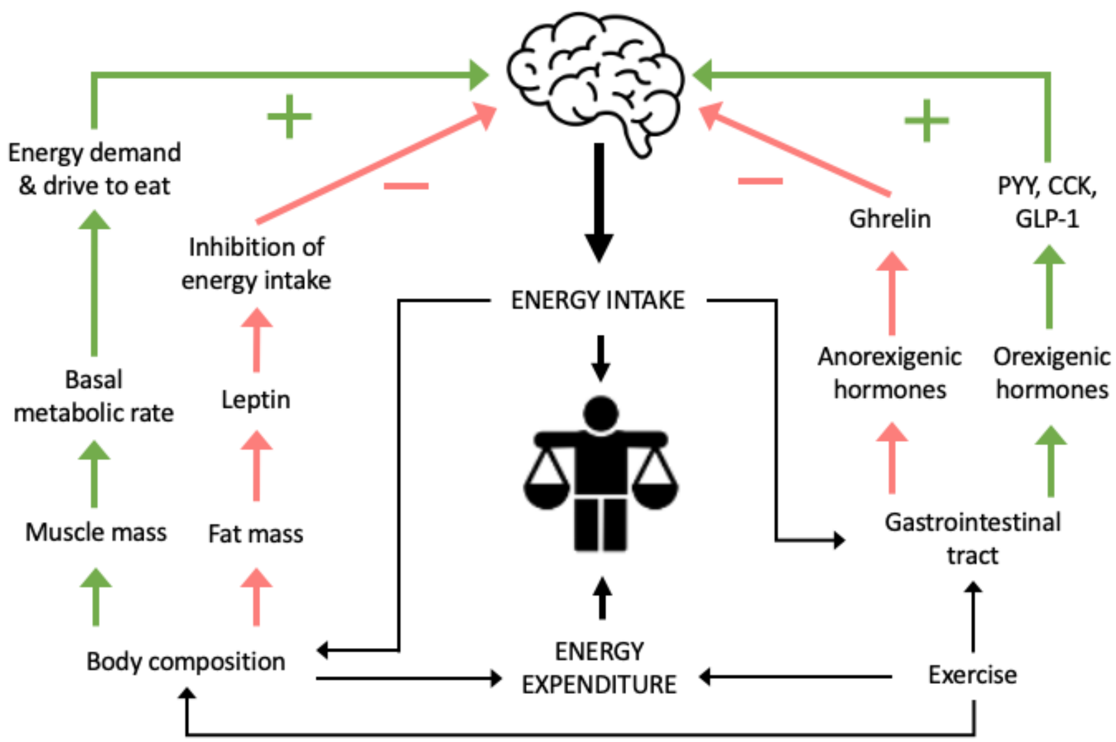


Figure 1.3.1: Schematic of body energy balance

1.3.1. Augmentation of Appetite

A balance of appetite-inducing (orexigenic) substances, such as ghrelin, and satiety-inducing (anorexigenic) hormones, such as peptide YY and leptin, dictates normal eating patterns. Metabolic and obesity surgery alters production of, and tissue sensitivity to, these appetite regulating hormones as part of the many mechanisms resulting in weight loss.

Ghrelin

Ghrelin is an orexigenic hormone produced by gastric parietal cells, predominantly in the fundus (Date *et al.* 2000), and stimulates neuropeptide Y (NPY) neurons in the hypothalamic arcuate nucleus to stimulate hunger (Kohno *et al.* 2003). Plasma levels surge just prior to eating and decrease shortly after food intake, illustrating the temporal association with hunger (Cummings *et al.* 2001). Hyperghrelinaemia resulting in hyperphagia can contribute to development of obesity, however this is uncommon and is usually related to pathological syndromes associated with hyperphagia, such as Prada-Willi syndrome (Kweh *et al.* 2015). Interestingly, fasting plasma ghrelin levels are lower in obese subjects with no diagnosed hyperphagic syndromes, compared with matched lean subjects (Korek *et al.* 2013; Tschop *et al.* 2001). These results likely represent a compensation for chronic positive energy balance.

The role of ghrelin in contributing to weight loss after MOS remains unclear. Sleeve gastrectomy tends to decrease plasma ghrelin levels post-operatively (McCarty, Jirapinyo & Thompson 2020), whereas gastric bypass has variable effect (Cummings *et al.* 2002; Garcia-Fuentes *et al.* 2008; Korner *et al.* 2009; Liou *et al.* 2008; Perez-Romero *et al.* 2010; Xu *et al.* 2019; Yang *et al.* 2018). A meta-analysis of 28 studies (653 patients) evaluating ghrelin levels post-SG demonstrated a decrease in ghrelin levels at an average follow-up period of 11 months post-operatively (McCarty, Jirapinyo & Thompson 2020). Another meta-analysis of 16 studies (325 patients) investigating plasma ghrelin levels post-RYGB found that RYGB resulted in an initial decrease, but overall increase in the long term (≥3 months) (Xu *et al.* 2019). One study exists evaluating mean ghrelin levels after OAGB demonstrating significant, albeit modest, decrease at 6 months (383pg/mL) and 12 months (452pg/mL) post-operatively, compared with pre-operative mean value (460pg/mL). Resection of the gastric fundus in SG compared with exclusion (but not resection) in gastric bypass could explain the difference in post-operative ghrelin levels between procedures. Ghrelin production from other organs, such as the pancreas, can also be upregulated post-operatively (Camacho-Ramírez *et al.* 2020), consistent with trends described above.

Peptide YY

Peptide tyrosine-tyrosine (or peptide YY; PYY) is an anorexigenic peptide produced by *L-cells* in the GIT, predominantly the ileum and colon. PYY is released post-prandially, depending on caloric load and nutrient composition (Batterham *et al.* 2006), imparting satiety through agonism of hypothalamic NPY *Y2* receptors (Batterham & Bloom 2003). Using a mouse model, Professor Batterham illustrated that peripheral intravenous infusion of PYY resulted in a dose-dependent reduction in food intake in wild-type mice, but not *Y2*-receptor knockout mice (Batterham & Bloom 2003). Building on these findings, using a randomised crossover study design, she found that when infused intravenously in humans for 90 minutes, PYY demonstrated significantly decreased food intake by 33% over 24 hours compared to saline infusion ($p<0.001$). The study relied on submission of food diaries by participants, which may be prone to recall bias, however given the short duration of the study, this is unlikely to be significant.

The impact of MOS on PYY secretion has been evaluated in multiple clinical trials, demonstrating increased post-prandial PYY levels >12 months after SG, RYGB and OAGB, with no major differences seen between procedures (Alamuddin *et al.* 2017; Dardzinska *et al.* 2017; Karamanakos *et al.* 2008; Ramon *et al.* 2012; Yang *et al.* 2018). Despite the relatively small size of these trials, all with fewer than 41 participants, the reproducibility of results bolsters validity and confirms the key role PYY plays in appetite reduction post-operatively.

Peptide YY is being investigated for use as a therapeutic target for obesity treatment. A study using intranasal PYY over 12 weeks encountered adverse effects such as nausea and vomiting with higher doses (600 micrograms three times daily), and no significant weight loss at lower doses (200 micrograms three times daily), limiting the efficacy of PYY for weight loss (Gantz *et al.* 2007). Altering the PYY formulation for slow-release has shown promise in a primate-model study, with no episodes of vomiting and good efficacy in reduction of oral intake (Rangwala *et al.* 2019). A weekly subcutaneous injection of PYY is currently under investigation by Novo Nordisk (Denmark) in a phase 1 clinical trial (registered trial/ accessed at:
https://www.clinicaltrials.gov/ct2/show/NCT03707990).

Adipose tissue and leptin

Adipose tissue is a metabolically active 'organ', capable of synthesising numerous bioactive molecules to regulate metabolic homeostasis (Coelho, Oliveira & Fernandes 2013). Accumulation of adipose tissue is determined by a balance between synthesis (lipogenesis), occurring during times of energy excess, and breakdown (lipolysis), occurring in times of metabolic stress (fasting, prolonged physical exertion). Complex interaction between pro- and anti-inflammatory adipokines confers a state of chronic, low-grade inflammation in obesity, contributing to development of numerous diseases including the 'metabolic syndrome' (Itoh *et al.* 2011).

Leptin, an anorexigenic peptide produced mainly by adipocytes, is instrumental in regulation of appetite and energy expenditure. Leptin counteracts the orexigenic signals induced by ghrelin and NPY neurons at the level of the hypothalamus, thereby regulating appetite (Friedman &

Halaas 1998). Leptin resistance, first identified over 20 years ago, is a multi-factorial pathological process that contributes to obesity (Caro *et al.* 1996). Mechanisms include defects in intracellular signalling associated with the leptin receptor, or through altered transport of leptin across the blood-brain barrier to the hypothalamus (Gruzdeva *et al.* 2019). Leptin resistance is likely to be a key factor in the failure of exogenous leptin as a therapeutic treatment for obesity (Tam, Lecoultre & Ravussin 2011).

Fasting plasma leptin levels are significantly elevated in obese subjects and decreased in underweight subjects, when compared to healthy control subjects (Korek *et al.* 2013). Further, weight loss in an overweight population through diet and exercise significantly decreases fasting plasma leptin levels, demonstrating total energy balance positively correlates with plasma leptin levels (Thong *et al.* 2000). Metabolic and obesity surgery similarly results in decreased plasma leptin levels, correlating with weight loss. Roux-en-Y gastric bypass, SG and OAGB all result in significant decreases in plasma leptin at 6 months and 12 or 18 months post-operatively, compared with pre-operative levels (Alamuddin *et al.* 2017; Liou *et al.* 2008; Salman *et al.* 2020). No significant difference was identified between RYGB and SG, whereas OAGB was evaluated separately.

As is apparent from the literature described above, no individual hormone or receptor is solely responsible for the changes in appetite post-MOS. There is a complex interplay between these systems that work together to change food intake. This is also significantly impacted by changes in psychology and the 'food reward' response (Al-Najim, Docherty & le Roux 2018).

1.3.2. Nutrient digestion and absorption

Neurohormonal changes may alter appetite and food intake, but surgical alteration of the GIT also alters chemical and mechanical digestion of food, subsequently affecting absorption of macronutrients (carbohydrates, protein, and fat) and micronutrients. This impacts total energy balance of the body by altering energy intake.

Carbohydrates

Dietary carbohydrates (CHO), in the form of poly- and di-saccharides, need to be broken down into monosaccharides for absorption, predominantly in the proximal small intestine and to a lesser degree in the ileum (Hall 2016).

Bypassing the proximal intestine, such as in gastric bypass surgery, is hypothesised to decrease CHO absorption and thus result in weight loss (Wang *et al.* 2012). Wang et al. tested this hypothesis, administering oral D-xylose (a monosaccharide) followed by frequent testing for plasma D-xylose concentration in the first 3 hours after ingestion. This was performed in the same patients prior to RYGB and 1 year post-operatively. The authors observed no difference in total absorption of D-xylose, but noted accelerated peak levels post-RYGB, suggesting hastened gastric emptying for small intestinal absorption. Other studies investigating this hypothesis also failed to find a significant alteration of total CHO absorption after gastric bypass (Odstrcil *et al.* 2010) or sleeve gastrectomy (Svane *et al.* 2019). The observation of accelerated peak blood glucose levels post-RYGB has also been reported in other studies (Jacobsen *et al.* 2013; Svane *et al.* 2019). Despite the small size of the gastric pouch following RYGB, there is not as much 'restriction' as would be expected, due to rapid food passage through the stoma into the small intestine (Dirksen *et al.* 2013). The lack of pylorus-regulated gastric emptying post-RYGB results in rapid delivery of CHO into the small intestine, resulting in a rapid peak of blood glucose level. This phenomenon can result in post-operative 'dumping syndrome'. Early dumping syndrome, 15-30 minutes after eating, is characterised by abdominal cramps and watery diarrhoea due to rapid fluid shift into the intestinal lumen in response to the hyperosmolar luminal contents. Late dumping syndrome, 1-4 hours after eating, is characterised by profound hypoglycaemia from a hyperinsulinaemic response to the rapid increase in blood glucose levels.

Protein

Dietary protein requires luminal and brush border enzymatic breakdown and enterocyte membranous transporters for absorption (Hall 2016). Gastric pepsin, maximally active at low-pH, initiates proteolysis, which is continued in the proximal intestine by pancreatic peptidases and completed by brush border enzymes to enable protein absorption (Hall 2016).

Reduced gastric capacity, acid and pepsinogen secretion, and in the case of gastric bypass, exclusion of the proximal intestine resulting in reduced surface area for absorption, can contribute to post-operative protein malabsorption (Ponsky, Brody & Pucci 2005). In a recent systematic review, however, Mahawar and Sharples concluded only minor impairment of protein digestion and absorption occurs post-RYGB (Mahawar & Sharples 2017). Despite this, protein malnutrition after MOS occurs in up to 40% of patients undergoing procedures with a significant 'malabsorptive' component, such as gastric bypass and biliopancreatic diversion (Suarez Llanos *et al.* 2015). Inadequate dietary protein intake occurs in many patients post-MOS, with few meeting the recommended 60g/day intake (Mechanick *et al.* 2020; Steenackers, Gesquiere & Matthys 2018); attributable to protein intolerance, food aversion and early satiety. (Moize *et al.* 2003). Daily protein supplementation after MOS increases loss of fat mass in preference to lean muscle mass when compared with daily intake of an isocaloric placebo (Schollenberger *et al.* 2016). The high rate of protein malnutrition is therefore most likely attributable to inadequate dietary intake, rather than intestinal malabsorption. Protein supplementation is common post-operatively, with routine use supported by the literature (Andreu *et al.* 2010).

Lipids

Under physiological conditions, dietary fat passes into the duodenum and elicits secretion of cholecystokinin (CCK) to stimulate excretion of bile and pancreatic enzymes into the intestinal lumen. Lipids are then emulsified by bile, increasing the surface area for interaction with lipases, and are transported by enterocytes as chylomicrons to be secreted into the lymphatic system (Hall 2016).

Surgical exclusion of the duodenum, as in RYGB and OAGB, can impair biliary and pancreatic secretion (Bastouly *et al.* 2009). Consequently, bile emulsification of fats is impaired, decreasing lipid surface area for lipase action. The reduced effective intestinal length after gastric bypass shortens the duration for digestion to occur and decreases available surface area for enterocyte absorption of chylomicrons.

A systematic review evaluating malabsorption after RYGB concluded that a modest amount of dietary fat malabsorption occurs post-operatively (Mahawar & Sharples 2017). Identified significant factors of malabsorption included greater faecal fat loss (Carswell *et al.* 2014; Kumar *et al.* 2011), and improvement of post-prandial plasma triglyceride (Griffo *et al.* 2014) and serum cholesterol (Pihlajamäki *et al.* 2010) profiles after RYGB.

Sleeve gastrectomy does not result in duodenal/jejunal exclusion, therefore differing from RYGB in how lipids are digested and absorbed. De Vuono *et al.* measured plasma levels of plant sterols (campesterol and sitosterol) as a marker of cholesterol absorption, before and 10 months after sleeve gastrectomy in 42 subjects and 20 non-obese controls (De Vuono *et al.* 2017). Plasma sterol levels, relative to dietary cholesterol intake, remained unchanged post-operatively when compared with pre-operative values, illustrating no change in cholesterol absorption post-SG. In another study of 25 subjects, Griffo *et al.* measured serum lipids three hours after ingestion of a standardised oral meal containing 9 grams of fat, before and two weeks after RYGB (n=10) or SG (n=15) (Griffo *et al.* 2014). The study demonstrated statistically significant reduction in fasting and post-prandial plasma triglycerides and cholesterol post-operatively in both operative groups, with a trend to greater improvement after RYGB, as expected. The difference between RYGB and SG failed to reach significance, likely due to the small sample size in a potentially underpowered study; the authors give no mention of a power calculation. These findings indicate that alteration in post-prandial lipid profile observed post-SG most likely relates to improved lipid metabolism rather than altered absorption.

Micronutrients and vitamins

Malnutrition in the obese population is counterintuitive but prevalent (Ernst *et al.* 2009; Peterson *et al.* 2016; Roust & DiBaise 2017; Wolf *et al.* 2015). Poor intake of vitamin- and mineral-rich foods (fruit and vegetables), sedentary lifestyle and history of restrictive dieting are all contributing factors. Intentional altered absorption from MOS can further exacerbate pre-existing dietary deficiencies. The most common nutritional deficiencies after MOS are vitamin B12, iron, calcium, and vitamin D (Roust & DiBaise 2017). Pre- and post-operative screening and replacement for vitamin and mineral deficiencies is routine in clinical practice.

Vitamin B12 is involved in the metabolism of every cell in the body, with particular importance in the neurological and haematological systems. Vitamin B12 is absorbed in the terminal ileum, relying on binding to *intrinsic factor* in the duodenum for both transport and absorption. Intrinsic factor is secreted by gastric parietal cells, located predominantly in the gastric fundus and cardia. Sleeve gastrectomy and gastric bypass procedures result in removal or exclusion of the gastric fundus, limiting the amount of intrinsic factor available for binding (Behrns, Smith

& Sarr 1994). As such, vitamin B12 deficiency is common after MOS, warranting regular blood testing and supplementation as required.

The chronic low-grade inflammatory state conferred by excess adipose tissue can cause anaemia through induction of hepcidin production and impaired iron absorption (Nemeth *et al.* 2004). Up to one-third of bariatric surgery candidates have pre-existing iron deficiency prior to MOS (Peterson *et al.* 2016). *Ferric* to *ferrous* conversion of dietary iron occurs in low-pH environments and is required for absorption in the duodenum and proximal jejunum. Reduced gastric acid secretion post-MOS due to gastric resection or exclusion impairs iron conversion and subsequent absorption (Smith *et al.* 1993). Gastric bypass further impairs intestinal surface area for iron absorption (Ruz *et al.* 2012). Consumption of iron-rich red meat can be difficult post-operatively, further increasing the risk of developing iron-deficiency (Nicoletti *et al.* 2015).

Calcium and vitamin D are integral for bone formation and remodelling, with deficiencies leading to osteoporosis and bone fractures. Both molecules are predominantly absorbed in the proximal midgut, with vitamin D, a liposoluble vitamin, requiring bile acids and pancreatic secretions for absorption. Bypassing the duodenum and proximal jejunum, such as in RYGB or OAGB, can impact absorption of these osteogenic nutrients. This is especially pertinent as vitamin-D and calcium deficiency is found in up to 80% and 14%, respectively, of bariatric patients prior to MOS (Roust & DiBaise 2017). After MOS, despite vitamin D supplementation and adequate calcium intake, calcium malabsorption and decreased bone mineral density can still occur (Schafer *et al.* 2015). In addition to the biochemical changes, weight loss post-operatively reduces mechanical stress-loading of bones, with resultant lower bone mineral density. The relative risk for bone fractures is more than doubled for patients post-MOS, (Nakamura *et al.* 2014).

1.3.3. Glucose metabolism

It is well-established that MOS has a profound impact on glucose metabolism (Douros, Tong & D'Alessio 2019). The STAMPEDE trial was a landmark study in the investigation of the impact of MOS on diabetes (Schauer *et al.* 2012). In this trial, 150 obese patients with diabetes were randomised to undergo intensive medical therapy alone, or in combination with RYGB or SG. At 12 months, the surgical cohorts (RYGB and SG) had significantly greater mean weight loss (29.4kg and 25.1kg respectively) and lower mean HbA1c (6.4% and 6.6% respectively) compared with the medical cohort (5.4kg and 7.5%). Ninety percent of patients completed 5-yr follow-up, with the surgical cohorts maintaining greater mean reduction in HbA1c (2.1%) compared with the medical cohort (0.3%) (Schauer *et al.* 2017). One criticism of the study was the limitation of a single-centre, single-surgeon study with questionable validity for generalisation. However, these results have since been replicated in subsequent studies; SLEEVEPASS and SM-BOSS (Peterli *et al.* 2018; Salminen *et al.* 2018).

Improvements in glucose handling are seen in the early post-operative period, demonstrating the significant metabolic impact, independent of weight loss, of MOS procedures (Yang *et al.* 2018). Improvements in fasting glucose and fasting insulin levels are seen as early as 3 days post-operatively, prior to any significant weight loss (Shankar *et al.* 2017). These findings are confounded by the significantly decreased caloric intake in such a post-operative cohort, offset by the surgical stress response inducing insulin resistance. Douros *et al* concluded in their comprehensive review of studies evaluating glucose metabolism post-MOS, that there are 'additional effects beyond acute energy balance on insulin clearance and sensitivity' (Douros, Tong & D'Alessio 2019). Research into the mechanisms through which gastrointestinal surgery augments glucose metabolism is in its infancy and presents a multitude of potential avenues of enquiry for therapeutic targets.

Alterations to gastrointestinal anatomy from MOS induces synergistic interaction between appetite augmentation, nutrient digestion / absorption, and glucose metabolism, resulting in weight loss and overall metabolic improvement. Recent evidence has challenged and disproven initial theories of operative weight loss to be due to either dietary restriction or malabsorption. The complex interplay between MOS and the endocrine/paracrine functions of gastrointestinal organs is an expanding area of ongoing research that is likely to have a major impact on future treatments of obesity. However, achieving the profoundly beneficial physiological sequelae of MOS does not come risk-free. The anatomical changes required to achieve such benefit create unavoidable risk of post-operative adverse outcomes. One such outcome, and the substantive topic of this thesis, is bile reflux, which can damage gastric and oesophageal tissues irreversibly, potentially resulting in carcinogenesis.

1.4. Bile Reflux and the Gastrointestinal Sequelae

Bile reflux, or duodenogastric reflux (DGR), is movement of small intestinal contents, including bile, into the stomach. When bilious refluxate reaches the oesophagus, the term duodenogastro-oesophageal reflux (DGOR) is used. In metabolic and obesity surgery, DGR can occur as retrograde movement from the duodenum or antegrade movement from the jejunum through a gastro-jejunostomy. Duodenogastro-oesophageal reflux can occur independently or concurrently with gastro-oesophageal reflux disease (GORD); defined as the reflux of acid, rather than bile. In health, the pyloric sphincter prevents most DGR, however a small amount of post-prandial DGR is considered physiological (Koek *et al.* 2005; Wormsley 1972). As such, DGR is often a post-surgical issue when pyloric sphincter function is compromised or abolished. The anatomical alterations of MOS can also impact the coordinated motility of the oesophagus, gastro-oesophageal junction (GOJ), and stomach, impairing normal antegrade movement of luminal contents. Normal physiological anti-reflux mechanisms include: coordinated oesophageal peristalsis for luminal clearance of any refluxed gastric contents; the intrinsic lower oesophageal sphincter (LOS) and extrinsic crural diaphragm as an anatomical & physiological barrier preventing gastro-oesophageal reflux, and; timely gastric emptying under appropriate intragastric pressure. Recurrent and prolonged exposure of the stomach and oesophagus to bile can result in mucosal damage, metaplasia, dysplasia and potentially neoplasia (Abdel-Latif *et al.* 2016; Farré *et al.* 2008; Ghatak *et al.* 2016).

1.4.1. Impact of MOS on Gastrointestinal Motility

Obesity itself can impair gastro-oesophageal function. Studies using high-resolution impedance manometry (HRIM), the gold standard for assessment of gastro-oesophageal motor function, demonstrate a direct relationship between BMI, intragastric pressure and gastro-oesophageal pressure gradient (Pandolfino *et al.* 2006; Tolone *et al.* 2014). Further, low resting LOS pressures and more frequent transient LOS relaxations are observed in obese populations, compared with matched lean subjects (Wu *et al.* 2007). The reversibility of these findings through non-surgical weight loss hasn't been prospectively evaluated utilising objective oesophageal function testing. However, non-surgical weight loss significantly improves subjective reflux symptoms (Singh *et al.* 2013), likely through reduction of intragastric pressure (and thus gastro-oesophageal pressure gradient) resulting from reduced intra-abdominal visceral adiposity.

Of the commonly performed MOS procedures in modern practice, sleeve gastrectomy has the most significant impact on the GOJ reflux barrier and is commonly termed a 'refluxogenic procedure'. Sleeve gastrectomy can lead to altered GOJ (intrinsic LOS and extrinsic crural diaphragm) function in numerous ways: disruption of the angle of His, dissection of the crural sling fibres and phreno-oesophageal ligament, subsequent development of a hiatus hernia (or intrathoracic sleeve migration), and high luminal sleeve pressures from decreased gastric compliance (law of Laplace). A recent comprehensive review of the effect of SG on gastrointestinal motility concluded that the impact on oesophageal motility remains debatable, due to methodological heterogeneity of clinical studies (Sioka *et al.* 2018). Two prospective clinical trials evaluating reflux barrier or GOJ function post-SG yield conflicting results; one showing increased LOS pressure post-operatively (8.2 mmHg pre-operatively to 21.2 mmHg post-operatively), the other showed decreased LOS pressure (17.1 mmHg to 12.4 mmHg) (Gorodner *et al.* 2015; Petersen *et al.* 2012). Del Genio *et al.* prospectively evaluated the impact of SG on LOS function, concluding that SG with preserved antral function, regular gastric tube size and maintained integrity of crural sling fibres has no impact on GOJ function (Del Genio *et al.* 2014). Using magnetic resonance imaging to reconstruct gastric structure, Quero *et al.* evaluated the angle of His pre- and post-SG, postulating that a more obtuse angle may contribute to observed post-operative reflux (Quero *et al.* 2020). They reported an increase in the oesophago-gastric insertion angle (of His) in 18/23 participants post-operatively, compared with pre-operative measurements (36° ± 11 vs. 51° ± 16; $p = 0.002$). This change was positively associated with lower GOJ tone ($p=0.01$) and more acid reflux events ($p<0.05$). Most recently, Professor Wendy Brown's research group published a comprehensive study using multi-modal investigation of the mechanics of gastric sleeve emptying (Johari *et al.* 2021a). Using a stress barium swallow, HRIM, and video fluoroscopy with volume stress testing, the authors defined a sequence of events for sleeve emptying; swallows result in proximal sleeve compartment filling and pressurisation causing small reflux events, which in turn trigger oesophageal and gastric peristalsis for bolus transit into the distal sleeve compartment and subsequent trans-pyloric flow. Of note, they reported largely normal oesophageal motor function, with low-normal LOS resting pressure and normal LOS relaxation. Their study demonstrated overall accelerated sleeve emptying on nuclear scintigraphy, compared with an obese control group, supporting findings from earlier studies (Vigneshwaran *et al.* 2016). Elucidating this sequential mechanism of gastric sleeve emptying has provided an explanation for the existing paradox whereby accelerated gastric emptying occurs in a so-called 'refluxogenic' procedure. Taken together, the presented data illustrate variable impact of SG on GOJ structure and function, with the most significant factor likely surgical technique given the disparity of results between research groups.

Bypass procedures, both RYGB and OAGB, have reported minimal impact on gastro-oesophageal function with most studies showing no significant gastro-oesophageal dysmotility (Naik, Choksi & Vaezi 2016). Two studies report a hypotonic LOS post-RYGB (Cassao *et al.* 2013; Valezi *et al.* 2012), which would suggest an increased incidence of GORD, however this is not seen. This could be explained by the small gastric pouch with no reservoir capacity, which empties rapidly into the jejunum thus reducing any possible reflux events (Dirksen *et al.* 2013). Motility assessment post-OAGB has only been comprehensively investigated in two studies, both by Salvatore Tolone *et al.* (Tolone *et al.* 2016; Tolone *et al.* 2019). In both studies the authors reported unchanged oesophageal motility and LOS function post-operatively but noted significantly decreased intragastric pressure and gastro-oesophageal pressure gradient when compared with pre-operative values. In the 2016 study, results following OAGB were also compared with a control group of patients undergoing sleeve gastrectomy, demonstrating the same statistically significant changes. Musella *et al.* also performed HRIM on patients post-OAGB, but only commented on LOS pressures, also reporting no change in LOS tone at 12-months post-operatively (Musella *et al.* 2021). Having a patent gastrojejunostomy, rather than a pyloric sphincter-regulated gastric outlet, provides a sound mechanistic explanation for these findings.

With equivocal data on the impact of sleeve gastrectomy on normal anti-reflux mechanisms, while acknowledging minimal impact post-gastric bypass, understanding the effect of bile reflux on gastric and oesophageal tissue is crucial in weighing the risks of MOS against the benefits.

1.4.2. Bile Physiology

Synthesis and excretion

Bile is a green-yellow pigmented, viscous fluid, produced by liver hepatocytes, comprised of water (98%), bile salts (1%), bilirubin and fats (cholesterol, lecithin and fatty acids) (Hall 2016). Bile salts are water-soluble end-products of cholesterol metabolism that are excreted in bile. *Bile salts* form from conjugation of *bile acid*s with taurine or glycine, which occurs as the bile is excreted from hepatocytes into bile canaliculi. Conjugation increases the hydrophilicity of bile acids, decreasing the passive diffusion across intestinal epithelial cell membranes. This maximises intestinal luminal concentration of bile acids to facilitate the key function of lipid digestion/absorption. It is the bile salts (i.e. conjugated bile acids) that can be injurious to the gastric and oesophageal mucosa when bile reflux occurs (McQuaid *et al.* 2011; Sun *et al.* 2015).

Hepatocytes excrete bile into canaliculi that coalesce to form progressively larger bile ducts, culminating with the *common bile duct* (Figure 1.4.1). The common bile duct drains into the second part of the duodenum at the *major duodenal ampulla (of Vater),* with bile flow being regulated by the *sphincter of Oddi*. Between meals, the sphincter of Oddi is closed resulting in diversion of bile into the gallbladder for storage. Ingested dietary amino-acids and fatty-acids enter the duodenum, triggering release of CCK from mucosal enteroendocrine cells. Cholecystokinin stimulates gallbladder contraction and sphincter of Oddi relaxation, enabling delivery of bile into the small intestine to facilitate digestion and metabolism.

Gallbladder emptying is impaired after gastric bypass, demonstrated in a prospective study comparing pre- and post-operative gallbladder emptying after RYGB with concurrent placement of a gastrostomy tube in the gastric remnant (Bastouly *et al.* 2009). Ultrasonographic assessment of gallbladder emptying was performed pre-operatively and one month post-operatively, both during oral ingestion of a liquid test meal and again with infusion of the same meal through the gastrostomy. Compared with pre-operative findings, significantly decreased maximum gallbladder ejection fraction, and increased residual volume of bile are observed in patients one-month post-RYGB. Cholecystokinin production is significantly reduced in response to oral fat ingestion after RYGB compared with an unoperated control group, however no significant difference in CCK response occurs after protein or glucose ingestion (Jensen *et al.* 2020). One physiological explanation is exclusion of the duodenum resulting in decreased CCK secretion, however in Bastouly's study, similar findings were observed regardless of whether the test meal was administered orally or via a gastrostomy into the gastric remnant (Bastouly *et al.* 2009). A more likely explanation is altered expression of intestinal CCK-secreting cells after RYGB. Expression of preprohormone CCK-encoding genes shown to be significantly lower in the BP limb and higher in the proximal common channel 60-days after RYGB compared with sham-operation in a weight-matched rat study (Zhang *et al.* 2019).

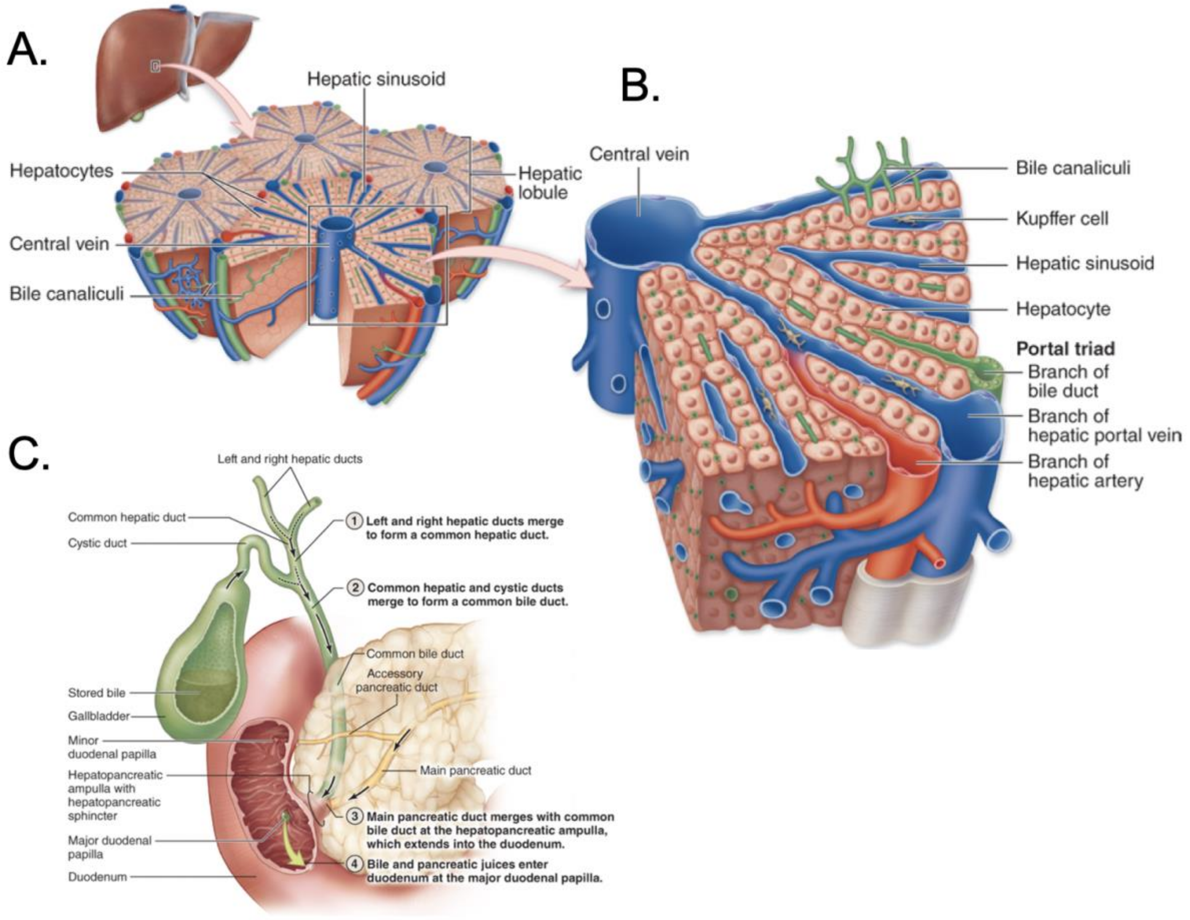


Figure 1.4.1: (A) hepatic lobules; (B) hepatocytes and sinusoids; (C) biliary tract.
Adapted from *Junqueira's Basic Histology: Text and Atlas, 15th Edition* (Mescher 2018), with permission from McGraw Hill LLC, USA.

Enterohepatic circulation

Relatively large amounts of bile acids are required daily for digestion of dietary fats encountered in a typical diet. To meet the demand, bile acids are recycled in the GIT through a highly efficient process termed *enterohepatic circulation*. Once bile acids reach the terminal ileum, 95% are re-absorbed by ileal enterocytes and enter the portal circulation to be returned to the liver. Enterohepatic cycling plays a key role controlling the rate of bile acid production. Biosynthesis of new bile acids is dependent on the rate of bile acid return through the portal system (Small, Dowling & Redinger 1972). An inverse relationship between synthesis and portal venous return of bile acids is observed when return is above ~7 mmol/day, however relatively constant high volume synthesis is seen with return <7 mmol/day (Small, Dowling & Redinger 1972).

There is inconclusive evidence about the impact of MOS on enterohepatic cycling. Sleeve gastrectomy may increase ileal reabsorption of bile acids, specifically taurine-conjugates (Wei *et al.* 2018), whereas RYGB may decrease ileal reabsorption (Chávez-Talavera *et al.* 2017; Seyfried *et al.* 2021). These observations are based on small, animal-based studies, however, limiting translatability to human physiology.

Bile functions

The primary functions of bile are to aid digestion by facilitating absorption of dietary fat and fat-soluble molecules, excretion of hydrophobic hepatic wastes and cholesterol homeostasis. The amphipathic nature of bile acids, containing hydrophilic and hydrophobic ends, enables interaction with both hydrophobic and hydrophilic molecules. This molecular feature is what enables the digestion and absorption of dietary fat and fat-soluble vitamins, as well as elimination of hydrophobic hepatic wastes. Digestion of dietary fat and fat-soluble molecules in the gut requires adequate enzymatic exposure through bile-emulsification, and absorption requires adequate intestinal brush border surface area.

More recent studies elucidate further functions of bile acids as ligands for several nuclear receptors, most significantly *farnesoid X receptor (FXR)* and *Takeda G protein-coupled receptor 5 (TGR5)*. Agonism of these receptors by bile acids significantly augments total body energy expenditure and metabolism (Molinaro, Wahlström & Marschall 2018). A positive correlation is noted between elevated plasma bile acids and increasing BMI in patients with obesity (Prinz *et* *al.* 2015); the authors proposing that the correlation may represent the positive total energy balance. However, persistently elevated serum bile acids have been observed in patients post-RYGB despite significant weight loss (Albaugh *et al.* 2015). This finding, not observed after sleeve gastrectomy (Zhang, Zhang & Zhou 2021), is at least partly explained by the expedited delivery of bile acids to the distal small intestine after RYGB; increasing bile acid re-absorption via the enterohepatic circulation and thus concentration in the portal circulation (Han *et al.* 2015).

Despite much research being undertaken to develop therapeutics targeting FXR and TGR5 (Schaap, Trauner & Jansen 2014), their role in obesity and weight loss remains unclear (Molinaro, Wahlström & Marschall 2018). Paradoxical effects of exogenously administered agonists and antagonists of FXR are reported; both capable of inducing weight loss and improving metabolism (Fang *et al.* 2015; Jiang *et al.* 2015). Further research into the effect of specific bile acids and their selective effect on FXR and TGR5 needs to be undertaken to develop potential therapeutic targets.

1.4.3. Sequelae of bile reflux

Impact on oesophageal mucosa

In GORD, refluxate can contain gastric acid, pepsin and in some individuals, bile acids. Physiological and pathological oesophageal reflux exposure is guided by the 2018 Lyon Consensus for GORD (Gyawali *et al.* 2018). The consensus determined distal oesophageal acid exposure time (pH <4.0) of less than 4% of the total monitoring period and fewer than 40 acidic (pH <4.0) reflux events is physiological. Acid exposure time >6% and >80 acidic reflux events is definitively abnormal, with intervening values indeterminate. When present in refluxate, bile acids form a synergistic combination with gastric acid (low-pH) causing more damage to the oesophageal mucosal barrier than each component acting alone (Farré *et al.* 2008). The degree of damage inflicted is both bile acid concentration-dependent and pH-dependent, with low-pH and high bile acid concentration solutions being more harmful (Farré *et al.* 2008).

Bile acids behave differently depending on the acidity of the residing medium (Kauer *et al.* 1997). Bile acids remain ionised in solutions with relatively high pH (>7), however become non-ionised when the pH nears their pKa (logarithmic acid dissociation constant; lower pKa value means the acid more fully dissociates in water). When in strongly acidic solutions (pH <2), bile acids precipitate irreversibly. Unconjugated bile acids in aqueous solution have pKa range of approximately 5.0 - 6.5, whereas conjugated bile acids have a lower pKa range of 3.0 – 4.0 (Cabral, Hamilton & Small 1986; Fini & Roda 1987). In GORD, most reflux events are acidic (defined as pH <4.0), resulting in a greater proportion of bile acids (when present) being in their non-ionised, hydrophobic form during which they can cross oesophageal epithelial cell membranes (mucosal barrier).

In GORD, reflux disrupts the oesophageal mucosal barrier by increasing epithelial permeability and widening intercellular spaces. Dilated intercellular space (DIS) is an early histological hallmark of GORD and occurs in non-erosive oesophageal reflux disease (Caviglia *et al.* 2005; Tobey *et al.* 1996). When exposed to bile acids *in vitro*, cultured human oesophageal epithelial cells exhibit disruption of intercellular junctions, manifested by alteration in expression of claudins and occludin; proteins involved in establishing epithelial intercellular tight junctions that control cellular flow of molecules. Ghatak *et al.* demonstrated disruption of tight junctions with exposure to a physiologic bile salts cocktail at pH 5, but no disruption with fluid at pH5 without bile salts, or with bile salts at higher pH (Ghatak *et al.* 2016). Similarly, Chen *et al.* demonstrated that exposure to bile salts (glycocholic acid and taurocholic acid) at pH 3 markedly reduced expression of claudins in cultured human oesophageal epithelial cells (Chen *et al.* 2012). These studies utilised *in vitro* cultured oesophageal cells, which lack the true regenerative characteristics of *in vivo* human tissue. This limits translation of findings to normal physiology but builds a foundation for future research. These studies provide important understanding of the synergistic effect of bile acids and acidic media. The combination impairs the oesophageal mucosal barrier, increasing susceptibility to the harmful effects of bile-containing refluxate.

Oesophagitis

Once intracellular, bile acids can damage oesophageal epithelial cells by upregulating production of inflammatory cytokines, such as *interleukin-8, cyclo-oxygenase-2,* and *prostaglandin E2* (Kawabe *et al.* 2004; Souza *et al.* 2009). Reflux oesophagitis, initially thought to be caused by direct caustic injury to epithelial cells by gastric acid or gastric fluids, is more recently thought to be cytokine-mediated (Souza *et al.* 2009). This hypothesis was tested in a rodent-model by fashioning an oesophago-gastro-duodenostomy to induce bile reflux. Direct caustic injury would result in epithelial cell death, subsequent acute inflammatory response, and basal cellular hyperplasia to replace the damaged squamous cells. Souza *et al*. found that appearance of inflammatory cells (T-lymphocytes) and basal cell hyperplasia both preceded any apparent epithelial damage, which first appeared 4-weeks post-operatively (Souza *et al.* 2009).

Elucidation of this mechanism is a significant step forward in understanding the pathophysiology behind the progressive GORD-oesophagitis-Barrett's oesophagus sequence.

Metaplasia (Barrett's Oesophagus)

Barrett's oesophagus (BO), as described by the Adelaide-born British surgeon Sir Norman Barrett, is the replacement of normal oesophageal squamous epithelium with metaplastic columnar epithelium (Barrett 1957). There remains disparity internationally about the histological features of the columnar epithelium defining BO. Australian and American guidelines require intestinal-type metaplasia with goblet cells for diagnosis (Spechler *et al.* 2011; Whiteman *et al.* 2015), contrasting with the British guidelines not requiring inclusion of goblet cells in metaplastic tissue (Fitzgerald *et al.* 2014).

Metaplasia fundamentally occurs as a protective response to chronic tissue damage (Burke & Tosh 2012), with Barrett's metaplasia a consequence of chronic gastro-oesophageal reflux (Spechler & Souza 2014). The GORD-oesophagitis-BO pathology sequence has been extensively investigated with the definitive cellular origin of columnar metaplasia in humans remaining unclear (Zhang *et al.* 2021). The possible aetiological origins of metaplastic cells include: phenotypic conversion of either differentiated oesophageal squamous epithelial cells (Wang 2017) or oesophageal stem cells (Seery 2002); proximal migration of primitive embryonic stem cells at the squamocolumnar junction (Jiang *et al.* 2017; Wang *et al.* 2011), and differentiation of circulating bone marrow stem cells (Sarosi *et al.* 2008; Zhang *et al.* 2021). In a recently published review of BO pathophysiology, Mukaisho *et al.* determined that short-segment BO (≤3cm from gastroesophageal junction) is likely resultant from a 'proximal migration' aetiology, whereas long-segment BO (>3cm) is likely from a 'phenotypic conversion' aetiology (Mukaisho *et al.* 2019). No single aetiological theory has been adopted to date, with majority of existing data elucidated from murine models, limiting translation to human cell lineage and physiology.

When present in gastro-oesophageal refluxate, bile contributes to alteration of gene expression influencing squamous and columnar differentiation. *In vitro* studies of cultured oesophageal cells demonstrate reduced stratification and squamous gene expression when exposed to a bile acid cocktail at pH 5 (Ghatak *et al.* 2013; Reveiller *et al.* 2012). Furthermore, trans-membranous epidermal growth factor receptor signalling is upregulated upon exposure to bile; resulting in cellular de-differentiation and proliferation to augment the response to tissue damage (Ghatak *et al.* 2013). Columnar cell differentiation is also influenced by transcription factors present in human intestinal cells but absent in normal oesophageal epithelium. When exposed to gastric acid and bile acids, Barrett's epithelial cells show increased expression of such transcription factors, whereas non-Barrett's epithelial cells do not (Huo *et al.* 2010; Reveiller *et al.* 2012). All the above-referenced studies used cultured human oesophageal cells, exposed to a 'physiological' bile salt cocktail for 10-15 minutes three times per day. This duration and frequency of bile exposure is underestimated in comparison to *in vivo* findings, however, with episodes of oesophageal bile reflux detected up to 78 times in a 24-hour period on ambulatory pH-bilirubin monitoring in patients with known BO (Marshall *et al.* 1998). Despite this limitation, these data still provide sound scientific basis for understanding the impact of bile on the pathophysiology of BO.

Dysplasia and carcinogenesis

Barrett's epithelial cells can become dysplastic and potentially neoplastic if they undergo genetic and epigenetic alterations to acquire tumourigenic potential (Hanahan & Weinberg 2011). Bile-induced oesophageal inflammation alters the cellular microenvironment, promoting oxidative deoxyribonucleic acid (DNA) damage and facilitating tumour development (Coussens & Werb 2002). Reflux-related oesophageal cancers are typically *adenocarcinomas*; neoplastic epithelial cells of glandular origin.

Barrett's epithelium and oesophageal adenocarcinoma cells show increased expression of nuclear factor-kappa B (NF-kB) compared with normal oesophageal epithelium (Abdel-Latif *et al.* 2004). Nuclear factor-kappa B is a cytoplasmic protein present in healthy cells and involved in normal cellular proliferation and programmed cell death (apoptosis). When exposed to bile acids, oesophageal epithelial tissue upregulates NF-kB expression in a time- and dose-dependent manner, pathologically altering cellular proliferation and preventing apoptosis, increasing the risk of cancer development (Abdel-Latif *et al.* 2016).

Patients with BO have a ~0.5% annual risk of developing adenocarcinoma; a cancer that portends a five-year survival rate of 20% (Australian Institute of Health and Welfare 2017a; Peters *et al.* 2019). Preventative strategies, such as chemoprevention and endoscopic surveillance, are key tenets of BO management. Proton pump inhibitor (PPI) therapy has proven an effective method of risk reduction for progression of BO to dysplasia or neoplasia. The strongest evidence for this comes from the *AspECT Trial;* a large, multicentre, randomised trial allocating 2557 participants with BO to receive esomeprazole at either high (40mg twice daily) or low dose (20mg daily), with or without aspirin (300mg daily) (Jankowski *et al.* 2018). This robust study, with 99.9% completion rate and median follow-up of 8.9 years, reported that high dose PPI is protective against mortality, oesophageal adenocarcinoma, and high-grade dysplasia, compared with low-dose PPI. The assumption that low-dose PPI is ineffective in protecting against dysplasia/neoplasia is false, however, with a 2014 meta-analysis concluding an associated overall 71% risk-reduction, noting inconsistent reporting of PPI dosages (Singh *et al.* 2014). The AspECT trial also demonstrated that aspirin is additive to PPI use in protecting against the same endpoints of mortality, dysplasia, and neoplasia. However, in a post-MOS cohort, concern regarding marginal ulceration prompts avoidance of non-steroidal anti-inflammatory drugs, which includes aspirin, as they unequivocally increase ulceration risk (Rodrigo *et al.* 2020). However, in this large retrospective analysis of hospital admissions for marginal ulceration post-MOS, Rodrigo *et al.* reported aspirin to be only a minor risk factor on univariate analysis, but a protective factor on multivariate analysis. The discrepancy possibly relates to pre-morbid microvascular disease being treated with aspirin, thereby improving tissue vascularity and reducing ischaemia; another key cause of marginal ulceration.

Endoscopic surveillance of BO is widely recommended by many international gastroenterological societies: the British Society of Gastroenterology; the European Society of Gastrointestinal Endoscopy; the American Gastroenterological Association, and; Cancer Council Australia (Fitzgerald *et al.* 2014; Sharma *et al.* 2020; Weusten *et al.* 2017; Whiteman *et al.* 2015). The purpose of surveillance programmes is to detect dysplasia and neoplasia early, enabling expedited treatment and improved outcomes. Australian guidelines for initial and repeat surveillance endoscopy are summarised in Table 1.4.1.

Biopsies taken as per *Seattle protocol (Levine et al. 2000)*:
- Any mucosal irregularity - Quadrantic biopsies every 2cm of affected oesophagus - *If known or suspected dysplasia* → quadrantic biopsies every 1cm
No dysplasia on endoscopy + biopsy
- Short segment Barrett's (<3cm) → Repeat endoscopy in 3-5 years - Long segment Barrett's (≥3cm) → Repeat endoscopy in 2-3 years
Indefinite results for dysplasia on biopsy
1. Repeat in 6 months 2. If no dysplasia → continue as above 3. If indefinite again → repeat in 6mo 4. If low-grade or high-grade dysplasia, or neoplasia, continue as below
Low grade dysplasia on biopsy
1. Repeat every 6 months taking quadrantic biopsies every 1cm 2. If 2 consecutive 6-monthly endoscopies show no dysplasia, can return to above protocol
High grade dysplasia or neoplasia
- Refer patient to specialist centre with appropriate multi-disciplinary expertise

Table 1.4.1: Recommendations for frequency of endoscopic surveillance of patients with Barrett's Oesophagus. *Adapted from Australian Clinical Practice Guidelines for BO* (Whiteman *et al.* 2015).

Despite widespread recommendation for endoscopic surveillance, there are potential harms: risks associated with endoscopy and any therapies instituted; potential for missed lesions, and persistent patient anxiety about their health. Further, approximately 85-90% of patients with non-dysplastic BO will not progress to developing dysplasia or malignancy (Hvid-Jensen *et al.* 2011; Peters *et al.* 2019). Recommendations for surveillance are largely based on retrospective, observational studies, with the efficacy and cost-effectiveness of such programmes being brought into question (Verbeek *et al.* 2014; Vissapragada *et al.* 2021). The annual risk of progression of non-dysplastic BO decreases with each consecutive endoscopy showing absence of dysplasia; from 0.32% after one endoscopy to 0.11% after five negative endoscopies (Peters *et al.* 2019). As such, targeted surveillance of higher risk groups, such as those with BO segments ≥2cm and/or dysplasia, have been proposed to improve cost-effectiveness of surveillance programmes (Lindblad *et al.* 2017). A large randomised controlled trial in the UK is currently underway to further investigate the utility of endoscopic surveillance, estimated to finish in 2022 (Old *et al.* 2015). The study is comparing regular endoscopic surveillance versus endoscopy on symptom development among patients with BO, with overall survival and cost-effectiveness as the key outcomes. This trial will hopefully provide clear evidence about the benefits, or lack thereof, of endoscopic surveillance.

1.4.4. Bile reflux after upper gastrointestinal surgery

Prior to the introduction of effective medical therapy for benign duodenal and gastric ulcer disease, surgery was frequently performed as primary treatment. Non-resectional techniques utilised disruption of vagal innervation to parietal cells, decreasing acid production. *Truncal vagotomy* (division of both anterior and posterior vagal trunks), while denervating gastric parietal cells, also denervates the pylorus, necessitating a drainage procedure for gastric emptying. Pyloroplasty and gastrojejunostomy are commonly used methods, however both demonstrate resultant duodenogastric reflux of bile, observed on biliary scintigraphy (Brough, Taylor & Torrance 1984) and endoscopy (Charitopoulos *et al.* 1994). *Highly selective vagotomy*, described by Johnston & Wilkinson in 1970, preserves pyloric innervation, eliminating the need for disruption of the pyloric anti-reflux mechanism (Johnston & Wilkinson 1970). Published studies demonstrate much lower rates of duodenogastric reflux compared with truncal vagotomy and drainage procedure (Dewar, Dixon & Johnston 1984). For severe or refractory ulcer disease, distal gastrectomy was often required, with reconstitution of the gastrointestinal tract predominantly using a Billroth II gastrojejunostomy (Figure 1.4.2). Studies arose reporting a link between the Billroth II reconstruction and cancer of the gastric stump (Morgenstern, Yamakawa & Seltzer 1973), with bile reflux cited as a potential causative factor. However these studies pre-date the discovery of *Helicobacter pylori* (Warren & Marshall 1983), an independent risk factor for development of gastric cancer (Kuipers 1999). More recently, a large population-based study was published, investigating the development of gastric cancer among patients who had undergone distal gastrectomy between 1964 - 2008 for benign ulcer disease (Lagergren, Lindam & Mason 2012). In a cohort of over 18,000 patients, 8,735 (46%) of whom underwent a Billroth II, the incidence of gastric stump cancer post-Billroth II was no different than the expected incidence in the standard population (73 cases post-Billroth II; 83 cases expected). Such a large population study, including patients post-*H. pylori* discovery and proton pump inhibitor development, provides much more meaningful context for the true risk of gastric stump cancer development in a modern healthcare system. Surgery for benign ulcer disease has been largely superseded by PPI therapy and *H. pylori* eradication. The popularity of weight loss surgery continues to grow however, with innovative procedures inciting ongoing concern for risk of duodenogastric reflux.

When the OAGB was first described, similar controversy surrounding the risk of bile reflux and carcinogenic potential was encountered due to the anatomical similarities to the Billroth II and the Mason gastric bypass (see Figure 1.4.2). Despite encouraging data on the efficacy and safety of the procedure (Almuhanna *et al.* 2021; Carandina *et al.* 2021), many surgeons report concern regarding the risk of subsequent gastric and oesophageal cancer (Mahawar *et al.* 2017). Five studies have evaluated bile reflux after OAGB, but utilise varied diagnostic protocols; two (from the same group) use biliary scintigraphy and upper gastrointestinal endoscopy (Saarinen *et al.* 2020; Saarinen *et al.* 2017); two use upper gastrointestinal endoscopy and gastric fluid analysis (Lasheen *et al.* 2019; Shenouda *et al.* 2018), and; one uses only upper gastrointestinal endoscopy (Keleidari *et al.* 2019). The variation in bile reflux incidence (7.8 - 55.5%) between studies reflects the diagnostic heterogeneity and impedes determination of the true incidence of bile reflux.

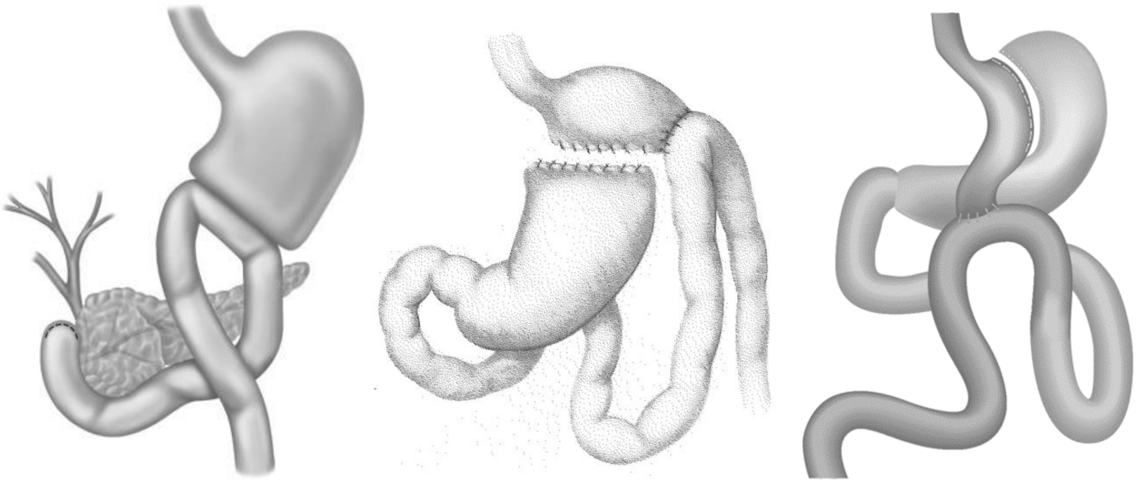


Figure 1.4.2:
Left: Billroth II; *Reproduced from 'ERCP in Surgically Altered Anatomy' (Lo 2019)*
Middle: Mason gastric bypass; *Reproduced from Linner et al. (Linner 1987)*
Right: One-anastomosis gastric bypass; *Reproduced from 'Mahawar et al (Mahawar et al. 2017)*
Images reproduced with permission from: Elsevier ©, Amsterdam, Netherlands (left and middle), and; Springer Nature©, Basingstoke, United Kingdom (right).

A more recently described MOS procedure, albeit much less frequently performed than OAGB (<0.1% of all procedures – IFSO 2021), is the *single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S)*; a modification on the BPD-DS utilising an ileal loop anastomosis (Figure 1.4.3) (Sánchez-Pernaute *et al. 2007*). Much like OAGB, there exists apprehension for adoption of this procedure due to concern regarding long term complications, such as chronic bile reflux (Clapp *et al.* 2021). A recently published meta-analysis explored occurrence of duodenogastric reflux post-SADI-S, demonstrating a reported incidence of only 1.23% (Portela *et al.* 2022). Retention of the pyloric sphincter proving crucial as a physical barrier to duodenogastric reflux.

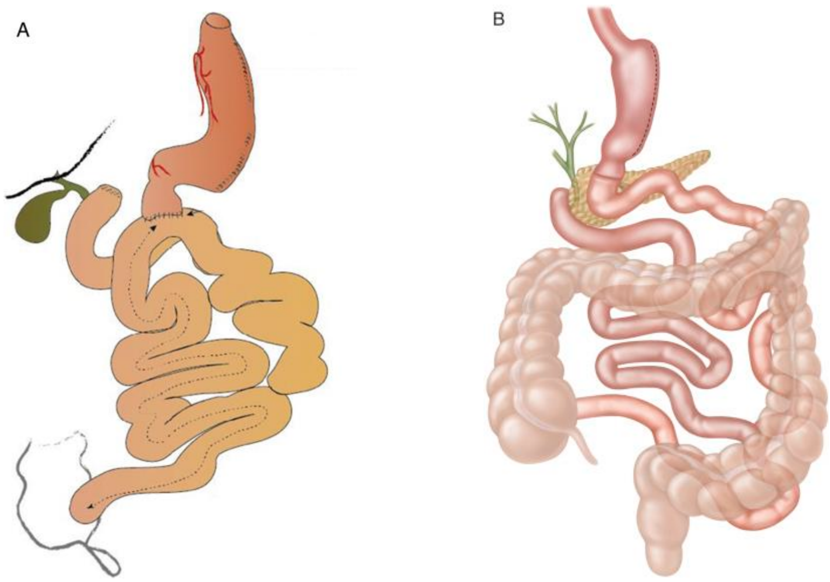


Figure 1.4.3:
A) Single anastomosis duodeno-ileal bypass with sleeve gastrectomy. *Reproduced from Brown et al. (Brown et al. 2021) with permission from Springer Nature©, Basingstoke, United Kingdom*
B) Biliopancreatic diversion with duodenal switch. *Reproduced from 'ERCP in Surgically Altered Anatomy' (Lo 2019) with permission from Elsevier ©, Amsterdam, Netherlands*.

Sleeve gastrectomy is frequently termed a 'refluxogenic' procedure with regards to gastroesophageal reflux. A recent systematic review and meta-analysis of over 10,000 patients reports an increase of reflux symptoms post-SG in 19% of patients and *de novo* reflux symptoms in 23% (Yeung *et al.*). Further, the long-term prevalence of oesophagitis and BO were reported as 28% and 8% respectively. The concern for bile reflux after SG is less than that of OAGB, largely because the pyloric sphincter remains intact as a barrier to duodenogastric reflux. However, a recent study assessing bile reflux using biliary scintigraphy in patients with *de novo* reflux symptoms post-SG, demonstrated bile reflux occurring in 32% of participants (7/22) (Braghetto *et al.* 2019).

Concern for gastric stump bile reflux after RYGB is negligible, given the long distance between the biliopancreatic limp and the gastric stump. However, the gastric remnant remains susceptible to duodenogastric reflux, evidenced to occur in up to 36% of patients 18-months post-operatively in a prospective cohort study (Sundbom, Hedenstrom & Gustavsson 2002). Almost half (9/22) of the patients in this study had undergone prior cholecystectomy, a condition known to promote duodenogastric reflux (Lake *et al.* 2021), however no significant difference in reflux was observed when compared with patients with an intact, functional gallbladder; possibly due to the small sample size. Despite such findings, disproportionate apprehension towards OAGB exists. Concern regarding gastric mucosal exposure to the potentially deleterious effects of bile cannot be limited to OAGB, when duodenogastric reflux occurs in 1/3 of patients SG and RYGB. This is especially pertinent in RYGB as the gastric remnant is inaccessible for endoscopic surveillance.

To date, very few studies have evaluated the incidence of bile reflux post-MOS, with a paucity of comparative studies and long-term follow-up studies evaluating carcinogenesis. The lack of a gold standard investigation for bile reflux diagnosis means heterogenous diagnostic protocols are utilised in the existing studies evaluating bile reflux post-MOS. Determination of an optimal method of assessment for bile reflux is warranted to enable accurate diagnosis.

1.5 Subjective and Objective Assessment of Reflux Disease

1.5.1 Symptom Assessment

Gastro-oesophageal reflux disease is the pathological diagnosis made when oesophageal reflux of gastric contents causes troublesome symptoms and/or complications, as outlined in the *Montreal definition* (Vakil *et al.* 2006). Typical reflux symptoms include heartburn and regurgitation, however atypical oesophageal and extra-oesophageal symptoms can arise, including: chest pain, dysphagia, cough, laryngitis and dental erosion (Vakil *et al.* 2006). Bile reflux into the oesophagus cannot be differentiated from acidic reflux by symptoms alone, although symptoms caused by bile reflux are often non-responsive to acid-suppression therapy (Tack *et al.* 2004).

Myriad questionnaires exist for assessment of GORD, each with varying characteristics and domains of evaluation. A systematic review of existing GORD questionnaires, undertaken in 2015, categorised questionnaires into 7 domains for evaluation; generic gastrointestinal, GORD-specific symptoms (oesophageal and extra-oesophageal as 2 distinct domains), diagnosis, response to treatment, quality of life, and paediatric (Bolier *et al.* 2015). Table 1.5.1 provides a summary of recommendations. Ultimately, no single questionnaire is suitable for all aspects of GORD assessment and selection is determined by desired outcome.

General practitioners (GP) are the first line of care for patients presenting with reflux symptoms, relying on symptom scores and response to oral therapies to facilitate diagnosis of GORD. Throughout his illustrious career, Professor John Dent, an internationally renowned, Adelaide-based gastroenterologist, has been involved in the development and refinement of numerous questionnaires to aid GP diagnosis of GORD. The *Carlsson-Dent Questionnaire* entered practice

RECOMMENDED ASSESSMENT TOOL	NOTES
Generic gastrointestinal	
Patient Assessment of Upper Gastrointestinal Symptom Severity Index (**PAGI-SYM)**	Assesses main symptom groupings of GERD, dyspepsia, and gastroparesis
Gastrointestinal Symptom Rating Scale **(GSRS)**	Ability to discriminate across different gastrointestinal disorders
GORD-specific	
Gastroesophageal Reflux Questionnaire **(GERQ)**	Extensive symptom questionnaire, less practical in everyday practice due to length
Reflux Questionnaire **(ReQuest)**	Extensive questionnaire with symptom and well-being sub-scales Assesses typical and atypical symptoms Has a shorter *ReQuest in Practice* for use in everyday clinical practice
Diagnosis	
Reflux Disease Questionnaire **(RDQ)**	Appropriate for symptom assessment and diagnosis
Gastroesophageal Reflux Disease Questionnaire **(GerdQ)**	Short, effective, validated questionnaire for diagnosis. Accuracy approaches that of gastroenterologists taking a patient history.
Response to treatment	
Proton Pump Inhibitor Acid Suppression Symptom Test **(PASS)**	Easily applicable in primary care settings for assessment of response to treatment solely
Reflux Disease Questionnaire **(RDQ)**	Useful in evaluating oesophageal symptoms in response to treatment
Reflux Symptom Index **(RSI)**	Useful for the assessment of extra-oesophageal symptoms in response to treatment
Quality of life	
Quality of Life in Reflux and Dyspepsia **(QOLRAD)** Patient Assessment of Upper GastroIntestinal Disorders-Quality of Life **(PAGI-QOL)**	Both QOLRAD and PAGI-QOL questionnaires are easy to administer with Likert scales. Self-administration by patients enhances content validity and reduces outcome bias.
Paediatric	
Infant Gastroesophageal Reflux Questionnaire Revised **(I-GERQ-R)**	Most useful for evaluating GERD symptoms and their change in response to treatment in infants. Some diagnostic value also.
Paediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire	Useful for assessment of symptoms and quality of life in children and adolescents

Table 1.5.1 – Summary of recommendations from systemic review of GERD questionnaires (Bolier *et al.* 2015).

in 1998 as a simple, structured questionnaire, using patient-experienced symptom descriptions for GORD diagnosis (Carlsson *et al.* 1998). Further evaluation of the questionnaire in a prospective cohort study demonstrated no diagnostic improvement over GP clinical judgement, limiting clinical utility (Numans & de Wit 2003). In an effort to develop a more effective diagnostic tool, the *Reflux Diagnostic Questionnaire (RDQ)* was constructed (Shaw *et al.* 2001). The RDQ pilot version, possessing many similarities to the *Carlsson-Dent Questionnaire,* was designed with assistance of a 'survey methodologist'. Alterations were then made after conducting cognitive interviews with 25 patients presenting with reflux symptoms to ascertain if the questions adequately covered the breadth of their reflux symptoms. The diagnostic accuracy of the RDQ was assessed in the DIAMOND study; a large multi-national clinical trial, led by Professor Dent, assessing accuracy of GORD diagnosis by RDQ compared with physicians and by trial of PPI therapy (Dent *et al.* 2010). Questionnaire scores, physician diagnosis, and response to PPI therapy were compared with upper GI endoscopy and ambulatory 48-hour wireless pH monitoring results to determine accuracy. Sensitivity and specificity, respectively, of the symptom-based diagnosis of GORD, were 62% and 67% for the RDQ, 63% and 63% for family practitioners, and 67% and 70% for gastroenterologists. Symptom response to PPI therapy (esomeprazole) was neither sensitive nor specific for the diagnosis of GORD.

Further analysis of data from the DIAMOND study was undertaken as a separate study to devise a simpler symptom questionnaire, the *GerdQ* (Jones *et al.* 2009). The impetus for the simpler questionnaire being to improve ability for reliable, rapid GORD diagnosis and provision of appropriate management; important in modern practice where consulting time is short, and compliance with numerous treatment guidelines is expected. The number, wording, and content of questions for GerdQ (see Table 1.5.2) were determined through analysis of RDQ questionnaire responses, along with qualitative patient interviews. Using a receiver-operating characteristic (ROC) curve, Jones *et al.* determined a cut-off value of 8 (those with score ≥8 have higher likelihood of GORD and <8 have low or no likelihood) to be optimal, with sensitivity and specificity being 64.6% and 71.4% respectively; comparable results to that of a specialist gastroenterologist. Validation studies comparing GerdQ scores with endoscopic findings and ambulatory reflux testing confirm reliable results. In a study of 169 patients with symptoms suggestive of GORD, a cut-off value of 8 demonstrated sensitivity and specificity of 78% and 50%, respectively, when compared with confirmed reflux on upper GI endoscopy or 24-hour pH-metry (Jonasson *et al.* 2013). On balance, the authors recommended a cut-off score of 9, which had lower sensitivity of 66%, but higher specificity of 64%. Further, comparison with 24-hour oesophageal pH-impedance monitoring demonstrates good correlation of GerdQ score ≥8 with key indicators of reflux (acid exposure time and total acid reflux events), with sensitivity of 78.9% and specificity 92.9% (Zaika *et al.* 2020). Lacy *et al.* compared GerdQ scores with findings on 48-hour wireless pH-recording, demonstrating that GerdQ was useful in discriminating between normal and abnormal acid reflux in patients off PPI therapy, but not those already on PPI therapy (Lacy, Chehade & Crowell 2011). These findings indicate that the optimal use for the GerdQ may be for patients presenting to their GP with previously untreated reflux-type symptoms, to avoid the need for invasive diagnostic tests.

No specific questionnaire exists to distinguish bile reflux from acidic reflux and very few studies investigating bile reflux have incorporated symptom questionnaires. The GerdQ has been used in one study examining bile reflux in nine patients after OAGB (Saarinen *et al.* 2017). Only two patients recorded GerdQ score >8: one demonstrating bile reflux into the gastric pouch, the other with no reflux. No extrapolation regarding GerdQ score correlation with positive bile reflux is possible due to the small sample size. Another trial, examining bile reflux after sleeve gastrectomy (Braghetto *et al.* 2019), classified reflux symptoms according to a *symptom index* (Wang *et al.* 2004). The indices of mild, moderate, and severe, give a likelihood of GORD according to graded frequency and subjective severity of the patient's symptoms. In developing the GerdQ, symptom frequency was used in preference to severity; patient focus groups preferred use of symptom frequency due to the challenge of subjective symptom severity determination. Further, using frequency alone gave a slightly better ROC curve (sensitivity 64% and specificity 67% for an optimal diagnosis cut-off) compared with severity alone, and a comparable curve compared with both frequency and severity (corresponding sensitivity 62% and specificity 67%) (Jones *et al.* 2009).

QUESTIONS *(prefix: During the previous week…)*	Score for frequency of symptom			
	0 days	1 day	2-3 days	4-7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards towards your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have a pain in the centre of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what a physician told you to take? (such as Mylanta, Gaviscon, etc.)	0	1	2	3
TOTAL SCORE: 0 to 2 points = 0% likelihood of GORD 3 to 7 points = 50% likelihood of GORD 8 to 10 points = 79% likelihood of GORD 11 to 18 points = 89% likelihood of GORD				

Table 1.5.2: *GerdQ* questions and score allocation (Jones *et al.* 2009).

Symptom questionnaires are of limited diagnostic value for bile reflux when used alone. Evaluation must be multi-modal, employing use of subjective questionnaires in conjunction with objective investigations. When patients have atypical symptoms for GORD, or symptoms refractory to PPI therapy, upper gastrointestinal endoscopy is often warranted to identify a cause and evaluate any tissue damage that may be present.

1.5.2 Endoscopic Assessment

Upper gastrointestinal endoscopy (UGIE) is not the primary investigation for *diagnosis* of gastro-oesophageal or bile reflux; absence of abnormal findings on UGIE does not rule out reflux disease. Rather, UGIE provides the opportunity to assess for sequelae of reflux disease by enabling macro- and microscopic assessment of gastric and oesophageal mucosa, while also enabling acquisition of gastric fluid for biochemical analysis.

Macroscopic and Microscopic Findings

In modern practice, the macroscopic appearance of oesophagitis during endoscopic examination is described using the *Los Angeles (LA) Classification*, which categorises appearances of oesophageal mucosa into four levels of severity (Figure 1.5.1). The LA classification system, backed by peer-reviewed, original research, was developed prospectively as a standardised method of grading oesophagitis (Armstrong *et al.* 1996; Lundell *et al.* 1999). Prior to its conception, over 30 different 'classifications' had been reported; illustrating a lack of consensus. When compared with the most widely used system at the time, the *Savary-Miller classification* (Savary & Miller 1978), the LA Classification demonstrated superior inter-observer agreement regardless of endoscopist experience (Rath *et al.* 2004). The use of ambiguous terminology in the Savary-Miller classification, such as 'erosion' and 'ulcer', contributes to the poor inter-observer reliability. When shown individually photographs of varying mucosal defects, poor agreement was observed between endoscopists in distinguishing 'ulcers' from 'erosions' (Lundell *et al.* 1999). Thus, the term 'mucosal break' was adopted in the development of the LA classification, minimising ambiguity. The LA classification has since become the most-commonly used tool globally for description of macroscopic oesophagitis (Dent 2008).

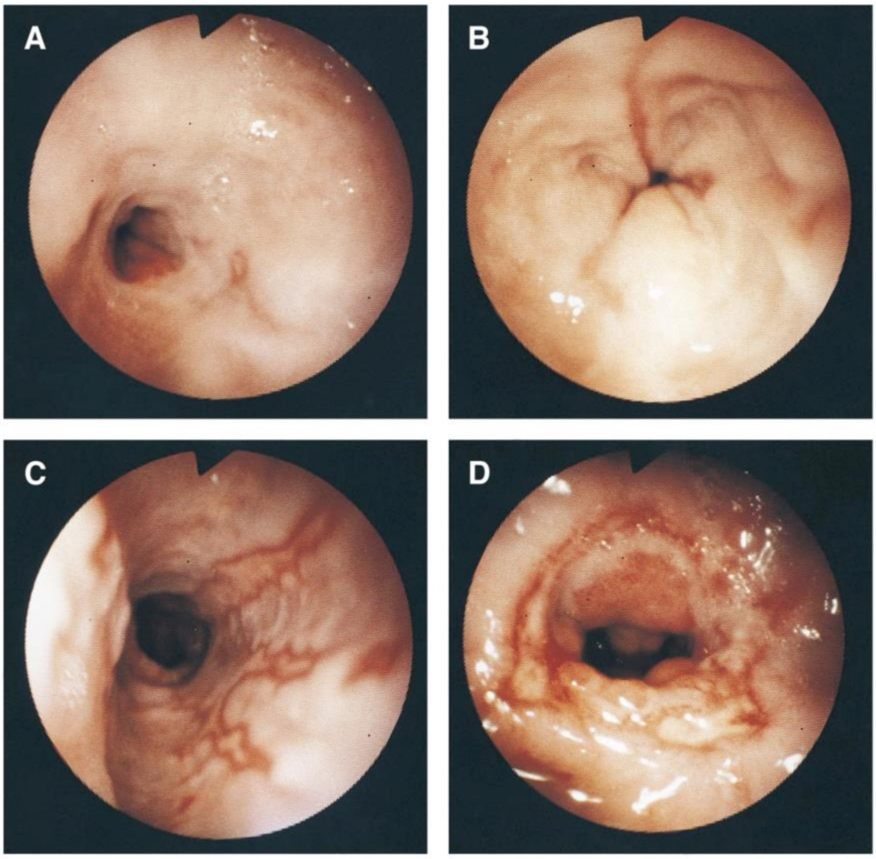


Figure 1.5.1: Endoscopic images depicting the grades of the *Los Angeles Classification*:

A) One (or more) mucosal break ≤5 mm long not extending between the tops of two mucosal folds
B) One (or more) mucosal break >5 mm long not extending between the tops of two mucosal folds
C) One (or more) mucosal break that is continuous between the tops of two mucosal folds but which involves ≤75% of the circumference
D) One (or more) mucosal break which involves at least 75% of the oesophageal circumference

Image reproduced (Armstrong *et al.* 1996) with permission from Elsevier©; Amsterdam, Netherlands .

Microscopically, the key features of reflux oesophagitis include: inflammatory cells in the squamous epithelium; basal zone hyperplasia, and; elongation of lamina propria papillae with capillary congestion (Collins *et al.* 1985). When present in gastroesophageal refluxate, bile acids increase mucosal permeability (see Chapter 1.4.3), however no major distinction can be made between bile-induced and acid-induced oesophagitis on routine histopathological analysis.

Gastritis arises from more diverse pathological causes compared with oesophagitis, warranting differentiation to define treatment. As such, the *Updated Sydney System* was developed by world experts in gastroenterology as a standardised tool for determining aetiology of gastritis based on histological findings (Price 1991; Stolte & Meining 2001). As outlined in the Updated Sydney System, bile reflux gastropathy is often characterised by: foveolar hyperplasia; lamina propria vasodilatation and congestion; oedema, and a paucity of inflammatory cells (Dixon *et al.* 1986). The *reflux gastritis score* is an aggregate scoring system, with scores of 0-3 allocated to severity of the histological features mentioned above. When evaluated in comparison to gastric fluid bile acid analysis, a score of >10 had a sensitivity of 60%, and specificity 83% for elevated gastric fluid bile acid concentration (Sobala *et al.* 1993). Upon further stepwise logistic regression analysis of reflux gastritis score components in the same study, the authors described an amended scoring system, the *bile reflux index*, reporting improved sensitivity and specificity of 70% and 85%, respectively. This study population was heterogenous, however, comprising patients from 5 different studies, some who had previously undergone gastric surgery resulting in antral resection or exclusion. As a result, not all patients had antral biopsies for histopathological review, a requirement of the Sydney system, instead using gastric body biopsies for analysis. No subgroup analysis was performed on the post-surgical cohort. In the context of this thesis topic, the requirement of antral biopsies therefore limits use of these scoring systems for assessment of bile reflux in a post-gastric bypass cohort. Further, these scoring systems have not been further validated in the past 20 years, over which time diagnostic techniques for bile reflux have improved (see Chapter 3). This original study used gastric fluid bile acid concentration as the diagnostic comparator for bile reflux; a technique which has limitations in the diagnosis of bile reflux, as described in the following section.

Gastric Fluid Analysis

Biochemical analysis of gastric fluid - collected at the time of UGIE - can be performed for bilirubin and/or specific bile acids, confirming bile reflux. Enzymatic colorimetric assay kits for bilirubin are widely used and provide reliable results (Parviainen 1997). Such assays use a reagent to react with bilirubin to form pigmented *azobilirubin,* which absorbs light at a wavelength of 600 nanometres. The amount of light absorbed enables calculation of bilirubin concentration. Another method is liquid chromatography-tandem mass spectrometry, which can be more accurate, providing a ratio of measured to known bile acid concentration of >97%, but the latter method is more complex and expensive (Mi *et al.* 2016).

Bile reflux occurs intermittently (Marshall *et al.* 1998), which may not coincide with the timing of UGIE and gastric fluid collection. In a study of 113 patients referred for investigation of reflux symptoms and 15 healthy controls, 24-hour ambulatory combined oesophageal pH and bilirubin monitoring was used to investigate oesophageal exposure to bilirubin (Marshall *et al.* 1998). Maximal exposure of the distal oesophagus to bile reflux, measured by presence of bilirubin, occurred while patients were recumbent, however, periods of elevated oesophageal mucosa exposure were noted intermittently during non-recumbent periods. It is also worth noting suction aspiration itself during UGIE leads to reduced intra-luminal pressure, potentially inducing bile reflux and distorting assessment of the true incidence (Muller-Lissner 1985). The dilutional effect of orally ingested water, saliva and any topical anaesthesia around the time of UGIE will also interfere with the measured concentration of bilirubin.

1.5.3. Utility in Metabolic and Obesity Surgery

Upper gastrointestinal endoscopy prior to MOS is not universally routine, despite recommendation in a recent position statement from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) (Brown *et al.* 2020). Unexpected findings on UGIE – gastritis, oesophagitis, hiatus hernia – results in modification of the surgical plan, delay, or cancellation in up to 16.5% of patients (Brown *et al.* 2020). Such occurrences have significant patient and healthcare system implications and must be considered. Selective UGIE for symptomatic patients may be reasonable, however up to 25% of asymptomatic patients have abnormal findings; the most common being gastritis, oesophagitis, and presence of a hiatus hernia. As such, selective pre-operative UGIE is only recommended for procedures with known lower risk of gastro-oesophageal or bile reflux, such as adjustable gastric banding and RYGB.

Post-operative UGIE after MOS is predominantly performed only for patients with post-operative symptoms, such as: reflux-type symptoms; regurgitation; chest or abdominal pain, and dysphagia. Severity of reflux symptoms correlates poorly with severity of oesophagitis and presence of BO. A study evaluating patients >3 years post-SG found that reflux symptoms were reported in only 33.4% of patients with *LA Grade C* oesophagitis and 57.2% with *Grade D* oesophagitis (Genco *et al.* 2017). Further, among patients with BO identified at follow-up, 26% denied any reflux symptoms. This study illustrates inappropriate reliance on symptoms to guide post-operative UGIE and highlights the risk of missing asymptomatic severe oesophagitis and BO, squandering the opportunity for early intervention. With increasing concern regarding gastro-oesophageal and bile reflux after SG and OAGB, post-operative surveillance UGIE by a surgical endoscopist or gastroenterologist is now recommended by IFSO at 1 year post-operatively, and every 2-3 years thereafter (Brown *et al.* 2020; De Luca *et al.* 2021; Fisher *et al.* 2021).

The role of MOS in our increasingly obese population is well-established, but improvements are sought. Operative techniques continue to evolve, with adverse outcomes and long-term risks often the driver for change. Currently performed procedures have proven to be effective for weight loss and metabolic improvements, but remain marred by risk of potential long-term harms, such as bile reflux, which remains under-investigated due to lack of standardised diagnostic techniques. To further understand the safety of these procedures, a reliable diagnostic method for bile reflux must be determined to enable clinical research into the incidence, severity, and sequelae. The research presented in this thesis addresses this key gap in the literature.

CHAPTER 2:

Research Aims, Methodology and Considerations

2.1 Aims

The overarching aim of the research in this dissertation is to investigate the incidence, severity, and impact of bile reflux after metabolic and obesity surgery. The studies comprising this research were undertaken to address the following specific aims:

1. **To determine the most effective technique(s) for diagnosis of bile reflux**.

2. **To devise a tailored approach for bile reflux diagnosis in a post-metabolic and obesity surgery cohort, and to determine patient tolerability of the proposed protocol.**

3. **To evaluate the post-operative incidence and severity of bile reflux after laparoscopic one-anastomosis gastric bypass, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy operations.**

4. **To examine the relationship between post-operative objective bile reflux, reflux-type symptoms, and objective findings of gastric and oesophageal tissue damage.**

2.2 Research outline

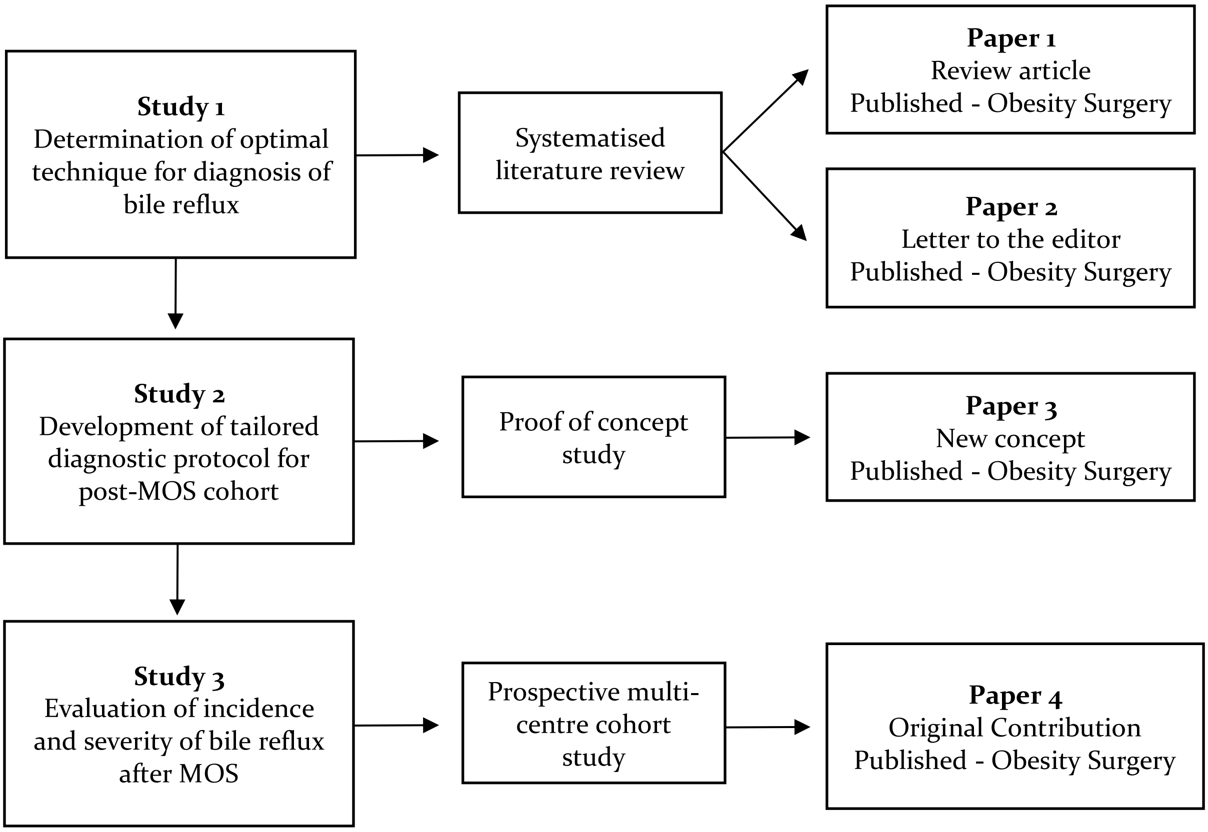


Figure 2.2.1: Research sequence and resulting publications

2.2.1 Study 1

The first study (Chapter 3) reviews and critically evaluates the literature regarding the diagnostic techniques available for diagnosis of bile reflux. A *systematised review* methodology was used. This includes elements of the systematic review process, but doesn't strictly adhere to the guidelines of a systematic review; in this case including a broader range of published data, not just randomised controlled trials for example (Grant & Booth 2009). As part of this study, a systematic search strategy was employed to identify all appropriate studies. A narrative review was then undertaken, evaluating identified techniques based on four key domains: efficacy, cost, patient acceptance, and availability/infrastructure requirements. The findings from this review enabled determination of the optimal investigation(s) for diagnosis of bile reflux.

2.2.2 Study 2

The second study (Chapter 4) builds on the findings from Study 1 to develop a diagnostic protocol for bile reflux, tailored for use in a cohort of patients post-MOS. The optimal investigations identified in Study 1 were critically analysed to identify limitations that would be encountered by the anatomical and physiological changes incurred by MOS. Modifications to the diagnostic protocols were devised to address the limitations. Study 2 assessed the accuracy, reproducibility of results, and patient tolerability of the modified protocol. The findings from this work aiding in the development of the study protocol for study 3.

2.2.3 Study 3

The third study (Chapter 5) - a prospective, multi-centre, multi-arm cohort study - forms the capstone work of this thesis. Participants were invited to enrol from the multidisciplinary obesity clinics of two public hospitals in Adelaide, Australia, and the private consulting rooms of four surgeons. Three trial arms were defined based on the operations participants were undergoing: OAGB, SG and RYGB. Enrolled participants underwent pre- and post-operative (at 6 months) assessment for bile reflux; the findings from studies 1 and 2 guiding the appropriate investigations. Analysis of the study results enabled determination of the incidence of bile reflux after these three MOS procedures, enabling direct comparison between them. These findings provide context for interpreting the role that post-operative bile reflux plays in ongoing gastroesophageal tissue damage and potential for carcinogenesis.

2.3 Considerations

2.3.1 Trial design

The trial design for Study 3 (Chapter 5) was a prospective multi-arm cohort study. Although a randomised controlled trial provides stronger scientific study design, clinical equipoise is lacking in this study context. The three procedures investigated in this study have their own nuances that guide individualised recommendations depending on patient characteristics. For example, patients with pre-existing reflux disease or Barrett's oesophagus are preferentially offered a RYGB rather than a potentially more refluxogenic procedure. Similarly, young patients may be offered a sleeve gastrectomy rather than RYGB or OAGB, due to lower risks of lifelong malabsorption and potential macro- / micronutrient deficiencies.

The trial is registered with the Australian New Zealand Clinical Trial Registry (ACTRN12618000806268).

2.3.2 Radiation exposure

Optimal pre- and post-operative comparison of bile reflux ideally involves identical investigations undertaken at both time points; however biliary scintigraphy was performed only post-operatively in the study presented. The radiation exposure from biliary scintigraphy is significant, warranting review and assessment by the radiation safety officer for informed investigators and patient informed consent. The effective radiation dose for the technique used in Study 3 (Chapter 5) is about 9 millisieverts (mSv) per patient test – see Appendix A (Radiation Dose and Risk Assessment). This is compared with naturally occurring background radiation exposure of about 2 mSv each year (United Nations Scientific Committee on the Effects of Atomic Radiation 2008). It is considered unethical to expose participants to an additional 9 mSv of radiation (totalling 9-times the background annual dose), when the knowledge sought is the occurrence of bile reflux in post-surgical, compared with normal, anatomy. Thus investigators chose to undertake post-operative investigation alone and ethical approval for the study was granted by The Queen Elizabeth Hospital (TQEH) and Calvary Health Care Adelaide Ethics Committees (TQEH - HREC/17/TQEH/185; Calvary – 18-CHREC-F001).

2.3.3 COVID-19 pandemic

The COVID-19 pandemic, extending from December 2019 to the present time, is having substantial impact on all clinical trials, with this current study being no exception (Asaad, Habibullah & Butler 2020; Sohrabi *et al.* 2021). Due to government placed restrictions, all non-essential medical treatments were ceased for 4 months during our recruitment/follow-up period. As a result, recruitment was halted, follow-up was delayed, and patients withdrew due to concerns about visiting hospitals during the pandemic (details in later sections of this thesis).

CHAPTER 3:

Detecting Bile Reflux – The Enigma of Bariatric Surgery

Eldredge T A, Myers J C, Kiroff G K, Shenfine J.
Detecting Bile Reflux – The Enigma of Bariatric Surgery.
Obesity Surgery. 2018 Feb;28(2):559-566.
DOI: 10.1007/s11695-017-3026-6.

Statement of Authorship

Title of Paper	Detecting Bile Reflux - the Enigma of Bariatric Surgery
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Eldredge T A, Myers J C, Kiroff G K, Shenfine J. Detecting Bile Reflux – The Enigma of Bariatric Surgery. Obes Surg. 2018 Feb;28(2):559-566. doi: 10.1007/s11695-017-3026-6

Principal Author

Name of Principal Author (Candidate)	Thomas Eldredge		
Contribution to the Paper	Conceived and designed research; Undertook literature review; Analysed the data and interpreted the findings; Drafted the manuscript including revisions.		
Overall percentage (%)	85%		
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	19/1/22

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 in 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	Jennifer C Myers		
Contribution to the Paper	Assisted in drafting of manuscript; Contributed to critical revision of manuscript for final submission.		
Signature		Date	22-1-2022

Name of Co-Author	George K Kiroff		
Contribution to the Paper	Contributed to critical revision of manuscript for final submission.		
Signature		Date	11/02/2022

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Jonathan Shenfine		
Contribution to the Paper	Conceived and designed research; Supervised the overall study; Contributed to critical revision of manuscript for final submission.		
Signature		Date	19/1/22

Detecting Bile Reflux – The Enigma of Bariatric Surgery

Authors: Thomas A Eldredge [1,2], Jennifer C Myers [1,2,3], George K Kiroff [1,3], Jonathan Shenfine [1,2]

Affiliations

1. Discipline of Surgery, School of Medicine, University of Adelaide, Adelaide, South Australia;
2. Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia;
3. Department of Surgery, Queen Elizabeth Hospital, Woodville South, South Australia.

Acknowledgments:

Thank you to Associate Professor Dylan Bartholomeusz (Royal Adelaide Hospital Nuclear Medicine Department), Ms. Josie Burfield and Mr. Marcus Tippett (Royal Adelaide Hospital Department of Gastrointestinal Investigation) for their input regarding the costing of investigations.

Conflict of interest

Author 1, Author 3 and Author 4 have no conflicts of interest, financial or otherwise, to declare. Author 2 provides educational activities for Medtronic Australasia.

Funding

No industry or other external funding was used for this research.

Abstract

Duodeno-gastro-esophageal reflux, or *bile reflux*, is a condition for which there is no diagnostic gold standard and it remains controversial in terms of carcinoma risk. This is pertinent in the context of an increasingly overweight population who are undergoing weight-loss operations that theoretically further increase the risk of bile reflux. This article reviews investigations for bile reflux based on efficacy, patient tolerability, cost and infrastructure requirements. At this time, whilst no gold standard exists, hepatobiliary scintigraphy is the least invasive investigation with good patient tolerability, sensitivity and reproducibility to be considered first-line for diagnosis of bile reflux. This review will guide clinicians investigating bile reflux.

Keywords: Bile reflux, fiberoptic spectrophotometry, impedance, scintigraphy, endoscopy

Abbreviations:

AUD	Australian dollars
DGER	Duodenogastroesophageal reflux
EGD	Esophagogastroduodenoscopy
HIDA	Hepatobiliary iminodiacetic acid
LES	Lower esophageal sphincter
MII-pH	Multi-channel intraluminal impedance-pH
SPECT	Single photon emission computed tomography

Introduction

Renewed interest in bile reflux follows the escalating obesity epidemic, for which an increasing number of patients are receiving surgical management. While obesity is an independent risk factor for development of gastroesophageal reflux, the anatomical alterations of weight-loss operations can also be refluxogenic (Barr *et al.* 2017). Duodenal contents - bile, bicarbonate and pancreatic enzymes - may reflux back into the stomach and esophagus, termed *duodenogastroesophageal reflux (DGER)* or *bile reflux*. It has been well-documented that bile acids, in conjunction with gastric acid, contribute to reflux-type symptoms (heartburn, regurgitation, waterbrash, etc.), erosive esophagitis and Barrett's esophagus (McQuaid *et al.* 2011; Sun *et al.* 2015). With more weight-loss operations, bile reflux post-bariatric surgery is becoming a pertinent area of investigation (Saarinen *et al.* 2017; Salama & Hassan 2017). There are several investigations validated for the diagnosis of acid gastro-esophageal reflux, however the detection of bile-containing refluxate with subsequent diagnosis of DGER is more difficult with no accepted gold standard. The objectives of this report are to review the current literature surrounding DGER investigations and evaluate their merit. We aim to assess whether a single diagnostic investigation is superior to all others for the diagnosis of DGER.

Methods

PubMed and EMBASE databases were searched for articles describing techniques for detection of DGER. Initial review, using search terms related to DGER, identified four key investigations: hepatobiliary scintigraphy; fiberoptic bilirubin monitoring (Bilitec®); esophagogastroduodenoscopy (EGD) with gastric fluid aspiration, and esophageal impedance-pH testing. These investigations were then included as search terms. A total of 621 abstracts were recalled and searched for information to determine suitability for inclusion. Where the title or abstract involved validation and/or comparison of techniques as part of the investigation of

DGER, the article was read in full. Thirty-eight articles were deemed relevant and a further 13 relevant studies were identified from examination of their full text bibliographies and these articles were included in the review (Table 1). The four techniques identified were critically evaluated based on the available literature in the domains of patient tolerability, cost, infrastructure requirements and sensitivity/specificity.

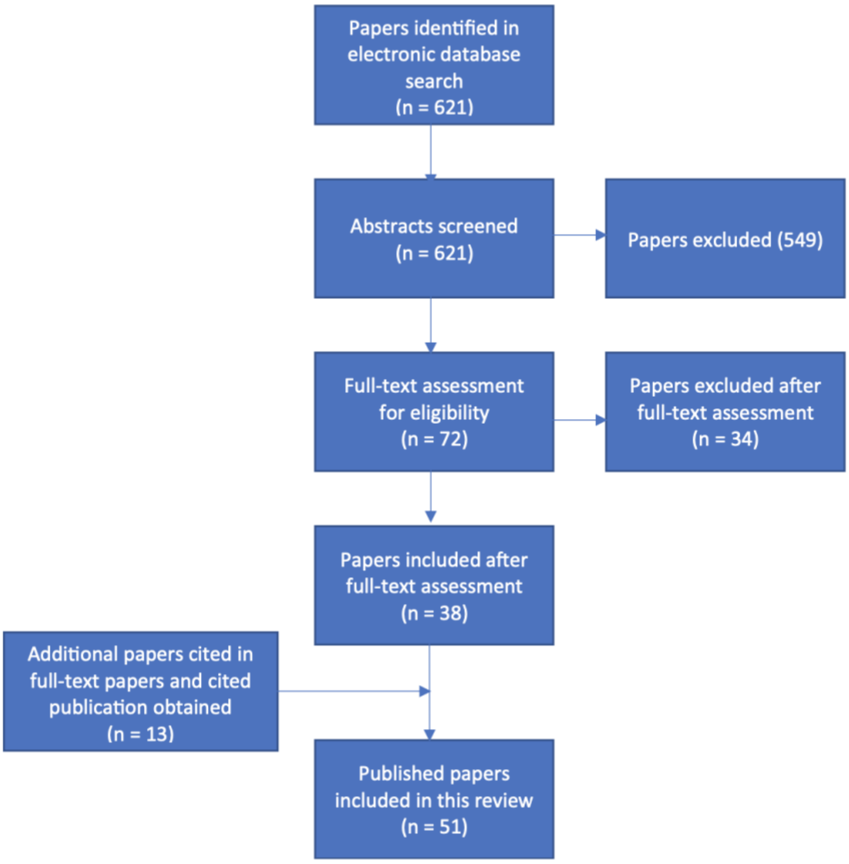


Table 1: Flow chart of systematic search and selection strategy.

Investigative Techniques

Hepatobiliary Iminodiacetic Acid Scintigraphy

Hepatobiliary iminodiacetic acid (HIDA) scintigraphy is a nuclear medicine diagnostic investigation. Iminodiacetic acid, combined with technetium-99m (Tc-99m) is injected intravenously as a radioactive tracer, and detected by an external gamma camera. Tc-99m circulates to the liver and is secreted in bile, allowing visualization of bile drainage through the biliary tree, into the duodenum, and, in cases of DGER, passing into the stomach and/or esophagus (Figure 1). Patients are instructed to fast for 2-6 hours, and positioned supine in front of the gamma camera for 1.5-2 hours (Tulchinsky *et al.* 2010). Pharmacologic agents such as cholecystokinin or morphine may enhance the diagnostic value of the examination, through gallbladder contraction and relaxation of the sphincter of Oddi. This technique was first used for detection of bile reflux post-gastric surgery in 1979 and has since been validated and utilized by many researchers and clinicians (Aydin, Yapar & Yapar 2001; Baulieu *et al.* 1986; Blue, Jackson & Ghaed 1984; Bonaz *et al.* 1988; Borsato *et al.* 1991; Castedal *et al.* 2000; Drane *et al.* 1987; Gerard, Gerczuk & Finestone 2007; Liron *et al.* 1997; Lujan Mompean *et al.* 1990; Mackie, Wisbey & Cuschieri 1982; Shaffer, McOrmond & Duggan 1980; Tolin *et al.* 1979).

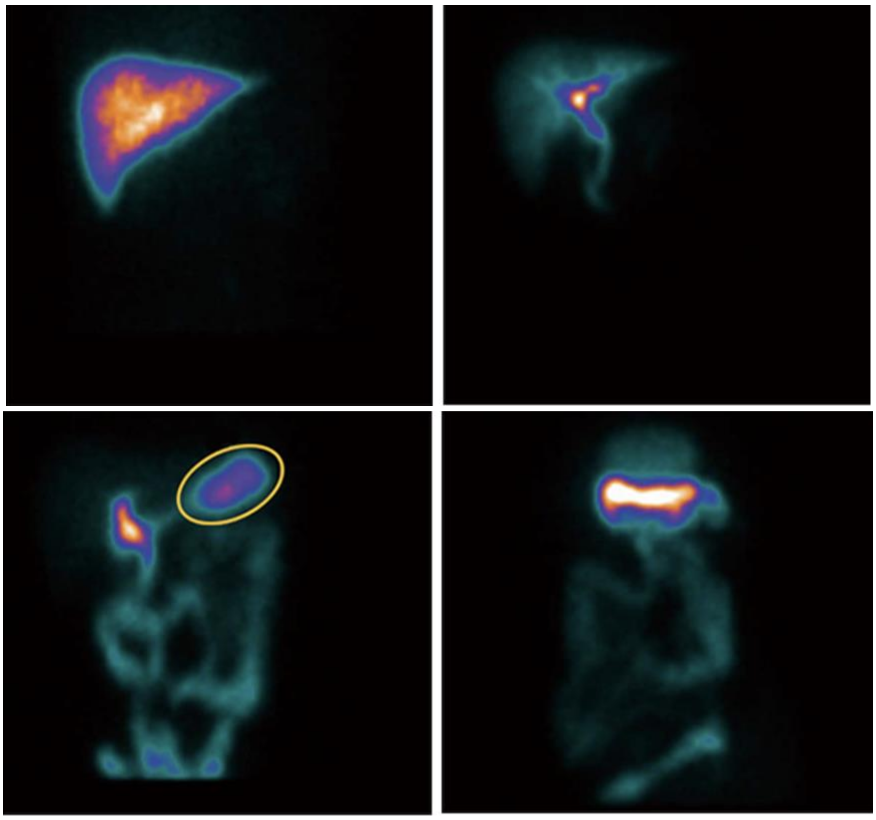


Figure 1: Example of HIDA scintigraphic images, sequentially from left to right, illustrating gastric localization of DGER, as indicated by the yellow circle. Image reproduced with permission from *World Journal of Gastroenterology* (Chen *et al.* 2013).

Scintigraphy is non-invasive. Research suggests that it is equally as reliable as gastric fluid aspiration in the detection of fasting bile reflux. Eriksson and colleagues compared scintigraphic imaging with fasting hourly output of aspirated gastric bile acids in 46 patients admitted for epigastric pain (Eriksson *et al.* 1988). The two methods corroborated the diagnosis of DGER in 80.4% of patients. However, a small sample size and lack of an asymptomatic control arm are notable limitations of this study. Scintigraphy is more sensitive for the diagnosis of DGER than aspiration of gastroesophageal fluid, with acceptable reproducibility (Chen *et al.* 2013; Mittal *et al.* 1994; Tolin *et al.* 1979). Chen *et al.* demonstrated this in a study of 99 patients with known DGER versus a control group of 70 healthy volunteers. All subjects underwent EGD with aspiration of gastric fluid, while 28 patients from the DGER group and 19 persons from the control group underwent HIDA scintigraphy. The sensitivity and specificity of EGD and bile acid analysis were 83.8% and 84.3% respectively. Twenty-eight patients (59.6%) were deemed to be DGER positive by EGD and bile acid analysis, compared with 37 patients (78.7%) by HIDA scintigraphy. Thus the reported reproducibility of HIDA scintigraphy is around 75%, however the short monitoring period (50 minutes) and lack of provocation in this study may understate it's true value (Sorgi *et al.* 1984).

Despite these advantages, scintigraphy lacks anatomical resolution, due to the overlap of organs/structures in a 2-dimensional image. The interpretation of the images during small volume DGER can be especially difficult due to the proximity of the gastric antrum to the left lobe of the liver and the duodenal-jejunal flexure. Combining computed tomography (CT) and single photon emission computed tomography (SPECT) can address this issue, but at a significantly increased cost (Lo, Huang & Fan 2015). Scintigraphy does not accurately quantify volume, concentration or the composition of the refluxate and the intermittent nature of bile reflux and the availability of longer-term monitoring techniques limits it's utility. Although there is no data on tolerability or acceptability, the radiation exposure (effective dose is 3 mSv; equivalent to 30 chest X-Rays) and the requirement to lie still for up to 2 hours are key considerations in this regard.

Fiberoptic Spectrophotometric Bilirubin Monitor

Bilitec 2000 (EB Neuro S.p.A., Florence, Italy) is a fiberoptic spectrophotometer, conceived by Paolo Bechi and colleagues in 1993, based on the principle that bilirubin absorbs light at a specific wavelength, which if detected, infers the presence of bile (Bechi *et al.* 1992). The cylindrical head of the Bilitec probe (9.5mm x 4mm) contains two light-emitting diodes; one blue (emitting at 470nm, corresponding as close as possible to the peak bilirubin absorbance of 450nm) and a reference green diode (565nm). The emitted light traverses a 2mm gap in the head of the probe, is reflected by a white polyvinyl chloride cap and returns to the photodiode in the proximal probe head. When bilious refluxate enters the gap, it will absorb the blue light. Thus by measuring the difference in absorption between the two emitted wavelengths, the concentration of bilirubin in the refluxate can be determined (Beer-Lambert Law). Bilitec thus detects bile acid reflux events when bile salt concentrations in the refluxate exceed 1mmol/L, a level in which esophageal epithelial permeability would be altered causing cell injury (Kiroff *et al.* 1987). The probe is inserted transnasally to the distal esophagus (5cm above the manometric-determined lower esophageal sphincter, LES) in a fasted patient and left *in situ* for 24 hours. Patients are discharged and instructed to resume normal daily activities while adhering to a strict 'white' diet, to avoid interference from coloured food or drink known to affect absorbance readings (Barrett *et al.* 1999).

Ambulatory Bilitec monitoring provides a reproducible, 24-hour measurement of the presence, duration of exposure and approximate concentration of bilirubin (surrogate marker for bile acids) (Manifold *et al.* 2001). *In-vitro* studies of gastric aspirates show a statistically significant correlation between the concentrations of bilirubin and bile acids, and both of these strongly correlate with bilirubin absorbance levels (Bechi *et al.* 1993; Fein *et al.* 1996; Stipa *et al.* 1997;

Vaezi, Lacamera & Richter 1994). These findings indicate that bilirubin is a suitable surrogate marker for bile reflux.

However, despite commercial availability of the device for over two decades, clinical uptake of the Bilitec system has been limited. There are many reasons for this. Although patient comfort and acceptance have not been specifically studied, similar catheter-based studies using significantly smaller probes are poorly tolerated (Wenner *et al.* 2007; Wong *et al.* 2005). In addition, Bilitec has decreased sensitivity when applied *in vivo* when compared to *in vitro* validation studies(Barrett *et al.* 2000; Bechi *et al.* 1993; Vaezi, Lacamera & Richter 1994). Barrett *et al.* artificially reproduced bile reflux in 32 patients with a mid-esophageal infusion of the patient's own aspirated gastric fluid (Barrett *et al.* 2000). Bilirubin absorbance values measured *in vitro* and *in vivo* were compared with total bile acid concentration and total bilirubin concentration of the fluid measured by enzymatic colorimetric assay. The correlations between assays and bilirubin monitoring in the *in vitro* and *in vivo* settings were significantly different with *in vivo* assessments yielding lower correlations than *in vitro* levels. Diagnostic yield can be improved by the additional concurrent assessment of acid reflux (by combining the 3mm Bilitec catheter probe with a 1.5mm single-sensor pH catheter) since most DGER events are acidic (Champion *et al.* 1994; Dai *et al.* 2002).

These differences between *in vitro* and *in vivo* may be partly explained by the following issues. Bilitec does not quantify bile acid concentration, and absorbance readings are affected both by the pH and dilution of the refluxate, so that whether a bile reflux event is 'significant' is unknown (Bechi 1995; Tibbling Grahn *et al.* 2002). The technique is further limited by non-clearance of the probe's sensor region, in which food particles and viscous material may remain longer in the sampling region than in the surrounding mucosa. Interference of Bilitec absorbance readings by solid and liquid meals was evaluated in 211 patients and 40 healthy subjects (Tack *et al.* 2003).

Major meal artifacts occurred in 19% of patients consuming solid meals and none consuming liquid meals. Ambulatory Bilitec monitoring therefore requires adherence to a white, liquid diet, which can impact upon the normal gastrointestinal condition during which reflux occurs.

Gastro-esophageal Fluid Aspiration and Analysis of Bile Acids

Direct aspiration of gastric and esophageal fluid allows for chemical analysis of the concentration and composition of the fluid and determination of the presence of bile acids. Aspiration can be performed either endoscopically under-vision during EGD, or via a naso-gastric tube, then liquid chromatography-tandem mass spectrometry can give quantitative bile acid analysis (Mi *et al.* 2016). Collection of fluid during EGD has the advantage of direct visualization of the fluid and allows an assessment of the esophageal and gastric mucosa with the further advantage of tissue biopsy. Important endoscopic features include: presence of a gastric bile lake; acute gastritis with erythema; thickening of the gastric folds or mucosal erosions (Chang *et al.* 2016; Vere *et al.* 2005). Histological findings include foveolar hypertrophy, intestinal metaplasia and acute or chronic inflammation (Vere *et al.* 2005). Obviously these findings are not specific for bile reflux, thus limiting the diagnostic value of endoscopic visualization and histological analysis when used in isolation (Stein *et al.* 1992).

The intermittent nature of bile reflux also limits the utility of isolated gastric and esophageal fluid aspirates. Reflux generally occurs maximally when supine, but can still occur sporadically when upright. In a study utilizing 24-hour ambulatory combined esophageal pH and bilirubin monitoring, esophageal exposure to bilirubin was evaluated in 113 patients (Marshall *et al.* 1998). The subjects were stratified into 3 groups based on absence and presence of erosive esophagitis and presence of Barrett's esophagus on endoscopy. The median percentage of esophageal bilirubin exposure time in patients with Barrett's esophagus was 16% with interquartile range of 5.0-38.2%. Maximal exposure occurred between 9 pm and 9 am while patients were recumbent, however periods of elevated exposure (above 0.14 units of absorbance) were noted intermittently during the 24-hour test. In addition, the reduced intra-luminal pressure with suction aspiration can induce reflux affecting validity (Muller-Lissner 1985). In the case of EGD, sedation and day-patient hospital admission significantly increases both cost, infrastructure requirements and patient acceptance.

Combined Multi-Channel Intraluminal Impedance-pH

Multi-channel intraluminal impedance monitoring detects the passage of a bolus through the esophagus, first described by Silny *et al.* in 1991 (Silny 1991). It is usually combined with pH testing to evaluate acid and non-acid reflux. The multi-channel intraluminal impedance-pH (MII-pH) probe has 6-8 pairs of impedance electrodes (at intervals on the probe. Each electrode is activated by a high-frequency (1kHz), low-amplitude (<6 μA), alternating current. The degree to which the contents of the esophagus impede the electrical current between any pair of adjacent electrodes allows the determination of the state of the bolus (gas, fluid or mixed), as well as the extent of movement and direction of a passing bolus. The addition of 1 or 2 pH sensors along the probe provides refluxate pH and enables quantification of acidic, weakly acidic and non-acidic reflux episodes.

A pre-calibrated probe, measuring 2.1mm in diameter, is placed trans-nasally in a fasted patient into the stomach; with one pH sensor sitting 5cm below the sphincter and one 5cm above. The probe remains *in situ* while the patient is discharged home to resume their usual activities, while documenting key events including meals, symptoms and recumbent periods. Upon termination of the 24 h test, data is uploaded for semi-automated computer analysis and interpretation.

MII-pH is highly-sensitive and reproducible for all types of reflux, regardless of acidity or composition (Bredenoord *et al.* 2005; Sifrim *et al.* 2004). Furthermore, MII-pH provides 24 hours of information pertaining to the number, proximal extent and nature of reflux episodes and allows for correlation with patient symptoms. An American study retrospectively evaluated 200 patients with persistent GERD symptoms despite twice daily proton pump inhibitor therapy (Sharma *et al.* 2008). They found that 39% of patients were symptomatic during non-acid reflux episodes and would have been misdiagnosed if investigated with pH testing alone. Similar results were observed by Zerbib *et al.*, while utilizing MII-pH testing in patients on and off proton pump inhibitor therapy, they found combined impedance-pH testing improved diagnostic yield by 4% and 17% in patients off and on anti-reflux therapy respectively (Zerbib *et al.* 2006).

Combined MII-pH is easier to perform than combined Bilitec-pH, as the former involves one catheter of 2.1mm diameter compared to two catheters of 3.5mm and 1.5mm. The MII-pH test does not objectively or specifically detect bile or bile acid reflux, instead using a combination of reflux data to act as surrogate markers for 'likely' bile reflux. So that while this technique is an advancement in detection of gastro-esophageal reflux, it is a measure of total reflux rather than a specific measure of DGER. In fact, Pace *et al.* noted that non-acid reflux and bile reflux should be considered as two distinct phenomena after assessing reflux with MII-pH and Bilitec simultaneously (Pace *et al.* 2007). In similarity to the Bilitec monitor patient compliance is important, which can prove difficult as the presence of the small-bore catheter in the throat region can irritate the nose and throat and carrying the data logger interferes with the ability to undertake normal daily activities (Wenner *et al.* 2007; Wong *et al.* 2005). One technique that could improve tolerability is to use a 3-hour post-prandial monitoring period, rather than 24 hours (Gourcerol *et al.* 2014). Gourcerol *et al* correlated the number of liquid reflux events in a 3-hour period and a 24-hour period, concluding that data from the 3-hour recording are likely to give as accurate assessment of GERD as 24-hour MII recording. Unfortunately, the impedance data interpretation is labor-intensive, as patient diary entries and auto analysis of impedance data must be carefully checked for antegrade and retrograde bolus movement.

Other Techniques

Other techniques developed for DGER detection are reported in the literature, however clinical uptake has been poor:

Sodium Ion Electrode

Sodium ion concentration is a marker for duodenal reflux, as the Na+ concentration in duodenal, pancreatic and biliary fluid is fairly constant at ~150mmol/L in contrast to gastric fluid Na+ concentration which varies significantly (Smythe, Bird & Johnson 1992). A British group developed a sodium ion-selective electrode which can be used to detect duodenal reflux events (Watson *et al.* 1996). In one patient study, electrode readings during or following swallows of solutions with varying sodium ion concentrations, and a mid-esophageal re-infusion of bile-containing gastric fluid aspirated from patients was evaluated. This showed very positive results but study conditions were highly controlled and artificial and non-representative of usual bile reflux conditions. Readings *in vivo* are again likely to be significantly affected by acidic environments (pH < 3) and food intake (Watson *et al.* 1996). It remains an experimental technique.

Intraluminal Gamma Detector

A custom-built cadmium telluride gamma detector, small enough to pass into the esophagus and stomach, can also be used following the principles of scintigraphy (Stoker *et al.* 1990). This has validated well against an external gamma camera. However, the internal detector is confounded by elevated radiation counts from radiolabelled bile outside of the gastrointestinal tract studied (i.e. in an adjacent loop of distal bowel). As such, although this ambulatory technique addresses the brief detection window of conventional scintigraphy patient discomfort is likely to limit use.

Ultrasonography

High-resolution colour Doppler ultrasonography of the pylorus allows for real-time detection of DGER events and quantification of reflux volume. First described by King *et al.* in 1984, the technique was evaluated further by Hausken *et al.* (Hausken *et al.* 2001; King *et al.* 1984). A probe placed over the epigastrium records retrograde flow of enteric contents through the pylorus into the stomach by applying Doppler principles. The frequency of reflux events and the distance of the colour signal from the pylorus determine the severity of the DGER. However, movement of the pylorus during respiration disrupts continuous visualization and proximal extent of reflux and duration of exposure cannot be determined. It has not been adopted in this field.

Cost

The cost-to-benefit ratio of the medical investigations is an important factor in healthcare systems. inappropriate tests can place unnecessary financial burden on patients, health insurers and governments. The cost to perform the above investigations for detection of bile reflux in Australia was determined, incorporating the price of consumable items as well as available government rebates. Labor and medication costs, re-useable equipment items and pre-existing infrastructure items were excluded from the calculation. The totals, shown in Table 2, represent the total cost to the Australian public healthcare system to perform the investigations. In addition to costs, Table 2 summarizes the test duration, limitations of each investigation and provides a recommendation for when each test should be considered.

Discussion

The intermittent nature of DGER poses a challenge in the development of an optimal investigation. Of the available techniques, HIDA scintigraphy is the least invasive, but only provides a short window for the capture of DGER events. A more complete DGER profile requires prolonged monitoring. Unfortunately, none of the current ambulatory techniques are ideal. Bilitec ambulatory monitoring was specifically developed for the detection of bile reflux, but is prone to errors, particularly false positive readings, while ambulatory pH and MII-pH monitoring do not directly detect bile reflux.

Patient tolerability is also of key importance. HIDA scintigraphy has superior patient tolerability over catheter-based techniques, as a short-duration, non-invasive investigation. No distinction can be made between available techniques based on cost due to the small financial margin between them (Table 2). EGD and HIDA scintigraphy have substantial infrastructure requirements, requiring a staffed endoscopy suite and gamma camera with computed tomography and SPECT imaging respectively. In contrast, MII-pH and Bilitec monitoring require a highly skilled health practitioner for placement of the specialized catheter and interpretation of acquired data. Infrastructure items were taken into consideration for this review, but not included in Table 2. Sensitivity and specificity data for each technique are lacking, limiting direct comparison of techniques. In available comparative studies, HIDA scintigraphy shows greater sensitivity and specificity over EGD and gastric fluid aspiration. Three studies confirmed this, with Chen *et al.* most recently reporting sensitivity and specificity of HIDA exceeding 83.8% and 84.3% respectively (Chen *et al.* 2013).

Test	Duration	Cost*	Limitations	When to use
HIDA scintigraphy	3 h	$210	– Short monitoring period – No information on concentration, duration or composition of reflux	– For diagnosis of bile reflux without requirement for characterization of refluxate or reflux profile
MII-pH	24 h	$190	– Poor patient tolerability – Not specific for bile reflux – Requires skilled staff for data interpretation	– Reflux symptoms refractory to medical therapy – Characterization of reflux profile
Bilitec	24 h	$230	– Poor patient tolerability – Non-clearance of probe tip – No quantifiable data on bile acid concentrations	– Estimation of duration of bile exposure
EGD + aspiration	~6 h	$240	– Significant infrastructure requirements – Invasive test requiring sedation – Risk of complications	– Persistent reflux symptoms – Dysphagia/odynophagia – Need for tissue visualization and biopsy

*Costs, shown in $AUD, include consumables and government rebates but are not inclusive of staff labor, medications (if required), and reusable equipment items

Table 2: Summary of recommendations. HIDA – hepatobiliary iminodiacetic acid; MII-pH – multichannel intraluminal impedance-pH; EGD – esophagogastroduodenoscopy.

Scope exists for further advances in techniques for detection of bile reflux. The use of a bile acid-specific biosensor has been conceptualized, utilizing polymers capable of forming covalent bonds with bile acids (Nehra 2010). This technique remains a concept not yet developed, but illustrates a potential area for advancement. On the horizon, wireless devices such as those used for pH monitoring (Bravo™, Medtronic, Minneapolis, USA) will potentially enhance the uptake of ambulatory recording techniques, with improved patient tolerability.

Conclusions

This review demonstrates that the literature lacks suitable comparative studies and so it is difficult to draw a conclusion that a single diagnostic investigation is superior to others for the diagnosis of DGER. However, there are distinct advantages and disadvantages between the investigative techniques. In terms of purely establishing the diagnosis of DGER, HIDA scintigraphy is non-invasive and accurate. For further characterization of the reflux profile, a more invasive and longer ambulatory test is required such as Bilitec (for DGER) and/or MII-pH monitoring (for acid and non-acid reflux). Finally, for visual assessment of esophageal mucosal integrity and determination of refluxate composition, EGD would be most appropriate to enable fluid aspiration and tissue biopsy.

References

Aydin, M, Yapar, AF & Yapar, Z 2001, 'Hepatobiliary scintigraphy to detect duodenogastric reflux: intravenous administration of Tc-99m pertechnetate to define the location of the stomach', *Clinical Nuclear Medicine*, vol. 26, no. 4, Apr, p. 360.

Barr, AC, Frelich, MJ, Bosler, ME, Goldblatt, MI & Gould, JC 2017, 'GERD and acid reduction medication use following gastric bypass and sleeve gastrectomy', *Surgical Endoscopy*, vol. 31, no. 1, Jan, pp. 410-415.

Barrett, MW, Myers, JC, Watson, DI & Jamieson, GG 1999, 'Dietary interference with the use of Bilitec to assess bile reflux', *Diseases of the Esophagus*, vol. 12, no. 1, pp. 60-64.

Barrett, MW, Myers, JC, Watson, DI & Jamieson, GG 2000, 'Detection of bile reflux: in vivo validation of the Bilitec fibreoptic system', *Diseases of the Esophagus*, vol. 13, no. 1, pp. 44-50.

Baulieu, F, Baulieu, JL, Dorval, E, Metman, E, Bertrand, J & Itti, R 1986, 'Scintigraphy in duodeno-gastric reflux: a new method of quantification', *Nuclear Medicine Communications*, vol. 7, no. 10, Oct, pp. 747-754.

Bechi, P 1995, 'Bilitec and "quantitation" of reflux: further acid comments', *Gastroenterology*, vol. 109, no. 3, Sep, pp. 1023-1024.

Bechi, P, Falciai, R, Baldini, F, Cosi, F, Pucciani, F & Boscherini, S 1992, 'New fiber optic sensor for ambulatory entero-gastric reflux detection', in *Fiber Optic Medical and Fluorescent Sensors and Applications,* Proc. SPIE, vol. 1648, pp. 130-135.

Bechi, P, Pucciani, F, Baldini, F, Cosi, F, Falciai, R, Mazzanti, R, Castagnoli, A, Passeri, A & Boscherini, S 1993, 'Long-term ambulatory enterogastric reflux monitoring. Validation of a new fiberoptic technique', *Digestive Diseases and Sciences*, vol. 38, no. 7, Jul, pp. 1297-1306.

Blue, PW, Jackson, JH & Ghaed, N 1984, 'Duodenogastroesophageal reflux. Demonstration with Tc-99m DISIDA imaging', *Clinical Nuclear Medicine*, vol. 9, no. 4, Apr, pp. 238-239.

Bonaz, B, Caravel, JP, Hostein, J, Bost, R & Fournet, J 1988, 'Scintigraphic study of duodenogastric reflux. Value of a computerized image-subtraction method', *Gastroenterologie Clinique et Biologique*, vol. 12, no. 5, May, pp. 436-440.

Borsato, N, Bonavina, L, Zanco, P, Saitta, B, Chierichetti, F, Peracchia, A & Ferlin, G 1991, 'Proposal of a modified scintigraphic method to evaluate duodenogastroesophageal reflux', *Journal of Nuclear Medicine*, vol. 32, no. 3, Mar, pp. 436-440.

Bredenoord, AJ, Weusten, BL, Timmer, R & Smout, AJ 2005, 'Reproducibility of multichannel intraluminal electrical impedance monitoring of gastroesophageal reflux', *American Journal of Gastroenterology*, vol. 100, no. 2, Feb, pp. 265-269.

Castedal, M, Bjornsson, E, Gretarsdottir, J, Fjalling, M & Abrahamsson, H 2000, 'Scintigraphic assessment of interdigestive duodenogastric reflux in humans: distinguishing between duodenal and biliary reflux material', *Scandinavian Journal of Gastroenterology*, vol. 35, no. 6, Jun, pp. 590-598.

Champion, G, Richter, JE, Vaezi, MF, Singh, S & Alexander, R 1994, 'Duodenogastroesophageal reflux: Relationship to pH and importance in Barrett's esophagus', *Gastroenterology*, vol. 107, no. 3, pp. 747-754.

Chang, WK, Lin, CK, Chuan, DC & Chao, YC 2016, 'Duodenogastric reflux: Proposed new endoscopic classification in symptomatic patients', *Journal of Medical Sciences (Taiwan)*, vol. 36, no. 1, pp. 1-5.

Chen, TF, Yadav, PK, Wu, RJ, Yu, WH, Liu, CQ, Lin, H & Liu, ZJ 2013, 'Comparative evaluation of intragastric bile acids and hepatobiliary scintigraphy in the diagnosis of duodenogastric reflux', *World Journal of Gastroenterology*, vol. 19, no. 14, pp. 211-217.

Dai, F, Gong, J, Zhang, R, Luo, JY, Zhu, YL & Wang, XQ 2002, 'Assessment of duodenogastric reflux by combined continuous intragastric pH and bilirubin monitoring', *World Journal of Gastroenterology*, vol. 8, no. 2, Apr, pp. 382-384.

Drane, WE, Karvelis, K, Johnson, DA & Silverman, ED 1987, 'Scintigraphic evaluation of duodenogastric reflux. Problems, pitfalls, and technical review', *Clinical Nuclear Medicine*, vol. 12, no. 5, May, pp. 377-384.

Eriksson, B, Emas, S, Jacobsson, H, Larsson, SA & Samuelsson, K 1988, 'Comparison of gastric aspiration and HIDA scintigraphy in detecting fasting duodenogastric bile reflux', *Scandinavian Journal of Gastroenterology*, vol. 23, no. 5, Jun, pp. 607-610.

Fein, M, Fuchs, KH, Bohrer, T, Freys, SM & Thiede, A 1996, 'Fiberoptic technique for 24-hour bile reflux monitoring. Standards and normal values for gastric monitoring', *Digestive Diseases and Sciences*, vol. 41, no. 1, Jan, pp. 216-225.

Gerard, PS, Gerczuk, P & Finestone, H 2007, 'Bile reflux in the esophagus demonstrated by HIDA scintigraphy', *Clinical Nuclear Medicine*, vol. 32, no. 3, Mar, pp. 224-225.

Gourcerol, G, Verin, E, Leroi, AM & Ducrotte, P 2014, 'Can multichannel intraluminal pH-impedance monitoring be limited to 3 hours? Comparison between ambulatory 24-hour and post-prandial 3-hour recording', *Diseases of the Esophagus*, vol. 27, no. 8, Nov-Dec, pp. 732-736.

Hausken, T, Li, XN, Goldman, B, Leotta, D, Odegaard, S & Martin, RW 2001, 'Quantification of gastric emptying and duodenogastric reflux stroke volumes using three-dimensional guided digital color Doppler imaging', *European Journal of Ultrasound*, vol. 13, no. 3, Jul, pp. 205-213.

King, PM, Adam, RD, Pryde, A, McDicken, WN & Heading, RC 1984, 'Relationships of human antroduodenal motility and transpyloric fluid movement: non-invasive observations with real-time ultrasound', *Gut*, vol. 25, no. 12, Dec, pp. 1384-1391.

Kiroff, GK, Devitt, PG, DeYoung, NJ & Jamieson, GG 1987, 'Bile salt-induced injury of rabbit oesophageal mucosa measured by hydrogen ion disappearance', *Australian and New Zealand Journal of Surgery*, vol. 57, no. 2, Feb, pp. 111-117.

Liron, R, Parrilla, P, Martinez de Haro, LF, Ortiz, A, Robles, R, Lujan, JA, Fuente, T & Andres, B 1997, 'Quantification of duodenogastric reflux in Barrett's esophagus', *American Journal of Gastroenterology*, vol. 92, no. 1, Jan, pp. 32-36.

Lo, RC, Huang, WL & Fan, YM 2015, 'Evaluation of bile reflux in HIDA images based on fluid mechanics', *Computers in Biology and Medicine*, vol. 60, May, pp. 51-65.

Lujan Mompean, JA, Parrilla Paricio, P, Robles Campos, R, Fuente Jimenez, T & Martinez Gomez, D 1990, 'Continuous 99mTc-HIDA infusion as a method for measuring duodenogastric reflux', *British Journal of Surgery*, vol. 77, no. 4, Apr, pp. 425-427.

Mackie, CR, Wisbey, ML & Cuschieri, A 1982, 'Milk 99Tcm-EHIDA test for enterogastric bile reflux', *British Journal of Surgery*, vol. 69, no. 2, Feb, pp. 101-104.

Manifold, DK, Anggiansah, A, Marshall, RE & Owen, WJ 2001, 'Reproducibility and intragastric variation of duodenogastric reflux using ambulatory gastric bilirubin monitoring', *Digestive Diseases and Sciences*, vol. 46, no. 1, Jan, pp. 78-85.

Marshall, REK, Anggiansah, A, Owen, WA & Owen, WJ 1998, 'The temporal relationship between oesophageal bile reflux and pH in gastro-oesophageal reflux disease', *European Journal of Gastroenterology and Hepatology*, vol. 10, no. 5, pp. 385-392.

McQuaid, KR, Laine, L, Fennerty, MB, Souza, R & Spechler, SJ 2011, 'Systematic review: the role of bile acids in the pathogenesis of gastro-oesophageal reflux disease and related neoplasia', *Alimentary Pharmacology and Therapeutics*, vol. 34, no. 2, Jul, pp. 146-165.

Mi, S, Lim, DW, Turner, JM, Wales, PW & Curtis, JM 2016, 'Determination of Bile Acids in Piglet Bile by Solid Phase Extraction and Liquid Chromatography-Electrospray Tandem Mass Spectrometry', *Lipids*, vol. 51, no. 3, Mar, pp. 359-372.

Mittal, BR, Ibrarullah, M, Agarwal, DK, Maini, A, Ali, W, Sikora, SS & Das, BK 1994, 'Comparative evaluation of scintigraphy and upper gastrointestinal tract endoscopy for detection of duodenogastric reflux', *Annals of Nuclear Medicine*, vol. 8, no. 3, Aug, pp. 183-186.

Muller-Lissner, SA 1985, 'Measurements of bile salt reflux are influenced by the method of collecting gastric juice', *Gastroenterology*, vol. 89, no. 6, Dec, pp. 1338-1341.

Nehra, D 2010, 'Bile in the esophagus-model for a bile acid biosensor', *Journal of Gastrointestinal Surgery*, vol. 14 Suppl 1, Feb, pp. S6-8.

Pace, F, Sangaletti, O, Pallotta, S, Molteni, P & Porro, GB 2007, 'Biliary reflux and non-acid reflux are two distinct phenomena: a comparison between 24-hour multichannel intraesophageal impedance and bilirubin monitoring', *Scandinavian Journal of Gastroenterology*, vol. 42, no. 9, Sep, pp. 1031-1039.

Saarinen, T, Rasanen, J, Salo, J, Loimaala, A, Pitkonen, M, Leivonen, M & Juuti, A 2017, 'Bile Reflux Scintigraphy After Mini-Gastric Bypass', *Obesity Surgery*, vol. 27, no. 8, Aug, pp. 2083-2089.

Salama, TMS & Hassan, MI 2017, 'Incidence of Biliary Reflux Esophagitis after Laparoscopic Omega Loop Gastric Bypass in Morbidly Obese Patients', *Journal of Laparoendoscopic and Advanced Surgical Techniques*, vol. 27, no. 6, pp. 618-622.

Shaffer, EA, McOrmond, P & Duggan, H 1980, 'Quantitative cholescintigraphy: assessment of gallbladder filling and emptying and duodenogastric reflux', *Gastroenterology*, vol. 79, no. 5 Pt 1, Nov, pp. 899-906.

Sharma, N, Agrawal, A, Freeman, J, Vela, MF & Castell, D 2008, 'An analysis of persistent symptoms in acid-suppressed patients undergoing impedance-pH monitoring', *Clinical Gastroenterology and Hepatology*, vol. 6, no. 5, May, pp. 521-524.

Sifrim, D, Castell, D, Dent, J & Kahrilas, PJ 2004, 'Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux', *Gut*, vol. 53, no. 7, Jul, pp. 1024-1031.

Silny, J 1991, 'Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility', *Neurogastroenterology and Motility*, vol. 3, no. 3, pp. 151-162.

Smythe, A, Bird, NC & Johnson, AG 1992, 'Continuous monitoring of sodium ion concentration in the human stomach--a new technique for the detection of duodenogastric reflux', *Digestion*, vol. 52, no. 1, pp. 20-25.

Sorgi, M, Wolverson, RL, Mosimann, F, Donovan, IA, Alexander-Williams, J & Harding, LK 1984, 'Sensitivity and reproducibility of a bile reflux test using 99mTc HIDA', *Scandinavian Journal of Gastroenterology. Supplement*, vol. 92, pp. 30-32.

Stein, HJ, Smyrk, TC, DeMeester, TR, Rouse, J & Hinder, RA 1992, 'Clinical value of endoscopy and histology in the diagnosis of duodenogastric reflux disease', *Surgery*, vol. 112, no. 4, Oct, pp. 796-803; discussion 803-794.

Stipa, F, Stein, HJ, Feussner, H, Kraemer, S & Siewert, JR 1997, 'Assessment of non-acid esophageal reflux: comparison between long-term reflux aspiration test and fiberoptic bilirubin monitoring', *Diseases of the Esophagus*, vol. 10, no. 1, Jan, pp. 24-28.

Stoker, DL, Williams, JG, MacLeod, MA & Colin-Jones, DG 1990, 'The evaluation of a gastric bile probe', *Nuclear Medicine Communications*, vol. 11, no. 11, Nov, pp. 777-790.

Sun, D, Wang, X, Gai, Z, Song, X, Jia, X & Tian, H 2015, 'Bile acids but not acidic acids induce Barrett's esophagus', *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 2, pp. 1384-1392.

Tack, J, Bisschops, R, Koek, G, Sifrim, D, Lerut, T & Janssens, J 2003, 'Dietary restrictions during ambulatory monitoring of duodenogastroesophageal reflux', *Digestive Diseases and Sciences*, vol. 48, no. 7, Jul, pp. 1213-1220.

Tibbling Grahn, L, Blackadder, L, Franzen, T & Kullman, E 2002, 'Gastric bile monitoring: an in vivo and in vitro study of Bilitec reliability', *Scandinavian Journal of Gastroenterology*, vol. 37, no. 11, Nov, pp. 1334-1337.

Tolin, RD, Malmud, LS, Stelzer, F, Menin, R, Makler, PT, Jr., Applegate, G & Fisher, RS 1979, 'Enterogastric reflux in normal subjects and patients with Bilroth II gastroenterostomy. Measurement of enterogastric reflux', *Gastroenterology*, vol. 77, no. 5, Nov, pp. 1027-1033.

Tulchinsky, M, Ciak, BW, Delbeke, D, Hilson, A, Holes-Lewis, KA, Stabin, MG & Ziessman, HA 2010, 'SNM practice guideline for hepatobiliary scintigraphy 4.0', *Journal of Nuclear Medicine Technology*, vol. 38, no. 4, Dec, pp. 210-218.

Vaezi, MF, Lacamera, RG & Richter, JE 1994, 'Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system', *American Journal of Physiology*, vol. 267, no. 6 Pt 1, Dec, pp. G1050-1057.

Vere, CC, Cazacu, S, Comanescu, V, Mogoanta, L, Rogoveanu, I & Ciurea, T 2005, 'Endoscopical and histological features in bile reflux gastritis', *Romanian Journal of Morphology and Embryology*, vol. 46, no. 4, pp. 269-274.

Watson, DI, Smythe, A, Mangnall, YF & Johnson, AG 1996, 'Detection of duodenal fluid in the oesophagus with a sodium ion selective electrode', *Journal of Gastroenterology and Hepatology*, vol. 11, no. 5, May, pp. 486-490.

Wenner, J, Johnsson, F, Johansson, J & Oberg, S 2007, 'Wireless esophageal pH monitoring is better tolerated than the catheter-based technique: results from a randomized cross-over trial', *American Journal of Gastroenterology*, vol. 102, no. 2, Feb, pp. 239-245.

Wong, WM, Bautista, J, Dekel, R, Malagon, IB, Tuchinsky, I, Green, C, Dickman, R, Esquivel, R & Fass, R 2005, 'Feasibility and tolerability of transnasal/per-oral placement of the wireless pH capsule vs. traditional 24-h oesophageal pH monitoring--a randomized trial', *Alimentary Pharmacology and Therapeutics*, vol. 21, no. 2, Jan 15, pp. 155-163.

Zerbib, F, Roman, S, Ropert, A, des Varannes, SB, Pouderoux, P, Chaput, U, Mion, F, Verin, E, Galmiche, JP & Sifrim, D 2006, 'Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy', *American Journal of Gastroenterology*, vol. 101, no. 9, Sep, pp. 1956-1963.

This article has been cited by:

Eldredge, TA, Bills, M, Myers, JC, Bartholomeusz, D, Kiroff, GK & Shenfine, J 2020, 'HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery', *Obesity Surgery*, vol. 30, no. 5, May, pp. 2038-2045.

Hoffman, I 2017*, 'Duodenogastroesophageal Reflux', in Y Vandenplas (ed.), *Gastroesophageal Reflux in Children: GER in Children*, Springer International Publishing, Cham, pp. 237-250. (*updated edition, in press)

Kassir, R, Lointier, P, Chouillard, E, Joumaa, S, Kassir, R & Sauvat, F 2018, 'Detecting Bile Reflux-the Enigma of Bariatric Surgery', *Obesity Surgery*, vol. 28, no. 7, Jul, pp. 2050-2051.

Othman, AAA, Dwedar, AAZ, ElSadek, HM, AbdElAziz, HR & Abdelrahman, AAF 2021, 'Bile reflux gastropathy: Prevalence and risk factors after therapeutic biliary interventions: A retrospective cohort study', *Ann Med Surg (Lond)*, vol. 72, Dec, p. 103168.

Park, JM, Yoon, SJ, Kim, JW & Chi, KC 2020, 'Laparoscopic Hiatal Hernia Repair and Roux-en-Y Conversion for Refractory Duodenogastroesophageal Reflux after Billroth I Distal Gastrectomy', *Journal of Gastric Cancer*, vol. 20, no. 3, Sep, pp. 337-343.

Pizza, F, D'Antonio, D, Lucido, FS, Tolone, S, Dell'Isola, C & Gambardella, C 2020, 'Postoperative Clinical-Endoscopic Follow-up for GERD and Gastritis After One Anastomosis Gastric Bypass for Morbid Obesity: How, When, and Why', *Obesity Surgery*, vol. 30, no. 11, Nov, pp. 4391-4400.

Portela, R, Marrerro, K, Vahibe, A, Galvani, C, Billy, H, Abu Dayyeh, B, Clapp, B & Ghanem, OM 2022, 'Bile Reflux After Single Anastomosis Duodenal-Ileal Bypass with Sleeve (SADI-S): a Meta-analysis of 2,029 Patients', *Obesity Surgery*, Feb 2022 (in press).

Saarinen, T, Pietiläinen, KH, Loimaala, A, Ihalainen, T, Sammalkorpi, H, Penttilä, A & Juuti, A 2020, 'Bile Reflux is a Common Finding in the Gastric Pouch After One Anastomosis Gastric Bypass', *Obesity Surgery*, vol. 30, no. 3, Mar, pp. 875-881.

Tang, Z-H, Wei, A, Zhang, Y-Y, Zou, Q & Yang, Z-Y 2020, 'Clinical application of gastrointestinal contrast-enhanced ultrasonography in diagnosis of gastric duodenal diseases', *World Chinese Journal of Digestology*, vol. 28, 08/28, pp. 745-754.

Uspenskiy, Y, Fominykh, Y & Gnutov, A 2021, 'Duodenogastroesophageal reflux: current state of issue', *Medical alphabet*, 01/15, pp. 11-15.

Voon, K, Huang, C-K, Patel, A, Wong, L-F, Lu, Y-C & Hsin, M-C 2021, 'Conversion of One-Anastomosis Gastric Bypass (OAGB) to Roux-en-Y Gastric Bypass (RYGB) is Effective in Dealing with Late Complications of OAGB: Experience from a Tertiary Bariatric Center and Literature Review', *J Metab Bariatr Surg*, vol. 10, no. 1, 6/, pp. 32-41.

3.1 Response to Letter-to-the-Editor for Study 1

Eldredge T A, Myers J C, Kiroff G K, Shenfine J.

Response to Letter to the Editor: Detecting Bile Reflux – The Enigma of Bariatric Surgery.

Obesity Surgery. 2018 Jul;28(7):2052. DOI: 10.1007/s11695-018-3277-x

Statement of Authorship

Title of Paper	Response to a Letter to the Editor Re: Detecting Bile Reflux—the Enigma of Bariatric Surgery
Publication Status	[X] Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Eldredge T A, Myers J C, Kiroff G K, et al. Response to Letter to the Editor: Detecting Bile Reflux – The Enigma of Bariatric Surgery. Obes Surg. 2018 Jul;28(7):2052. doi: 10.1007/s11695-018-3277-x

Principal Author

Name of Principal Author (Candidate)	Thomas Eldredge		
Contribution to the Paper	Reviewed the author's response; Undertook review of literature and analysed data; Drafted the response manuscript including revisions.		
Overall percentage (%)	90%		
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	19/1/22

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 in 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	Jennifer C Myers		
Contribution to the Paper	Contributed to critical revision of manuscript for final submission.		
Signature		Date	22-1-2022

Name of Co-Author	George K Kiroff		
Contribution to the Paper	Read and approved final submission		
Signature		Date	11/02/2022

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Jonathan Shenfine		
Contribution to the Paper	Read and approved final submission		
Signature		Date	19/1/22

Response to Letter to the Editor Re: Detecting Bile Reflux – The Enigma of Bariatric Surgery

Authors: Thomas A Eldredge [1,2], Jennifer C Myers [1,2,3], George K Kiroff [1,3], Jonathan Shenfine [1,2]

Affiliations

1. Discipline of Surgery, School of Medicine, University of Adelaide, Adelaide, South Australia;
2. Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia;
3. Department of Surgery, Queen Elizabeth Hospital, Woodville South, South Australia.

Conflict of interest

TE, GK and JS have no conflicts of interest, financial or otherwise, to declare. JM provides educational activities for Medtronic Australasia.

Funding

No industry or other external funding was used for this research.

Invited response from Editor of Obesity Surgery to the following 'Letter to the Editor':

Detecting Bile Reflux-the Enigma of Bariatric Surgery.
Kassir R, Lointier P, Chouillard E, Joumaa S, Kassir R, Sauvat F.
Obesity Surgery. 2018 Jul;28(7):2050-2051.
DOI: 10.1007/s11695-018-3267-z.

To the Editor:

We thank Dr Kassir *et al.* for their knowledgeable comments and interest in our review article. The primary objective of our article was to review techniques currently available for investigating bile reflux, to guide clinicians wishing to evaluate pre- or post-operative symptomatic patients. Recommendations of systematic pre-bariatric surgery investigations were outside of the scope of the article, however we agree that surgeons should observe common practices of pre-operative work-up, by undertaking endoscopy and other oesophageal function tests as clinically indicated.

Ambulatory pH testing is an effective method of measuring acid reflux, however offers no insight into the presence of bile in the refluxate. Unfortunately, as identified in our review, there is little or no systematic approach to measuring bile reflux after bariatric surgery. A HIDA scan is relatively easy to perform in patients who have undergone any type of bariatric procedure, to document the presence or absence of bile reflux.

We would also like to thank the authors of this letter for identifying surgical techniques that may reduce the incidence of bile reflux. With the single anastomosis gastric bypass (SAGB) procedure gaining popularity, surgeons must consider the potential risk of bile reflux in their selection of surgical technique. When surveyed, surgeons who do not perform the SAGB voiced concern regarding the risk of bile reflux and the risk of gastric and oesophageal cancers (Mahawar *et al.*).

Studies evaluating bile reflux after bariatric surgery are lacking and there is a need for quantitative data in this cohort.

References:

Mahawar KK, Borg C, Kular KS, et al. Understanding Objections to One Anastomosis (Mini) Gastric Bypass: A Survey of 417 Surgeons Not Performing this Procedure.Obes Surg. 2017 Sep;27(9):2222-2228.

CHAPTER 4:

HIDA and seek: Challenges of scintigraphy to diagnose bile reflux post-bariatric surgery

Eldredge T A, Bills M, Myers J C, Bartholomeusz D, Kiroff G K, Shenfine J.
HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery.
Obesity Surgery. 2020 May;30(5):2038-2045.
DOI: 10.1007/s11695-020-04510-7

Statement of Authorship

Title of Paper	HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery
Publication Status	[X] Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Eldredge T A, Bills M, Myers J C, Bartholomeusz D, Kiroff G K, Shenfine J. HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery. Obes Surg. 2020 Mar; doi: 10.1007/s11695-020-04510-7

Principal Author

Name of Principal Author (Candidate)	Thomas Eldredge		
Contribution to the Paper	Conceived and designed research; Undertook literature review; Recruited and consented participants; Analysed the data and interpreted the findings; Drafted the manuscript including revisions for submission.		
Overall percentage (%)	80%		
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	19/1/22

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 in 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	Madison Bills		
Contribution to the Paper	Assisted in research design; Performed investigations; Analysed the data and interpreted the findings; Assisted in drafting the manuscript including critical revision for submission.		
Signature		Date	25/01/2022

Name of Co-Author	Jennifer C Myers		
Contribution to the Paper	Assisted in research design; Contributed to literature review; Assisted in drafting the manuscript including critical revision for submission.		
Signature		Date	22-1-2022

Please cut and paste additional co-author pa

Name of Co-Author	Dylan Bartholomeusz		
Contribution to the Paper	Assisted in research design; Analysed the data and interpreted the findings; Contributed to critical revision of the manuscript for submission.		
Signature		Date	25.1.22

Name of Co-Author	George K Kiroff		
Contribution to the Paper	Contributed to conception and design of research; Contributed to critical revision of the manuscript for submission.		
Signature		Date	11/02/2022

Name of Co-Author	Jonathan Shenfine		
Contribution to the Paper	Conceived and designed research; Supervised the overall study; Performed weight loss operations on participants; Contributed to critical revision of the manuscript for submission.		
Signature		Date	19/1/22

HIDA and seek: Challenges of scintigraphy to diagnose bile reflux post-bariatric surgery

Authors: Thomas A Eldredge [1, 2], Madison Bills [4], Jennifer C Myers [1, 2], Dylan Bartholomeusz [4, 5], George K Kiroff [1, 2], Jonathan Shenfine [1, 3]

Affiliations

1. Discipline of Surgery, University of Adelaide, Adelaide, South Australia;
2. Department of Surgery, The Queen Elizabeth Hospital, South Australia;
3. Department of Surgery, Flinders Medical Centre, South Australia;
4. Department of Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital and SA Medical Imaging, South Australia
5. Department of Gastroenterology, Royal Adelaide Hospital, South Australia

Acknowledgments:

Thank you to Mr Harsh Kanhere, Mr Markus Trochsler, Mr Shalvin Prasad and Mr Philip Game for allowing us to enrol their patients for our trial.

Funding

T.A.E is the recipient of the Richard Jepson Research Scholarship from the Royal Australasian College of Surgeons.

Abstract

Introduction:

Oesophageal bile reflux after bariatric surgery may trigger development of Barrett's oesophagus. Gastro-oesophageal reflux of bile is captured by hepatobiliary iminodiacetic acid (HIDA) scintigraphy, however anatomical and physiological changes after bariatric surgery warrant protocol modifications to optimise bile reflux detection.

Methods:

HIDA scintigraphy occurred 6-months after either sleeve gastrectomy, Roux-en-Y gastric bypass or one-anastomosis gastric bypass. Standard HIDA scanning involves: (i) 6hr fast and 24hr abstinence from opioids; (ii) IV administration of 99mTc di-isopropyl iminodiacetic acid; (iii) dual anterior/posterior 60-minute dynamic scanning of the duodenum, stomach and oesophagus. Three challenges were identified and modifications were implemented, namely: (1) Anatomical localisation of refluxed bile on planar scintigraphy was improved by adding a SPECT/CT for 3-dimensional imaging; (2) Impaired cholecystokinin-controlled gallbladder emptying, following bypassed duodenum, was addressed by ingestion of a 'fatty meal'; and (3) intestinal hypomotility after gastric bypass was counteracted by longer scan duration (75-90min), to allow bile to pass beyond the gastro-jejunal anastomosis.

Results:

HIDA scan was undertaken in 18 patients, 13 of whom underwent the modified protocol. The tailored protocol ameliorated issues identified with the standard HIDA scan protocol, thus, accurate anatomical localisation was achieved in all patients; no delayed gallbladder emptying was observed; and bile was observed beyond the gastro-jejunal anastomosis in all gastric bypass patients. The modified technique was well-tolerated by patients.

Conclusion:

A tailored HIDA scan protocol with addition of a SPECT-CT scan; ingestion of a fatty meal; and prolonged scanning duration, results in enhanced bile reflux detection in post-bariatric surgical patients.

Key Words: Bile reflux, HIDA scintigraphy, sleeve gastrectomy, gastric bypass

Abbreviations:

CCK	Cholecystokinin
CT	Computed tomography
HIDA	Hepatobiliary iminodiacetic acid
IV	Intravenous
OAGB	One-anastomosis gastric bypass
ROI	Region of interest
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
SPECT	Single photon emission computed tomography

Introduction:

Oesophageal bile reflux is an issue following bariatric surgery (Bruzzi, Chevallier & Czernichow 2017). Altered gastrointestinal anatomy following some bariatric procedures increases potential for bile to reflux into the remaining stomach and the oesophagus (Braghetto *et al.* 2019; Facchiano *et al.* 2016; Saarinen *et al.* 2017). This is concerning, as bile acids may act synergistically with gastric hydrochloric acid to induce Barrett's metaplasia, a known precursor to adenocarcinoma (Abdel-Latif *et al.* 2016; Chen *et al.* 2012; Ghatak *et al.* 2013; Huo *et al.* 2010; Reveiller *et al.* 2012). While all bariatric procedures alter the anatomy and physiology of the upper digestive tract, controversy specifically surrounds the one-anastomosis gastric bypass (Mahawar *et al.* 2017; Mahawar *et al.* 2013). Thus, the detection and diagnosis of bile reflux is important and while there is no gold standard diagnostic investigation, hepatobiliary iminodiacetic acid (HIDA) scintigraphy is an effective, non-invasive technique with acceptable sensitivity and specificity (Eldredge *et al.* 2018). The aims of this study are to: (1) develop a tailored HIDA scanning protocol that can be utilised after the three most common forms of bariatric surgery, to enable more accurate detection and diagnosis of bile reflux; and (2) evaluate patient tolerability and acceptability of HIDA scintigraphy.

Methods:

As part of a current prospective cohort study, HIDA scintigraphy is undertaken six-months post-operatively in patients after either laparoscopic sleeve gastrectomy (SG); laparoscopic Roux-en-Y gastric bypass (RYGB); or laparoscopic one-anastomosis gastric bypass (OAGB). Hence an optimal HIDA scan protocol specifically to evaluate bile reflux in this cohort is required.

Subjects

Participants aged 18-60 years and eligible for weight loss surgery (National Health and Medical Research Council 2013) were invited to participate in this study. Exclusion criteria include: (1)

previous bariatric, oesophago-gastric or hepatobiliary surgery (including cholecystectomy); (2) body mass index >65 kg/m^2; (3) major psychiatric illness; (4) pregnant or breastfeeding; and (5) large abdominal hernia(e).

Operative techniques

Sleeve gastrectomy was performed using a linear stapler commencing 4-7cm from the pylorus and continuing to the angle of His, with gastric tube calibration using a 36Fr bougie in most cases (1 case used a 52Fr bougie). RYGB was performed using a 5-6cm gastric pouch calibrated over a 36Fr bougie in all cases. Alimentary limb length ranged from 100-120cm and biliopancreatic limb length ranged from 50-80cm. OAGB was performed using the Rutledge technique (Rutledge, Kular & Manchanda 2019) with the addition of an anti-reflux mechanism in all cases, suturing the biliopancreatic limb to the gastric pouch just proximal to the anastomosis. All cases used a 36Fr bougie for gastric pouch calibration and biliopancreatic limb lengths ranged from 150-200cm. Hiatoplasty was not performed in any cases.

HIDA Scan Acquisition

The standard HIDA protocol at our centre involves a 6-hour fast and 24-hour abstinence from opioid medications prior to intravenous (IV) administration of 150-180 MBq of the radiopharmaceutical, Technetium ^{99m}Tc di-isopropyl iminodiacetic acid (Disofenin; *Hepatolite®*, Pharmalucence Inc, MA, USA). Peak liver uptake of ^{99m}Tc Disofenin is known to occur by 10 minutes post-injection and peak gallbladder accumulation by 30-40 minutes. Visualisation of gallbladder activity and intestinal activity occurs by 60 minutes post-injection in individuals with normal hepatobiliary function. HIDA imaging is obtained with dual anterior/posterior 60-minute dynamic images of the abdomen using a Siemens Symbia T16 SPECT-CT camera (Siemens Healthcare GmbH, Munich, Germany), to assess gallbladder excretion of bile, intestinal activity and potential duodenogastro-oesophageal reflux. Image acquisition for 5 seconds per frame was used, to capture short reflux events.

Scan Protocol Modifications

Prior to study commencement, we identified post-operative anatomical localisation as a potential issue for bile reflux identification and quantification. Further, while scanning the second gastric bypass patient (OAGB – fourth patient scanned overall), we identified impaired gallbladder emptying and also delayed enteric transit of radio-labelled bile. These identified challenges led us to seek appropriate modifications to the standard HIDA protocol.

<u>Post-bariatric surgery anatomy</u>:

Accurate localisation of anatomy can be difficult after bariatric surgery, impacting the utility of HIDA to detect the presence and severity of bile reflux. In a 2017 study evaluating bile reflux after OAGB, a Single Photon Emission Computed Tomography (SPECT) - Computed Tomography (CT) (SPECT-CT) scan was utilised for anatomical localisation (Saarinen *et al.* 2017). SPECT-CT has the unique advantage of amalgamating the anatomical data obtained by CT, with the functional data obtained by scintigraphy. It is superior for anatomical localisation when compared with SPECT or scintigraphy alone, aiding differentiation between the gastric pouch and small intestine (Arun *et al.* 2013; Jacene *et al.* 2008). Thus, the first modification to the standard HIDA protocol was to include a SPECT acquisition, with low-dose CT, immediately following the completion of dynamic imaging. The SPECT parameters were: 128 x 128 matrix, non-circular orbit, with 'step-and-shoot' protocol of 15 s per view for 60 views.

<u>Delayed gallbladder emptying</u>:

In healthy individuals, food entering the duodenum stimulates enteroendocrine cells to release cholecystokinin (CCK), triggering gallbladder contraction and release of bile. However, after gastric bypass surgery (RYGB or OAGB) food bypasses the duodenum, which can impair gallbladder emptying (Bastouly *et al.* 2009). CCK-analogues and triglyceride fat emulsions ('fatty meal') can provoke gallbladder emptying. IV injection of CCK-analogues means quicker and more complete gallbladder emptying than an orally ingested fatty meal (Krishnamurthy & Brown 2002). CCK-analogues are no longer available for use in Australia. Fatty meals, however, remain effective for gallbladder provocation (Braghetto *et al.* 2019). The fourth patient enrolled in this current study (who subsequently underwent an OAGB) demonstrated impaired gallbladder emptying at 60 minutes, prompting ad-hoc administration of a fatty meal (60mL Calogen®; Nutricia, a Danone Company, Paris, France) and prolonged scan time (further 60 minutes). Gallbladder emptying and intestinal transit was visualised 45 minutes after Calogen®administration. Giving rise to the second modification to the HIDA protocol, to include a standardised fatty meal (60mL Calogen®), ingested 30 minutes after tracer administration, to allow time for the gallbladder to fill with radiolabelled bile prior to emptying. The intended physiological outcome was to stimulate jejunal enteroendocrine cells to produce cholecystokinin, resulting in gallbladder contraction and ejection of bile.

<u>Intestinal hypomotility</u>:

Observed delayed enteric transit in gastric bypass patients prompted extension of HIDA imaging duration as the third modification to the acquisition protocol. As described above, Calogen® administration in the fourth patient, stimulated gallbladder emptying and intestinal transit after 45 minutes, guiding the time span of our modified protocol (Figure 1). Delayed static imaging, up to 120 minutes after the initial dose administration, was added to the protocol to detect delayed bile reflux activity into the gastric pouch or oesophagus.

HIDA Scan Analysis

Scintigraphic images were evaluated by a nuclear medicine technologist (MB) and a surgical registrar (TE), then reviewed by a dual-trained senior nuclear medicine physician/ gastroenterologist (DB). The CT images enabled corroboration with planar scintigraphy for correct anatomical localisation. Regions of interest (ROI) were drawn over the gastric pouch and oesophagus. Bile reflux was quantified as the percentage of tracer found within the gastric pouch and/or oesophagus ROIs, compared with total biliary excretion.

Tolerability of imaging technique

A secondary outcome of the study was to assess the patient tolerability of HIDA scintigraphy. Immediately after the conclusion of the HIDA scan, participants were invited to complete a questionnaire comprising six questions evaluating their perception of the level of invasiveness, comfort/ discomfort and degree of willingness to undergo the test again (Appendix B).

Results:

Five patients underwent the standard HIDA scanning protocol, inclusive of SPECT-CT (3 female; mean age 46.8 yrs, SD 10.9; 2 - SG, 2 - OAGB, 1 - RYGB). The modified HIDA scanning protocol (Figure 1), including patients with ad-hoc modifications, was performed in 13 patients (10 female; mean age 41.2 yrs, SD 10.9; 2 - SG, 6 - OAGB, 5 - RYGB). The mean time from operation to modified HIDA scan was 7 months (SD 0.7).

Using this new methodology, accurate anatomical delineation of organs was achieved in all patients. Bilary reflux into the gastric pouch/sleeve was observed in 2/4 (50%) SG patients, 6/8 (75%) OAGB participants and no RYGB patients (0/6, 0%). In patients with reflux positive scans, the mean percentage of bile reflux into the gastric pouch in SG patients was 9.4% (SD 0.0001), contrasting with 2.0% (SD 0.01) in OAGB patients. In addition to bile reflux to the gastric pouch, reflux to the mid-oesophagus was documented in 1/6 (16.7%%) OAGB patients (Figure 2).

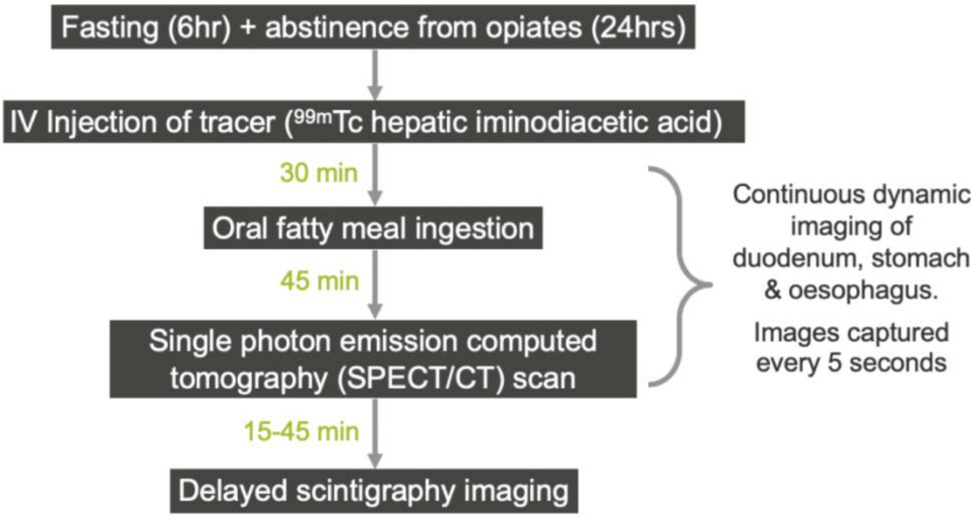


Figure 1: Modified HIDA scintigraphy protocol used for imaging of bile reflux in this study.

Prior to routine administration of Calogen®, delayed gallbladder emptying (>60mins afer IV tracer injection) and prolonged small bowel transit was visualised in 2 patients, both of whom had undergone OAGB. Both patients were administed ad-hoc Calogen®, with subsequent effective gallbladder emptying. After commencement of routine Calogen® administration, no patients displayed inadequate gallbladder emptying. Prolongation of scan duration led to adequate transit of radio-labelled bile through the small intestine, with tracer observed distal to the gastro-jejunal anastomosis in all gastric bypass patients.

Evalation of subject participation determined the modified HIDA scan was non-invasive (question 1; median 4, IQR 4-4), tolerable (question 4; median 3.5, IQR 3-4) and comfortable during (question 2; median 4, IQR 3-4) and after scanning (question 3; median 5, IQR 4-5). All patients reported that they would undertake the procedure again, except one who was unsure. Free-text responses describing the worst aspect of the procedure (question 6, N=10) included: lying still (N=3), holding hands above head during scanning (N=3), and lying on their back (N=2). Two patients described reflux symptoms after ingestion of the fatty meal, both of whom had visible reflux on HIDA scanning. One patient reported acute abdominal pain five-hours after the scan, which was self-limiting. It remains unclear whether the abdominal pain was associated with the HIDA scan protocol.

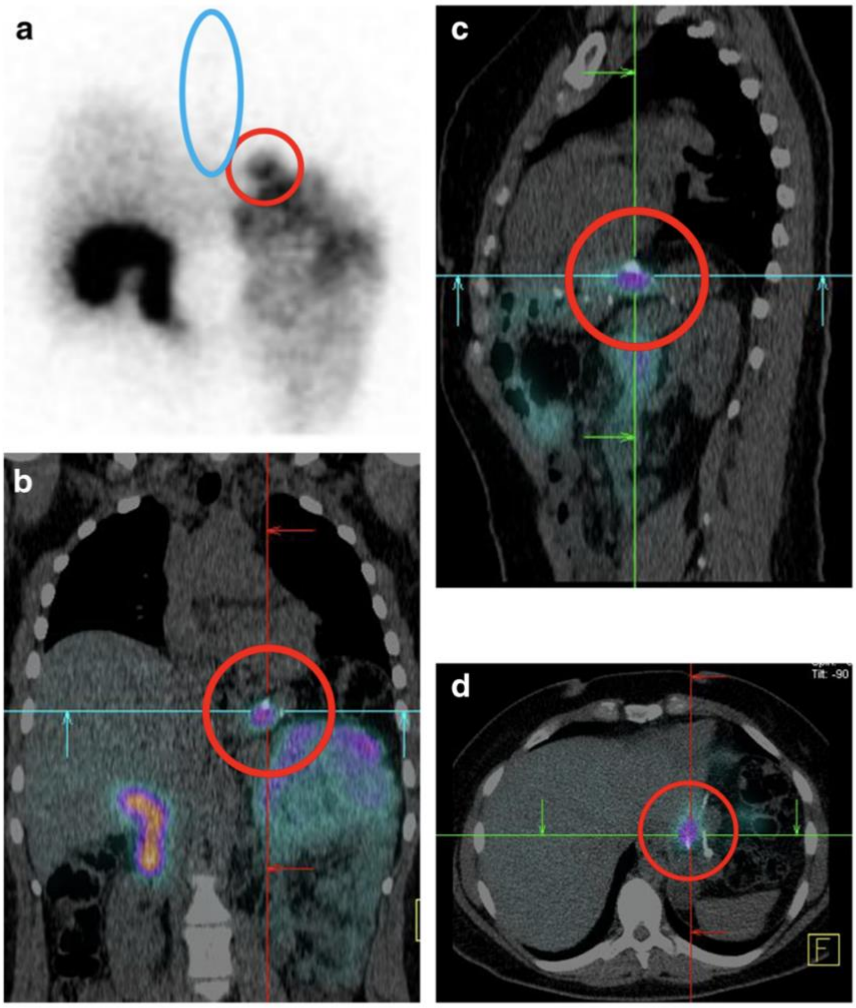


Figure 2: A: scintigraphic image showing reflux into gastric pouch (red circle) and oesophagus (blue cirlce); B-D: coronal (B), sagittal (C) and axial (D) fused CT images, confirming localisation of reflux in the gastric pouch (red circle).

Discussion

Accurate HIDA scintigraphy results rely on knowledge of the expected anatomy and anticipated physiological changes related to the type of bariatric surgery performed. The gastric sleeve/pouch post-operatively in SG and gastric bypass procedures can sit retro-hepatically and make localisation on scintigraphic images difficult. Furthermore, gastric bypass results in anastomosis of small intestine to the gastric pouch, thereby obscuring differentiation of radiolabelled bile refluxing in the gastric pouch or sitting in the small intestine as expected. Physiologically, bypass of the duodenum in RYGB/OAGB can impact hormonally-controlled gallbladder contraction and delivery of bile into the intestines, with resultant hypomotility. These issues necessitated HIDA scan protocol modifications. Additionally, certain post-operative gastric sleeve morphologies, seen on post-operative water-soluble contrast upper gastrointestinal series, can also result in higher severity of reflux (Toro *et al.* 2014), however this was not evaluated as part of this study.

The challenge of confirming gastric and oesophageal reflux of tracer on planar scintigraphy was ameliorated by adding a SPECT-CT, providing fused physiological data with 3-dimensional anatomical images. This enabled accurate regions of interest to be defined and correct localisation and subsequent quantification of reflux of biliary origin (Figure 2). The use of hybrid SPECT-CT in nuclear medical imaging has seen rapid growth over the past 2 decades (Kashyap *et al.* 2013). When anatomical localisation is paramount, such as locating a bile leak after hepatobiliary surgery or reflux in the present study, SPECT-CT is superior when compared to SPECT or planar scintigraphy alone (Arun *et al.* 2013; Jacene *et al.* 2008). This present study supports routine use of SPECT-CT for diagnosis of bile reflux in this setting, a recommendation shared by a recent review of the role and application of SPECT/CT in a variety of applications, including gastrointestinal imaging (Israel *et al.* 2019).

Prior to routine administration of Calogen®, delayed gallbladder emptying was observed in 2 patients after OAGB. Both RYGB and OAGB result in bypass of the duodenum, which may decrease cholecystokinin (CCK) release from duodenal enteroendocrine cells, impacting subsequent gallbladder emptying. Only one published study has compared pre- and post-operative gallbladder emptying after bariatric surgery (Bastouly *et al.* 2009). In this study, patients underwent open RYGB with placement of a gastrostomy tube in the gastric remnant.

Ultrasonographic assessment of gallbladder emptying was performed pre-operatively, and one month post-operatively both during oral ingestion of a liquid test meal and again with infusion of the same meal through the gastrostomy. Compared with pre-operative findings, significantly decreased maximum gallbladder ejection fraction and increased residual volume were observed post-operatively. No significant difference in ejection fraction or residual volume was observed between the oral meal and the gastrostomy meal. These findings suggest a role of endogenous CCK, which was not evaluated in this study. A comprehensive review of studies evaluating CCK levels post-RYGB, indicates unchanged or increased CCK secretion occurs post-operatively, while recognising it is an under-researched area, with variable results (Steinert *et al.* 2017). In the present study, gallbladder emptying was improved by oral ingestion of a lipid-rich 'fatty meal' (Figure 3), which may be explained by high-concentration fatty-acid-induced release of endogenous CCK by jejunal enteroendocrine cells.

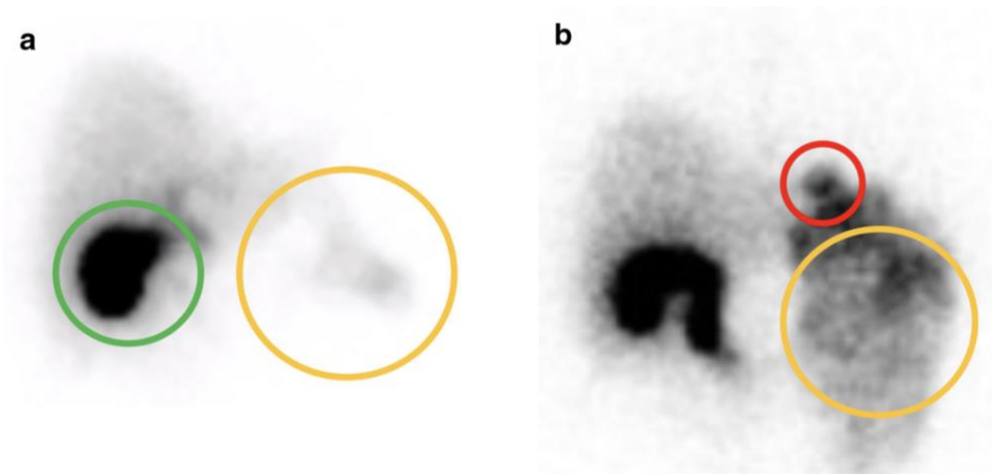


Figure 3: Scintigraphic images showing; (A) delayed gallbladder (green circle) emptying and small bowel (orange circle) transit 60 minutes after IV ^{99m}Tc Disofenin administration; and (B) improved gallbladder emptying and transit 45 minutes after 'fatty meal' ingestion, with reflux seen in gastric pouch (red circle).

Small intestinal motility can also be affected by bariatric surgery. Three published studies evaluated small intestinal motility after SG (Melissas *et al.* 2013; Shah *et al.* 2010; Trung *et al.* 2013). A Japanese study, using cine MRI during an oral glucose tolerance test, noted increased small intestine contraction frequency and faster transit of fluid after SG, when compared with the same patient's pre-operative cine MRI (Trung *et al.* 2013). Further, Shah and Melissas separately reported faster gastric emptying and small bowel transit time in patients post-SG, using semi-solid radiolabelled meals and scintigraphic detection (Melissas *et al.* 2013; Shah *et al.* 2010). All three of these studies, however, incorporate gastric transit time in their assessment of small bowel transit time. There is a paucity of published studies evaluating gastrointestinal motility after RYGB, with the few that exist largely evaluating gastric pouch emptying. Dirksen *et al* studied intestinal motility as well as gastric emptying in patients post-RYGB, using scintigraphy following ingestion of radiolabelled solid and liquid meals (Dirksen *et al.* 2013). Compared with a non-operative control group, post-operative RYGB patients had quicker gastric pouch emptying, but slower small intestinal transit, for both solids and liquids. Such heterogenous results allow no definitive conclusions to be drawn regarding the impact of bariatric surgery on enteric motility. In the present study, prolonged small intestinal transit of bile was observed for two patients, neither of whom were diabetic. Given the potential for post-operative intestinal hypomotility, HIDA scan imaging duration was lengthened to allow time for bile to reach the gastro-jejunal anastomosis and beyond.

Four previous studies utilised HIDA scintigraphy to evaluate bile reflux into either the gastric pouch/sleeve (Braghetto *et al.* 2019; Saarinen *et al.* 2017) or the excluded stomach after bariatic surgery (Sundbom, Hedenstrom & Gustavsson 2002; Vella *et al.* 2017). To evaluate bile reflux after OAGB, Saarinen *et al* utilised a similar protocol to the current study, incorporating SPECT-CT and delayed static images, but did not use any provocation agents (e.g. Calogen®) (Saarinen *et al.* 2017). The authors made no comment regarding delayed gallbladder emptying, suggesting this may not have been prevalent in their cohort of eight patients. Braghetto *et al* assessed bile reflux post-SG in patients with *de novo* reflux symptoms (Braghetto *et al.* 2019). Their study utilised an extended scanning period (90-120 min) with fatty-meal provocation after 60 min, however reflux was not quantified and instead reported subjectively as only present or absent. Gastric localisation was achieved by oral ingestion of ^{99m}Tc sulphur colloid (in water) after 90 or 120 min, rather than utilisation of SPECT-CT. Remnant gastropathy from chronic bile reflux post-RYGB was identified in two studies (Sundbom, Hedenstrom & Gustavsson 2002; Vella *et al.* 2017). Sundbom *et al* group's protocol utilised a 90-min HIDA scan with IV CCK provocation at 20mins, and gastric remnant localisation with IV ^{99m}Tc pertechnetate, because it is secreted into the gastric lumen. Short episodes of bile reflux may have been missed with this protocol, which only captured scintigraphic image frames every 2 minutes (Sundbom, Hedenstrom & Gustavsson 2002). The published study by Vella *et al*, did not describe their scanning protocol and noted only positive or negative scan results (Vella *et al.* 2017). No SPECT-CT was performed in either study.

The notable lack of a standardised scanning protocol for HIDA scingtigraphy in a post-bariatic surgical cohort undoubtedly impacts generalisability of results. We acknowledge the inherent variability in individual physiology as a barrier to standardisation, as observed by inconsistent gallbladder emptying and enteric hypomotility. Six months was selected as a standardised follow-up timepoint to allow patients to recover from surgery and return to their normal lifestyle. We recognise that weight loss is likely to extend beyond this timeframe and thus reflux incidence and severity at later follow-up is worthy of examination in a future study, applying the techniques established by the present study. Other limitations include the observational nature of this study and the lack of experimental rigour of a randomised trial. The present trial design required reactionary interventions to be conceived and implemented to address issues that arose for HIDA scanning in this cohort. Another key limitation of our study is the exclusion of patients who had previously undergone a cholecystectomy, which can increase prevalence and severity of bile reflux (Atak *et al.* 2012; Kunsch *et al.* 2009). Known high rates of gallbladder disease in pre- and post-bariatric surgical cohorts calls for further research to optimise scintigraphy protocols for post-cholecystectomy patients.

The use of Likert-type scales was helpful for quantifying patient experiences, while noting inherent limitations such as *central tendency bias* and *acquiescence bias* (James, Demaree & Wolf 1984; Lichtenstein & Bryan 1965).

Conclusion

The current controversy surrounding bile reflux after bariatric surgery necessitates a standardised and accurate approach to diagnosis. HIDA scintigraphy is an effective and well tolerated investigation, however we have identified and rectified issues in the use of this technique for post bariatric surgery patients. Modifying the standard HIDA scanning protocol by adding a SPECT-CT scan; ingestion of a fatty meal; and prolonged scanning duration results in enhanced gastric visualisation and quantification of bile reflux. This modified HIDA scan protocol could form the basis of a standard approach to investigation of bile reflux in bariatric patients undergoing weight-loss surgery.

Conflict of interest

No conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Human Research Ethics Committee of The Queen Elizabeth Hospital (TQEH) gave ethical approval for the study (HREC/17/TQEH/185).

Informed consent

Informed consent was obtained from all participants enrolled in the study.

References

Abdel-Latif, MM, Inoue, H, Kelleher, D & Reynolds, JV 2016, 'Factors regulating nuclear factor-kappa B activation in esophageal cancer cells: Role of bile acids and acid', *Journal of Cancer Research and Therapeutics*, vol. 12, no. 1, Jan-Mar, pp. 364-373.

Arun, S, Santhosh, S, Sood, A, Bhattacharya, A & Mittal, BR 2013, 'Added value of SPECT/CT over planar Tc-99m mebrofenin hepatobiliary scintigraphy in the evaluation of bile leaks', *Nuclear Medicine Communications*, vol. 34, no. 5, May, pp. 459-466.

Atak, I, Ozdil, K, Yucel, M, Caliskan, M, Kilic, A, Erdem, H & Alimoglu, O 2012, 'The effect of laparoscopic cholecystectomy on the development of alkaline reflux gastritis and intestinal metaplasia', *Hepato-Gastroenterology*, vol. 59, no. 113, Jan-Feb, pp. 59-61.

Bastouly, M, Arasaki, CH, Ferreira, JB, Zanoto, A, Borges, FG & Del Grande, JC 2009, 'Early changes in postprandial gallbladder emptying in morbidly obese patients undergoing Roux-en-Y gastric bypass: correlation with the occurrence of biliary sludge and gallstones', *Obesity Surgery*, vol. 19, no. 1, Jan, pp. 22-28.

Braghetto, I, Gonzalez, P, Lovera, C, Figueroa-Giralt, M & Pineres, A 2019, 'Duodenogastric biliary reflux assessed by scintigraphic scan in patients with reflux symptoms after sleeve gastrectomy: preliminary results', *Surgery for Obesity and Related Diseases*, vol. 15, no. 6, Jun, pp. 822-826.

Bruzzi, M, Chevallier, JM & Czernichow, S 2017, 'One-Anastomosis Gastric Bypass: Why Biliary Reflux Remains Controversial?', *Obesity Surgery*, vol. 27, no. 2, Feb, pp. 545-547.

Chen, X, Oshima, T, Shan, J, Fukui, H, Watari, J & Miwa, H 2012, 'Bile salts disrupt human esophageal squamous epithelial barrier function by modulating tight junction proteins', *American Journal of Physiology: Gastrointestinal and Liver Physiology*, vol. 303, no. 2, Jul 15, pp. G199-208.

Dirksen, C, Damgaard, M, Bojsen-Moller, KN, Jorgensen, NB, Kielgast, U, Jacobsen, SH, Naver, LS, Worm, D, Holst, JJ, Madsbad, S, Hansen, DL & Madsen, JL 2013, 'Fast pouch emptying, delayed small intestinal transit, and exaggerated gut hormone responses after Roux-en-Y gastric bypass', *Neurogastroenterology and Motility*, vol. 25, no. 4, Apr, pp. 346-e255.

Eldredge, TA, Myers, JC, Kiroff, GK & Shenfine, J 2018, 'Detecting Bile Reflux-the Enigma of Bariatric Surgery', *Obesity Surgery*, vol. 28, no. 2, Feb, pp. 559-566.

Facchiano, E, Leuratti, L, Veltri, M & Lucchese, M 2016, 'Laparoscopic Conversion of One Anastomosis Gastric Bypass to Roux-en-Y Gastric Bypass for Chronic Bile Reflux', *Obesity Surgery*, vol. 26, no. 3, Mar, pp. 701-703.

Ghatak, S, Reveiller, M, Toia, L, Ivanov, A, Godfrey, TE & Peters, JH 2013, 'Bile acid at low pH reduces squamous differentiation and activates EGFR signaling in esophageal squamous cells in 3-D culture', *Journal of Gastrointestinal Surgery*, vol. 17, no. 10, Oct, pp. 1723-1731.

Huo, X, Zhang, HY, Zhang, XI, Lynch, JP, Strauch, ED, Wang, JY, Melton, SD, Genta, RM, Wang, DH, Spechler, SJ & Souza, RF 2010, 'Acid and bile salt-induced CDX2 expression differs in esophageal squamous cells from patients with and without Barrett's esophagus', *Gastroenterology*, vol. 139, no. 1, Jul, pp. 194-203.e191.

Israel, O, Pellet, O, Biassoni, L, De Palma, D, Estrada-Lobato, E, Gnanasegaran, G, Kuwert, T, la Fougere, C, Mariani, G, Massalha, S, Paez, D & Giammarile, F 2019, 'Two decades of SPECT/CT - the coming of age of a technology: An updated review of literature evidence', *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 46, no. 10, Sep, pp. 1990-2012.

Jacene, H, Goetze, S, Patel, H, Wahl, R & Ziessman, H 2008, 'Advantages of Hybrid SPECT/CT vs SPECT Alone', *The Open Medical Imaging Journal*, vol. 2, 09/26.

James, L, Demaree, R & Wolf, G 1984, 'Estimating Within-Group Interrater Reliability With and Without Response Bias', *Journal of Applied Psychology*, vol. 69, 02/01, pp. 85-98.

Kashyap, R, Dondi, M, Paez, D & Mariani, G 2013, 'Hybrid imaging worldwide-challenges and opportunities for the developing world: a report of a Technical Meeting organized by IAEA', *Seminars in Nuclear Medicine*, vol. 43, no. 3, May, pp. 208-223.

Krishnamurthy, GT & Brown, PH 2002, 'Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction', *Journal of Nuclear Medicine*, vol. 43, no. 12, Dec, pp. 1603-1610.

Kunsch, S, Neesse, A, Huth, J, Steinkamp, M, Klaus, J, Adler, G, Gress, TM & Ellenrieder, V 2009, 'Increased Duodeno-Gastro-Esophageal Reflux (DGER) in symptomatic GERD patients with a history of cholecystectomy', *Zeitschrift für Gastroenterologie*, vol. 47, no. 8, Aug, pp. 744-748.

Lichtenstein, E & Bryan, JH 1965, 'Acquiescence and the mmpi: An item reversal approach', *Journal of Abnormal Psychology*, vol. 70, Aug, pp. 290-293.

Mahawar, KK, Borg, CM, Kular, KS, Courtney, MJ, Sillah, K, Carr, WRJ, Jennings, N, Madhok, B, Singhal, R & Small, PK 2017, 'Understanding Objections to One Anastomosis (Mini) Gastric Bypass: A Survey of 417 Surgeons Not Performing this Procedure', *Obesity Surgery*, vol. 27, no. 9, Sep, pp. 2222-2228.

Mahawar, KK, Jennings, N, Brown, J, Gupta, A, Balupuri, S & Small, PK 2013, '"Mini" gastric bypass: systematic review of a controversial procedure', *Obesity Surgery*, vol. 23, no. 11, Nov, pp. 1890-1898.

Melissas, J, Leventi, A, Klinaki, I, Perisinakis, K, Koukouraki, S, de Bree, E & Karkavitsas, N 2013, 'Alterations of global gastrointestinal motility after sleeve gastrectomy: a prospective study', *Annals of Surgery*, vol. 258, no. 6, pp. 976-982.

National Health and Medical Research Council 2013, *Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia.*, National Health and Medical Research Council, Melbourne, Accessed 17/9/19, <https://www.nhmrc.gov.au/about-us/publications/clinical-practice-guidelines-management-overweight-and-obesity>.

Reveiller, M, Ghatak, S, Toia, L, Kalatskaya, I, Stein, L, D'Souza, M, Zhou, Z, Bandla, S, Gooding, WE, Godfrey, TE & Peters, JH 2012, 'Bile exposure inhibits expression of squamous differentiation genes in human esophageal epithelial cells', *Annals of Surgery*, vol. 255, no. 6, Jun, pp. 1113-1120.

Rutledge, R, Kular, K & Manchanda, N 2019, 'The Mini-Gastric Bypass original technique', *International Journal of Surgery*, vol. 61, Jan, pp. 38-41.

Saarinen, T, Rasanen, J, Salo, J, Loimaala, A, Pitkonen, M, Leivonen, M & Juuti, A 2017, 'Bile Reflux Scintigraphy After Mini-Gastric Bypass', *Obesity Surgery*, vol. 27, no. 8, Aug, pp. 2083-2089.

Shah, S, Shah, P, Todkar, J, Gagner, M, Sonar, S & Solav, S 2010, 'Prospective controlled study of effect of laparoscopic sleeve gastrectomy on small bowel transit time and gastric emptying half-time in morbidly obese patients with type 2 diabetes mellitus', *Surgery for Obesity and Related Diseases*, vol. 6, no. 2, pp. 152-157.

Steinert, RE, Feinle-Bisset, C, Asarian, L, Horowitz, M, Beglinger, C & Geary, N 2017, 'Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB', *Physiological Reviews*, vol. 97, no. 1, Jan, pp. 411-463.

Sundbom, M, Hedenstrom, H & Gustavsson, S 2002, 'Duodenogastric bile reflux after gastric bypass: a cholescintigraphic study', *Digestive Diseases and Sciences*, vol. 47, no. 8, Aug, pp. 1891-1896.

Toro, JP, Lin, E, Patel, AD, Davis, SS, Jr., Sanni, A, Urrego, HD, Sweeney, JF, Srinivasan, JK, Small, W, Mittal, P, Sekhar, A & Moreno, CC 2014, 'Association of radiographic morphology with early gastroesophageal reflux disease and satiety control after sleeve gastrectomy', *Journal of the American College of Surgeons*, vol. 219, no. 3, Sep, pp. 430-438.

Trung, VN, Yamamoto, H, Furukawa, A, Yamaguchi, T, Murata, S, Yoshimura, M, Murakami, Y, Sato, S, Otani, H, Ugi, S, Morino, K, Maegawa, H & Tani, T 2013, 'Enhanced Intestinal Motility during Oral Glucose Tolerance Test after Laparoscopic Sleeve Gastrectomy: Preliminary Results Using Cine Magnetic Resonance Imaging', *PloS One*, vol. 8, no. 6, pp. e65739-e65739.

Vella, E, Hovorka, Z, Yarbrough, DE & McQuitty, E 2017, 'Bile reflux of the remnant stomach following Roux-en-Y gastric bypass: an etiology of chronic abdominal pain treated with remnant gastrectomy', *Surgery for Obesity and Related Diseases*, vol. 13, no. 8, Aug, pp. 1278-1283.

CHAPTER 5:

Once in a Bile – The Incidence of Bile Reflux Post-Bariatric Surgery

Eldredge T A, Bills M, Ting Y Y, Dimitri M, Watson M W, Harris M C, Myers J C, Bartholomeusz D, Kiroff G K, Shenfine J.
Once in a Bile – The Incidence of Bile Reflux Post-Bariatric Surgery.
Obesity Surgery. 2022 Feb (Published online 28/2/22).
DOI: 10.1007/s11695-022-05977-2

Statement of Authorship

Title of Paper	Once in a Bile - The Incidence of Bile Reflux Post-Bariatric Surgery
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Eldredge T A, Bills M, Ting Y Y, Dimitri M, Watson M, Harris M, Myers J C, Bartholomeusz D, Kiroff G K, Shenfine J. Once in a Bile - The Incidence of Bile Reflux Post-Bariatric Surgery. Obes Surg. 2022 Feb; DOI: 10.1007/s11695-022-05977-2

Principal Author

Name of Principal Author (Candidate)	Thomas Eldredge		
Contribution to the Paper	Conceived and designed research; Undertook literature review; Recruited and consented participants; Analysed the data and interpreted the findings; Undertook statistical analysis; Drafted the manuscript including revisions for submission.		
Overall percentage (%)	75%		
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	19/1/22

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 in 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	Madison Bills		
Contribution to the Paper	Assisted in research design; Performed HIDA investigations; Analysed part of the data and interpreted the findings.		
Signature		Date	25/01/2022

Name of Co-Author	Ying Yang Ting		
Contribution to the Paper	Assisted in participant follow-up and data collection.		
Signature		Date	19/1/2022

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Mikayla Dimitri		
Contribution to the Paper	Performed HIDA investigations; Analysed part of the data and interpreted the findings.		
Signature		Date	24/01/2022

Name of Co-Author	Matthew Watson		
Contribution to the Paper	Assisted in participant follow-up and data collection.		
Signature		Date	19/01/2022

Name of Co-Author	Mark Harris		
Contribution to the Paper	Assisted in participant follow-up and data collection.		
Signature		Date	21/01/2022

Name of Co-Author	Jennifer C Myers		
Contribution to the Paper	Assisted in research design; Contributed to literature review; Co-supervised the overall study; Assisted in drafting the manuscript including critical revision for submission.		
Signature		Date	22-1-2022

Name of Co-Author	Dylan Bartholomeusz		
Contribution to the Paper	Assisted in research design; Supervised part of the overall study; Analysed part of the data and interpreted the findings; Contributed to revision of the manuscript for submission.		
Signature	ext here	Date	25.1.2022

Name of Co-Author	George K Kiroff		
Contribution to the Paper	Contributed to conception and design of research; Co-supervised the overall study; Performed portion of endoscopic procedures on participants; Contributed to critical revision of the manuscript for submission.		
Signature		Date	11/02/2022

Name of Co-Author	Jonathan Shenfine		
Contribution to the Paper	Conceived and designed research; Supervised the overall study; Performed weight loss operations on participants; Contributed to critical revision of the manuscript for submission.		
Signature		Date	19/1/22

Once in a Bile –The Incidence of Bile Reflux Post-Bariatric Surgery

Authors: Thomas A Eldredge [1, 2], Madison Bills [3], Ying Yang Ting [1, 2], Mikayla Dimitri [3], Matthew Watson [2], Mark Harris [2], Jennifer C Myers [1, 2], Dylan Bartholomeusz [3, 4], George K Kiroff [1, 2], Jonathan Shenfine [1]

Affiliations

1. Discipline of Surgery, University of Adelaide, Adelaide, South Australia;
2. Department of Surgery, The Queen Elizabeth Hospital, South Australia;
3. Department of Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital and SA Medical Imaging, South Australia
4. Department of Gastroenterology, Royal Adelaide Hospital, South Australia

Acknowlegments

Thank you to Mr Harsh Kanhere, Mr Markus Trochsler, Mr Shalvin Prasad, Mr Philip Game, Mr Jacob Chisholm and A/Prof Lilian Kow for their support of our study and allowing us to invite their patients to participate. Thank you also to: Mr Martin Bruening for performing endoscopies for our trial; Ms Suzanne Edwards for her expert statistical assistance; and Mr Lou Nesci, SA Pathology, for performing bile acid and bilirubin assays.

Funding

T.E is a recipient of the Richard Jepson Research Scholarship from the Royal Australasian College of Surgeons.

Abstract

Purpose:

Excellent metabolic improvement following one anastomosis gastric bypass (OAGB) remains compromised by the risk of esophageal bile reflux and theoretical carcinogenic potential. No 'gold standard' investigation exists for esophageal bile reflux, with diverse methods employed in the few studies evaluating it post-obesity surgery. As such, data on the incidence and severity of esophageal bile reflux is limited, with comparative studies lacking. This study aims to use specifically tailored biliary scintigraphy and upper gastrointestinal endoscopy protocols to evaluate esophageal bile reflux after OAGB, sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB).

Methods:

Fifty-eight participants underwent OAGB (20), SG (15) or RYGB (23) between November 2018 - July 2020. Pre-operative reflux symptom assessment and gastroscopy were performed and repeated post-operatively at 6-months along with biliary scintigraphy.

Results:

Gastric reflux of bile was identified by biliary scintigraphy in 14 OAGB (70%), one RYGB (5%) and four SG participants (31%), with a mean of 2.9% (SD 1.5) reflux (% of total radioactivity). One participant (OAGB) demonstrated esophageal bile reflux. *De novo* macro- or microscopic gastroesophagitis occurred in 11 OAGB (58%), 8 SG (57%), and 7 RYGB (30%) participants. Thirteen participants had worsened reflux symptoms post-operatively (OAGB – 4; SG – 7; RYGB – 2). Scintigraphic esophageal bile reflux bore no statistical association with *de novo* gastroesophagitis, or reflux symptoms.

Conclusion:

Despite high incidence of gastric bile reflux post-OAGB, esophageal bile reflux is rare. With scarce literature of tumour development post-OAGB, frequent low volume gastric bile reflux likely bears little clinical consequence, however longer-term studies are needed.

Key points:

- Low volume gastric pouch bile reflux occurs frequently after OAGB and SG
- Esophageal bile reflux is rare after OAGB and SG
- *De novo* gastroesophagitis occurs equally after SG & OAGB, unrelated to bile reflux
- Reports of gastroesophageal cancer after OAGB are rare, with questionable

Abbreviations:

BMI	Body mass index
BP	Biliopancreatic
CT	Computed tomography
DGER	Duodenogastroesophageal reflux
EWL	Excess weight loss
GERD	Gastroesophageal reflux disease
HIDA	Hepatobiliary iminodiacetic acid
IV	Intravenous
MOS	Metabolic and obesity surgery
OAGB	One-anastomosis gastric bypass
PPI	Proton pump inhibitor
ROI	Region of interest
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
SPECT	Single photon emission computed tomography
UGIE	Upper gastrointestinal endoscopy

Introduction

The one anastomosis gastric bypass (OAGB) is deservedly the third-most performed metabolic and obesity surgery (MOS) procedure globally (IFSO 2021). Large meta-analyses demonstrate equivalent, if not superior, metabolic outcomes compared with Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG); the two most popular MOS operations (Jia *et al.* 2020; Wang *et al.* 2017). Despite equivalence, OAGB has not been adopted with enthusiasm, due to concerns around the potential impact of post-operative esophageal bile reflux. This is often termed Duodeno-Gastro-Esophageal reflux (DGER) but strictly this is not a correct term regarding post-OAGB anatomy. The potential for bile reflux stems from the anatomical similarities with both the Mason gastric bypass and the Billroth II procedure, both of which were also controversially associated with both duodenogastric and esophageal bile reflux and thus a potential cancer risk. No gold standard investigation exists to diagnose esophageal bile reflux, and heterogenous diagnostic protocols are evident in the few studies that evaluate esophageal bile reflux post-OAGB. This study aims to elucidate the incidence and severity of esophageal bile reflux post-OAGB, with direct comparison to SG and RYGB, by utilising a specifically developed diagnostic protocol tailored for a post-MOS cohort.

Methods

Participants

Eligible participants (inclusion / exclusion criteria defined in Figure 1) from multidisciplinary obesity clinics of two public and four private hospitals in Adelaide, Australia, were invited to participate. The type of procedure undertaken was determined by informed patient preference; participants undergoing OAGB, SG and RYGB were included, forming the three arms of this prospective cohort study. Randomisation to procedure was not possible due to lacking clinical equipoise.

To enable inferential statistical tests on study findings, a power analysis was conducted, which determined a target sample size of 24 participants per trial arm (72 total), using *Fisher's Exact Conditional Test for Two Proportions*, assuming a power of 80% and significance level or alpha of 0.05 (i.e. 80% or greater chance of finding a statistically significant difference when there is one). The calculation assumed a 45% difference between worst (50%) and best (5%) incidence of bile reflux between procedures; a 'best estimate' from limited published data. The calculation included design effect or variance inflation factor to account for multiple surgeons and an additional 10% of patients per arm (for potential loss to follow-up), to minimize bias related to attrition reducing the effective sample size.

Follow-up occurred at 6 months post-operatively; an expected timepoint at which participants have returned to a stable lifestyle. After study commencement, follow-up was impacted by government-mandated restrictions regarding elective medical investigations/ treatments during the COVID-19 pandemic.

<u>Data collection</u>

The following data were collected pre-operatively and again at follow-up: full medical history; height, weight, and body mass index (BMI); blood tests (lipid studies, Hba1c, fasting glucose, biochemical panel, and full blood exam); reflux symptom assessment, and macro- & microscopic gastroesophageal assessment by upper gastrointestinal endoscopy (UGIE), along with gastric fluid aspiration for bilirubin analysis. In addition, tailored biliary scintigraphy was performed at 6-months post-operatively. No pre-operative scintigraphy was performed; an ethical decision to limit radiation exposure for participants.

<u>Symptom assessment</u>

The *GerdQ* was utilised as a validated, self-administered, patient-centred questionnaire with similar diagnostic accuracy for symptom-based diagnosis of gastroesophageal reflux to that of a gastroenterologist (Jonasson *et al.* 2013; Jones *et al.* 2009).

Endoscopy

Endoscopy was performed under intravenous sedation with oropharyngeal topical anaesthesia using lignocaine/phenylephrine (CoPhenylcaine™, ENT Technologies, Melbourne, Australia). Mucosal biopsies were taken from the gastric antrum (where present), gastro-jejunal anastomosis (where present), gastric body, and distal esophagus for histopathological analysis. The endoscopist documented: any visible bile in the stomach, macroscopic gastritis, esophagitis (Armstrong *et al.* 1996), anastomotic erosion/ulceration, and details of any hiatus hernia.

Gastric fluid, aspirated via the endoscope channel, was immediately transferred to storage tubes, and placed in a -80^{o} Celsius freezer prior to batched bilirubin analysis utilising enzymatic colorimetric assay (Parviainen 1997) by an accredited state-wide pathology laboratory (SA Pathology, Adelaide, Australia).

Biliary scintigraphy

Our previously described modified biliary scintigraphy protocol, tailored for a post-MOS cohort (Eldredge *et al.* 2020), was performed 6 months post-operatively.

Surgical Technique

Seven surgeons were involved in this study. Techniques were largely identical among surgeons, with differences outlined below. All procedures were completed laparoscopically or robotically (for 2 cases), with standard 4-port placement and an epigastric liver retractor. Stapled anastomoses utilised the EndoGIA™ or Signia™ stapling systems (Medtronic, Minneapolis, USA).

OAGB

One-anastomosis gastric bypass was predominantly performed by one surgeon (n=17/20). A stapled gastric pouch was fashioned over a 36 Fr. bougie, extending to the *incisura angularis*. Small variation in biliopancreatic (BP) limb length was observed (150-200cm) and an antecolic, end-to-side gastro-jejunal stapled anastomosis was constructed. The remaining bowel defect was hand-sewn with a 2/0 barbed, absorbable suture (V-loc™, Medtronic, Minneapolis USA). An 'anti-reflux' stitch was placed between the afferent loop of the jejunum and the lateral aspect of the gastric pouch. Petersen's space was not closed.

SG

Sleeve gastrectomy was performed by five surgeons. Two participants underwent robotic (da Vinci Xi, Intuitive Surgical, Sunnyvale, USA), rather than laparoscopic procedures, using identical port placement and a liver retraction device, and two participants had a concurrent cruroplasty. The stomach was mobilised along the greater curvature and posteriorly to visualise the diaphragmatic crura. Gastric stapling commenced ~6cm proximal to the pylorus, ending at the angle of His with a 36 Fr. bougie (or 48 Fr./52 Fr. in 2 cases) for luminal calibration.

RYGB

Roux-en-Y gastric bypass was performed by five surgeons. Minor variations in BP- and alimentary limb lengths were observed. A small, stapled gastric pouch was fashioned over a 36 Fr. Bougie. An antecolic, end-to-side gastro-jejunal stapled anastomosis was performed with a 50-80cm BP limb. A stapled jejuno-jejunostomy was performed using a 100-110 cm alimentary limb. The resulting anastomotic defect was closed with 2/0 monofilament (Monocryl®, Ethicon, Somerville, USA) or barbed V-loc™ absorbable suture. Mesenteric defects were routinely closed.

Statistics

Statistical analysis was undertaken by the lead author (TE), with assistance of our Unit's statistician. Descriptive statistics included mean (standard deviation) or median (interquartile range) as appropriate. Binary and ordinal logistic generalized estimating equations models and linear mixed-effects models were applied depending on the outcome variable (binary, ordinal, or continuous), controlling for repeated measures over time and adjusting for clustering on hospitals. P values of <0.05 were considered significant.

Results

Participants

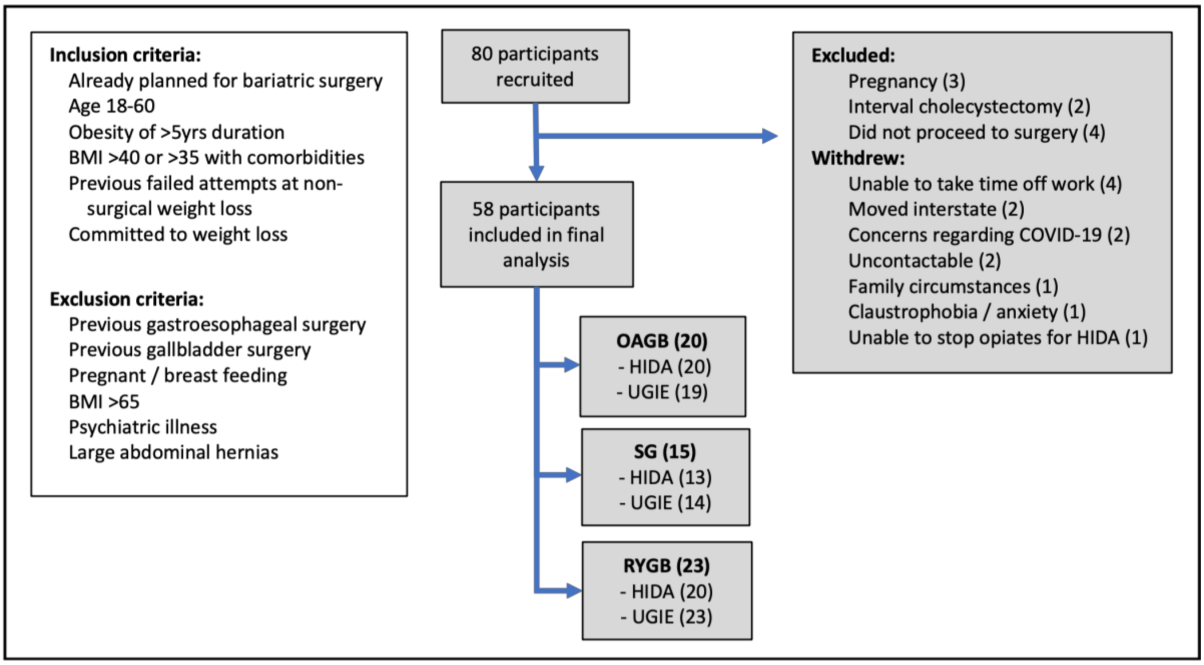


Figure 1: Participant inclusion flow-chart. BMI, body mass index; HIDA, hepatobiliary iminodiacetic acid scintigraphy; UGIE, upper gastrointestinal endoscopy).

Eighty participants were invited to participate between November 2018 and July 2020. Nine participants were excluded after enrolment and 13 withdrew, thus 58 participants were evaluated before and after surgery: OAGB, n=20; SG, n=15; RYGB, n=23 (see Figure 1). Forty-five participants were female (78%) and participant mean age was 41.8 years (SD 9.92). Mean time lapse from surgery to follow-up endoscopy was 250 days (SD 90.6), and time to biliary scintigraphy was 248 days (SD 65.5). Pandemic-related shutdowns resulted in a bi-modal distribution of follow-up times, with peaks at 200 days and 300 days.

Reflux symptoms

The OAGB was the only procedure showing a statistically significant decrease in GerdQ score post-operatively (Figure 2; Table 1). Post-operative proton pump inhibitor (PPI) usage varied among patient groups. Overall, more participants were using PPI therapy post-operatively compared with pre-operatively in all operative groups. Some participants ceased PPI medication post-operatively (OAGB – 2; SG – 0; RYGB – 2), while others were newly prescribed PPI therapy (OAGB – 5; SG – 3; RYGB – 4).

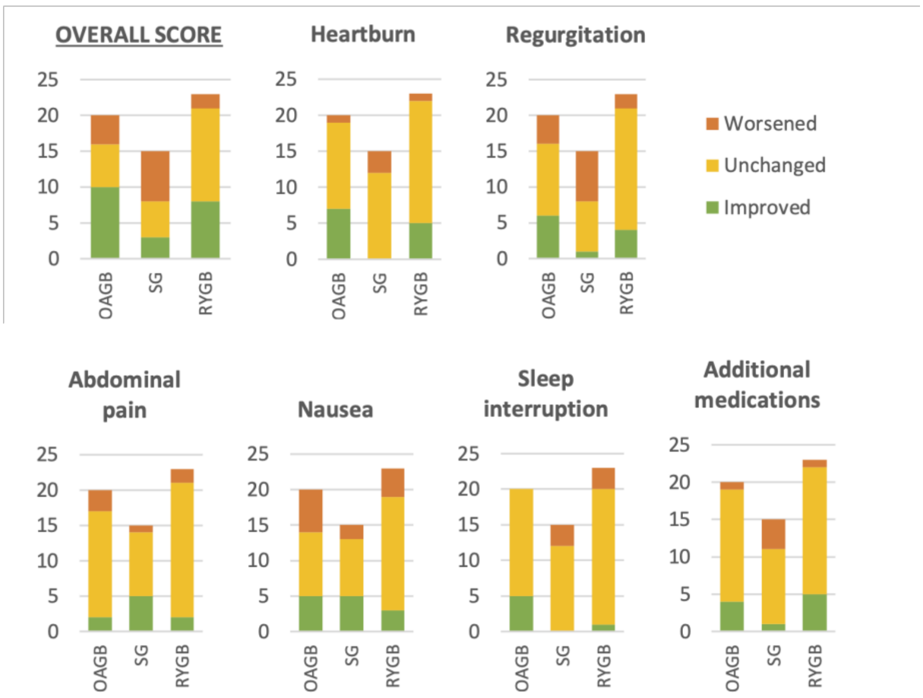


Figure 2: Results from GerdQ questionnaire, by category.

OAGB (N=20)	**Pre-op**	**Post-op**	***p-value***
BMI (kg/m^2)	45.7 (6.9)	32.4 (4.7)	**<0.0001**
%EWL		67.5 (18.3)	
Comorbidities			
Diabetes mellitus	5	1	**0.03**
HbA1c (%)	5.86 (1.1)	5.2 (0.4)	**<0.0001**
Fasting glucose (mmol/L)	5.63 (1.5)	4.37 (0.6)	**<0.001**
Insulin (n=)	0	0	-
Oral medication (n=)	5	1	**0.03**
Dyslipidaemia			
Total cholesterol (mmol/L)	4.63 (1.0)	4.34 (1.0)	0.29
Lipid-lowering therapy (n=)	5	1	**0.03**
Hypertension			
Antihypertensives (n=)	6	5	0.56
Reflux symptoms			
GerdQ score	7.6 (3.1)	6.4 (2.5)	**0.02**
PPI therapy (n=)	5	8	0.24
SG (N=15)	**Pre-op**	**Post-op**	***p-value***
BMI (kg/m^2)	45.1 (6.1)	34.6 (6.2)	**<0.0001**
%EWL		55.6 (18.5)	
Comorbidities			
Diabetes mellitus	1	1	-
HbA1c (%)	5.48 (0.4)	5.12 (0.3)	0.078
Fasting glucose (mmol/L)	5.18 (0.9)	4.1 (0.6)	**0.006**
Insulin (n=)	1	0	-
Oral medication (n=)	0	1	-
Dyslipidaemia			
Total cholesterol (mmol/L)	5.60 (1.9)	5.57 (3.7)	0.93
Lipid-lowering therapy (n=)	2	3	0.31
Hypertension			
Antihypertensives (n=)	5	3	0.13
Reflux symptoms			
GerdQ score	5.9 (3.5)	6.9 (2.9)	0.09
PPI therapy (n=)	0	3	0.05
RYGB (N=23)	**Pre-op**	**Post-op**	***p-value***
BMI (kg/m^2)	43.8 (6.3)	32.0 (5.6)	**<0.001**
%EWL		68.4 (25.4)	
Comorbidities			
Diabetes mellitus	6	3	0.06
HbA1c (%)	5.78 (0.8)	5.28 (0.4)	**0.001**
Fasting glucose (mmol/L)	5.45 (1.3)	4.56 (0.5)	**0.003**
Insulin (n=)	0	0	-
Oral medication (n=)	6	3	0.06
Dyslipidaemia			
Total cholesterol (mmol/L)	4.36 (1.0)	3.94 (0.7)	0.10
Lipid-lowering therapy (n=)	6	4	0.14
Hypertension			
Antihypertensives (n=)	7	3	**0.03**
Reflux symptoms			
GerdQ score	5.9 (2.9)	6.7 (2.3)	0.08
PPI therapy (n=)	7	9	0.41

Table 1: Pre- and post-operative results for biometric measurements and comorbidity resolution. Results presented as mean (SD) where applicable.

Endoscopy

Fifty-six participants (56/58; 97%) underwent UGIE, with findings summarised in Table 2. *De novo* gastritis or erosion/ulceration was observed macroscopically in nine participants and histologically in six participants. Sometimes macroscopic gastritis was not supported by microscopic findings and vice versa. Six participants (OAGB - 2; SG - 1; RYGB - 3) had macroscopic gastritis in the absence of microscopic findings, whereas three (OAGB – 1; SG - 2) participants had converse findings. *De novo* microscopic esophagitis was identified in eleven participants (OAGB – 5; SG – 4; RYGB – 2), however this was only macroscopically evident in 2 participants (SG – 1; RYGB – 1). One participant, post-SG had *de novo* intestinal metaplasia on distal esophageal biopsies; however, the absence of macroscopic changes suggests a sampling error. Early histological features of gastritis (foveolar hyperplasia) were observed in one OAGB patient, and esophagitis (basal cell hyperplasia) in nine participants (OAGB– 5; SG– 3; RYGB– 1).

Overall, *de novo* macro- or microscopic gastroesophagitis was seen in eleven participants post-OAGB (58%), eight post-SG (57%), and five post-RYGB (22%). Conversely, resolution of macroscopic esophagitis was observed in all patients post-OAGB with no *de novo* development of macroscopic findings. There was no statistical association between *de novo* gastroesophagitis and positive scintigraphy or worsened reflux symptoms.

Gastric fluid analysis

Twenty-eight participants had pre-operative gastric fluid analysis for bilirubin (OAGB – 11; SG – 4; RYGB – 13) and 35 had post-operative analysis (OAGB – 14; SG – 7; RYGB – 14). No pre-operative samples measured elevated bilirubin (reference range 2-24 micromol/L). Post-operatively, elevated bilirubin levels were measured for three participants (157-498 micromol/L), all post-OAGB. No significant association was observed between elevated gastric fluid bilirubin and worsened symptoms, gastroesophagitis or positive scintigraphy.

Operation type	**Pre-op**	**Post-op**	***De-novo* post-op**	***p-value****
OAGB	20 (100%)	19 (95%)		
Normal	6 (30%)	4 (21%)		0.72
Stomach				
Macroscopic gastritis	2 (10%)	1 (5%)	1 (5%)	-
Macroscopic erosion	1 (5%)	3 (16%)	3 (16%)	0.34
Foveolar hyperplasia	0	1 (5%)	1 (5%)	0.07
H. Pylori positive gastritis	4 (20%)	0	0	0.11
Histological acute inflammation	0	3 (16%)	3 (16%)	0.11
Histological chronic inflammation	8 (40%)	0	0	**0.003**
Esophagus				
LA grade A esophagitis	3 (15%)	0	0	0.23
LA grade B esophagitis	1 (5%)	0	0	-
Basal cell hyperplasia	0	5 (26%)	5 (26%)	**0.02**
Histological esophagitis	5 (25%)	5 (26%)	5 (26%)	-
Intestinal metaplasia	0	0	0	-
SG	15 (100%)	14 (93%)		
Normal	7 (47%)	2 (14%)		0.11
Stomach				
Macroscopic gastritis	2 (13%)	2 (14%)	2 (14%)	-
Macroscopic erosion	1 (7%)	0	0	-
Foveolar hyperplasia	0	0	0	-
H. Pylori positive gastritis	0	1 (7%)	1 (7%)	0.48
Histological acute inflammation	2 (13%)	5 (36%)	3 (21%)	0.21
Histological chronic inflammation	6 (40%)	0	0	**0.02**
Esophagus				
LA grade A esophagitis	1 (7%)	0	0	-
LA grade B esophagitis	0	1 (7%)	1 (7%)	0.48
Basal cell hyperplasia	0	3 (21%)	3 (21%)	0.10
Histological esophagitis	1 (7%)	4 (28%)	4 (28%)	0.17
Intestinal metaplasia	0	1 (7%)	1 (7%)	0.48
RYGB	23 (100%)	23 (100%)		
Normal	4 (17%)	9 (39%)		0.19
Stomach				
Macroscopic gastritis	0	1 (4%)	1 (4%)	-
Macroscopic erosion	0	2 (9%)	2 (9%)	0.49
Foveolar hyperplasia	0	0	0	-
H. Pylori positive gastritis	2 (9%)	0	0	0.49
Histological acute inflammation	1 (4%)	0	0	-
Histological chronic inflammation	13 (57%)	0	0	**<0.001**
Esophagus				
LA grade A esophagitis	3 (13%)	1 (4%)	1 (4%)	0.61
LA grade B esophagitis	1 (4%)	0	0	-
Basal cell hyperplasia	0	1 (4%)	1 (4%)	-
Histological esophagitis	4 (17%)	4 (17%)	2 (9%)	-
Intestinal metaplasia	1 (4%)	0	0	-

Table 2: Results from upper gastrointestinal endoscopy and histopathological assessment (* p-value calculated using Fisher's exact test).

Biliary scintigraphy

Fifty-three participants underwent scintigraphy (91%), with reflux of bile into the gastric pouch/sleeve most frequently identified in OAGB participants (70%), and to a lesser extent post-SG (31%) (Table 3). Esophageal reflux of bile was demonstrated in only one participant post-OAGB (Figure 3). Mean percentage of reflux activity within the gastric pouch/sleeve in positive studies was low for all surgical techniques. Participants who underwent OAGB had higher likelihood of positive duodenogastric reflux on scintigraphy compared with SG (odds ratio – 1.48, 95% CI: 1.00 – 2.20, p=0.05) and RYGB (odds ratio – 44.33, 95% CI: 2.93 – 670.32, p=0.01). There was no statistical association between duodenogastric reflux seen on biliary scintigraphy and *de novo* gastroesophagitis or worsened reflux symptoms.

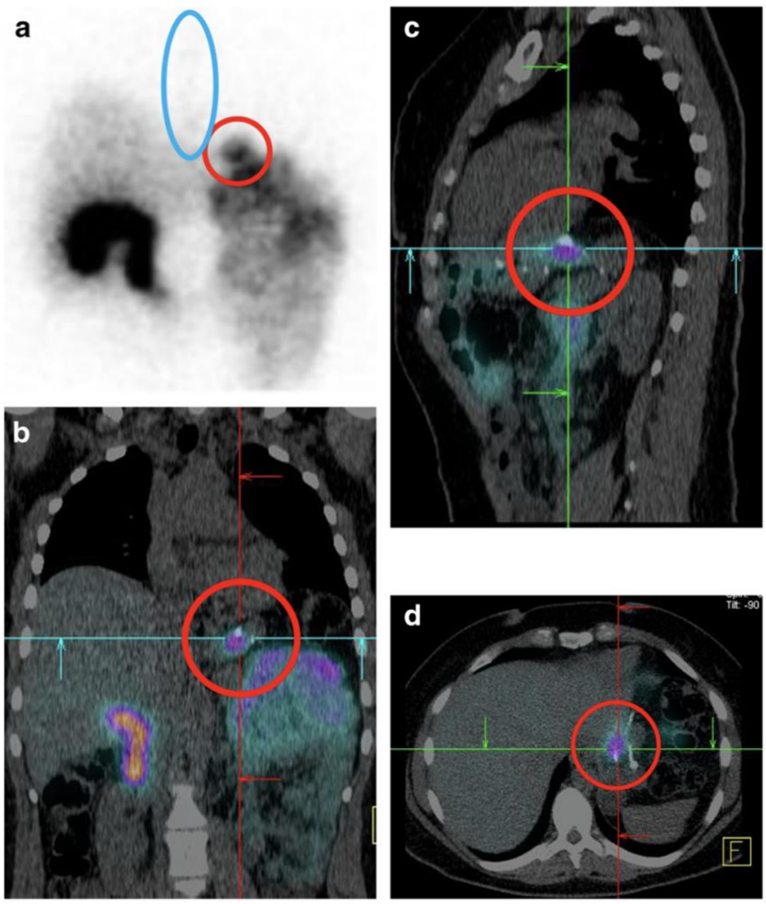


Figure 3: A- scintigraphic image showing reflux into gastric pouch (red circle) and esophagus (blue circle); B-D: coronal (B), sagittal (C) and axial (D) fused CT images, confirming localisation of reflux in the gastric pouch (red circle).

	OAGB	SG	RYGB
No. scanned / total each group	20/20	13/15	20/23
Reflux into pouch/sleeve	14 (70%)	4 (31%)	1 (5%)
Reflux into esophagus	1 (5%)	0	0
Reflux into gastric remnant	0	n/a	4 (17%)
Mean % reflux activity in pouch	2.9 (1.5)	4.1 (1.3)	2.05

Table 3: Biliary scintigraphy results.

Weight loss and comorbidity improvement

All operative groups demonstrated significant weight loss, with the greatest mean percentage excess weight loss and decrease in BMI observed for OAGB and RYGB, with less for SG (Table 1). Post-operatively, greatest improvement in glycaemic control occurred after OAGB, with significant decreases in mean HbA1c, fasting glucose, and diabetic medication usage. The RYGB and SG groups also showed improvements in glycaemic control, albeit to a lesser degree and varying statistical significance (Table 1). Improvements of hypercholesterolaemia and hypertension were observed for OAGB and RYGB, again with varying statistical significance (Table 1). No statistical significance between groups was observed for weight loss and comorbidity improvement, however the study was not powered for such comparison.

Discussion

This prospective study revealed that low volume reflux of bile into the gastric pouch/sleeve is common after OAGB and SG, when compared with RYGB. The presence of duodenogastric reflux on scintigraphy had no association with reflux symptoms, nor mucosal damage of the stomach and esophagus. In contrast, esophageal bile reflux is rare, only occurring in a single patient post-OAGB.

Diagnosing bile reflux is challenging, with no single investigation deemed superior in a systematised review of available diagnostic techniques (Eldredge *et al.* 2018). Macro- and microscopic findings of gastroesophagitis lack specificity and thus require adjunctive investigations to confirm bile as the inciting factor. The *Sydney System* of histological assessment can aid determination of bile-related gastritis (Stolte & Meining 2001). This system cannot be used in patients who have undergone gastric bypass, due to requirement of a gastric antrum biopsy. Obtaining gastric fluid for bilirubin analysis is similarly limited, due to the intermittent nature of bile reflux and dilutional impact of swallowed secretions. Biliary scintigraphy, with modifications tailored to the anatomical and physiological changes after MOS, becomes a specific and well-tolerated investigation with good sensitivity and reproducibility (Eldredge *et al.* 2020). Combining scintigraphy for diagnosis of bile reflux, with UGIE for macro- and microscopic mucosal assessment should now be considered the gold standard for investigation (Eldredge *et al.* 2018).

Esophageal bile reflux after OAGB has been investigated previously in five studies (Keleidari *et al.* 2021; Keleidari *et al.* 2019; Lasheen *et al.* 2019; Saarinen *et al.* 2020; Saarinen *et al.* 2017; Shenouda *et al.* 2018). Diagnostic techniques varied, with Saarinen *et al*. being the only other group using biliary scintigraphy (Saarinen *et al.* 2020). Their protocol was similar to the current study, incorporating SPECT-CT and delayed static images, but omitted any provocation agents. In their two published studies, they report duodenogastric reflux incidence of 55.5% and 31.6%, lower than in this current study. Differing scintigraphy protocols may account for this discrepancy; adding a provocation agent more accurately emulates dietary intake to stimulate gallbladder emptying, improving test sensitivity (Krishnamurthy & Brown 2002). Esophageal bile reflux was rarely observed in the current study, consistent with Saarinen's results; one patient in each study demonstrating low volume reflux of bile into the esophagus. Low extent/severity of total reflux activity was reported in both studies, with Saarinen reporting mean activity 5.2% compared with 2.9% in the current study.

Gastroesophageal reflux (GERD) after SG has been widely reported. A recent meta-analysis of over 10,000 patients found worsened reflux symptoms post-SG in 19% of patients, *de novo* symptoms in 23%, and long-term Barrett's esophagus prevalence of 8% (Yeung *et al.* 2020). While this review failed to elaborate on prevalence of gastric and esophageal bile reflux, a more recent study by Braghetto *et al.* assessed this using biliary scintigraphy in patients with *de novo* reflux symptoms post-SG (Braghetto *et al.* 2019). Duodenogastric reflux was detected in 32% of patients (7/22), consistent with our results of 31% (4/13). Their scintigraphy protocol utilised an oral provocation agent but didn't incorporate SPECT-CT for anatomical localisation; anatomical alterations post-SG cause less interference for scan interpretation compared with bypass procedures. Even though selection bias was evident (only symptomatic patients were enrolled), their study was like ours, in that no statistical association between symptoms and positive reflux on scintigraphy was found. Roux-en-Y gastric bypass is lauded for ameliorating GERD post-operatively (Suter 2020); mechanistically attributable to hastened gastric emptying through an unrestricted gastrojejunostomy (Dirksen *et al.* 2013). Similarly, OAGB reduces GERD post-operatively, with reduced acid exposure time and lower number of acidic reflux events on impedance-pH demonstrated 12-months post-operatively (Eskandaros *et al.* 2021; Musella *et al.* 2021).

The significance of demonstrated gastric and esophageal bile reflux is the potential for associated tissue damage rather than simply the presence, frequency, or severity. Duodeno-gastric reflux can occur physiologically and is of minimal concern (Koek *et al.* 2005), whereas esophageal bile has the potential to be associated with mucosal damage. Esophageal mucosa exposure to bile acids increases epithelial permeability and promotes intracellular translocation of bile acids (McQuaid *et al.* 2011). Once intracellular, bile acids can incite an inflammatory response, causing oxidative DNA damage and cell death, thus potentially initiating an esophagitis-Barrett's-adenocarcinoma sequence (Bernstein *et al.* 2009). The current study demonstrated *de novo* gastroesophagitis in 58% (n=11/19) of participants post-OAGB, compared with 39.5% reported by Saarinen *et al.* (Saarinen *et al.* 2020). Interestingly, the current study showed resolution of macroscopic esophagitis in all patients post-OAGB with no *de novo* development of macroscopic findings. This is consistent with a recent randomised controlled trial demonstrating complete endoscopic regression of pre-operative Los Angeles grade A or B esophagitis in 90% of patients at 12-months post-OAGB (Eskandaros *et al.* 2021). The long, narrow gastric pouch and widely patent gastrojejunostomy proposed as likely mechanistic explanations (Musella *et al.* 2021). Studies by Lasheen and Shenouda reported post-operative gastroesophagitis in 32.5% of patients at 9 months and 55% at 6 months, respectively, however no comment was made about whether these findings were *de novo* post-operative findings or had been present pre-operatively (Lasheen *et al.* 2019; Shenouda *et al.* 2018). Our study showed no association between *de novo* gastroesophagitis and positive reflux on scintigraphy, contrasting with a positive association reported by Saarinen's group (Saarinen *et al.* 2020). This may represent a type-2 error given the relatively small sample size.

Despite known histopathological links between esophageal mucosa exposure to bile and carcinogenesis, in the 20 years since OAGB conception, only two cases of gastric pouch / distal esophageal malignancy have been reported (Aggarwal *et al.* 2019; Runkel & Runkel 2019); both were adenocarcinomas of the distal esophagus/gastroesophageal junction, diagnosed two years post-operatively. One patient had known Los Angeles grade C esophagitis preoperatively, the other had no pre-operative UGIE performed. Linking post-operative bile reflux with carcinogenesis is confounded in these cases by the unclear pre-operative presence of malignancy. Further to this, a recent study compared esophageal histological changes 30-weeks after OAGB, loop esophagojejunostomy or sham-operation in rats (M'Harzi *et al.* 2020). The authors demonstrated no development of pre-cancerous or cancerous gastro-esophageal lesions after OAGB, compared with development of intestinal metaplasia in 42% of patients post-esophagojejunostomy. Similarly, based on long-term evidence from studies of patients having a Billroth II procedure, concerns of bile-related carcinogenesis may be unfounded. In a population-based study of over 18,000 patients, the incidence of gastric stump cancer post-Billroth II was no different than the expected incidence in the standard population (73/8,735 cases post-Billroth II versus 83 predicted) (Lagergren, Lindam & Mason 2012). These studies show that the actual rate of malignancy is almost certainly incredibly low, with no demonstrable link to bile reflux. Were this to be true, it would raise concern regarding RYGB, as the gastric remnant remains exposed to bile reflux from the duodenum but can never be easily visualised again. This was clearly shown in our study with 17% of RYGB patients having gastric remnant bile reflux on scintigraphy.

The number of SG procedures being performed eclipses OAGB by more than 6-times (IFSO 2021). With the current study demonstrating equivalent rates of *de novo* gastroesophagitis between SG and OAGB, irrespective of presence of bile, the concern surrounding carcinogenesis after OAGB must therefore be extrapolated to SG. The high prevalence of Barrett's esophagus after SG (Yeung *et al.* 2020) is alarming in the context of a procedure in which a large portion of stomach is resected and discarded: the optimal surgical conduit for esophagectomy should cancer arise. Regardless of procedure, therefore, emphasis should be placed on post-operative endoscopic surveillance, enabling early detection and treatment of Barrett's; an opinion shared by the International Federation for the Surgery of Obesity and Metabolic Disorders (Brown *et al.* 2020).

There are limitations in this study. Participants were not randomised to their procedure, resulting in inherent selection bias: participants with pre-existing reflux or Barrett's esophagus on pre-operative endoscopy were positively selected for RYGB to minimise post-operative reflux (Suter 2020). The relatively small sample size will increase the likelihood of type 2 error. Equally, below-target sample size could result in an underpowered study, however the difference in bile reflux incidence between groups was underestimated in the power calculation, ameliorating this sample size difference. Although no association between frequency of duodenogastric reflux and gastroesophagitis was demonstrated in this study, the short follow-up period may underestimate the impact bile has on gastroesophageal mucosal integrity over the long term. Finally, due to COVID-19 related government placed restrictions, all non-essential medical treatments were ceased for 4 months during our recruitment/follow-up period. As a result, recruitment was halted, follow-up was delayed, and patients withdrew due to concerns about visiting hospitals during the pandemic.

Conclusion

In this study, duodenogastric reflux occurred frequently after OAGB, but was of low volume and not associated with worsened reflux symptoms. The rarity of esophageal bile reflux, combined with post-operative resolution of macroscopic reflux esophagitis in 100% of cases post-OAGB, supports the assertion of OAGB as a safe procedure with regards to esophageal bile reflux and thus carcinogenic potential. The short follow-up period of this study may limit evaluation of the impact of chronic low volume duodenogastric reflux on gastric mucosa. This quandary necessitates a recommendation for further medium and long-term evaluation in this cohort of patients. However, with only two cases of malignancy post-OAGB reported in 20 years, both with no correlation to a bile aetiology, it is likely that the theoretical carcinogenic risk remains exactly that: theoretical.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Human Research Ethics Committees of The Queen Elizabeth Hospital (TQEH) and Calvary Health Care Adelaide gave ethical approval for the study (TQEH - HREC/17/TQEH/185; Calvary – 18-CHREC-F001).

INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study.

CLINICAL TRIAL REGISTRY:

Australian New Zealand Clinical Trials Registry number ACTRN12618000806268.

References

Aggarwal, S, Bhambri, A, Singla, V, Dash, NR & Sharma, A 2019, 'Adenocarcinoma of oesophagus involving gastro-oesophageal junction following mini-gastric bypass/one anastomosis gastric bypass', *Journal of Minimal Access Surgery*, vol. 16, no. 2, Feb 18, pp. 175-178.

Armstrong, D, Bennett, JR, Blum, AL, Dent, J, De Dombal, FT, Galmiche, JP, Lundell, L, Margulies, M, Richter, JE, Spechler, SJ, Tytgat, GN & Wallin, L 1996, 'The endoscopic assessment of esophagitis: a progress report on observer agreement', *Gastroenterology*, vol. 111, no. 1, Jul, pp. 85-92.

Bernstein, H, Bernstein, C, Payne, CM & Dvorak, K 2009, 'Bile acids as endogenous etiologic agents in gastrointestinal cancer', *World Journal of Gastroenterology*, vol. 15, no. 27, Jul 21, pp. 3329-3340.

Braghetto, I, Gonzalez, P, Lovera, C, Figueroa-Giralt, M & Pineres, A 2019, 'Duodenogastric biliary reflux assessed by scintigraphic scan in patients with reflux symptoms after sleeve gastrectomy: preliminary results', *Surgery for Obesity and Related Diseases*, vol. 15, no. 6, Jun, pp. 822-826.

Brown, WA, Johari Halim Shah, Y, Balalis, G, Bashir, A, Ramos, A, Kow, L, Herrera, M, Shikora, S, Campos, GM, Himpens, J & Higa, K 2020, 'IFSO Position Statement on the Role of Esophago-Gastro-Duodenal Endoscopy Prior to and after Bariatric and Metabolic Surgery Procedures', *Obesity Surgery*, vol. 30, no. 8, Aug, pp. 3135-3153.

Dirksen, C, Damgaard, M, Bojsen-Moller, KN, Jorgensen, NB, Kielgast, U, Jacobsen, SH, Naver, LS, Worm, D, Holst, JJ, Madsbad, S, Hansen, DL & Madsen, JL 2013, 'Fast pouch emptying, delayed small intestinal transit, and exaggerated gut hormone responses after Roux-en-Y gastric bypass', *Neurogastroenterology and Motility*, vol. 25, no. 4, Apr, pp. 346-e255.

Eldredge, TA, Bills, M, Myers, JC, Bartholomeusz, D, Kiroff, GK & Shenfine, J 2020, 'HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery', *Obesity Surgery*, vol. 30, no. 5, May, pp. 2038-2045.

Eldredge, TA, Myers, JC, Kiroff, GK & Shenfine, J 2018, 'Detecting Bile Reflux-the Enigma of Bariatric Surgery', *Obesity Surgery*, vol. 28, no. 2, Feb, pp. 559-566.

Eskandaros, MS, Abbass, A, Zaid, MH & Darwish, AA 2021, 'Laparoscopic One Anastomosis Gastric Bypass Versus Laparoscopic Roux-en-Y Gastric Bypass Effects on Pre-existing Mild-to-Moderate Gastroesophageal Reflux Disease in Patients with Obesity: a Randomized Controlled Study', *Obesity Surgery*, vol. 31, no. 11, Nov, pp. 4673-4681.

IFSO 2021, *Sixth Global Registry Report*, International Federation for the Surgery of Obesity and Metabolic Disorders, Viewed: 9/11/2021, <https://www.ifso.com/ifso-registry.php>.

Jia, D, Tan, H, Faramand, A & Fang, F 2020, 'One Anastomosis Gastric Bypass Versus Roux-en-Y Gastric Bypass for Obesity: a Systematic Review and Meta-Analysis of Randomized Clinical Trials', *Obesity Surgery*, vol. 30, no. 4, Apr, pp. 1211-1218.

Jonasson, C, Wernersson, B, Hoff, DA & Hatlebakk, JG 2013, 'Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease', *Alimentary Pharmacology and Therapeutics*, vol. 37, no. 5, Mar, pp. 564-572.

Jones, R, Junghard, O, Dent, J, Vakil, N, Halling, K, Wernersson, B & Lind, T 2009, 'Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care', *Alimentary Pharmacology and Therapeutics*, vol. 30, no. 10, Nov 15, pp. 1030-1038.

Keleidari, B, Dehkordi, MM, Shahraki, MS, Ahmadi, ZS, Heidari, M, Hajian, A & Nasaj, HT 2021, 'Bile reflux after one anastomosis gastric bypass surgery: A review study', *Ann Med Surg (Lond)*, vol. 64, Apr, p. 102248.

Keleidari, B, Mahmoudieh, M, Davarpanah Jazi, AH, Melali, H, Nasr Esfahani, F, Minakari, M & Mokhtari, M 2019, 'Comparison of the Bile Reflux Frequency in One Anastomosis Gastric Bypass and Roux-en-Y Gastric Bypass: a Cohort Study', *Obesity Surgery*, vol. 29, no. 6, Jun, pp. 1721-1725.

Koek, GH, Vos, R, Sifrim, D, Cuomo, R, Janssens, J & Tack, J 2005, 'Mechanisms underlying duodeno-gastric reflux in man', *Neurogastroenterology and Motility*, vol. 17, no. 2, Apr, pp. 191-199.

Krishnamurthy, GT & Brown, PH 2002, 'Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction', *Journal of Nuclear Medicine*, vol. 43, no. 12, Dec, pp. 1603-1610.

Lagergren, J, Lindam, A & Mason, RM 2012, 'Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study', *International Journal of Cancer*, vol. 131, no. 6, Sep 15, pp. E1048-1052.

Lasheen, M, Mahfouz, M, Salama, TMS & Salem, HE-DM 2019, 'Biliary reflux gastritis after Mini Gastric Bypass: The effect of Bilirubin level', *Archives of Surgery and Clinical Research*, vol. 3, pp. 027-031.

M'Harzi, L, Chevallier, JM, Certain, A, Autret, G, Levenson, G, Louis, D, Poghosyan, T, Berger, A, Rahmi, G, Broudin, C, Clément, O, Douard, R, Tavitian, B & Bruzzi, M 2020, 'Long-Term Evaluation of Biliary Reflux on Esogastric Mucosae after One-Anastomosis Gastric Bypass and Esojejunostomy in Rats', *Obesity Surgery*, vol. 30, no. 7, Jul, pp. 2598-2605.

McQuaid, KR, Laine, L, Fennerty, MB, Souza, R & Spechler, SJ 2011, 'Systematic review: the role of bile acids in the pathogenesis of gastro-oesophageal reflux disease and related neoplasia', *Alimentary Pharmacology and Therapeutics*, vol. 34, no. 2, Jul, pp. 146-165.

Musella, M, Vitiello, A, Berardi, G, Velotti, N, Pesce, M & Sarnelli, G 2021, 'Evaluation of reflux following sleeve gastrectomy and one anastomosis gastric bypass: 1-year results from a randomized open-label controlled trial', *Surgical Endoscopy*, vol. 35, no. 12, Dec, pp. 6777-6785.

Parviainen, MT 1997, 'A modification of the acid diazo coupling method (Malloy-Evelyn) for the determination of serum total bilirubin', *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 57, no. 3, May, pp. 275-279.

Runkel, M & Runkel, N 2019, 'Esophago-Gastric Cancer after One Anastomosis Gastric Bypass (OAGB)', *Chirurgia*, vol. 114, no. 6, Nov-Dec, pp. 686-692.

Saarinen, T, Pietiläinen, KH, Loimaala, A, Ihalainen, T, Sammalkorpi, H, Penttilä, A & Juuti, A 2020, 'Bile Reflux is a Common Finding in the Gastric Pouch After One Anastomosis Gastric Bypass', *Obesity Surgery*, vol. 30, no. 3, Mar, pp. 875-881.

Saarinen, T, Rasanen, J, Salo, J, Loimaala, A, Pitkonen, M, Leivonen, M & Juuti, A 2017, 'Bile Reflux Scintigraphy After Mini-Gastric Bypass', *Obesity Surgery*, vol. 27, no. 8, Aug, pp. 2083-2089.

Shenouda, MM, Harb, SE, Mikhail, SAA, Mokhtar, SM, Osman, AMA, Wassef, ATS, Rizkallah, NNH, Milad, NM, Anis, SE, Nabil, TM, Zaki, NS & Halepian, A 2018, 'Bile Gastritis Following Laparoscopic Single Anastomosis Gastric Bypass: Pilot Study to Assess Significance of Bilirubin Level in Gastric Aspirate', *Obesity Surgery*, vol. 28, no. 2, Feb, pp. 389-395.

Stolte, M & Meining, A 2001, 'The updated Sydney system: classification and grading of gastritis as the basis of diagnosis and treatment', *Canadian Journal of Gastroenterology*, vol. 15, no. 9, Sep, pp. 591-598.

Suter, M 2020, 'Gastroesophageal Reflux Disease, Obesity, and Roux-en-Y Gastric Bypass: Complex Relationship-a Narrative Review', *Obesity Surgery*, vol. 30, no. 8, Aug, pp. 3178-3187.

Wang, FG, Yu, ZP, Yan, WM, Yan, M & Song, MM 2017, 'Comparison of safety and effectiveness between laparoscopic mini-gastric bypass and laparoscopic sleeve gastrectomy: A meta-analysis and systematic review', *Medicine (Baltimore)*, vol. 96, no. 50, Dec, p. e8924.

Yeung, KTD, Penney, N, Ashrafian, L, Darzi, A & Ashrafian, H 2020, 'Does Sleeve Gastrectomy Expose the Distal Esophagus to Severe Reflux?: A Systematic Review and Meta-analysis', *Annals of Surgery*, vol. 271, no. 2, Feb, pp. 257-265.

Additional supporting information for the article

Supplement 5A – Results from Investigation Tolerability Questionnaire

Table 5A-1: Number of participants who completed the investigation tolerability questionnaire

	ENDOSCOPY	SCINTIGRAPHY
OAGB	19	17
SG	11	11
RYGB	22	18
TOTAL	**52**	**46**

Figure 5A-1: Results from all participants for Question 1 (top) - Q4 (bottom); blue box denotes median value with lateral arms representing interquartile range.

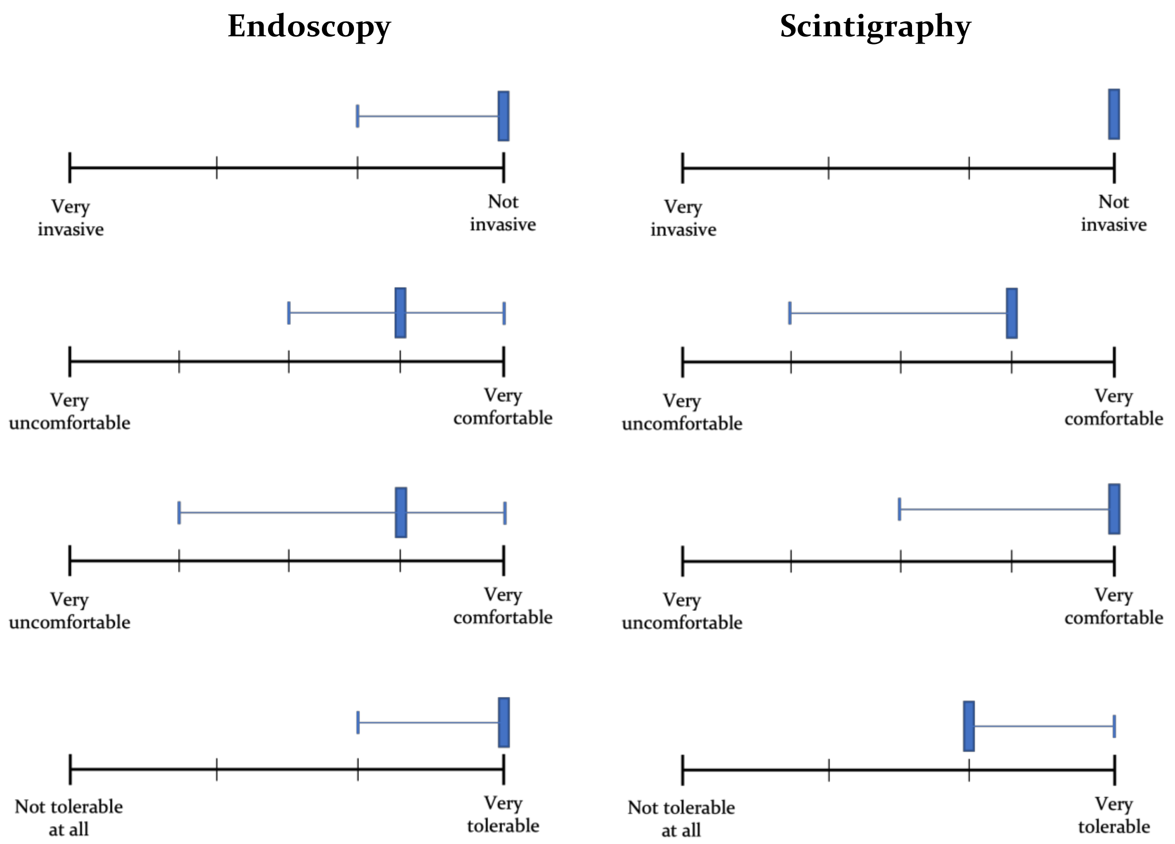
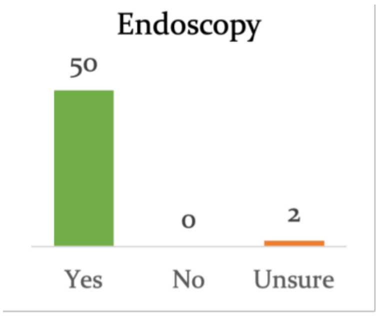
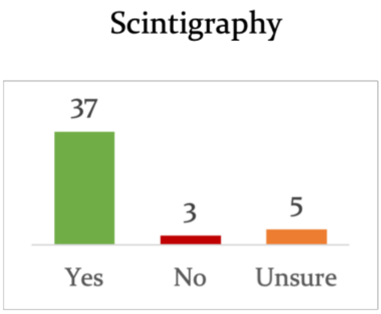


Table 5A-2: Results from Question 5; open text responses of worst aspect of investigation

COMMENT	N=
ENDOSCOPY	
No comment	23
Fasting	7
Waiting for procedure	4
Taking time off work/life	2
Sore throat afterwards	2
Nasal oxygen prongs causing irritation	2
Intravenous cannulation	2
Anxiety about procedure	1
Use of topical anaesthesia rather than sedation (patient preference after discussion with anaesthetist)	1
Low blood pressure	1
Type of food offered after procedure	1
Throat spray (topical anaesthesia)	1
Wearing gown in waiting room	1
Chest pain after procedure	1
Distance to travel for procedure	1
Protective 'Bite block' uncomfortable	1
Generally uncomfortable	1
SCINTIGRAPHY	
No comment	13
Lying still on back for 2 hours during procedure	14
Consuming 'fatty meal'	6
Having to place arms above head	5
Taking time off work/life	2
Migraine	1
Sore tailbone	1
Fasting	1
Waiting around for procedure	1
Needing to go to the toilet	1
Back pain (inability to take usual opiate medication)	1

Figure 5A-2: Results from question 6 – 'Would you undergo this procedure again?'





Appendix 5A – Discussion of results from Supplement 5A

Participants were invited to complete a questionnaire (see Appendix B) at the conclusion of their follow-up investigations, comprising six questions evaluating perception of the level of invasiveness, comfort/discomfort, and degree of willingness to undergo endoscopy or biliary scintigraphy again. Ninety-three percent (52/56) and 87% (46/53) of participants who underwent endoscopy and biliary scintigraphy, respectively, completed the questionnaire.

As summarised in Figure 5A-1, respondents determined that UGIE was from their perspective non-invasive (question 1; median 4, IQR 3-4), very tolerable (question 4; median 4, IQR 3-4) and that they were comfortable during (question 2; median 4, IQR 3-5) and after the procedure (question 3; median 4, IQR 2-5). Modified biliary scintigraphy was found to be slightly less tolerable (question 4; median 3, IQR 3-4), but patients felt more comfortable after the investigation (question 3; median 5, IQR 3-5).

The most frequently reported worst aspects of endoscopy were unrelated to the procedure itself (Table 5A-2): having to fast (n=7), and time spent waiting for procedure (n=4). Frequent responses regarding biliary scintigraphy surrounded consumption of the fatty meal (n=6) and physical positioning; difficulty lying supine and still for the duration of investigation (N=14), and holding arms extended above head during scanning (N=5). Table 5a-2 contains the full list of comments. Interestingly, one patient reported acute abdominal pain 5 h after the scan, which was self-limiting. Given no temporal association with IV tracer administration or fatty meal consumption, it is unlikely that the abdominal pain was related to the scan. There are no reports in the existing literature with similar occurrences.

Anxiety surrounding medical scans is common, with a systematic scoping review on the topic demonstrating an incidence of up to 83% in patients undergoing a scan for cancer-related illnesses (mammography, positron-emission tomography, or CT) (Bui *et al.* 2021). The authors acknowledge that anxiety is often related to fear of cancer diagnosis or recurrence, but also noted that 'scanxiety' is related to unpleasant, dehumanising, and often claustrophobic experiences, unrelated to diagnosis. Overall, in the presented study, most participants stated they would undergo both procedures again: with 50/52 patients willing to undergo endoscopy while two patients were unsure; and 37/46 patients willing to undergo biliary scintigraphy, with three patients unwilling, and five patients were unsure (Figure 5A-2). Majority of the reported 'worse aspects' of the investigations related to physical discomfort and making time for the scan; likely reflecting the voluntary and exploratory nature of this study, rather than relating to an individual patient diagnosis. Regardless, the proposed tailored investigations are well-tolerated by participants, with areas for improvement surrounding patient comfort.

CHAPTER 6:

Conclusions and Future Directions

6.1 Conclusions

Aim 1

- **To determine the most effective technique for diagnosis of bile reflux.**

The lack of a gold-standard diagnostic investigation for bile reflux presented a significant knowledge gap in the development of our study protocol. The results from Study 1 (Chapter 3) determined that no single investigation is sufficient for comprehensive evaluation of bile reflux into gastric remnant or oesophagus. Rather, the studies presented show: the information being sought guides the optimal investigation to use; obtaining a diagnosis of bile reflux differs from characterising a 24-hour reflux profile, which further differs from evaluation of the potential mucosal injury incurred by any reflux present. The body of work in this thesis focused on diagnosis and sequelae of bile reflux and identified the optimal combination of investigations to achieve this outcome.

The ideal tool for diagnosis of bile reflux is one that has longitudinal monitoring (rather than single timepoint), specifically detects bile rather than a surrogate marker such as pH and is minimally invasive. The research presented in Chapter 3, reveals biliary scintigraphy as the most suitable option based on these criteria: it is non-invasive and bile is specifically detected, however, the period of assessment is short, lasting approximately 60 minutes. In comparison to endoscopy and gastric fluid analysis, scintigraphy is more sensitive for diagnosis of bile reflux. Chen *et al.* compared the two techniques in 70 controls and 99 patients with suspected bile reflux diagnosed based on: reflux-type symptoms refractory to PPI therapy; macro- or microscopic gastritis on upper GI endoscopy; visible bile in the stomach at > 1 endoscopic examination, or elevated absorbance for bilirubin readings in gastric luminal fluid using the Bilitec probe. In the Chen study, all subjects underwent endoscopy with acquisition of gastric mucosal biopsies and aspiration of gastric fluid for analysis, while 47 participants (including 19 controls) underwent biliary scintigraphy. Twenty-eight patients (59.6%) were deemed to have bile reflux on endoscopy & gastric fluid analysis; defined as superficial mucosal inflammation with elevated concentration of total bile acids in gastric fluid. Whereas, 37 (78.7%) patients were diagnosed using biliary scintigraphy, evidenced by increased local radioactivity in the stomach. Further, reproducibility of scintigraphy findings was demonstrated in a group of eleven patients who underwent repeat scintigraphy within 2 weeks, with eight (72.7%) showing identical findings; similar results to a previous study reporting reproducible scintigraphic findings of bile reflux in 15/20 (75%) of patients (Sorgi *et al.* 1984). The discrepant results likely representing the intermittent nature of bile reflux.

Since publication of Study 1, additional published studies with prospective evaluation of duodenogastric reflux are scant. Other than the studies discussed under *Aim 4* (below), just one prospective study reports evaluating PPI-refractory GORD symptoms with HRM, MII-pH and Bilitec monitoring. In this study, MII-pH and Bilitec were conducted concurrently following HRM, to obtain a complete 24-hour reflux profile. Notably, 16% of patients opted to only undertake one trans-nasal catheter investigation, and 7% did not complete the full period of monitoring (<20 hours). Participant reasons for not completing all investigations were not included; however, intolerance of an invasive procedure is likely a contributing factor.

In contrast, the findings from Study 1 and Study 3 illustrate that biliary scintigraphy is an accurate, reproducible, and non-invasive investigation, and is the best technique currently available for diagnosis of bile reflux in this patient cohort, post bariatric surgery. In combination with upper GI endoscopy for macro- and microscopic assessment of tissue damage resulting from any present reflux, this diagnostic approach provides full assessment of the extent and sequelae of bile reflux and both procedures were well tolerated (see later).

Aim 2

- **To devise a tailored approach for bile reflux diagnosis in a post-metabolic and obesity surgery cohort, and to determine patient tolerability of the proposed protocol.**

Study 2 identified three key modifications to our biliary scintigraphy protocol to improve diagnostic yield: addition of SPECT-CT imaging; administration of a 'fatty meal'; and prolonged scanning duration.

Quantitation of bile reflux using scintigraphy requires calculation of radioactivity counts of radiolabelled bile within a 'region of interest', denominated by the total counts; localisation can be challenging on 2-dimensional planar images, however, due to altered GIT configuration post-operatively. Published research indicates the addition of SPECT-CT to scintigraphic imaging significantly improves anatomical localisation, fusing anatomical and functional information to improve diagnostic certainty. When compared to standard SPECT images alone, addition of fused CT images improved localisation of both abnormal and physiologic findings in 87% (68/78) cases and diagnostic certainty in 24% (34/144) cases for experienced nuclear medicine physicians (Jacene *et al.* 2008). SPECT combined with magnetic resonance imaging (MRI) as a multimodal imaging system (Bouziotis & Fiorini 2014) provides additional benefits including: significantly reduced radiation exposure and improved soft tissue contrast when compared with CT. Few SPECT/MRI systems exist, with this emerging technology limited to the pre-clinical, research-based setting, with no commercially available system largely due to challenges in developing MRI-compatible components (Hutton *et al.* 2018). Clinical application of SPECT/MRI is largely focused on neuro-oncology, where soft tissue differentiation is paramount, with limited utility for gastrointestinal imaging. As such, in the context of bile reflux, SPECT-CT provides the best utility of current technology.

Gallbladder emptying is impaired after gastric bypass (Bastouly *et al.* 2009). In Study 2 (Chapter 4) delayed gallbladder emptying was noted during post-operative scintigraphy for the second gastric bypass (OAGB) patient undergoing follow-up. Ad-hoc administration of a triglyceride fat emulsion (60mL Calogen®; Nutricia, a Danone Company, Paris, France) as a 'fatty meal' improved gallbladder emptying in the study presented, enabling optimised assessment of any present duodenogastric or duodenogastro-oesophageal reflux. Fatty meals are known to be effective for gallbladder provocation in biliary scintigraphy as an alternative to intravenous CCK-analogues, which are no longer available for clinical use (Krishnamurthy & Brown 2002). The intended physiological mechanism of the fatty meal in post-gastric bypass patients is stimulation of (potentially upregulated) CCK-secreting cells in the jejunal common channel. No further instances of impaired gallbladder emptying were encountered upon incorporation of a routine fatty meal into the study protocol for all patients.

Intravenously administered radio-labelled tracer (technetium 99mTc di-isopropyl iminodiacetic acid used in the current study) must be metabolised by the liver prior to excretion in bile, with peak liver uptake known to occur by 10 minutes post administration. Sufficient gallbladder filling time with radiolabelled bile is also needed prior to fatty meal provocation, with peak gallbladder accumulation by 30-40 minutes post administration. Further, small intestinal motility can be altered by MOS, whereby faster small bowel transit is observed post-SG compared with the same patient's pre-operative findings, and slower small bowel transit demonstrated after RYGB compared with a non-operated control group (Dirksen *et al.* 2013; Melissas *et al.* 2013; Shah *et al.* 2010). The studies evaluating motility post-SG included gastric emptying along with their evaluation of small bowel transit time. This approach confounds their conclusion regarding post-operative small bowel hypermotility, as gastric emptying is shown to be more rapid post-operatively for both liquid and semi-solid meals (Johari *et al.* 2021b). With the potential for post-operative small intestinal hypomotility, a longer scanning duration was adopted in Studies 2 & 3 to optimise detection of any bile reflux; the intermittent nature of bile reflux also favouring prolonged scanning duration. Enhanced diagnostic information from prolonging scan duration must be balanced with patient comfort, with 20/46 (43%) of participants noting physical discomfort during the scan.

Tolerability of clinical investigations is paramount for uptake and routine use in clinical practice. The proposed diagnostic protocol outlined in Study 1 and the modifications determined in Study 2 were well received by participants, who deemed endoscopy and scintigraphy to be non-invasive, tolerable, and comfortable (Supplement 5A & Appendix 5A).

The reported worst aspects of endoscopy (fasting and time spent waiting) are inherent to the procedure with improvements not easily incorporated. Poorly received aspects of the modified biliary scintigraphy related to consumption of the fatty meal and physical positioning, which are more amenable to improvements. The fatty meal utilised in my study is an unflavoured triglyceride emulsion containing predominantly vegetable oil, sold as a ready-to-use nutritional supplement (Calogen®; Nutricia, a Danone Company, Paris, France). Other studies have used milk-based products, either bought or made in-house (Kakhki, Zakavi & Davoudi 2007; Krishnamurthy & Brown 2002). Use of milk-based products alone is a limitation, due to dietary intolerances (i.e. lactose), and dietary choices (i.e. vegan). No published studies to date compare tolerability or efficacy of different preparations of a 'fatty meal'. Having a milk-based option available alongside a supplement such as Calogen, may improve patient-choice and acceptance, however comparative studies of physiological stimulus and resultant measurements are necessary. Patient positioning for the HIDA scan is important for optimal image acquisition, with a balance between patient comfort and necessary positioning warranted. Padded boards and cushions are commonplace and were used in the presented study, albeit limited by the physical contraints of the scanner.

Since publication of Study 2, further studies investigating bile reflux using scintigraphy in non-operative or post-operative cohorts are yet to emerge in the literature. A very recent meta-analysis of studies evaluating bile reflux after single anastomosis duodenal-ileal bypass with sleeve (an emerging but infrequently performed MOS procedure) identified no studies utilising scintigraphy for diagnosis (Portela *et al.* 2022). However, the time lapse from study protocol development to publication provides optimism that future published studies will incorporate this optimised methodology. Despite the identified issues with the modified diagnostic protocol, an overwhelming majority of participants would undergo both endoscopy and scintigraphy again, demonstrating excellent participant acceptability.

Aim 3

- **To evaluate the post-operative incidence and severity of bile reflux after laparoscopic one-anastomosis gastric bypass, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy operations.**

Study 3 (Chapter 5) demonstrated that low volume bile reflux into the stomach occurs frequently after OAGB (70%; n= 14/20) and SG (31%; n=4/13), compared with RYGB (5%; n=1/20). Reflux of bile into the oesophagus occurs infrequently, with only one patient demonstrating oesophageal bile reflux, post-OAGB, in our study.

Previously reports of bile reflux incidence post-OAGB range from 8-55%, however the diagnostic protocols used in these studies were variable (Keleidari *et al.* 2019; Lasheen *et al.* 2019; Saarinen *et al.* 2020; Saarinen *et al.* 2017; Shenouda *et al.* 2018). The most comprehensive protocol thus far by Saarinen *et al. (*published after our study commencement), utilised both biliary scintigraphy and upper GI endoscopy to demonstrate a bile reflux incidence of 31.6% and 55.5% in their two published studies of 2017 and 2020.

Study 3 (Chapter 5) and Saarinen's 2020 paper are both prospective studies with objective follow-up at 6-months post-surgery, however Saarinen's study presents data from one aspect of a larger randomised clinical trial comparing OAGB and RYGB. The larger study protocol does not report a power calculation for this aspect of the trial, suggesting a pre-hoc determination of 40 consecutive patients, all post-OAGB, compared with our statistically determined sample size of 24 participants per study arm. As such, it is unclear if the study was appropriately powered based on the reported findings.

Our diagnostic protocol differs from Saarinen, utilising a fatty meal during biliary scintigraphy to stimulate gallbladder emptying; more closely emulating normal physiological conditions of intestinal passage of bile compared with a fasted patient, thereby increasing test sensitivity (Krishnamurthy & Brown 2002). This likely accounts for the higher incidence of detected duodenogastric reflux reported in our study. Quantitation of bile reflux in patients with positive scintigraphy demonstrated low mean total volume of reflux (2.9%; SD 1.5), comparable with findings from Saarinen *et al.* (mean 5.2%). Similar methods of quantitation were employed; both using computed calculation of mean radiation counts within a region of interest compared with total extrahepatic radiation counts.

Bile reflux after sleeve gastrectomy was prospectively investigated in one other study. Braghetto *et al.* demonstrated bile reflux on scintigraphy in 31.8% (n=7/22) of participants post-SG, consistent with our findings (Braghetto *et al.* 2019). Diagnostic protocols were comparable, with both studies incorporating symptom questionnaires, upper GI endoscopy, and biliary scintigraphy, however Braghetto did not take mucosal biopsies, or incorporate use of a SPECT-CT scan as part of the scintigraphy protocol. The gastrointestinal anatomical alterations post-SG do not significantly obscure delineation of organs on scintigraphy compared with gastric bypass procedures. Further, Braghetto's study did not perform quantitation of reflux volume, which is significantly enhanced by use of SPECT-CT. While their decision to not incorporate this into their protocol is understandable, as it extends study length and increases radiation exposure, lack of SPECT-CT decreases sensitivity for identification of duodenogastric reflux. Volume of bile reflux post-SG in our study was low, with mean total volume of 4.1% (SD 1.3).

Roux-en-Y gastric bypass is widely considered to be the MOS procedure of choice for patients with co-existing GORD as an anti-reflux procedure (Suter 2020). Similarly, bile reflux into the gastric pouch post-RYGB is uncommon due to the length of the alimentary limb. Study 3 (Chapter 5) supports these assertions with only 1-in-20 patients (5%) demonstrating low volume bile reflux into the gastric pouch. In current literature, no study has investigated the relationship of varying alimentary limb lengths with the incidence of bile reflux. Perhaps of greater concern post-RYGB is duodenogastric reflux of bile into the gastric remnant, observed in 20% (n= 4/20) of patients in our study; results supported by an earlier scintigraphic study by Sundbom *et al.* reporting an incidence of 36% patients (n=8/22) with bile reflux post-RYGB (Sundbom, Hedenstrom & Gustavsson 2002). Of note, nine patients in the 2002 report had undergone cholecystectomy prior to the study, which may be a factor contributing to increased duodenogastric bile reflux (Atak *et al.* 2012; Kunsch *et al.* 2009; Lake *et al.* 2021; Manifold, Anggiansah & Owen 2000). Gastric remnant disease - such as gastritis, ulceration, or malignancy

– is difficult to identify and treat due to a lack of direct endoscopic access, as well as non-specific symptoms, most commonly upper abdominal pain, and nausea (Tornese *et al.* 2019; Vella *et al.* 2017). Gastric remnant malignancy is rare, however, with only 17 reported cases to date (Tornese *et al.* 2019). These findings suggest that bile reflux into the gastric remnant is of similar or greater clinical concern to gastric pouch reflux, warranting further investigation in symptomatic patients in which no aetiology can be identified. Given a significant area of concern for surgeons not performing OAGB is the development of bile-related gastric stump cancer (Mahawar *et al.* 2017), it is curious that such concern is not shared for RYGB and the remnant stomach, rendered inaccessible for future endoscopic assessment.

Aim 4

- **To examine the relationship between post-operative objective bile reflux, reflux-type symptoms, and objective findings of gastric and oesophageal tissue damage.**

The presence of bile reflux is moot if patients remain asymptomatic and no tissue damage is incurred. In Study 3 (Chapter 5), positive bile reflux on scintigraphy was not associated with either worsened post-operative reflux symptoms or development of *de novo* post-operative gastro-oesophagitis.

Participants in the OAGB arm, with the highest incidence of scintigraphic bile reflux, were the only operative arm showing a statistically significant improvement of mean reflux symptom score (GerdQ) post-operatively. These findings contrast with Saarinen's study, reporting a significant association between *de novo* post-operative symptoms and positive duodenogastric reflux on scintigraphy. Saarinen did not utilise a validated reflux symptom questionnaire, however, rather noting the presence of 'reflux symptoms' or eating difficulties. One patient with such symptoms had an anastomotic stricture, which cannot be attributed to duodenogastric reflux alone. Further, our tailored study protocol is likely more sensitive for bile reflux diagnosis, detecting more asymptomatic participants.

In our study, 58% (11/19) of participants post-OAGB demonstrated *de novo* gastro-oesophagitis, again showing no association with positive bile reflux. Of these, only four demonstrated macroscopic inflammation, limited to the stomach, with the remainder being histological diagnoses. Our findings are comparable with existing studies. Saarinen *et al.* reported *de novo* gastro-oesophagitis in 39.5% (15/38) of participants, with only six having macroscopic findings (Saarinen *et al.* 2020). Lasheen and Shenouda reported post-operative gastro-oesophagitis in 32.5% of patients at 9 months, and 55% at 6 months, respectively, however no comment was made about whether these findings were *de novo* post-operative findings or were present pre-operatively (Lasheen *et al.* 2019; Shenouda *et al.* 2018). Macroscopic oesophagitis is of greater concern, with potential for development of BO and/or neoplasia. In Study 3 (Chapter 5), all patients in the OAGB group with pre-operative macroscopic oesophagitis (LA grade A or B) showed resolution on post-operative UGIE with no *de novo* macroscopic oesophagitis observed in any other patients. This is consistent with a recent randomised controlled trial demonstrating complete endoscopic regression of pre-operative Los Angeles grade A or B oesophagitis in 90% of patients at 12-months post-OAGB (Eskandaros *et al.* 2021). The predominant finding of microscopic gastro-oesophagitis in the absence of macroscopic inflammation could represent the relatively short follow-up time frame of 6 months. A recently published study evaluating oesophageal pathology at endoscopy, 2-years post-OAGB, identified 48% (24/50) of participants with LA grade A (n=20) or grade B (n=4) oesophagitis (Szymański *et al.* 2021). The authors also note, however, that oesophagitis (macroscopic or microscopic – no distinction was made) was *de novo* in only 36% (18/50) participants, and do not comment on pre-operative findings, making interpretation of their reported numbers challenging.

Sleeve gastrectomy is widely reported to be refluxogenic (Assalia *et al.* 2020). Our findings in Study 3 support this assertion; the SG cohort had the greatest number of patients with worsened reflux symptom scores post-operatively. Longer term studies reinforce these findings, with patients reporting more frequent reflux symptoms and acid-suppression medication usage compared with patients post-RYGB, up to 4 years post-operatively (Thorsen *et al.* 2021). Further, gastro-oesophageal reflux is the most common cause for revision surgery post-SG (Wölnerhanssen *et al.* 2021). Lower incidence of bile reflux post-SG compared with OAGB is expected, with retention of the pyloric sphincter acting as a biliary anti-reflux mechanism. Despite the incidence of bile reflux after SG being half that of OAGB, Study 3 demonstrated comparable incidence of *de novo* gastro-oesophagitis; 58% for OAGB compared with 57% for SG. These findings confound the role bile acids have in *de novo* gastro-oesophagitis, however the frequent occurrence of bile reflux post-SG is cause for concern, given the known synergistic inflammatory potential of bile acids and gastric acid (Chapter 1.4.3).

Development of BO and subsequent oesophageal malignancy are key concerns in interpreting the significance of post-operative reflux disease, with or without bile reflux. A comprehensive systematic review and subsequent position statement from IFSO determined that approximately 1.9% of patients will develop *de novo* BO post-MOS, regardless of the procedure undertaken (Fisher *et al.* 2021). They found the highest risk procedure to be sleeve gastrectomy, which portends overall cumulative incidence of *de novo* BO in 4.6% of patients within 5 years. In comparison, the overall cumulative incidence of BO in obese patients prior to MOS is 0.9-2.1% as reported in two systematic reviews (Fisher *et al.* 2021; Qumseya *et al.* 2020). Progression of non-dysplastic BO occurs in 13% of patients, demonstrated in a large longitudinal population study of >12,000 patients with BO diagnosis (Peters *et al.* 2019). The annual risk of malignant progression decreases further with each consecutive endoscopy showing absence of dysplasia; from 0.32% after one endoscopy to 0.11% after five negative endoscopies performed at least 1 year apart. Fortunately, development of gastro-oesophageal malignancy is rare after MOS. A comprehensive retrospective observational study of patients with gastro-oesophageal cancer after MOS from 75 centres in 25 countries identified 64 cases post-RYGB, 43 cases post-SG, and 2 cases post-OAGB (Parmar *et al.* 2021). The study relied on individual data entry by collaborators via an opt-in process after invitation through personal networks or email distribution lists through IFSO, the British Obesity and Metabolic Surgery Society, and the Association of Upper Gastrointestinal Surgery (UK). This approach minimises publication bias but has inherent recall bias in the retrospective nature of the study. Regardless, this study is the most comprehensive to date in determining the true rate of malignancy post-MOS. A denominator of total procedures performed is not provided, denying incidence calculation and comparison with the incidence of gastric and oesophageal cancer in the general population (17.4 per 100,000 globally) (Rawla & Barsouk 2019). The mean lag time from surgery to diagnosis of malignancy was 9.4 ± 7.1 years for RYGB, 5.9 ± 4.1 years for SG, and 2.0 ± 1.4 years after OAGB. As outlined in the discussion section of Study 3 (Chapter 5), the two malignancies diagnosed post-OAGB do not represent causation. Pre-operative malignant status in these patients was unknown: one patient had LA grade C oesophagitis and no biopsies obtained, and the other did not undergo pre-operative endoscopy (Aggarwal *et al.* 2019; Runkel & Runkel 2019). The short time frame for neoplasia development post-SG supports the IFSO recommendation of surveillance post- operative endoscopy at 1 year, followed by repeat endoscopy every 2-3 years thereafter (Brown *et al.* 2020). At present the same timeframes are recommended by IFSO for patients post-OAGB, with no routine post-operative endoscopy deemed necessary for RYGB. The data presented in this thesis in Study 3 supports this recommendation.

6.2 Future directions

Mechanics of altered motility post-OAGB

The mechanics of gastric and oesophageal function after RYGB and SG have been thoroughly investigated (Cassao *et al.* 2013; Dirksen *et al.* 2013; Fiorillo *et al.* 2020; Johari *et al.* 2020; Johari *et al.* 2021a; Johari *et al.* 2021b; Naik, Choksi & Vaezi 2016; Quero *et al.* 2020; Valezi *et al.* 2012), however OAGB hasn't been subjected to such rigour. Only one group, Tolone *et al*., has evaluated gastro-oesophageal motility using HRIM post-OAGB (Tolone *et al.* 2016; Tolone *et al.* 2019). Both studies report oesophageal motility and LOS function were unchanged post-operatively but noted decreased intragastric pressure and gastro-oesophageal pressure gradient, when compared with pre-operative values. Musella *et al.* also performed HRIM in patients post-OAGB, but only commented on LOS pressures, also reporting no change in LOS tone at 12-months post-operatively (Musella *et al.* 2021). There are no formal studies on gastric emptying post-OAGB reported in the literature. HRIM is considered the gold standard for assessment of gastro-oesophageal motor function but doesn't provide information about gastric emptying. Recently reported studies utilise magnetic resonance imaging and scintigraphy for dynamic gastric volumetric analysis post-sleeve gastrectomy to further understand the mechanics and expected rates of gastric emptying post-operatively (Fiorillo *et al.* 2020; Johari *et al.* 2021a; Johari *et al.* 2021b; Quero *et al.* 2020). Applying such techniques to evaluate OAGB post-meal emptying rates, in conjunction with luminal pressure and flow using HRIM, will provide further knowledge on the impact of surgery on gastro-oesophageal function, particularly in relation to oesophageal bile reflux potential.

Duodenogastric reflux after cholecystectomy

After cholecystectomy, the bile reservoir function is lost, altering delivery of bile into the duodenum, and potentially increasing the risk of duodenogastric bile reflux. Two prospective cohort studies utilising UGIE, 24-hour pH manometry and Bilitec 2000 monitoring, report increased occurrence of duodenogastric reflux post-cholecystectomy (Atak *et al.* 2012; Kunsch *et al.* 2009). These findings are supported by a recent retrospective analysis of over 250 patients investigated for functional dyspepsia, showing patients post-cholecystectomy had significantly more severe abdominal pain ($P < 0.05$), gastric erythema ($P < 0.03$), and gastritis ($P < 0.05$), than patients without cholecystectomy (Lake *et al.* 2021). The Swedish Obese Subjects study found that cholecystectomy is approximately 4-times more common in patients with obesity, prior to MOS, compared with a reference control group (Torgerson *et al.* 2003). Further, they demonstrated post-MOS, cholecystectomy is 4-times more common within 2 years of surgery, compared with the control group. In Study 3 of this thesis, patients with previous cholecystectomy were excluded to facilitate appropriate acquisition and interpretation of biliary scintigraphy images. Further study regarding the incidence and severity of oesophageal bile reflux in patients post-MOS with prior cholecystectomy is warranted, as this may further influence surgical decision making and individualise procedure selection. Such a study is likely to also require further modification of scintigraphy protocols to enable reliable objective assessment of bile reflux.

6.3 Concluding remarks

The overarching aim of this thesis is to accurately determine the incidence and severity of duodenogastric reflux and duodenogastro-oesophageal reflux after the three most-commonly performed MOS procedures, namely SG, RYGB and OAGB. The underlying motivation is to further understand the safety and efficacy of these procedures, to enable surgeons to make evidence-based informed decision making for optimal individualised surgical care of their patients.

The body of research presented demonstrates the following findings:

1. Frequent duodenogastric reflux through a freely patent gastrojejunostomy post-OAGB; less frequent duodenogastric reflux post-SG due the pyloric anti-reflux mechanism, and even less post-RYGB due to the long alimentary limb distancing biliary secretions from the stomach.
2. Duodenogastric reflux (gastric bile reflux) is of minimal clinical consequence and occurs physiologically in small volumes.
3. Duodenogastro-oesophageal reflux (oesophageal bile reflux) is of much greater concern, due to the known role of bile acids in contributing to the development of oesophagitis, BO, and carcinogenesis.
4. The most noteworthy finding in this research is a high incidence of duodenogastric reflux post-OAGB, with rare occurrence of duodenogastro-oesophageal reflux, suggesting effective gastric clearance of expected duodenogastric refluxate. This is supported by resolution of pre-operative macroscopic oesophagitis in 100% of patients post-OAGB with no *de novo* development of macroscopic findings.

Overall, the conclusion drawn from the research presented is that OAGB is a safe procedure with regards to risk for duodenogastro-oesophageal reflux, dispelling a major concern and criticism of the procedure. Ongoing concern remains however regarding the risk of post-operative gastro-oesophageal reflux and development of oesophageal mucosal injury post-SG. Finally, my research findings support the consensus of RYGB as a safe procedure with regards to low risk for reflux disease, for both duodenogastro-oesophageal and gastro-oesophageal tissue injury. With emerging studies demonstrating likely superiority of OAGB over SG and RYGB with regards to metabolic improvements and adverse outcomes, increased utilisation of OAGB is likely to be observed going forward, translating to improved patient outcomes.

~ o O o ~

APPENDICES

Government of South Australia
SA Health

Appendix A

Ethics of Human Research Committee Radiation Dose and Risk Assessment

Study Title: Bile Reflux Post-Bariatric Surgery: A Cohort Study

Principal Investigators: Dr Thomas Eldredge, Dr Jennifer Myers, A/Prof. George Kiroff, Dr Jon Shenfine, A/Prof Dylan Bartholomeusz, Ms Madison Bills

Study Details

As part of this research study, each participant will undergo a hepatobiliary SPECT-CT scan for research purposes. aged 18-60. Volunteers who are pregnant or breast feeding will be excluded from the study. The procedures will be performed at the Royal Adelaide Hospital on a GE Discovery 670 SPECT-CT system. SPECT-CT hepatobiliary imaging involves exposure to radiation from two separate sources: gamma rays from the radiopharmaceutical and X-rays generated by the CT apparatus.

Radiation dose from the radiopharmaceutical.

The radiopharmaceutical used will be Tc-99m labelled disofenin (Hepatolite).

The administered activity is 180 MBq. Using data from [1] based on biokinetic modelling, the estimated radiation doses from the radiopharmaceutical are as follows:

- The effective dose from the radiopharmaceutical is 2.9 mSv.
- The maximum absorbed dose from the radiopharmaceutical is 20 mSv to the Gall Bladder wall.
- The absorbed dose to the uterus is 2 mSv.

Radiation dose from the CT

The CT parameters used for a typical patient undergoing hepatobiliary SPECT-CT procedure at the RAH are listed in Table 1.

Table 1: CT protocol acquisition parameters

KVp	120
Scan length (mm)	400
Collimation (mm)	16 x 1.25
Number of CT acquisitions	1
mAs	96

Radiation doses from the CT were estimated using CT expo software [1]. Details of the calculation are provided in the appendix. The estimated effective dose from the CT is 6.3 mSv.
The Absorbed dose to the gall bladder from the CT is 8.9 mSv. The dose to the uterus is 1.4 mSv.

Dose Summary

The estimated effective dose from this research study is 9.2 mSv

The highest effective dose to an organ is 28.9 mSv to the Gall Bladder wall
The effective dose to the uterus is 3.4 mSv

The ARPANSA risk category is IIb

Risks and dose constraints

When assessing research proposals involving ionizing radiation, the Human Research Ethics Committee should consider the balance between the likely benefits and risks associated with any radiation exposure using criteria specified in the Code of Practice. The document also provides radiation dose constraints for research participants and categorises risk and the benefits required to justify the risks.

The South Australian Government Gazette of 6 October 2011 provides for an exemption to regulation 44 of the Radiation Protection and Control (Ionising Radiation) Regulations 2015 “any person who conducts in vivo research involving the use of ionising radiation on a human being, provided that it is conducted in accordance with the Code of Practice published by the Australian Radiation Protection and Nuclear Safety Agency entitled Exposure of humans to ionizing radiation for research purposes, published as Radiation Protection Series No. 8 on 27 May 2005 [2], and as subsequently amended from time to time, and the requirement set out in the Schedule is complied with."

The Code of Practice provides radiation dose constraints for research participants and categorises risk and the benefits required to justify the risks. Excerpts from the document that are relevant to this proposal are included below.

The exposure of 9.2 mSv proposed here exceeds the recommended effective dose constraint of 5 mSv. Independent verification of the dose estimate provided here by another physicist is required and will be arranged.

The ARPANSA Code of Practice characterises the associated risks as ‘low’ and states “The dose range of 2 to 20 mSv covers the annual doses received by most radiation workers in the course of their employment, and most diagnostic radiological procedures. To justify the risks a moderate benefit will be needed. The benefit will be more directly aimed at the diagnosis, cure or prevention of disease"

Patient Information Sheet

The Code of Practice states “The researcher must provide the research participant with sufficient written information about the purpose, methods, radiation dose, associated risks and any discomforts of the radiation exposure to enable the research participant to give informed consent." and recommends that the patient information sheet include a statement of the form:

This research study involves exposure to a significant amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 9 mSv. The benefits from the study should be weighed against the possible detrimental effects of radiation, including an increased risk of fatal cancer. In this particular study, the risk is moderate and the estimated risk of such harm is about 1 in 1000. For comparison, this risk is about 250 times lower than the cancer mortality rate in the general population of about one case in every four people.

Ben Crouch
Medical Physics Registrar
2 August 2017
Royal Adelaide Hospital
North Terrace, Adelaide, 5000
Phone: 08 8222 5478
Email: Benjamin.crouch@sa.gov.au

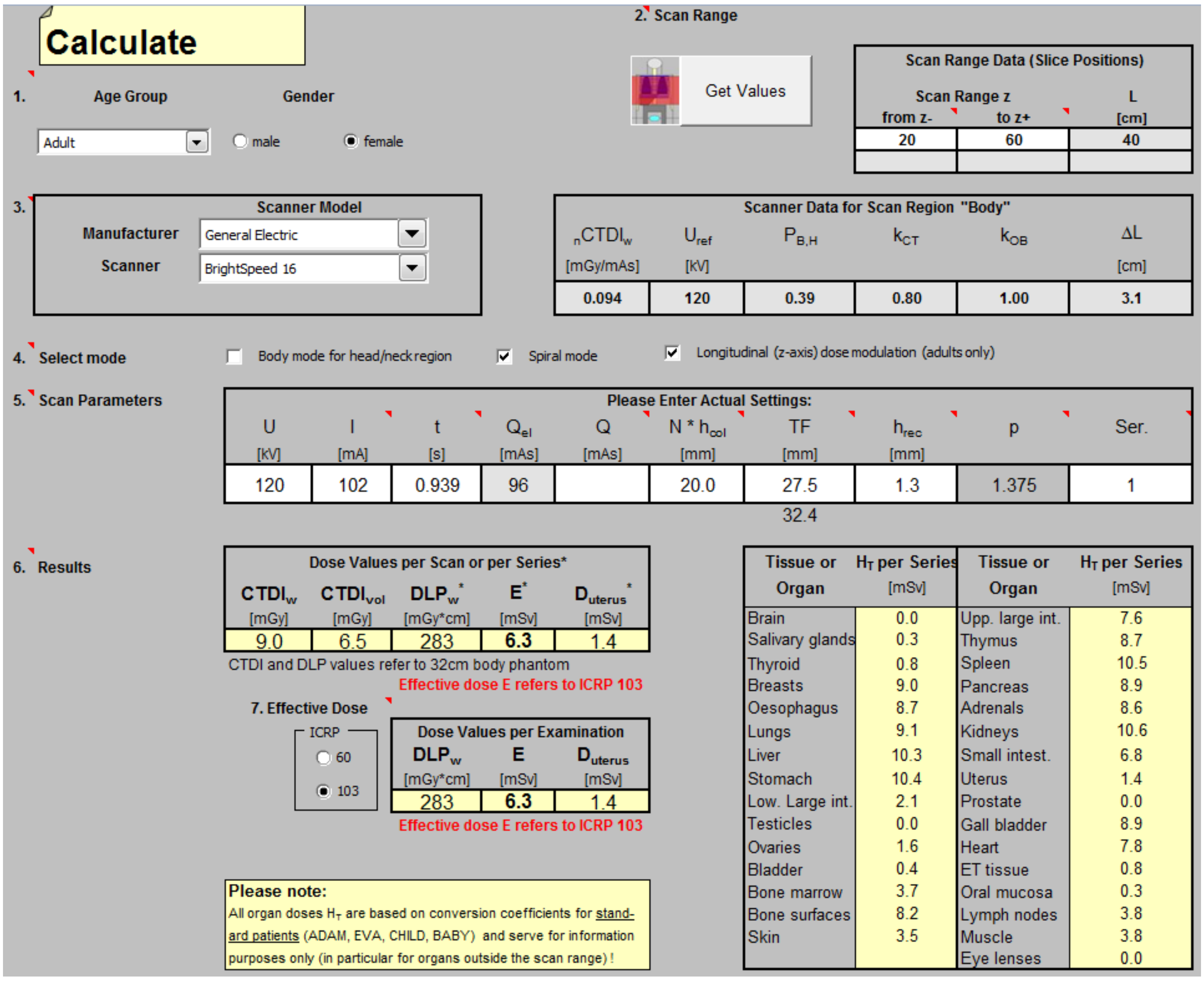
References

[1] Science and Technology for Radiology, *CT Expo Dosimetry Software,* Buchholz: SASCRAD, 2001.

[2] ARPANSA, "RPS Publication 8: Exposure of Humans to Ionizing Radiation for Research Purposes," ARPANSA, Barton, 2005.

Appendix

CT expo calculation. The Female dose was used here as this was the higher of the two genders.



Calculate

2. Scan Range

Get Values

Scan Range Data (Slice Positions)		
Scan Range z from z-	to z+	L [cm]
20	60	40

1. Age Group: Adult — Gender: ○ male ◉ female

3. Scanner Model

Manufacturer: General Electric

Scanner: BrightSpeed 16

Scanner Data for Scan Region "Body"					
$_nCTDI_w$ [mGy/mAs]	U_{ref} [kV]	$P_{B,H}$	k_{CT}	k_{OB}	ΔL [cm]
0.094	120	0.39	0.80	1.00	3.1

4. Select mode: ☐ Body mode for head/neck region ☑ Spiral mode ☑ Longitudinal (z-axis) dose modulation (adults only)

5. Scan Parameters — Please Enter Actual Settings:

U [kV]	I [mA]	t [s]	Q_{el} [mAs]	Q [mAs]	$N * h_{col}$ [mm]	TF [mm]	h_{rec} [mm]	p	Ser.
120	102	0.939	96		20.0	27.5	1.3	1.375	1
						32.4			

6. Results

Dose Values per Scan or per Series*				
$CTDI_w$ [mGy]	$CTDI_{vol}$ [mGy]	DLP_w* [mGy*cm]	E* [mSv]	D_{uterus}* [mSv]
9.0	6.5	283	6.3	1.4

CTDI and DLP values refer to 32cm body phantom

Effective dose E refers to ICRP 103

7. Effective Dose

ICRP: ○ 60 ◉ 103

Dose Values per Examination		
DLP_w [mGy*cm]	E [mSv]	D_{uterus} [mSv]
283	6.3	1.4

Effective dose E refers to ICRP 103

Please note:
All organ doses H_T are based on conversion coefficients for standard patients (ADAM, EVA, CHILD, BABY) and serve for information purposes only (in particular for organs outside the scan range)!

Tissue or Organ	H_T per Series [mSv]	Tissue or Organ	H_T per Series [mSv]
Brain	0.0	Upp. large int.	7.6
Salivary glands	0.3	Thymus	8.7
Thyroid	0.8	Spleen	10.5
Breasts	9.0	Pancreas	8.9
Oesophagus	8.7	Adrenals	8.6
Lungs	9.1	Kidneys	10.6
Liver	10.3	Small intest.	6.8
Stomach	10.4	Uterus	1.4
Low. Large int.	2.1	Prostate	0.0
Testicles	0.0	Gall bladder	8.9
Ovaries	1.6	Heart	7.8
Bladder	0.4	ET tissue	0.8
Bone marrow	3.7	Oral mucosa	0.3
Bone surfaces	8.2	Lymph nodes	3.8
Skin	3.5	Muscle	3.8
		Eye lenses	0.0

end

Royal Adelaide Hospital
Nuclear Medicine, PET & Bone Densitometry
North Terrace, Adelaide, SA, 5000

PHYSICS AND RADIATION SAFETY SECTION
Phone: (08) 8222 5408
Fax: (08) 8222 5949

RADIATION SAFETY REPORT
(Confirmation report)

Title:
Bile Reflux Post-Bariatric Surgery: A Cohort Study

Comment:
This is to confirm that I have verified the dosimetry calculations carried out by Ben Crouch for this study, as required by the ARPANSA Code of Practice "Exposure of Humans to Ionizing Radiation for Research Purposes". Based on the data given, the doses detailed in his report of 2 August 2017 are an accurate estimate of the doses which will be received by participants.

Yours sincerely

Yuri Matyagin, Ph.D.
Medical Physicist
SA Medical Imaging (SAMI)
RAH campus
Email: Yuri.Matyagin@sa.gov.au
Tel: (08) 8222 0741

3 August 2017

Government of South Australia
SA Health

Appendix B

Investigation Tolerability Questionnaire

Name: ____

Patient Identification #: ___________________
(To be completed by investigators)

Please tick the tests that you underwent:

☐ Endoscopy
☐ HIDA scan

For each test that you underwent, please answer the following questions by selecting the response that best represents your feelings.

Government of South Australia
SA Health

ENDOSCOPY

How invasive did you find the procedure?

- ☐ very invasive
- ☐ slightly invasive
- ☐ unsure
- ☐ not invasive

How comfortable did you feel during the procedure?

- ☐ very uncomfortable
- ☐ slightly uncomfortable
- ☐ neither comfortable nor uncomfortable
- ☐ comfortable
- ☐ very comfortable

How comfortable were you after the procedure?

- ☐ very uncomfortable
- ☐ slightly uncomfortable
- ☐ neither comfortable nor uncomfortable
- ☐ comfortable
- ☐ very comfortable

Overall, how tolerable did you find the procedure?

- ☐ Not tolerable at all
- ☐ slightly intolerable
- ☐ tolerable
- ☐ very tolerable

What was the worst aspect of the investigation, in your opinion? (Open text)

Would you undergo this procedure again?

- ☐ Yes
- ☐ No
- ☐ Unsure

Government of South Australia
SA Health

HIDA SCAN

How invasive did you find the procedure?

☐ very invasive
☐ slightly invasive
☐ unsure
☐ not invasive

How comfortable did you feel during the procedure?

☐ very uncomfortable
☐ slightly uncomfortable
☐ neither comfortable nor uncomfortable
☐ comfortable
☐ very comfortable

How comfortable were you after the procedure?

☐ very uncomfortable
☐ slightly uncomfortable
☐ neither comfortable nor uncomfortable
☐ comfortable
☐ very comfortable

Overall, how tolerable did you find the procedure?

☐ Not tolerable at all
☐ slightly intolerable
☐ tolerable
☐ very tolerable

What was the worst aspect of the investigation, in your opinion? (Open text)

Would you undergo this procedure again?

☐ Yes
☐ No
☐ Unsure

Appendix C

Awards and Prizes

2021 –**Early Career Researcher Award**

Australian & New Zealand Metabolic and Obesity Surgery Society Annual Conference 2021

2019 – **Best Poster/Mini-oral Presentation (Clinical)**

The Queen Elizabeth Hospital Research Expo 2019

2019 – **Richard Jepson Research Scholarship**

Royal Australasian College of Surgeons

2019 – **Basil Hetzel Institute Travel Grant**

The Hospital Research Foundation, South Australia

Appendix D

Other publications during candidature

I was a co-investigator/author for the following publications during my candidature

Gricks B, **Eldredge T A**, Bessell J, Shenfine J. *Outcomes of 325 One Anastomosis Gastric Bypass Operations. An Australian Case Series.* Under review, following re-submission including suggested minor revisions to ANZ J Surg, Feb 2022 (awaiting outcome).

Han J, **Eldredge T A,** McQuillan P, Prasad S. *Rare Complication of Diaphragmatic Hernia in a Live Donor Nephrectomy Patient*. ANZ J Surg. 2021 Apr;91(4):E235-E237. doi: 10.1111/ans.16296.

Barbaro A, **Eldredge T A,** Shenfine J. *Diagnosing Anastomotic Leak post-Esophagectomy: A Systematic Review*. Dis Esophagus. 2021 Feb 10;34(2):doaa076. doi: 10.1093/dote/doaa076.

Harley S J D, **Eldredge T A,** Warren L R, Shenfine J. *Low Impact: Junior Surgeons' Perception of their Own Research.* The Bulletin – Royal College of Surgeons of England. 2019 Jan;101(1):44-46. doi: 10.1308/rcsbull.2019.44

Eldredge T A, Harley S J D, Warren L R, Shenfine J. *Doctor-Doctor: The Impact of Early Career Higher Degrees in Surgical Research.* ANZ J Surg. 2018 Sep;88(9):820-822. doi: 10.1111/ans.14552

BIBLIOGRAPHY

Abdel-Latif, MM, Inoue, H, Kelleher, D & Reynolds, JV 2016, 'Factors regulating nuclear factor-kappa B activation in esophageal cancer cells: Role of bile acids and acid', *Journal of Cancer Research and Therapeutics*, vol. 12, no. 1, Jan-Mar, pp. 364-373.

Abdel-Latif, MM, O'Riordan, J, Windle, HJ, Carton, E, Ravi, N, Kelleher, D & Reynolds, JV 2004, 'NF-kappaB activation in esophageal adenocarcinoma: relationship to Barrett's metaplasia, survival, and response to neoadjuvant chemoradiotherapy', *Annals of Surgery*, vol. 239, no. 4, Apr, pp. 491-500.

Aggarwal, S, Bhambri, A, Singla, V, Dash, NR & Sharma, A 2019, 'Adenocarcinoma of oesophagus involving gastro-oesophageal junction following mini-gastric bypass/one anastomosis gastric bypass', *Journal of Minimal Access Surgery*, vol. 16, no. 2, Feb 18, pp. 175-178.

Al-Najim, W, Docherty, NG & le Roux, CW 2018, 'Food Intake and Eating Behavior After Bariatric Surgery', *Physiological Reviews*, vol. 98, no. 3, Jul 1, pp. 1113-1141.

Alamuddin, N, Vetter, ML, Ahima, RS, Hesson, L, Ritter, S, Minnick, A, Faulconbridge, LF, Allison, KC, Sarwer, DB, Chittams, J, Williams, NN, Hayes, MR, Loughead, JW, Gur, R & Wadden, TA 2017, 'Changes in Fasting and Prandial Gut and Adiposity Hormones Following Vertical Sleeve Gastrectomy or Roux-en-Y-Gastric Bypass: an 18-Month Prospective Study', *Obesity Surgery*, vol. 27, no. 6, Jun, pp. 1563-1572.

Albaugh, VL, Flynn, CR, Cai, S, Xiao, Y, Tamboli, RA & Abumrad, NN 2015, 'Early Increases in Bile Acids Post Roux-en-Y Gastric Bypass Are Driven by Insulin-Sensitizing, Secondary Bile Acids', *Journal of Clinical Endocrinology and Metabolism*, vol. 100, no. 9, Sep, pp. E1225-1233.

Alden, JF 1977, 'Gastric and jejunoileal bypass. A comparison in the treatment of morbid obesity', *Archives of Surgery*, vol. 112, no. 7, Jul, pp. 799-806.

Allender, S, Gleeson, E, Crammond, B, Sacks, G, Lawrence, M, Peeters, A, Loff, B & Swinburn, B 2012, 'Policy change to create supportive environments for physical activity and healthy eating: which options are the most realistic for local government?', *Health Promotion International*, vol. 27, no. 2, Jun, pp. 261-274.

Almuhanna, M, Soong, TC, Lee, WJ, Chen, JC, Wu, CC & Lee, YC 2021, 'Twenty years' experience of laparoscopic 1-anastomosis gastric bypass: surgical risk and long-term results', *Surgery for Obesity and Related Diseases*, vol. 17, no. 5, May, pp. 968-975.

Alsumali, A, Eguale, T, Bairdain, S & Samnaliev, M 2018, 'Cost-Effectiveness Analysis of Bariatric Surgery for Morbid Obesity', *Obesity Surgery*, vol. 28, no. 8, Aug, pp. 2203-2214.

Altieri, MS, Yang, J, Nie, L, Blackstone, R, Spaniolas, K & Pryor, A 2018, 'Rate of revisions or conversion after bariatric surgery over 10 years in the state of New York', *Surgery for Obesity and Related Diseases*, vol. 14, no. 4, Apr, pp. 500-507.

American Society of Anesthesiologists 2014, *ASA Physical Status Classification System*, American Society of Anesthesiologists, Viewed: 4/9/19, <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system>.

Andreu, A, Moizé, V, Rodríguez, L, Flores, L & Vidal, J 2010, 'Protein intake, body composition, and protein status following bariatric surgery', *Obesity Surgery*, vol. 20, no. 11, Nov, pp. 1509-1515.

Armstrong, D, Bennett, JR, Blum, AL, Dent, J, De Dombal, FT, Galmiche, JP, Lundell, L, Margulies, M, Richter, JE, Spechler, SJ, Tytgat, GN & Wallin, L 1996, 'The endoscopic assessment of esophagitis: a progress report on observer agreement', *Gastroenterology*, vol. 111, no. 1, Jul, pp. 85-92.

Arun, S, Santhosh, S, Sood, A, Bhattacharya, A & Mittal, BR 2013, 'Added value of SPECT/CT over planar Tc-99m mebrofenin hepatobiliary scintigraphy in the evaluation of bile leaks', *Nuclear Medicine Communications*, vol. 34, no. 5, May, pp. 459-466.

Asaad, M, Habibullah, NK & Butler, CE 2020, 'The Impact of COVID-19 on Clinical Trials', *Annals of Surgery*, vol. 272, no. 3, Sep 1, pp. e222-e223.

Assalia, A, Gagner, M, Nedelcu, M, Ramos, AC & Nocca, D 2020, 'Gastroesophageal Reflux and Laparoscopic Sleeve Gastrectomy: Results of the First International Consensus Conference', *Obesity Surgery*, vol. 30, no. 10, Oct, pp. 3695-3705.

Atak, I, Ozdil, K, Yucel, M, Caliskan, M, Kilic, A, Erdem, H & Alimoglu, O 2012, 'The effect of laparoscopic cholecystectomy on the development of alkaline reflux gastritis and intestinal metaplasia', *Hepato-Gastroenterology*, vol. 59, no. 113, Jan-Feb, pp. 59-61.

Australian Institute of Health and Welfare 2017a, *Cancer in Australia 2017*, Australian Government, Canberra, Viewed: 4/9/19, <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2017/summary>.

Australian Institute of Health and Welfare 2017b, *Weight loss surgery in Australia 2014–15: Australian hospital statistics.*, Australian Government, Canberra, Viewed: 4/9/19, <https://www.aihw.gov.au/reports/overweight-obesity/ahs-2014-15-weight-loss-surgery/contents/table-of-contents>.

Australian Institute of Health and Welfare 2019, *Overweight and obesity: an interactive insight*, Australian Government, Canberra, Viewed: 4/9/19, <https://www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity-an-interactive-insight/contents/what-is-overweight-and-obesity>.

Aydin, M, Yapar, AF & Yapar, Z 2001, 'Hepatobiliary scintigraphy to detect duodenogastric reflux: intravenous administration of Tc-99m pertechnetate to define the location of the stomach', *Clinical Nuclear Medicine*, vol. 26, no. 4, Apr, p. 360.

Backman, B, Brown, D, Cottrell, J, Campbell, A, Clancy, W, Halim Shah, YJ, Chadwick, C, Budin, A, MacCormick, A, Caterson, I & Brown, W 2020, *The Bariatric Surgery Registry Annual Report, 2020*, Monash University, Department of Epidemiology and Preventive Medicine, Viewed: 13/9/21, <https://www.monash.edu/medicine/sphpm/registries/bariatric/reports-publications>.

Barr, AC, Frelich, MJ, Bosler, ME, Goldblatt, MI & Gould, JC 2017, 'GERD and acid reduction medication use following gastric bypass and sleeve gastrectomy', *Surgical Endoscopy*, vol. 31, no. 1, Jan, pp. 410-415.

Barrett, MW, Myers, JC, Watson, DI & Jamieson, GG 1999, 'Dietary interference with the use of Bilitec to assess bile reflux', *Diseases of the Esophagus*, vol. 12, no. 1, pp. 60-64.

Barrett, MW, Myers, JC, Watson, DI & Jamieson, GG 2000, 'Detection of bile reflux: in vivo validation of the Bilitec fibreoptic system', *Diseases of the Esophagus*, vol. 13, no. 1, pp. 44-50.

Barrett, NR 1957, 'The lower esophagus lined by columnar epithelium', *Surgery*, vol. 41, no. 6, Jun, pp. 881-894.

Bastouly, M, Arasaki, CH, Ferreira, JB, Zanoto, A, Borges, FG & Del Grande, JC 2009, 'Early changes in postprandial gallbladder emptying in morbidly obese patients undergoing Roux-en-Y gastric bypass: correlation with the occurrence of biliary sludge and gallstones', *Obesity Surgery*, vol. 19, no. 1, Jan, pp. 22-28.

Batterham, RL & Bloom, SR 2003, 'The gut hormone peptide YY regulates appetite', *Annals of the New York Academy of Sciences*, vol. 994, Jun, pp. 162-168.

Batterham, RL, Heffron, H, Kapoor, S, Chivers, JE, Chandarana, K, Herzog, H, Le Roux, CW, Thomas, EL, Bell, JD & Withers, DJ 2006, 'Critical role for peptide YY in protein-mediated satiation and body-weight regulation', *Cell Metabolism*, vol. 4, no. 3, Sep, pp. 223-233.

Baulieu, F, Baulieu, JL, Dorval, E, Metman, E, Bertrand, J & Itti, R 1986, 'Scintigraphy in duodeno-gastric reflux: a new method of quantification', *Nuclear Medicine Communications*, vol. 7, no. 10, Oct, pp. 747-754.

Beamish, AJ & Olbers, T 2019, 'Metabolic and bariatric surgery in adolescents', *Nature Reviews: Gastroenterology & Hepatology*, vol. 16, no. 10, Oct, pp. 585-587.

Bechi, P 1995, 'Bilitec and "quantitation" of reflux: further acid comments', *Gastroenterology*, vol. 109, no. 3, Sep, pp. 1023-1024.

Bechi, P, Falciai, R, Baldini, F, Cosi, F, Pucciani, F & Boscherini, S 1992, 'New fiber optic sensor for ambulatory entero-gastric reflux detection', in *Fiber Optic Medical and Fluorescent Sensors and Applications,* Proc. SPIE, vol. 1648, pp. 130-135.

Bechi, P, Pucciani, F, Baldini, F, Cosi, F, Falciai, R, Mazzanti, R, Castagnoli, A, Passeri, A & Boscherini, S 1993, 'Long-term ambulatory enterogastric reflux monitoring. Validation of a new fiberoptic technique', *Digestive Diseases and Sciences*, vol. 38, no. 7, Jul, pp. 1297-1306.

Behrns, KE, Smith, CD & Sarr, MG 1994, 'Prospective evaluation of gastric acid secretion and cobalamin absorption following gastric bypass for clinically severe obesity', *Digestive Diseases and Sciences*, vol. 39, no. 2, Feb, pp. 315-320.

Bernstein, H, Bernstein, C, Payne, CM & Dvorak, K 2009, 'Bile acids as endogenous etiologic agents in gastrointestinal cancer', *World Journal of Gastroenterology*, vol. 15, no. 27, Jul 21, pp. 3329-3340.

Bingham, J, Kaufman, J, Hata, K, Dickerson, J, Beekley, A, Wisbach, G, Swann, J, Ahnfeldt, E, Hawkins, D, Choi, Y, Lim, R & Martin, M 2017, 'A multicenter study of routine versus selective intraoperative leak testing for sleeve gastrectomy', *Surgery for Obesity and Related Diseases*, vol. 13, no. 9, Sep, pp. 1469-1475.

Blue, PW, Jackson, JH & Ghaed, N 1984, 'Duodenogastroesophageal reflux. Demonstration with Tc-99m DISIDA imaging', *Clinical Nuclear Medicine*, vol. 9, no. 4, Apr, pp. 238-239.

Bogers, RP, Bemelmans, WJ, Hoogenveen, RT, Boshuizen, HC, Woodward, M, Knekt, P, van Dam, RM, Hu, FB, Visscher, TL, Menotti, A, Thorpe, RJ, Jr., Jamrozik, K, Calling, S, Strand, BH & Shipley, MJ 2007, 'Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons', *Archives of Internal Medicine*, vol. 167, no. 16, Sep 10, pp. 1720-1728.

Bolier, EA, Kessing, BF, Smout, AJ & Bredenoord, AJ 2015, 'Systematic review: questionnaires for assessment of gastroesophageal reflux disease', *Diseases of the Esophagus*, vol. 28, no. 2, Feb-Mar, pp. 105-120.

Bonaz, B, Caravel, JP, Hostein, J, Bost, R & Fournet, J 1988, 'Scintigraphic study of duodenogastric reflux. Value of a computerized image-subtraction method', *Gastroenterologie Clinique et Biologique*, vol. 12, no. 5, May, pp. 436-440.

Borisenko, O, Lukyanov, V & Ahmed, AR 2018, 'Cost-utility analysis of bariatric surgery', *British Journal of Surgery*, vol. 105, no. 10, Sep, pp. 1328-1337.

Borsato, N, Bonavina, L, Zanco, P, Saitta, B, Chierichetti, F, Peracchia, A & Ferlin, G 1991, 'Proposal of a modified scintigraphic method to evaluate duodenogastroesophageal reflux', *Journal of Nuclear Medicine*, vol. 32, no. 3, Mar, pp. 436-440.

Bouziotis, P & Fiorini, C 2014, 'SPECT/MRI: dreams or reality?', *Clinical and Translational Imaging*, vol. 2, no. 6, 2014/12/01, pp. 571-573.

Braghetto, I, Gonzalez, P, Lovera, C, Figueroa-Giralt, M & Pineres, A 2019, 'Duodenogastric biliary reflux assessed by scintigraphic scan in patients with reflux symptoms after sleeve gastrectomy: preliminary results', *Surgery for Obesity and Related Diseases*, vol. 15, no. 6, Jun, pp. 822-826.

Bredenoord, AJ, Weusten, BL, Timmer, R & Smout, AJ 2005, 'Reproducibility of multichannel intraluminal electrical impedance monitoring of gastroesophageal reflux', *American Journal of Gastroenterology*, vol. 100, no. 2, Feb, pp. 265-269.

Broadbent, R, Tracey, M & Harrington, P 1993, 'Laparoscopic Gastric Banding: a preliminary report', *Obesity Surgery*, vol. 3, no. 1, Feb, pp. 63-67.

Brough, WA, Taylor, TV & Torrance, HB 1984, 'The surgical factors influencing duodenogastric reflux', *British Journal of Surgery*, vol. 71, no. 10, Oct, pp. 770-773.

Brown, WA, de Leon Ballesteros, GP, Ooi, G, Higa, K, Himpens, J, Torres, A, Shikora, S, Kow, L, Herrera, MF & on behalf of the, IatfrtloS-SO 2021, 'Single Anastomosis Duodenal-Ileal Bypass with Sleeve Gastrectomy/One Anastomosis Duodenal Switch (SADI-S/OADS) IFSO Position Statement—Update 2020', *Obesity Surgery*, vol. 31, no. 1, 2021/01/01, pp. 3-25.

Brown, WA, Johari Halim Shah, Y, Balalis, G, Bashir, A, Ramos, A, Kow, L, Herrera, M, Shikora, S, Campos, GM, Himpens, J & Higa, K 2020, 'IFSO Position Statement on the Role of Esophago-

Gastro-Duodenal Endoscopy Prior to and after Bariatric and Metabolic Surgery Procedures', *Obesity Surgery*, vol. 30, no. 8, Aug, pp. 3135-3153.

Bruzzi, M, Chevallier, JM & Czernichow, S 2017, 'One-Anastomosis Gastric Bypass: Why Biliary Reflux Remains Controversial?', *Obesity Surgery*, vol. 27, no. 2, Feb, pp. 545-547.

Buchwald, H, Buchwald, JN & McGlennon, TW 2014, 'Systematic review and meta-analysis of medium-term outcomes after banded Roux-en-Y gastric bypass', *Obesity Surgery*, vol. 24, no. 9, Sep, pp. 1536-1551.

Buchwald, H & Oien, DM 2013, 'Metabolic/bariatric surgery worldwide 2011', *Obesity Surgery*, vol. 23, no. 4, Apr, pp. 427-436.

Buchwald, H & Varco, RL 1971, 'A bypass operation for obese hyperlipidemic patients', *Surgery*, vol. 70, no. 1, Jul, pp. 62-70.

Bui, KT, Liang, R, Kiely, BE, Brown, C, Dhillon, HM & Blinman, P 2021, 'Scanxiety: a scoping review about scan-associated anxiety', *BMJ open*, vol. 11, no. 5, pp. e043215-e043215.

Burke, ZD & Tosh, D 2012, 'Barrett's metaplasia as a paradigm for understanding the development of cancer', *Current Opinion in Genetics and Development*, vol. 22, no. 5, Oct, pp. 494-499.

Burton, PR & Brown, WA 2011, 'The mechanism of weight loss with laparoscopic adjustable gastric banding: induction of satiety not restriction', *International Journal of Obesity*, vol. 35 Suppl 3, Sep, pp. S26-30.

Cabral, DJ, Hamilton, JA & Small, DM 1986, 'The ionization behavior of bile acids in different aqueous environments', *Journal of Lipid Research*, vol. 27, no. 3, Mar, pp. 334-343.

Camacho-Ramírez, A, Mayo-Ossorio, M, Pacheco-García, JM, Almorza-Gomar, D, Ribelles-García, A, Belmonte-Núñez, A, Prada-Oliveira, JA & Pérez-Arana, GM 2020, 'Pancreas is a preeminent source of ghrelin after sleeve gastrectomy in Wistar rats', *Histology and Histopathology*, vol. 35, no. 8, Aug, pp. 801-809.

Carandina, S, Soprani, A, Zulian, V & Cady, J 2021, 'Long-Term Results of One Anastomosis Gastric Bypass: a Single Center Experience with a Minimum Follow-Up of 10 Years', *Obesity Surgery*, vol. 31, no. 8, Aug, pp. 3468-3475.

Carlsson, R, Dent, J, Bolling-Sternevald, E, Johnsson, F, Junghard, O, Lauritsen, K, Riley, S & Lundell, L 1998, 'The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease', *Scandinavian Journal of Gastroenterology*, vol. 33, no. 10, Oct, pp. 1023-1029.

Caro, JF, Kolaczynski, JW, Nyce, MR, Ohannesian, JP, Opentanova, I, Goldman, WH, Lynn, RB, Zhang, PL, Sinha, MK & Considine, RV 1996, 'Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance', *Lancet*, vol. 348, no. 9021, Jul 20, pp. 159-161.

Carswell, KA, Vincent, RP, Belgaumkar, AP, Sherwood, RA, Amiel, SA, Patel, AG & le Roux, CW 2014, 'The effect of bariatric surgery on intestinal absorption and transit time', *Obesity Surgery*, vol. 24, no. 5, May, pp. 796-805.

Cassao, BD, Herbella, FA, Silva, LC & Vicentine, FP 2013, 'Esophageal motility after gastric bypass in Roux-en-Y for morbid obesity: high resolution manometry findings', *Arquivos Brasileiros de Cirurgia Digestiva*, vol. 26 Suppl 1, pp. 22-25.

Castedal, M, Bjornsson, E, Gretarsdottir, J, Fjalling, M & Abrahamsson, H 2000, 'Scintigraphic assessment of interdigestive duodenogastric reflux in humans: distinguishing between duodenal and biliary reflux material', *Scandinavian Journal of Gastroenterology*, vol. 35, no. 6, Jun, pp. 590-598.

Caviglia, R, Ribolsi, M, Maggiano, N, Gabbrielli, AM, Emerenziani, S, Guarino, MP, Carotti, S, Habib, FI, Rabitti, C & Cicala, M 2005, 'Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure', *American Journal of Gastroenterology*, vol. 100, no. 3, Mar, pp. 543-548.

Champion, G, Richter, JE, Vaezi, MF, Singh, S & Alexander, R 1994, 'Duodenogastroesophageal reflux: Relationship to pH and importance in Barrett's esophagus', *Gastroenterology*, vol. 107, no. 3, pp. 747-754.

Chang, WK, Lin, CK, Chuan, DC & Chao, YC 2016, 'Duodenogastric reflux: Proposed new endoscopic classification in symptomatic patients', *Journal of Medical Sciences (Taiwan)*, vol. 36, no. 1, pp. 1-5.

Charitopoulos, NC, Karkanias, GG, Dimitraki, TV, Papadimitriou, C & Golematis, BC 1994, 'Postoperative alkaline reflux gastritis following vagotomy', *Hepato-Gastroenterology*, vol. 41, no. 6, Dec, pp. 542-545.

Chávez-Talavera, O, Baud, G, Spinelli, V, Daoudi, M, Kouach, M, Goossens, JF, Vallez, E, Caiazzo, R, Ghunaim, M, Hubert, T, Lestavel, S, Tailleux, A, Staels, B & Pattou, F 2017, 'Roux-en-Y gastric bypass increases systemic but not portal bile acid concentrations by decreasing hepatic bile acid uptake in minipigs', *International Journal of Obesity*, vol. 41, no. 4, Apr, pp. 664-668.

Chen, TF, Yadav, PK, Wu, RJ, Yu, WH, Liu, CQ, Lin, H & Liu, ZJ 2013, 'Comparative evaluation of intragastric bile acids and hepatobiliary scintigraphy in the diagnosis of duodenogastric reflux', *World Journal of Gastroenterology*, vol. 19, no. 14, pp. 211-217.

Chen, X, Oshima, T, Shan, J, Fukui, H, Watari, J & Miwa, H 2012, 'Bile salts disrupt human esophageal squamous epithelial barrier function by modulating tight junction proteins', *American Journal of Physiology: Gastrointestinal and Liver Physiology*, vol. 303, no. 2, Jul 15, pp. G199-208.

Chu, CA, Gagner, M & Quinn, T 2002, 'Two-stage laparoscopic biliopancreatic diversion with duodenal switch: An alternative approach to super-super morbid obesity', *Surgical Endoscopy*, vol. 16, 01/01, p. S069.

Clapp, B, Badaoui, JN, Gamez, JA, Vivar, A & Ghanem, OM 2021, 'Reluctance in duodenal switch adoption: an international survey among bariatric surgeons', *Surgery for Obesity and Related Diseases*, vol. 17, no. 10, Oct, pp. 1760-1765.

Coelho, M, Oliveira, T & Fernandes, R 2013, 'Biochemistry of adipose tissue: an endocrine organ', *Archives of Medical Science*, vol. 9, no. 2, Apr 20, pp. 191-200.

Collins, BJ, Elliott, H, Sloan, JM, McFarland, RJ & Love, AH 1985, 'Oesophageal histology in reflux oesophagitis', *Journal of Clinical Pathology*, vol. 38, no. 11, Nov, pp. 1265-1272.

Cornejo-Pareja, I, Clemente-Postigo, M & Tinahones, FJ 2019, 'Metabolic and Endocrine Consequences of Bariatric Surgery', *Frontiers in Endocrinology*, vol. 10, p. 626.

Coussens, LM & Werb, Z 2002, 'Inflammation and cancer', *Nature*, vol. 420, no. 6917, Dec 19-26, pp. 860-867.

Cummings, DE, Purnell, JQ, Frayo, RS, Schmidova, K, Wisse, BE & Weigle, DS 2001, 'A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans', *Diabetes*, vol. 50, no. 8, Aug, pp. 1714-1719.

Cummings, DE, Weigle, DS, Frayo, RS, Breen, PA, Ma, MK, Dellinger, EP & Purnell, JQ 2002, 'Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery', *New England Journal of Medicine*, vol. 346, no. 21, May 23, pp. 1623-1630.

Dai, F, Gong, J, Zhang, R, Luo, JY, Zhu, YL & Wang, XQ 2002, 'Assessment of duodenogastric reflux by combined continuous intragastric pH and bilirubin monitoring', *World Journal of Gastroenterology*, vol. 8, no. 2, Apr, pp. 382-384.

Dardzinska, JA, Kaska, L, Wisniewski, P, Aleksandrowicz-Wrona, E & Malgorzewicz, S 2017, 'Fasting and post-prandial peptide YY levels in obese patients before and after mini versus Roux-en-Y gastric bypass', *Minerva Chirurgica*, vol. 72, no. 1, Feb, pp. 24-30.

Date, Y, Kojima, M, Hosoda, H, Sawaguchi, A, Mondal, MS, Suganuma, T, Matsukura, S, Kangawa, K & Nakazato, M 2000, 'Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans', *Endocrinology*, vol. 141, no. 11, Nov, pp. 4255-4261.

De Luca, M, Piatto, G, Merola, G, Himpens, J, Chevallier, JM, Carbajo, MA, Mahawar, K, Sartori, A, Clemente, N, Herrera, M, Higa, K, Brown, WA & Shikora, S 2021, 'IFSO Update Position Statement on One Anastomosis Gastric Bypass (OAGB)', *Obesity Surgery*, vol. 31, no. 7, Jul, pp. 3251-3278.

De Vuono, S, Ricci, MA, Siepi, D, Boni, M, Gentili, A, Scavizzi, M, Daviddi, G, Labate, P, Roscini, AR & Lupattelli, G 2017, 'Laparoscopic sleeve gastrectomy modifies cholesterol synthesis but not cholesterol absorption', *Obesity Research & Clinical Practice*, vol. 11, no. 1, Jan-Feb, pp. 118-122.

Deitel, M 2018, 'A Brief History of Bariatric Surgery to the Present', in M Deitel (ed.), *Essentials of Mini – One Anastomosis Gastric Bypass*, Springer International Publishing, Cham, pp. 1-15.

Del Genio, G, Tolone, S, Limongelli, P, Brusciano, L, D'Alessandro, A, Docimo, G, Rossetti, G, Silecchia, G, Iannelli, A, del Genio, A, del Genio, F & Docimo, L 2014, 'Sleeve gastrectomy and development of "de novo" gastroesophageal reflux', *Obesity Surgery*, vol. 24, no. 1, Jan, pp. 71-77.

Demerdash, HM, Sabry, AA & Arida, EA 2018, 'Role of serotonin hormone in weight regain after sleeve gastrectomy', *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 78, no. 1-2, Feb - Apr, pp. 68-73.

Dent, J 2008, 'Endoscopic grading of reflux oesophagitis: the past, present and future', *Best Practice & Research: Clinical Gastroenterology*, vol. 22, no. 4, pp. 585-599.

Dent, J, Vakil, N, Jones, R, Bytzer, P, Schoning, U, Halling, K, Junghard, O & Lind, T 2010, 'Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study', *Gut*, vol. 59, no. 6, Jun, pp. 714-721.

Dewar, P, Dixon, MF & Johnston, D 1984, 'Bile reflux and degree of gastritis in patients with gastric ulcer: before and after operation', *Journal of Surgical Research*, vol. 37, no. 4, Oct, pp. 277-284.

Dimitriadis, E, Daskalakis, M, Kampa, M, Peppe, A, Papadakis, JA & Melissas, J 2013, 'Alterations in gut hormones after laparoscopic sleeve gastrectomy: a prospective clinical and laboratory investigational study', *Annals of Surgery*, vol. 257, no. 4, Apr, pp. 647-654.

Dirksen, C, Damgaard, M, Bojsen-Moller, KN, Jorgensen, NB, Kielgast, U, Jacobsen, SH, Naver, LS, Worm, D, Holst, JJ, Madsbad, S, Hansen, DL & Madsen, JL 2013, 'Fast pouch emptying, delayed small intestinal transit, and exaggerated gut hormone responses after Roux-en-Y gastric bypass', *Neurogastroenterology and Motility*, vol. 25, no. 4, Apr, pp. 346-e255.

Dixon, MF, O'Connor, HJ, Axon, AT, King, RF & Johnston, D 1986, 'Reflux gastritis: distinct histopathological entity?', *Journal of Clinical Pathology*, vol. 39, no. 5, May, pp. 524-530.

Douros, JD, Tong, J & D'Alessio, DA 2019, 'The Effects of Bariatric Surgery on Islet Function, Insulin Secretion, and Glucose Control', *Endocrine Reviews*, vol. 40, no. 5, Oct 1, pp. 1394-1423.

Drane, WE, Karvelis, K, Johnson, DA & Silverman, ED 1987, 'Scintigraphic evaluation of duodenogastric reflux. Problems, pitfalls, and technical review', *Clinical Nuclear Medicine*, vol. 12, no. 5, May, pp. 377-384.

Eldredge, TA, Bills, M, Myers, JC, Bartholomeusz, D, Kiroff, GK & Shenfine, J 2020, 'HIDA and Seek: Challenges of Scintigraphy to Diagnose Bile Reflux Post-Bariatric Surgery', *Obesity Surgery*, vol. 30, no. 5, May, pp. 2038-2045.

Eldredge, TA, Myers, JC, Kiroff, GK & Shenfine, J 2018, 'Detecting Bile Reflux-the Enigma of Bariatric Surgery', *Obesity Surgery*, vol. 28, no. 2, Feb, pp. 559-566.

Eriksson, B, Emas, S, Jacobsson, H, Larsson, SA & Samuelsson, K 1988, 'Comparison of gastric aspiration and HIDA scintigraphy in detecting fasting duodenogastric bile reflux', *Scandinavian Journal of Gastroenterology*, vol. 23, no. 5, Jun, pp. 607-610.

Ernst, B, Thurnheer, M, Schmid, SM & Schultes, B 2009, 'Evidence for the necessity to systematically assess micronutrient status prior to bariatric surgery', *Obesity Surgery*, vol. 19, no. 1, Jan, pp. 66-73.

Eskandaros, MS, Abbass, A, Zaid, MH & Darwish, AA 2021, 'Laparoscopic One Anastomosis Gastric Bypass Versus Laparoscopic Roux-en-Y Gastric Bypass Effects on Pre-existing Mild-to-

Moderate Gastroesophageal Reflux Disease in Patients with Obesity: a Randomized Controlled Study', *Obesity Surgery*, vol. 31, no. 11, Nov, pp. 4673-4681.

Facchiano, E, Leuratti, L, Veltri, M & Lucchese, M 2016, 'Laparoscopic Conversion of One Anastomosis Gastric Bypass to Roux-en-Y Gastric Bypass for Chronic Bile Reflux', *Obesity Surgery*, vol. 26, no. 3, Mar, pp. 701-703.

Fakhry, TK, Mhaskar, R, Schwitalla, T, Muradova, E, Gonzalvo, JP & Murr, MM 2019, 'Bariatric surgery improves nonalcoholic fatty liver disease: a contemporary systematic review and meta-analysis', *Surgery for Obesity and Related Diseases*, vol. 15, no. 3, Mar, pp. 502-511.

Fang, S, Suh, JM, Reilly, SM, Yu, E, Osborn, O, Lackey, D, Yoshihara, E, Perino, A, Jacinto, S, Lukasheva, Y, Atkins, AR, Khvat, A, Schnabl, B, Yu, RT, Brenner, DA, Coulter, S, Liddle, C, Schoonjans, K, Olefsky, JM, Saltiel, AR, Downes, M & Evans, RM 2015, 'Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance', *Nature Medicine*, vol. 21, no. 2, Feb, pp. 159-165.

Farré, R, Van, M, De Vos, R, Geboes, K, Depoortere, I, Vanden Berghe, P, Fornari, F, Blondeau, K, Mertens, V, Tack, J & Sifrim, D 2008, 'Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair integrity and provoke dilated intercellular Spaces', *Dysphagia*, vol. 24, no. 2, p. 254.

Fein, M, Fuchs, KH, Bohrer, T, Freys, SM & Thiede, A 1996, 'Fiberoptic technique for 24-hour bile reflux monitoring. Standards and normal values for gastric monitoring', *Digestive Diseases and Sciences*, vol. 41, no. 1, Jan, pp. 216-225.

Fini, A & Roda, A 1987, 'Chemical properties of bile acids. IV. Acidity constants of glycine-conjugated bile acids', *Journal of Lipid Research*, vol. 28, no. 7, Jul, pp. 755-759.

Fiorillo, C, Quero, G, Dallemagne, B, Curcic, J, Fox, M & Perretta, S 2020, 'Effects of Laparoscopic Sleeve Gastrectomy on Gastric Structure and Function Documented by Magnetic Resonance Imaging Are Strongly Associated with Post-operative Weight Loss and Quality of Life: a Prospective Study', *Obesity Surgery*, vol. 30, no. 12, Dec, pp. 4741-4750.

Fisher, OM, Chan, DL, Talbot, ML, Ramos, A, Bashir, A, Herrera, MF, Himpens, J, Shikora, S, Higa, KD, Kow, L & Brown, WA 2021, 'Barrett's Oesophagus and Bariatric/Metabolic Surgery-IFSO 2020 Position Statement', *Obesity Surgery*, vol. 31, no. 3, Mar, pp. 915-934.

Fitzgerald, RC, di Pietro, M, Ragunath, K, Ang, Y, Kang, JY, Watson, P, Trudgill, N, Patel, P, Kaye, PV, Sanders, S, O'Donovan, M, Bird-Lieberman, E, Bhandari, P, Jankowski, JA, Attwood, S, Parsons, SL, Loft, D, Lagergren, J, Moayyedi, P, Lyratzopoulos, G & de Caestecker, J 2014, 'British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus', *Gut*, vol. 63, no. 1, Jan, pp. 7-42.

Fobi, MA & Lee, H 1994, 'SILASTIC ring vertical banded gastric bypass for the treatment of obesity: two years of follow-up in 84 patients [corrected]', *Journal of the National Medical Association*, vol. 86, no. 2, Feb, pp. 125-128.

Friedman, JM & Halaas, JL 1998, 'Leptin and the regulation of body weight in mammals', *Nature*, vol. 395, no. 6704, Oct 22, pp. 763-770.

Gagner, M, Hutchinson, C & Rosenthal, R 2016, 'Fifth International Consensus Conference: current status of sleeve gastrectomy', *Surgery for Obesity and Related Diseases*, vol. 12, no. 4, May, pp. 750-756.

Gantz, I, Erondu, N, Mallick, M, Musser, B, Krishna, R, Tanaka, WK, Snyder, K, Stevens, C, Stroh, MA, Zhu, H, Wagner, JA, Macneil, DJ, Heymsfield, SB & Amatruda, JM 2007, 'Efficacy and safety of intranasal peptide YY3-36 for weight reduction in obese adults', *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 5, May, pp. 1754-1757.

García-Caballero, M & Carbajo, M 2004, 'One anastomosis gastric bypass: a simple, safe and efficient surgical procedure for treating morbid obesity', *Nutricion Hospitalaria*, vol. 19, no. 6, Nov-Dec, pp. 372-375.

Garcia-Fuentes, E, Garrido-Sanchez, L, Garcia-Almeida, JM, Garcia-Arnes, J, Gallego-Perales, JL, Rivas-Marin, J, Morcillo, S, Cardona, I & Soriguer, F 2008, 'Different effect of laparoscopic Roux-en-Y gastric bypass and open biliopancreatic diversion of Scopinaro on serum PYY and ghrelin levels', *Obesity Surgery*, vol. 18, no. 11, Nov, pp. 1424-1429.

Genco, A, Soricelli, E, Casella, G, Maselli, R, Castagneto-Gissey, L, Di Lorenzo, N & Basso, N 2017, 'Gastroesophageal reflux disease and Barrett's esophagus after laparoscopic sleeve gastrectomy: a possible, underestimated long-term complication', *Surgery for Obesity and Related Diseases*, vol. 13, no. 4, Apr, pp. 568-574.

Gerard, PS, Gerczuk, P & Finestone, H 2007, 'Bile reflux in the esophagus demonstrated by HIDA scintigraphy', *Clinical Nuclear Medicine*, vol. 32, no. 3, Mar, pp. 224-225.

Ghatak, S, Reveiller, M, Toia, L, Ivanov, A, Godfrey, TE & Peters, JH 2013, 'Bile acid at low pH reduces squamous differentiation and activates EGFR signaling in esophageal squamous cells in 3-D culture', *Journal of Gastrointestinal Surgery*, vol. 17, no. 10, Oct, pp. 1723-1731.

Ghatak, S, Reveiller, M, Toia, L, Ivanov, AI, Zhou, Z, Redmond, EM, Godfrey, TE & Peters, JH 2016, 'Bile Salts at Low pH Cause Dilation of Intercellular Spaces in In Vitro Stratified Primary Esophageal Cells, Possibly by Modulating Wnt Signaling', *Journal of Gastrointestinal Surgery*, vol. 20, no. 3, Mar, pp. 500-509.

Gorodner, V, Buxhoeveden, R, Clemente, G, Sole, L, Caro, L & Grigaites, A 2015, 'Does laparoscopic sleeve gastrectomy have any influence on gastroesophageal reflux disease? Preliminary results', *Surgical Endoscopy*, vol. 29, no. 7, Jul, pp. 1760-1768.

Gourcerol, G, Verin, E, Leroi, AM & Ducrotte, P 2014, 'Can multichannel intraluminal pH-impedance monitoring be limited to 3 hours? Comparison between ambulatory 24-hour and post-prandial 3-hour recording', *Diseases of the Esophagus*, vol. 27, no. 8, Nov-Dec, pp. 732-736.

Grant, MJ & Booth, A 2009, 'A typology of reviews: an analysis of 14 review types and associated methodologies', *Health Information and Libraries Journal*, vol. 26, no. 2, Jun, pp. 91-108.

Griffen, WO, Jr., Young, VL & Stevenson, CC 1977, 'A prospective comparison of gastric and jejunoileal bypass procedures for morbid obesity', *Annals of Surgery*, vol. 186, no. 4, Oct, pp. 500-509.

Griffo, E, Nosso, G, Lupoli, R, Cotugno, M, Saldalamacchia, G, Vitolo, G, Angrisani, L, Cutolo, PP, Rivellese, AA & Capaldo, B 2014, 'Early improvement of postprandial lipemia after bariatric surgery in obese type 2 diabetic patients', *Obesity Surgery*, vol. 24, no. 5, May, pp. 765-770.

Gruzdeva, O, Borodkina, D, Uchasova, E, Dyleva, Y & Barbarash, O 2019, 'Leptin resistance: underlying mechanisms and diagnosis', *Diabetes, metabolic syndrome and obesity : targets and therapy*, vol. 12, pp. 191-198.

Gumbs, AA, Gagner, M, Dakin, G & Pomp, A 2007, 'Sleeve Gastrectomy for Morbid Obesity', *Obesity Surgery*, vol. 17, no. 7, 2007/07/01, pp. 962-969.

Gyawali, CP, Kahrilas, PJ, Savarino, E, Zerbib, F, Mion, F, Smout, A, Vaezi, M, Sifrim, D, Fox, MR, Vela, MF, Tutuian, R, Tack, J, Bredenoord, AJ, Pandolfino, J & Roman, S 2018, 'Modern diagnosis of GERD: the Lyon Consensus', *Gut*, vol. 67, no. 7, Jul, pp. 1351-1362.

Hajibandeh, S, Hajibandeh, S, Abdelkarim, M, Shehadeh, A, Mohsin, MM, Khan, KA & Morgan, R 2020, 'Closure versus non-closure of mesenteric defects in laparoscopic Roux-en-Y gastric bypass: a systematic review and meta-analysis', *Surgical Endoscopy*, vol. 34, no. 8, Aug, pp. 3306-3320.

Hall, JE 2016, *Guyton and Hall Textbook of Medical Physiology*, 13th edn, Elsevier, Philadelphia.

Hallberg, D & Forsell, P 1985, 'Ballongband vid behandling av massiv övervikt', *Svensk Kirurgi*, vol. 43, no. 2, p. 106.

Halverson, JD, Wise, L, Wazna, MF & Ballinger, WF 1978, 'Jejunoileal bypass for morbid obesity. A critical appraisal', *American Journal of Medicine*, vol. 64, no. 3, Mar, pp. 461-475.

Han, H, Wang, L, Du, H, Jiang, J, Hu, C, Zhang, G, Liu, S, Zhang, X, Liu, T & Hu, S 2015, 'Expedited Biliopancreatic Juice Flow to the Distal Gut Benefits the Diabetes Control After Duodenal-Jejunal Bypass', *Obesity Surgery*, vol. 25, no. 10, Oct, pp. 1802-1809.

Hanahan, D & Weinberg, RA 2011, 'Hallmarks of cancer: the next generation', *Cell*, vol. 144, no. 5, Mar 4, pp. 646-674.

Hausken, T, Li, XN, Goldman, B, Leotta, D, Odegaard, S & Martin, RW 2001, 'Quantification of gastric emptying and duodenogastric reflux stroke volumes using three-dimensional guided digital color Doppler imaging', *European Journal of Ultrasound*, vol. 13, no. 3, Jul, pp. 205-213.

Henrikson, V 1994, 'Can Small Bowel Resection Be Defended as Therapy for Obesity?', *Obesity Surgery*, vol. 4, no. 1, February 01, pp. 54-55.

Hess, DS & Hess, DW 1998, 'Biliopancreatic diversion with a duodenal switch', *Obesity Surgery*, vol. 8, no. 3, Jun, pp. 267-282.

Holst, JJ, Madsbad, S, Bojsen-Møller, KN, Svane, MS, Jørgensen, NB, Dirksen, C & Martinussen, C 2018, 'Mechanisms in bariatric surgery: Gut hormones, diabetes resolution, and weight loss', *Surgery for Obesity and Related Diseases*, vol. 14, no. 5, May, pp. 708-714.

Hopkins, KD & Lehmann, ED 1995, 'Successful medical treatment of obesity in 10th century Spain', *Lancet*, vol. 346, no. 8972, Aug 12, p. 452.

Huo, X, Zhang, HY, Zhang, XI, Lynch, JP, Strauch, ED, Wang, JY, Melton, SD, Genta, RM, Wang, DH, Spechler, SJ & Souza, RF 2010, 'Acid and bile salt-induced CDX2 expression differs in esophageal squamous cells from patients with and without Barrett's esophagus', *Gastroenterology*, vol. 139, no. 1, Jul, pp. 194-203.e191.

Hutchison, RL & Hutchison, AL 2010, 'César Roux and his original 1893 paper', *Obesity Surgery*, vol. 20, no. 7, Jul, pp. 953-956.

Hutton, BF, Occhipinti, M, Kuehne, A, Mathe, D, Kovacs, N, Waiczies, H, Erlandsson, K, Salvado, D, Carminati, M, Montagnani, GL, Short, SC, Ottobrini, L, van Mullekom, P, Piemonte, C, Bukki, T, Nyitrai, Z, Papp, Z, Nagy, K, Niendorf, T, de Francesco, I, Fiorini, C & consortium, I 2018, 'Development of clinical simultaneous SPECT/MRI', *British Journal of Radiology*, vol. 91, no. 1081, Jan, p. 20160690.

Hvid-Jensen, F, Pedersen, L, Drewes, AM, Sørensen, HT & Funch-Jensen, P 2011, 'Incidence of adenocarcinoma among patients with Barrett's esophagus', *New England Journal of Medicine*, vol. 365, no. 15, Oct 13, pp. 1375-1383.

IFSO 2021, *Sixth Global Registry Report*, International Federation for the Surgery of Obesity and Metabolic Disorders, Viewed: 9/11/2021, <https://www.ifso.com/ifso-registry.php>.

Inge, TH, Courcoulas, AP, Jenkins, TM, Michalsky, MP, Brandt, ML, Xanthakos, SA, Dixon, JB, Harmon, CM, Chen, MK, Xie, C, Evans, ME & Helmrath, MA 2019, 'Five-Year Outcomes of Gastric Bypass in Adolescents as Compared with Adults', *New England Journal of Medicine*, vol. 380, no. 22, May 30, pp. 2136-2145.

Inge, TH, Jenkins, TM, Xanthakos, SA, Dixon, JB, Daniels, SR, Zeller, MH & Helmrath, MA 2017, 'Long-term outcomes of bariatric surgery in adolescents with severe obesity (FABS-5+): a prospective follow-up analysis', *Lancet Diabetes Endocrinol*, vol. 5, no. 3, Mar, pp. 165-173.

Inge, TH, King, WC, Jenkins, TM, Courcoulas, AP, Mitsnefes, M, Flum, DR, Wolfe, BM, Pomp, A, Dakin, GF, Khandelwal, S, Zeller, MH, Horlick, M, Pender, JR, Chen, JY & Daniels, SR 2013, 'The effect of obesity in adolescence on adult health status', *Pediatrics*, vol. 132, no. 6, Dec, pp. 1098-1104.

Israel, O, Pellet, O, Biassoni, L, De Palma, D, Estrada-Lobato, E, Gnanasegaran, G, Kuwert, T, la Fougere, C, Mariani, G, Massalha, S, Paez, D & Giammarile, F 2019, 'Two decades of SPECT/CT - the coming of age of a technology: An updated review of literature evidence', *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 46, no. 10, Sep, pp. 1990-2012.

Itoh, M, Suganami, T, Hachiya, R & Ogawa, Y 2011, 'Adipose tissue remodeling as homeostatic inflammation', *Int J Inflam*, vol. 2011, p. 720926.

Jacene, H, Goetze, S, Patel, H, Wahl, R & Ziessman, H 2008, 'Advantages of Hybrid SPECT/CT vs SPECT Alone', *The Open Medical Imaging Journal*, vol. 2, 09/26.

Jacobsen, SH, Bojsen-Møller, KN, Dirksen, C, Jørgensen, NB, Clausen, TR, Wulff, BS, Kristiansen, VB, Worm, D, Hansen, DL, Holst, JJ, van Hall, G & Madsbad, S 2013, 'Effects of gastric bypass surgery on glucose absorption and metabolism during a mixed meal in glucose-tolerant individuals', *Diabetologia*, vol. 56, no. 10, Oct, pp. 2250-2254.

James, L, Demaree, R & Wolf, G 1984, 'Estimating Within-Group Interrater Reliability With and Without Response Bias', *Journal of Applied Psychology*, vol. 69, 02/01, pp. 85-98.

Jankowski, JAZ, de Caestecker, J, Love, SB, Reilly, G, Watson, P, Sanders, S, Ang, Y, Morris, D, Bhandari, P, Brooks, C, Attwood, S, Harrison, R, Barr, H & Moayyedi, P 2018, 'Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial', *Lancet*, vol. 392, no. 10145, Aug 4, pp. 400-408.

Jensen, CZ, Bojsen-Møller, KN, Svane, MS, Holst, LM, Hermansen, K, Hartmann, B, Wewer Albrechtsen, NJ, Kuhre, RE, Kristiansen, VB, Rehfeld, JF, Clausen, TR, Holst, JJ & Madsbad, S 2020, 'Responses of gut and pancreatic hormones, bile acids, and fibroblast growth factor-21 differ to glucose, protein, and fat ingestion after gastric bypass surgery', *American Journal of Physiology: Gastrointestinal and Liver Physiology*, vol. 318, no. 4, Apr 1, pp. G661-g672.

Jia, D, Tan, H, Faramand, A & Fang, F 2020, 'One Anastomosis Gastric Bypass Versus Roux-en-Y Gastric Bypass for Obesity: a Systematic Review and Meta-Analysis of Randomized Clinical Trials', *Obesity Surgery*, vol. 30, no. 4, Apr, pp. 1211-1218.

Jiang, C, Xie, C, Lv, Y, Li, J, Krausz, KW, Shi, J, Brocker, CN, Desai, D, Amin, SG, Bisson, WH, Liu, Y, Gavrilova, O, Patterson, AD & Gonzalez, FJ 2015, 'Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction', *Nat Commun*, vol. 6, Dec 15, p. 10166.

Jiang, M, Li, H, Zhang, Y, Yang, Y, Lu, R, Liu, K, Lin, S, Lan, X, Wang, H, Wu, H, Zhu, J, Zhou, Z, Xu, J, Lee, D-K, Zhang, L, Lee, Y-C, Yuan, J, Abrams, JA, Wang, TC, Sepulveda, AR, Wu, Q, Chen, H, Sun, X, She, J, Chen, X & Que, J 2017, 'Transitional basal cells at the squamous-columnar junction generate Barrett's oesophagus', *Nature*, vol. 550, no. 7677, pp. 529-533.

Johari, Y, Lim, G, Wickremasinghe, A, Yue, H, Seah, J, Ooi, G, Playfair, J, Laurie, C, Beech, P, Yap, K, Hebbard, G, Brown, W & Burton, P 2020, 'Pathophysiological Mechanisms of GASTRO-ESOPHAGEAL Reflux Following Sleeve Gastrectomy', *Annals of Surgery*, Nov 18.

Johari, Y, Wickremasinghe, A, Kiswandono, P, Yue, H, Ooi, G, Laurie, C, Hebbard, G, Beech, P, Yap, K, Brown, W & Burton, P 2021a, 'Mechanisms of Esophageal and Gastric Transit Following Sleeve Gastrectomy', *Obesity Surgery*, vol. 31, no. 2, Feb, pp. 725-737.

Johari, Y, Yue, H, Laurie, C, Hebbard, G, Beech, P, Yap, KS, Brown, W & Burton, P 2021b, 'Expected Values of Esophageal Transit and Gastric Emptying Scintigraphy Post-uncomplicated Sleeve Gastrectomy', *Obesity Surgery*, vol. 31, no. 8, Aug, pp. 3727-3737.

Johnston, D, Dachtler, J, Sue-Ling, HM, King, RF & Martin l, G 2003, 'The Magenstrasse and Mill operation for morbid obesity', *Obesity Surgery*, vol. 13, no. 1, Feb, pp. 10-16.

Johnston, D & Wilkinson, AR 1970, 'Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer', *British Journal of Surgery*, vol. 57, no. 4, Apr, pp. 289-296.

Jonasson, C, Wernersson, B, Hoff, DA & Hatlebakk, JG 2013, 'Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease', *Alimentary Pharmacology and Therapeutics*, vol. 37, no. 5, Mar, pp. 564-572.

Jones, R, Junghard, O, Dent, J, Vakil, N, Halling, K, Wernersson, B & Lind, T 2009, 'Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care', *Alimentary Pharmacology and Therapeutics*, vol. 30, no. 10, Nov 15, pp. 1030-1038.

Jonnalagadda, S & Likhitsup, A 2019, 'Postsurgical Endoscopic Anatomy', in V Chandrasekhara, BJ Elmunzer, MA Khashab & VR Muthusamy (eds), *Clinical Gastrointestinal Endoscopy (Third Edition)*, Elsevier, Philadelphia, pp. 124-140.e123.

Kakhki, VR, Zakavi, SR & Davoudi, Y 2007, 'Normal values of gallbladder ejection fraction using 99mTc-sestamibi scintigraphy after a fatty meal formula', *Journal of Gastrointestinal and Liver Diseases*, vol. 16, no. 2, Jun, pp. 157-161.

Karamanakos, SN, Vagenas, K, Kalfarentzos, F & Alexandrides, TK 2008, 'Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study', *Annals of Surgery*, vol. 247, no. 3, Mar, pp. 401-407.

Kashyap, R, Dondi, M, Paez, D & Mariani, G 2013, 'Hybrid imaging worldwide-challenges and opportunities for the developing world: a report of a Technical Meeting organized by IAEA', *Seminars in Nuclear Medicine*, vol. 43, no. 3, May, pp. 208-223.

Kauer, WK, Peters, JH, DeMeester, TR, Feussner, H, Ireland, AP, Stein, HJ & Siewert, RJ 1997, 'Composition and concentration of bile acid reflux into the esophagus of patients with gastroesophageal reflux disease', *Surgery*, vol. 122, no. 5, Nov, pp. 874-881.

Kawabe, A, Shimada, Y, Soma, T, Maeda, M, Itami, A, Kaganoi, J, Kiyono, T & Imamura, M 2004, 'Production of prostaglandinE2 via bile acid is enhanced by trypsin and acid in normal human esophageal epithelial cells', *Life Sciences*, vol. 75, no. 1, May 21, pp. 21-34.

Keleidari, B, Dehkordi, MM, Shahraki, MS, Ahmadi, ZS, Heidari, M, Hajian, A & Nasaj, HT 2021, 'Bile reflux after one anastomosis gastric bypass surgery: A review study', *Ann Med Surg (Lond)*, vol. 64, Apr, p. 102248.

Keleidari, B, Mahmoudieh, M, Davarpanah Jazi, AH, Melali, H, Nasr Esfahani, F, Minakari, M & Mokhtari, M 2019, 'Comparison of the Bile Reflux Frequency in One Anastomosis Gastric Bypass and Roux-en-Y Gastric Bypass: a Cohort Study', *Obesity Surgery*, vol. 29, no. 6, Jun, pp. 1721-1725.

King, PM, Adam, RD, Pryde, A, McDicken, WN & Heading, RC 1984, 'Relationships of human antroduodenal motility and transpyloric fluid movement: non-invasive observations with real-time ultrasound', *Gut*, vol. 25, no. 12, Dec, pp. 1384-1391.

Kiroff, GK, Devitt, PG, DeYoung, NJ & Jamieson, GG 1987, 'Bile salt-induced injury of rabbit oesophageal mucosa measured by hydrogen ion disappearance', *Australian and New Zealand Journal of Surgery*, vol. 57, no. 2, Feb, pp. 111-117.

Koek, GH, Vos, R, Sifrim, D, Cuomo, R, Janssens, J & Tack, J 2005, 'Mechanisms underlying duodeno-gastric reflux in man', *Neurogastroenterology and Motility*, vol. 17, no. 2, Apr, pp. 191-199.

Kohno, D, Gao, HZ, Muroya, S, Kikuyama, S & Yada, T 2003, 'Ghrelin directly interacts with neuropeptide-Y-containing neurons in the rat arcuate nucleus: Ca2+ signaling via protein kinase

A and N-type channel-dependent mechanisms and cross-talk with leptin and orexin', *Diabetes*, vol. 52, no. 4, Apr, pp. 948-956.

Korek, E, Krauss, H, Gibas-Dorna, M, Kupsz, J, Piatek, M & Piatek, J 2013, 'Fasting and postprandial levels of ghrelin, leptin and insulin in lean, obese and anorexic subjects', *Przegląd Gastroenterologiczny*, vol. 8, no. 6, pp. 383-389.

Korner, J, Inabnet, W, Febres, G, Conwell, IM, McMahon, DJ, Salas, R, Taveras, C, Schrope, B & Bessler, M 2009, 'Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass', *International Journal of Obesity*, vol. 33, no. 7, Jul, pp. 786-795.

Kremen, AJ, Linner, JH & Nelson, CH 1954, 'An experimental evaluation of the nutritional importance of proximal and distal small intestine', *Annals of Surgery*, vol. 140, no. 3, Sep, pp. 439-448.

Krishnamurthy, GT & Brown, PH 2002, 'Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction', *Journal of Nuclear Medicine*, vol. 43, no. 12, Dec, pp. 1603-1610.

Kuipers, EJ 1999, 'Review article: exploring the link between Helicobacter pylori and gastric cancer', *Alimentary Pharmacology and Therapeutics*, vol. 13, no. s1, pp. 3-11.

Kumar, R, Lieske, JC, Collazo-Clavell, ML, Sarr, MG, Olson, ER, Vrtiska, TJ, Bergstralh, EJ & Li, X 2011, 'Fat malabsorption and increased intestinal oxalate absorption are common after Roux-en-Y gastric bypass surgery', *Surgery*, vol. 149, no. 5, May, pp. 654-661.

Kunsch, S, Neesse, A, Huth, J, Steinkamp, M, Klaus, J, Adler, G, Gress, TM & Ellenrieder, V 2009, 'Increased Duodeno-Gastro-Esophageal Reflux (DGER) in symptomatic GERD patients with a history of cholecystectomy', *Zeitschrift für Gastroenterologie*, vol. 47, no. 8, Aug, pp. 744-748.

Kuzmak, LI 1986, 'Silicone gastric banding : a simple and effective operation for morbid obesity', *Contemporary Surgery*, vol. 28, 1986, pp. 13-18.

Kweh, FA, Miller, JL, Sulsona, CR, Wasserfall, C, Atkinson, M, Shuster, JJ, Goldstone, AP & Driscoll, DJ 2015, 'Hyperghrelinemia in Prader-Willi syndrome begins in early infancy long before the onset of hyperphagia', *American Journal of Medical Genetics. Part A*, vol. 167a, no. 1, Jan, pp. 69-79.

Kwok, CS, Pradhan, A, Khan, MA, Anderson, SG, Keavney, BD, Myint, PK, Mamas, MA & Loke, YK 2014, 'Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis', *International Journal of Cardiology*, vol. 173, no. 1, Apr 15, pp. 20-28.

Lacy, BE, Chehade, R & Crowell, MD 2011, 'A prospective study to compare a symptom-based reflux disease questionnaire to 48-h wireless pH monitoring for the identification of gastroesophageal reflux (revised 2-26-11)', *American Journal of Gastroenterology*, vol. 106, no. 9, Sep, pp. 1604-1611.

Lagergren, J, Lindam, A & Mason, RM 2012, 'Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study', *International Journal of Cancer*, vol. 131, no. 6, Sep 15, pp. E1048-1052.

Lake, A, Rao, SSC, Larion, S, Spartz, H & Kavuri, S 2021, 'Bile Reflux Gastropathy and Functional Dyspepsia', *Journal of Neurogastroenterology and Motility*, vol. 27, no. 3, Jul 30, pp. 400-407.

Lasheen, M, Mahfouz, M, Salama, TMS & Salem, HE-DM 2019, 'Biliary reflux gastritis after Mini Gastric Bypass: The effect of Bilirubin level', *Archives of Surgery and Clinical Research*, vol. 3, pp. 027-031.

Lee, WJ, Yu, PJ, Wang, W, Chen, TC, Wei, PL & Huang, MT 2005, 'Laparoscopic Roux-en-Y versus mini-gastric bypass for the treatment of morbid obesity: a prospective randomized controlled clinical trial', *Annals of Surgery*, vol. 242, no. 1, Jul, pp. 20-28.

Levine, DS, Blount, PL, Rudolph, RE & Reid, BJ 2000, 'Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus', *American Journal of Gastroenterology*, vol. 95, no. 5, May, pp. 1152-1157.

Lichtenstein, E & Bryan, JH 1965, 'Acquiescence and the mmpi: An item reversal approach', *Journal of Abnormal Psychology*, vol. 70, Aug, pp. 290-293.

Lin, Z & Qu, S 2020, 'Legend of Weight Loss: a Crosstalk Between the Bariatric Surgery and the Brain', *Obesity Surgery*, vol. 30, no. 5, May, pp. 1988-2002.

Lindblad, M, Bright, T, Schloithe, A, Mayne, GC, Chen, G, Bull, J, Bampton, PA, Fraser, RJ, Gatenby, PA, Gordon, LG & Watson, DI 2017, 'Toward More Efficient Surveillance of Barrett's Esophagus: Identification and Exclusion of Patients at Low Risk of Cancer', *World Journal of Surgery*, vol. 41, no. 4, Apr, pp. 1023-1034.

Linner, JH 1987, 'Overview of surgical techniques for the treatment of morbid obesity', *Gastroenterology Clinics of North America*, vol. 16, no. 2, Jun, pp. 253-272.

Liou, JM, Lin, JT, Lee, WJ, Wang, HP, Lee, YC, Chiu, HM & Wu, MS 2008, 'The serial changes of ghrelin and leptin levels and their relations to weight loss after laparoscopic minigastric bypass surgery', *Obesity Surgery*, vol. 18, no. 1, Jan, pp. 84-89.

Liron, R, Parrilla, P, Martinez de Haro, LF, Ortiz, A, Robles, R, Lujan, JA, Fuente, T & Andres, B 1997, 'Quantification of duodenogastric reflux in Barrett's esophagus', *American Journal of Gastroenterology*, vol. 92, no. 1, Jan, pp. 32-36.

Lo, RC, Huang, WL & Fan, YM 2015, 'Evaluation of bile reflux in HIDA images based on fluid mechanics', *Computers in Biology and Medicine*, vol. 60, May, pp. 51-65.

Lo, SK 2019, 'ERCP in Surgically Altered Anatomy', in TH Baron, RA Kozarek & DL Carr-Locke (eds), *ERCP (Third Edition)*, Elsevier, Philadelphia, pp. 288-307.e281.

Lujan Mompean, JA, Parrilla Paricio, P, Robles Campos, R, Fuente Jimenez, T & Martinez Gomez, D 1990, 'Continuous 99mTc-HIDA infusion as a method for measuring duodenogastric reflux', *British Journal of Surgery*, vol. 77, no. 4, Apr, pp. 425-427.

Lundell, LR, Dent, J, Bennett, JR, Blum, AL, Armstrong, D, Galmiche, JP, Johnson, F, Hongo, M, Richter, JE, Spechler, SJ, Tytgat, GN & Wallin, L 1999, 'Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification', *Gut*, vol. 45, no. 2, Aug, pp. 172-180.

M'Harzi, L, Chevallier, JM, Certain, A, Autret, G, Levenson, G, Louis, D, Poghosyan, T, Berger, A, Rahmi, G, Broudin, C, Clément, O, Douard, R, Tavitian, B & Bruzzi, M 2020, 'Long-Term Evaluation of Biliary Reflux on Esogastric Mucosae after One-Anastomosis Gastric Bypass and Esojejunostomy in Rats', *Obesity Surgery*, vol. 30, no. 7, Jul, pp. 2598-2605.

Mackie, CR, Wisbey, ML & Cuschieri, A 1982, 'Milk 99Tcm-EHIDA test for enterogastric bile reflux', *British Journal of Surgery*, vol. 69, no. 2, Feb, pp. 101-104.

Magouliotis, DE, Tzovaras, G, Tasiopoulou, VS, Christodoulidis, G & Zacharoulis, D 2020, 'Closure of Mesenteric Defects in Laparoscopic Gastric Bypass: a Meta-Analysis', *Obesity Surgery*, vol. 30, no. 5, May, pp. 1935-1943.

Mahawar, KK, Borg, CM, Kular, KS, Courtney, MJ, Sillah, K, Carr, WRJ, Jennings, N, Madhok, B, Singhal, R & Small, PK 2017, 'Understanding Objections to One Anastomosis (Mini) Gastric Bypass: A Survey of 417 Surgeons Not Performing this Procedure', *Obesity Surgery*, vol. 27, no. 9, Sep, pp. 2222-2228.

Mahawar, KK, Jennings, N, Brown, J, Gupta, A, Balupuri, S & Small, PK 2013, '"Mini" gastric bypass: systematic review of a controversial procedure', *Obesity Surgery*, vol. 23, no. 11, Nov, pp. 1890-1898.

Mahawar, KK, Kumar, P, Parmar, C, Graham, Y, Carr, WR, Jennings, N, Schroeder, N, Balupuri, S & Small, PK 2016, 'Small Bowel Limb Lengths and Roux-en-Y Gastric Bypass: a Systematic Review', *Obesity Surgery*, vol. 26, no. 3, Mar, pp. 660-671.

Mahawar, KK & Sharples, AJ 2017, 'Contribution of Malabsorption to Weight Loss After Roux-en-Y Gastric Bypass: a Systematic Review', *Obesity Surgery*, vol. 27, no. 8, Aug, pp. 2194-2206.

Manifold, DK, Anggiansah, A, Marshall, RE & Owen, WJ 2001, 'Reproducibility and intragastric variation of duodenogastric reflux using ambulatory gastric bilirubin monitoring', *Digestive Diseases and Sciences*, vol. 46, no. 1, Jan, pp. 78-85.

Manifold, DK, Anggiansah, A & Owen, WJ 2000, 'Effect of cholecystectomy on gastroesophageal and duodenogastric reflux', *American Journal of Gastroenterology*, vol. 95, no. 10, Oct, pp. 2746-2750.

Marshall, REK, Anggiansah, A, Owen, WA & Owen, WJ 1998, 'The temporal relationship between oesophageal bile reflux and pH in gastro-oesophageal reflux disease', *European Journal of Gastroenterology and Hepatology*, vol. 10, no. 5, pp. 385-392.

Marsk, R, Jonas, E, Gartzios, H, Stockeld, D, Granstrom, L & Freedman, J 2009, 'High revision rates after laparoscopic vertical banded gastroplasty', *Surgery for Obesity and Related Diseases*, vol. 5, no. 1, Jan-Feb, pp. 94-98.

Mason, EE 1982, 'Vertical banded gastroplasty for obesity', *Archives of Surgery*, vol. 117, no. 5, May, pp. 701-706.

Mason, EE & Ito, C 1967, 'Gastric bypass in obesity', *Surgical Clinics of North America*, vol. 47, no. 6, Dec, pp. 1345-1351.

McCarty, TR, Jirapinyo, P & Thompson, CC 2020, 'Effect of Sleeve Gastrectomy on Ghrelin, GLP-1, PYY, and GIP Gut Hormones: A Systematic Review and Meta-analysis', *Annals of Surgery*, vol. 272, no. 1, Jul, pp. 72-80.

McQuaid, KR, Laine, L, Fennerty, MB, Souza, R & Spechler, SJ 2011, 'Systematic review: the role of bile acids in the pathogenesis of gastro-oesophageal reflux disease and related neoplasia', *Alimentary Pharmacology and Therapeutics*, vol. 34, no. 2, Jul, pp. 146-165.

Mechanick, JI, Apovian, C, Brethauer, S, Garvey, WT, Joffe, AM, Kim, J, Kushner, RF, Lindquist, R, Pessah-Pollack, R, Seger, J, Urman, RD, Adams, S, Cleek, JB, Correa, R, Figaro, MK, Flanders, K, Grams, J, Hurley, DL, Kothari, S, Seger, MV & Still, CD 2020, 'Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists', *Surgery for Obesity and Related Diseases*, vol. 16, no. 2, Feb, pp. 175-247.

Melissas, J, Leventi, A, Klinaki, I, Perisinakis, K, Koukouraki, S, de Bree, E & Karkavitsas, N 2013, 'Alterations of global gastrointestinal motility after sleeve gastrectomy: a prospective study', *Annals of Surgery*, vol. 258, no. 6, pp. 976-982.

Mescher, AL 2018, 'Organs Associated with the Digestive Tract', in *Junqueira's Basic Histology: Text and Atlas, 15e*, McGraw-Hill Education, New York, NY.

Mi, S, Lim, DW, Turner, JM, Wales, PW & Curtis, JM 2016, 'Determination of Bile Acids in Piglet Bile by Solid Phase Extraction and Liquid Chromatography-Electrospray Tandem Mass Spectrometry', *Lipids*, vol. 51, no. 3, Mar, pp. 359-372.

Michielson, D, Van Hee, R & Hendrickx, L 1996, 'Complications of Biliopancreatic Diversion Surgery as Proposed by Scopinaro in the Treatment of Morbid Obesity', *Obesity Surgery*, vol. 6, no. 5, Oct, pp. 416-420.

Milic, S, Lulic, D & Stimac, D 2014, 'Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations', *World Journal of Gastroenterology*, vol. 20, no. 28, Jul 28, pp. 9330-9337.

Mingrone, G, Panunzi, S, De Gaetano, A, Guidone, C, Iaconelli, A, Nanni, G, Castagneto, M, Bornstein, S & Rubino, F 2015, 'Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial', *Lancet*, vol. 386, no. 9997, Sep 5, pp. 964-973.

Mittal, BR, Ibrarullah, M, Agarwal, DK, Maini, A, Ali, W, Sikora, SS & Das, BK 1994, 'Comparative evaluation of scintigraphy and upper gastrointestinal tract endoscopy for detection of duodenogastric reflux', *Annals of Nuclear Medicine*, vol. 8, no. 3, Aug, pp. 183-186.

Moize, V, Geliebter, A, Gluck, ME, Yahav, E, Lorence, M, Colarusso, T, Drake, V & Flancbaum, L 2003, 'Obese patients have inadequate protein intake related to protein intolerance up to 1 year following Roux-en-Y gastric bypass', *Obesity Surgery*, vol. 13, no. 1, Feb, pp. 23-28.

Molinaro, A, Wahlström, A & Marschall, HU 2018, 'Role of Bile Acids in Metabolic Control', *Trends in Endocrinology and Metabolism*, vol. 29, no. 1, Jan, pp. 31-41.

Morgenstern, L, Yamakawa, T & Seltzer, D 1973, 'Carcinoma of the gastric stump', *American Journal of Surgery*, vol. 125, no. 1, Jan, pp. 29-38.

Mukaisho, KI, Kanai, S, Kushima, R, Nakayama, T, Hattori, T & Sugihara, H 2019, 'Barretts's carcinogenesis', *Pathology International*, vol. 69, no. 6, Jun, pp. 319-330.

Muller-Lissner, SA 1985, 'Measurements of bile salt reflux are influenced by the method of collecting gastric juice', *Gastroenterology*, vol. 89, no. 6, Dec, pp. 1338-1341.

Musella, M, Vitiello, A, Berardi, G, Velotti, N, Pesce, M & Sarnelli, G 2021, 'Evaluation of reflux following sleeve gastrectomy and one anastomosis gastric bypass: 1-year results from a randomized open-label controlled trial', *Surgical Endoscopy*, vol. 35, no. 12, Dec, pp. 6777-6785.

Naef, M, Mouton, WG, Naef, U, van der Weg, B, Maddern, GJ & Wagner, HE 2011, 'Esophageal dysmotility disorders after laparoscopic gastric banding--an underestimated complication', *Annals of Surgery*, vol. 253, no. 2, Feb, pp. 285-290.

Naik, RD, Choksi, YA & Vaezi, MF 2016, 'Consequences of bariatric surgery on oesophageal function in health and disease', *Nature Reviews: Gastroenterology & Hepatology*, vol. 13, no. 2, Feb, pp. 111-119.

Nakamura, KM, Haglind, EG, Clowes, JA, Achenbach, SJ, Atkinson, EJ, Melton, LJ, 3rd & Kennel, KA 2014, 'Fracture risk following bariatric surgery: a population-based study', *Osteoporosis International*, vol. 25, no. 1, Jan, pp. 151-158.

National Health and Medical Research Council 2013, *Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia.*, National Health and Medical Research Council, Melbourne, Accessed 17/9/19, <https://www.nhmrc.gov.au/about-us/publications/clinical-practice-guidelines-management-overweight-and-obesity>.

Nehra, D 2010, 'Bile in the esophagus-model for a bile acid biosensor', *Journal of Gastrointestinal Surgery*, vol. 14 Suppl 1, Feb, pp. S6-8.

Nemeth, E, Rivera, S, Gabayan, V, Keller, C, Taudorf, S, Pedersen, BK & Ganz, T 2004, 'IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin', *Journal of Clinical Investigation*, vol. 113, no. 9, May, pp. 1271-1276.

Nguyen, NT, Magno, CP, Lane, KT, Hinojosa, MW & Lane, JS 2008, 'Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004', *Journal of the American College of Surgeons*, vol. 207, no. 6, Dec, pp. 928-934.

Nicoletti, CF, de Oliveira, BA, Barbin, R, Marchini, JS, Salgado Junior, W & Nonino, CB 2015, 'Red meat intolerance in patients submitted to gastric bypass: a 4-year follow-up study', *Surgery for Obesity and Related Diseases*, vol. 11, no. 4, Jul-Aug, pp. 842-846.

Numans, ME & de Wit, NJ 2003, 'Reflux symptoms in general practice: diagnostic evaluation of the Carlsson-Dent gastro-oesophageal reflux disease questionnaire', *Alimentary Pharmacology and Therapeutics*, vol. 17, no. 8, Apr, pp. 1049-1055.

Odstrcil, EA, Martinez, JG, Santa Ana, CA, Xue, B, Schneider, RE, Steffer, KJ, Porter, JL, Asplin, J, Kuhn, JA & Fordtran, JS 2010, 'The contribution of malabsorption to the reduction in net energy absorption after long-limb Roux-en-Y gastric bypass', *American Journal of Clinical Nutrition*, vol. 92, no. 4, Oct, pp. 704-713.

Olbers, T, Beamish, AJ, Gronowitz, E, Flodmark, CE, Dahlgren, J, Bruze, G, Ekbom, K, Friberg, P, Gothberg, G, Jarvholm, K, Karlsson, J, Marild, S, Neovius, M, Peltonen, M & Marcus, C 2017, 'Laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity (AMOS): a prospective, 5-year, Swedish nationwide study', *Lancet Diabetes Endocrinol*, vol. 5, no. 3, Mar, pp. 174-183.

Old, O, Moayyedi, P, Love, S, Roberts, C, Hapeshi, J, Foy, C, Stokes, C, Briggs, A, Jankowski, J & Barr, H 2015, 'Barrett's Oesophagus Surveillance versus endoscopy at need Study (BOSS): protocol and analysis plan for a multicentre randomized controlled trial', *Journal of Medical Screening*, vol. 22, no. 3, Sep, pp. 158-164.

Pace, F, Sangaletti, O, Pallotta, S, Molteni, P & Porro, GB 2007, 'Biliary reflux and non-acid reflux are two distinct phenomena: a comparison between 24-hour multichannel intraesophageal impedance and bilirubin monitoring', *Scandinavian Journal of Gastroenterology*, vol. 42, no. 9, Sep, pp. 1031-1039.

Pandolfino, JE, El-Serag, HB, Zhang, Q, Shah, N, Ghosh, SK & Kahrilas, PJ 2006, 'Obesity: a challenge to esophagogastric junction integrity', *Gastroenterology*, vol. 130, no. 3, Mar, pp. 639-649.

Parmar, C, Zakeri, R, Abouelazayem, M, Shin, TH, Aminian, A, Mahmoud, T, Abu Dayyeh, BK, Wee, MY, Fischer, L, Daams, F & Mahawar, K 2021, 'Esophageal and gastric malignancies after bariatric surgery: a retrospective global study', *Surgery for Obesity and Related Diseases*, in press, DOI: 10.1016/j.soard.2021.11.024.

Parviainen, MT 1997, 'A modification of the acid diazo coupling method (Malloy-Evelyn) for the determination of serum total bilirubin', *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 57, no. 3, May, pp. 275-279.

Payne, JH & DeWind, LT 1969, 'Surgical treatment of obesity', *American Journal of Surgery*, vol. 118, no. 2, Aug, pp. 141-147.

Payne, JH, Dewind, LT & Commons, RR 1963, 'Metabolic observations in patients with jejunocolic shunts', *American Journal of Surgery*, vol. 106, Aug, pp. 273-289.

Perez-Romero, N, Serra, A, Granada, ML, Rull, M, Alastrue, A, Navarro-Diaz, M, Romero, R & Fernandez-Llamazares, J 2010, 'Effects of two variants of Roux-en-Y Gastric bypass on metabolism behaviour: focus on plasma ghrelin concentrations over a 2-year follow-up', *Obesity Surgery*, vol. 20, no. 5, May, pp. 600-609.

Peterli, R, Wölnerhanssen, BK, Peters, T, Vetter, D, Kröll, D, Borbély, Y, Schultes, B, Beglinger, C, Drewe, J, Schiesser, M, Nett, P & Bueter, M 2018, 'Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial', *JAMA*, vol. 319, no. 3, Jan 16, pp. 255-265.

Peters, Y, Honing, J, Kievit, W, Kestens, C, Pestman, W, Nagtegaal, ID, van der Post, RS & Siersema, PD 2019, 'Incidence of Progression of Persistent Nondysplastic Barrett's Esophagus to Malignancy', *Clinical Gastroenterology and Hepatology*, vol. 17, no. 5, Apr, pp. 869-877.e865.

Petersen, WV, Meile, T, Kuper, MA, Zdichavsky, M, Konigsrainer, A & Schneider, JH 2012, 'Functional importance of laparoscopic sleeve gastrectomy for the lower esophageal sphincter in patients with morbid obesity', *Obesity Surgery*, vol. 22, no. 3, Mar, pp. 360-366.

Peterson, LA, Cheskin, LJ, Furtado, M, Papas, K, Schweitzer, MA, Magnuson, TH & Steele, KE 2016, 'Malnutrition in Bariatric Surgery Candidates: Multiple Micronutrient Deficiencies Prior to Surgery', *Obesity Surgery*, vol. 26, no. 4, Apr, pp. 833-838.

Pihlajamäki, J, Grönlund, S, Simonen, M, Käkelä, P, Moilanen, L, Pääkkönen, M, Pirinen, E, Kolehmainen, M, Kärjä, V, Kainulainen, S, Uusitupa, M, Alhava, E, Miettinen, TA & Gylling, H 2010, 'Cholesterol absorption decreases after Roux-en-Y gastric bypass but not after gastric banding', *Metabolism: Clinical and Experimental*, vol. 59, no. 6, Jun, pp. 866-872.

Ponsky, TA, Brody, F & Pucci, E 2005, 'Alterations in gastrointestinal physiology after Roux-en-Y gastric bypass', *Journal of the American College of Surgeons*, vol. 201, no. 1, Jul, pp. 125-131.

Pontiroli, AE & Morabito, A 2011, 'Long-term prevention of mortality in morbid obesity through bariatric surgery. a systematic review and meta-analysis of trials performed with gastric banding and gastric bypass', *Annals of Surgery*, vol. 253, no. 3, Mar, pp. 484-487.

Portela, R, Marrerro, K, Vahibe, A, Galvani, C, Billy, H, Abu Dayyeh, B, Clapp, B & Ghanem, OM 2022, 'Bile Reflux After Single Anastomosis Duodenal-Ileal Bypass with Sleeve (SADI-S): a Meta-analysis of 2,029 Patients', *Obesity Surgery*, 9/2/22.

Price, AB 1991, 'The Sydney System: histological division', *Journal of Gastroenterology and Hepatology*, vol. 6, no. 3, May-Jun, pp. 209-222.

PricewaterhouseCoopers 2015, *Weighing the Cost of Obesity: a Case for Action*, PwC Australia, Australia, Viewed: 4/9/19, <https://www.pwc.com.au/publications/healthcare-obesity.html>.

Printen, KJ & Mason, EE 1973, 'Gastric surgery for relief of morbid obesity', *Archives of Surgery*, vol. 106, no. 4, Apr, pp. 428-431.

Prinz, P, Hofmann, T, Ahnis, A, Elbelt, U, Goebel-Stengel, M, Klapp, BF, Rose, M & Stengel, A 2015, 'Plasma bile acids show a positive correlation with body mass index and are negatively associated with cognitive restraint of eating in obese patients', *Frontiers in Neuroscience*, vol. 9, p. 199.

Quero, G, Fiorillo, C, Dallemagne, B, Mascagni, P, Curcic, J, Fox, M & Perretta, S 2020, 'The Causes of Gastroesophageal Reflux after Laparoscopic Sleeve Gastrectomy: Quantitative Assessment of the Structure and Function of the Esophagogastric Junction by Magnetic Resonance Imaging and High-Resolution Manometry', *Obesity Surgery*, vol. 30, no. 6, Jun, pp. 2108-2117.

Qumseya, B, Gendy, S, Wallace, A, Yang, D, Estores, D, Ayzengart, A & Draganov, PV 2020, 'Prevalence of Barrett's esophagus in obese patients undergoing pre-bariatric surgery evaluation: a systematic review and meta-analysis', *Endoscopy*, vol. 52, no. 7, Jul, pp. 537-547.

Ramon, JM, Salvans, S, Crous, X, Puig, S, Goday, A, Benaiges, D, Trillo, L, Pera, M & Grande, L 2012, 'Effect of Roux-en-Y gastric bypass vs sleeve gastrectomy on glucose and gut hormones: a prospective randomised trial', *Journal of Gastrointestinal Surgery*, vol. 16, no. 6, Jun, pp. 1116-1122.

Rangwala, SM, D'Aquino, K, Zhang, YM, Bader, L, Edwards, W, Zheng, S, Eckardt, A, Lacombe, A, Pick, R, Moreno, V, Kang, L, Jian, W, Arnoult, E, Case, M, Jenkinson, C, Chi, E, Swanson, RV, Kievit, P, Grove, K, Macielag, M, Erion, MD, SinhaRoy, R & Leonard, JN 2019, 'A Long-Acting PYY(3-36) Analog Mediates Robust Anorectic Efficacy with Minimal Emesis in Nonhuman Primates', *Cell Metabolism*, vol. 29, no. 4, Apr 2, pp. 837-843.e835.

Rath, HC, Timmer, A, Kunkel, C, Endlicher, E, Grossmann, J, Hellerbrand, C, Herfarth, HH, Lock, G, Sahrbacher, U, Schölmerich, J, Kullmann, F & Messmann, H 2004, 'Comparison of interobserver agreement for different scoring systems for reflux esophagitis: Impact of level of experience', *Gastrointestinal Endoscopy*, vol. 60, no. 1, Jul, pp. 44-49.

Rawla, P & Barsouk, A 2019, 'Epidemiology of gastric cancer: global trends, risk factors and prevention', *Przegląd Gastroenterologiczny*, vol. 14, no. 1, pp. 26-38.

Ren, CJ, Patterson, E & Gagner, M 2000, 'Early results of laparoscopic biliopancreatic diversion with duodenal switch: a case series of 40 consecutive patients', *Obesity Surgery*, vol. 10, no. 6, Dec, pp. 514-523; discussion 524.

Renehan, AG, Tyson, M, Egger, M, Heller, RF & Zwahlen, M 2008, 'Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies', *Lancet*, vol. 371, no. 9612, Feb 16, pp. 569-578.

Reveiller, M, Ghatak, S, Toia, L, Kalatskaya, I, Stein, L, D'Souza, M, Zhou, Z, Bandla, S, Gooding, WE, Godfrey, TE & Peters, JH 2012, 'Bile exposure inhibits expression of squamous differentiation genes in human esophageal epithelial cells', *Annals of Surgery*, vol. 255, no. 6, Jun, pp. 1113-1120.

Ri, M, Aikou, S & Seto, Y 2018, 'Obesity as a surgical risk factor', *Ann Gastroenterol Surg*, vol. 2, no. 1, Jan, pp. 13-21.

Rodrigo, DC, Jill, S, Daniel, M, Kimberly, C & Maher, EC 2020, 'Which Factors Correlate with Marginal Ulcer After Surgery for Obesity?', *Obesity Surgery*, vol. 30, no. 12, Dec, pp. 4821-4827.

Rosenthal, RJ, Diaz, AA, Arvidsson, D, Baker, RS, Basso, N, Bellanger, D, Boza, C, El Mourad, H, France, M, Gagner, M, Galvao-Neto, M, Higa, KD, Himpens, J, Hutchinson, CM, Jacobs, M, Jorgensen, JO, Jossart, G, Lakdawala, M, Nguyen, NT, Nocca, D, Prager, G, Pomp, A, Ramos, AC, Rosenthal, RJ, Shah, S, Vix, M, Wittgrove, A & Zundel, N 2012, 'International Sleeve Gastrectomy Expert Panel Consensus Statement: best practice guidelines based on experience of >12,000 cases', *Surgery for Obesity and Related Diseases*, vol. 8, no. 1, Jan-Feb, pp. 8-19.

Roust, LR & DiBaise, JK 2017, 'Nutrient deficiencies prior to bariatric surgery', *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 20, no. 2, Mar, pp. 138-144.

Runkel, M & Runkel, N 2019, 'Esophago-Gastric Cancer after One Anastomosis Gastric Bypass (OAGB)', *Chirurgia*, vol. 114, no. 6, Nov-Dec, pp. 686-692.

Rutledge, R 2001, 'The mini-gastric bypass: experience with the first 1,274 cases', *Obesity Surgery*, vol. 11, no. 3, Jun, pp. 276-280.

Rutledge, R, Kular, K & Manchanda, N 2019, 'The Mini-Gastric Bypass original technique', *International Journal of Surgery*, vol. 61, Jan, pp. 38-41.

Ruz, M, Carrasco, F, Rojas, P, Codoceo, J, Inostroza, J, Basfi-Fer, K, Valencia, A, Csendes, A, Papapietro, K, Pizarro, F, Olivares, M, Westcott, JL, Hambidge, KM & Krebs, NF 2012, 'Heme- and nonheme-iron absorption and iron status 12 mo after sleeve gastrectomy and Roux-en-Y gastric bypass in morbidly obese women', *American Journal of Clinical Nutrition*, vol. 96, no. 4, Oct, pp. 810-817.

Saarinen, T, Pietiläinen, KH, Loimaala, A, Ihalainen, T, Sammalkorpi, H, Penttilä, A & Juuti, A 2020, 'Bile Reflux is a Common Finding in the Gastric Pouch After One Anastomosis Gastric Bypass', *Obesity Surgery*, vol. 30, no. 3, Mar, pp. 875-881.

Saarinen, T, Rasanen, J, Salo, J, Loimaala, A, Pitkonen, M, Leivonen, M & Juuti, A 2017, 'Bile Reflux Scintigraphy After Mini-Gastric Bypass', *Obesity Surgery*, vol. 27, no. 8, Aug, pp. 2083-2089.

Saber, AA, Elgamal, MH & McLeod, MK 2008, 'Bariatric surgery: the past, present, and future', *Obesity Surgery*, vol. 18, no. 1, Jan, pp. 121-128.

Salama, TMS & Hassan, MI 2017, 'Incidence of Biliary Reflux Esophagitis after Laparoscopic Omega Loop Gastric Bypass in Morbidly Obese Patients', *Journal of Laparoendoscopic and Advanced Surgical Techniques*, vol. 27, no. 6, pp. 618-622.

Salman, AA, Sultan, A, Abdallah, A, Abdelsalam, A, Mikhail, HMS, Tourky, M, Omar, MG, Youssef, A, Ahmed, RA, Elkassar, H, Seif El Nasr, SM, Shaaban, HE, Atallah, M, GabAllah, GMK & Salman, MA 2020, 'Effect of weight loss induced by laparoscopic sleeve gastrectomy on liver histology and serum adipokine levels', *Journal of Gastroenterology and Hepatology*, Mar 9.

Salminen, P, Helmiö, M, Ovaska, J, Juuti, A, Leivonen, M, Peromaa-Haavisto, P, Hurme, S, Soinio, M, Nuutila, P & Victorzon, M 2018, 'Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial', *JAMA*, vol. 319, no. 3, pp. 241-254.

Salmon, PA 1971, 'The results of small intestine bypass operations for the treatment of obesity', *Surgery, Gynecology and Obstetrics*, vol. 132, no. 6, Jun, pp. 965-979.

Sánchez-Pernaute, A, Rubio Herrera, MA, Pérez-Aguirre, E, García Pérez, JC, Cabrerizo, L, Díez Valladares, L, Fernández, C, Talavera, P & Torres, A 2007, 'Proximal Duodenal–Ileal End-to-Side Bypass with Sleeve Gastrectomy: Proposed Technique', *Obesity Surgery*, vol. 17, no. 12, 2007/12/01, pp. 1614-1618.

Sarosi, G, Brown, G, Jaiswal, K, Feagins, LA, Lee, E, Crook, TW, Souza, RF, Zou, YS, Shay, JW & Spechler, SJ 2008, 'Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus', *Diseases of the Esophagus*, vol. 21, no. 1, pp. 43-50.

Savary, M & Miller, G 1978, *The Esophagus: Handbook and atlas of endoscopy*, Verlag Gassmann AG, Solothurn, Switzerland.

Schaap, FG, Trauner, M & Jansen, PL 2014, 'Bile acid receptors as targets for drug development', *Nature Reviews: Gastroenterology & Hepatology*, vol. 11, no. 1, Jan, pp. 55-67.

Schafer, AL, Weaver, CM, Black, DM, Wheeler, AL, Chang, H, Szefc, GV, Stewart, L, Rogers, SJ, Carter, JT, Posselt, AM, Shoback, DM & Sellmeyer, DE 2015, 'Intestinal Calcium Absorption Decreases Dramatically After Gastric Bypass Surgery Despite Optimization of Vitamin D Status', *Journal of Bone and Mineral Research*, vol. 30, no. 8, Aug, pp. 1377-1385.

Schauer, PR, Bhatt, DL, Kirwan, JP, Wolski, K, Aminian, A, Brethauer, SA, Navaneethan, SD, Singh, RP, Pothier, CE, Nissen, SE & Kashyap, SR 2017, 'Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes', *New England Journal of Medicine*, vol. 376, no. 7, Feb 16, pp. 641-651.

Schauer, PR, Kashyap, SR, Wolski, K, Brethauer, SA, Kirwan, JP, Pothier, CE, Thomas, S, Abood, B, Nissen, SE & Bhatt, DL 2012, 'Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes', *New England Journal of Medicine*, vol. 366, no. 17, pp. 1567-1576.

Schollenberger, AE, Karschin, J, Meile, T, Küper, MA, Königsrainer, A & Bischoff, SC 2016, 'Impact of protein supplementation after bariatric surgery: A randomized controlled double-blind pilot study', *Nutrition*, vol. 32, no. 2, Feb, pp. 186-192.

Scopinaro, N, Gianetta, E, Civalleri, D, Bonalumi, U & Bachi, V 1979, 'Bilio-pancreatic bypass for obesity: II. Initial experience in man', *British Journal of Surgery*, vol. 66, no. 9, Sep, pp. 618-620.

Scott, HW, Jr., Dean, RH, Shull, HJ & Gluck, F 1977, 'Results of jejunoileal bypass in two hundred patients with morbid obesity', *Surgery, Gynecology and Obstetrics*, vol. 145, no. 5, Nov, pp. 661-673.

Scott, HW, Jr., Dean, RH, Shull, HJ & Gluck, FW 1976, 'Metabolic complications of jejunoileal bypass operations for morbid obesity', *Annual Review of Medicine*, vol. 27, pp. 397-405.

Seery, JP 2002, 'Stem cells of the oesophageal epithelium', *Journal of Cell Science*, vol. 115, no. Pt 9, May 1, pp. 1783-1789.

Services Australia 2021, *Medicare Item Reports*, Australian Government, Accessed 25/8/21, <http://medicarestatistics.humanservices.gov.au/>.

Seyfried, F, Phetcharaburanin, J, Glymenaki, M, Nordbeck, A, Hankir, M, Nicholson, JK, Holmes, E, Marchesi, JR & Li, JV 2021, 'Roux-en-Y gastric bypass surgery in Zucker rats induces bacterial and systemic metabolic changes independent of caloric restriction-induced weight loss', *Gut Microbes*, vol. 13, no. 1, Jan-Dec, pp. 1-20.

Shaffer, EA, McOrmond, P & Duggan, H 1980, 'Quantitative cholescintigraphy: assessment of gallbladder filling and emptying and duodenogastric reflux', *Gastroenterology*, vol. 79, no. 5 Pt 1, Nov, pp. 899-906.

Shah, S, Shah, P, Todkar, J, Gagner, M, Sonar, S & Solav, S 2010, 'Prospective controlled study of effect of laparoscopic sleeve gastrectomy on small bowel transit time and gastric emptying half-time in morbidly obese patients with type 2 diabetes mellitus', *Surgery for Obesity and Related Diseases*, vol. 6, no. 2, pp. 152-157.

Shankar, SS, Mixson, LA, Chakravarthy, M, Chisholm, R, Acton, AJ, Jones, R, Mattar, SG, Miller, DL, Petry, L, Beals, CR, Stoch, SA, Kelley, DE & Considine, RV 2017, 'Metabolic improvements following Roux-en-Y surgery assessed by solid meal test in subjects with short duration type 2 diabetes', *BMC Obesity*, vol. 4, p. 10.

Sharma, N, Agrawal, A, Freeman, J, Vela, MF & Castell, D 2008, 'An analysis of persistent symptoms in acid-suppressed patients undergoing impedance-pH monitoring', *Clinical Gastroenterology and Hepatology*, vol. 6, no. 5, May, pp. 521-524.

Sharma, P, Shaheen, NJ, Katzka, D & Bergman, J 2020, 'AGA Clinical Practice Update on Endoscopic Treatment of Barrett's Esophagus With Dysplasia and/or Early Cancer: Expert Review', *Gastroenterology*, vol. 158, no. 3, Feb, pp. 760-769.

Shaw, MJ, Talley, NJ, Beebe, TJ, Rockwood, T, Carlsson, R, Adlis, S, Fendrick, AM, Jones, R, Dent, J & Bytzer, P 2001, 'Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease', *American Journal of Gastroenterology*, vol. 96, no. 1, Jan, pp. 52-57.

Shenouda, MM, Harb, SE, Mikhail, SAA, Mokhtar, SM, Osman, AMA, Wassef, ATS, Rizkallah, NNH, Milad, NM, Anis, SE, Nabil, TM, Zaki, NS & Halepian, A 2018, 'Bile Gastritis Following Laparoscopic Single Anastomosis Gastric Bypass: Pilot Study to Assess Significance of Bilirubin Level in Gastric Aspirate', *Obesity Surgery*, vol. 28, no. 2, Feb, pp. 389-395.

Sifrim, D, Castell, D, Dent, J & Kahrilas, PJ 2004, 'Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux', *Gut*, vol. 53, no. 7, Jul, pp. 1024-1031.

Silny, J 1991, 'Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility', *Neurogastroenterology and Motility*, vol. 3, no. 3, pp. 151-162.

Singh, M, Lee, J, Gupta, N, Gaddam, S, Smith, BK, Wani, SB, Sullivan, DK, Rastogi, A, Bansal, A, Donnelly, JE & Sharma, P 2013, 'Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial', *Obesity (Silver Spring)*, vol. 21, no. 2, Feb, pp. 284-290.

Singh, S, Garg, SK, Singh, PP, Iyer, PG & El-Serag, HB 2014, 'Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis', *Gut*, vol. 63, no. 8, Aug, pp. 1229-1237.

Sioka, E, Tzovaras, G, Perivoliotis, K, Bakalis, V, Zachari, E, Magouliotis, D, Tassiopoulou, V, Potamianos, S, Kapsoritakis, A, Poultsidi, A, Tepetes, K, Chatzitheofilou, C & Zacharoulis, D 2018, 'Impact of Laparoscopic Sleeve Gastrectomy on Gastrointestinal Motility', *Gastroenterology Research and Practice*, vol. 2018, p. 4135813.

Small, DM, Dowling, RH & Redinger, RN 1972, 'The enterohepatic circulation of bile salts', *Archives of Internal Medicine*, vol. 130, no. 4, Oct, pp. 552-573.

Smith, CD, Herkes, SB, Behrns, KE, Fairbanks, VF, Kelly, KA & Sarr, MG 1993, 'Gastric acid secretion and vitamin B12 absorption after vertical Roux-en-Y gastric bypass for morbid obesity', *Annals of Surgery*, vol. 218, no. 1, Jul, pp. 91-96.

Smythe, A, Bird, NC & Johnson, AG 1992, 'Continuous monitoring of sodium ion concentration in the human stomach--a new technique for the detection of duodenogastric reflux', *Digestion*, vol. 52, no. 1, pp. 20-25.

Sobala, GM, O'Connor, HJ, Dewar, EP, King, RF, Axon, AT & Dixon, MF 1993, 'Bile reflux and intestinal metaplasia in gastric mucosa', *Journal of Clinical Pathology*, vol. 46, no. 3, Mar, pp. 235-240.

Sohrabi, C, Mathew, G, Franchi, T, Kerwan, A, Griffin, M, Soleil C Del Mundo, J, Ali, SA, Agha, M & Agha, R 2021, 'Impact of the coronavirus (COVID-19) pandemic on scientific research and implications for clinical academic training - A review', *International Journal of Surgery*, vol. 86, pp. 57-63.

Sorgi, M, Wolverson, RL, Mosimann, F, Donovan, IA, Alexander-Williams, J & Harding, LK 1984, 'Sensitivity and reproducibility of a bile reflux test using 99mTc HIDA', *Scandinavian Journal of Gastroenterology. Supplement*, vol. 92, pp. 30-32.

Souza, RF, Huo, X, Mittal, V, Schuler, CM, Carmack, SW, Zhang, HY, Zhang, X, Yu, C, Hormi-Carver, K, Genta, RM & Spechler, SJ 2009, 'Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury', *Gastroenterology*, vol. 137, no. 5, Nov, pp. 1776-1784.

Spechler, SJ, Sharma, P, Souza, RF, Inadomi, JM & Shaheen, NJ 2011, 'American Gastroenterological Association technical review on the management of Barrett's esophagus', *Gastroenterology*, vol. 140, no. 3, Mar, pp. e18-52; quiz e13.

Spechler, SJ & Souza, RF 2014, 'Barrett's esophagus', *New England Journal of Medicine*, vol. 371, no. 9, Aug 28, pp. 836-845.

Steenackers, N, Gesquiere, I & Matthys, C 2018, 'The relevance of dietary protein after bariatric surgery: what do we know?', *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 21, no. 1, Jan, pp. 58-63.

Stein, HJ, Smyrk, TC, DeMeester, TR, Rouse, J & Hinder, RA 1992, 'Clinical value of endoscopy and histology in the diagnosis of duodenogastric reflux disease', *Surgery*, vol. 112, no. 4, Oct, pp. 796-803; discussion 803-794.

Steinert, RE, Feinle-Bisset, C, Asarian, L, Horowitz, M, Beglinger, C & Geary, N 2017, 'Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB', *Physiological Reviews*, vol. 97, no. 1, Jan, pp. 411-463.

Stipa, F, Stein, HJ, Feussner, H, Kraemer, S & Siewert, JR 1997, 'Assessment of non-acid esophageal reflux: comparison between long-term reflux aspiration test and fiberoptic bilirubin monitoring', *Diseases of the Esophagus*, vol. 10, no. 1, Jan, pp. 24-28.

Stoker, DL, Williams, JG, MacLeod, MA & Colin-Jones, DG 1990, 'The evaluation of a gastric bile probe', *Nuclear Medicine Communications*, vol. 11, no. 11, Nov, pp. 777-790.

Stolte, M & Meining, A 2001, 'The updated Sydney system: classification and grading of gastritis as the basis of diagnosis and treatment', *Canadian Journal of Gastroenterology*, vol. 15, no. 9, Sep, pp. 591-598.

Suarez Llanos, JP, Fuentes Ferrer, M, Alvarez-Sala-Walther, L, Garcia Bray, B, Medina Gonzalez, L, Breton Lesmes, I & Moreno Esteban, B 2015, 'Protein Malnutrition Incidence Comparison after Gastric Bypass Versus Biliopancreatic Diversion', *Nutricion Hospitalaria*, vol. 32, no. 1, Jul 1, pp. 80-86.

Sun, D, Wang, X, Gai, Z, Song, X, Jia, X & Tian, H 2015, 'Bile acids but not acidic acids induce Barrett's esophagus', *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 2, pp. 1384-1392.

Sundbom, M, Hedenstrom, H & Gustavsson, S 2002, 'Duodenogastric bile reflux after gastric bypass: a cholescintigraphic study', *Digestive Diseases and Sciences*, vol. 47, no. 8, Aug, pp. 1891-1896.

Suter, M 2020, 'Gastroesophageal Reflux Disease, Obesity, and Roux-en-Y Gastric Bypass: Complex Relationship-a Narrative Review', *Obesity Surgery*, vol. 30, no. 8, Aug, pp. 3178-3187.

Svane, MS, Bojsen-Møller, KN, Martinussen, C, Dirksen, C, Madsen, JL, Reitelseder, S, Holm, L, Rehfeld, JF, Kristiansen, VB, van Hall, G, Holst, JJ & Madsbad, S 2019, 'Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy', *Gastroenterology*, vol. 156, no. 6, May, pp. 1627-1641.e1621.

Szymański, M, Marek, I, Wilczyński, M, Janczy, A, Bigda, J, Kaska, Ł & Proczko-Stepaniak, M 2021, 'Evaluation of esophageal pathology in a group of patients 2 years after one-anastomosis gastric bypass (OAGB) - Cohort study', *Obesity Research & Clinical Practice*, viewed Dec 15, in press, DOI: 10.1016/j.orcp.2021.12.001.

Tack, J, Bisschops, R, Koek, G, Sifrim, D, Lerut, T & Janssens, J 2003, 'Dietary restrictions during ambulatory monitoring of duodenogastroesophageal reflux', *Digestive Diseases and Sciences*, vol. 48, no. 7, Jul, pp. 1213-1220.

Tack, J, Koek, G, Demedts, I, Sifrim, D & Janssens, J 2004, 'Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both?', *American Journal of Gastroenterology*, vol. 99, no. 6, Jun, pp. 981-988.

Tam, CS, Lecoultre, V & Ravussin, E 2011, 'Novel strategy for the use of leptin for obesity therapy', *Expert Opinion on Biological Therapy*, vol. 11, no. 12, pp. 1677-1685.

The Obesity Collective 2019, *Weighing in: Australia's Growing Obesity Epidemic*, Viewed: 20/12/21, <https://www.obesityaustralia.org/publications-and-documents>.

Thong, FS, Hudson, R, Ross, R, Janssen, I & Graham, TE 2000, 'Plasma leptin in moderately obese men: independent effects of weight loss and aerobic exercise', *American Journal of Physiology: Endocrinology and Metabolism*, vol. 279, no. 2, Aug, pp. E307-313.

Thorsen, B, Gjeilo, KH, Sandvik, J, Follestad, T, Græslie, H & Nymo, S 2021, 'Self-Reported Gastrointestinal Symptoms Two To Four Years After Bariatric Surgery. A Cross-Sectional Study Comparing Roux-en-Y Gastric Bypass and Laparoscopic Sleeve Gastrectomy', *Obesity Surgery*, vol. 31, no. 10, Oct, pp. 4338-4346.

Tibbling Grahn, L, Blackadder, L, Franzen, T & Kullman, E 2002, 'Gastric bile monitoring: an in vivo and in vitro study of Bilitec reliability', *Scandinavian Journal of Gastroenterology*, vol. 37, no. 11, Nov, pp. 1334-1337.

Tobey, NA, Carson, JL, Alkiek, RA & Orlando, RC 1996, 'Dilated intercellular spaces: a morphological feature of acid reflux--damaged human esophageal epithelium', *Gastroenterology*, vol. 111, no. 5, Nov, pp. 1200-1205.

Tolin, RD, Malmud, LS, Stelzer, F, Menin, R, Makler, PT, Jr., Applegate, G & Fisher, RS 1979, 'Enterogastric reflux in normal subjects and patients with Bilroth II gastroenterostomy. Measurement of enterogastric reflux', *Gastroenterology*, vol. 77, no. 5, Nov, pp. 1027-1033.

Tolone, S, Cristiano, S, Savarino, E, Lucido, FS, Fico, DI & Docimo, L 2016, 'Effects of omega-loop bypass on esophagogastric junction function', *Surgery for Obesity and Related Diseases*, vol. 12, no. 1, Jan, pp. 62-69.

Tolone, S, Limongelli, P, del Genio, G, Brusciano, L, Rossetti, G, Amoroso, V, Schettino, P, Avellino, M, Gili, S & Docimo, L 2014, 'Gastroesophageal reflux disease and obesity: do we need to perform reflux testing in all candidates to bariatric surgery?', *International Journal of Surgery*, vol. 12 Suppl 1, pp. S173-177.

Tolone, S, Musella, M, Savarino, E, Cristiano, S, Docimo, L & Deitel, M 2019, 'Esophagogastric junction function and gastric pressure profile after minigastric bypass compared with Billroth II', *Surgery for Obesity and Related Diseases*, vol. 15, no. 4, Apr, pp. 567-574.

Torgerson, JS, Lindroos, AK, Näslund, I & Peltonen, M 2003, 'Gallstones, gallbladder disease, and pancreatitis: cross-sectional and 2-year data from the Swedish Obese Subjects (SOS) and SOS reference studies', *American Journal of Gastroenterology*, vol. 98, no. 5, May, pp. 1032-1041.

Tornese, S, Aiolfi, A, Bonitta, G, Rausa, E, Guerrazzi, G, Bruni, PG, Micheletto, G & Bona, D 2019, 'Remnant Gastric Cancer After Roux-en-Y Gastric Bypass: Narrative Review of the Literature', *Obesity Surgery*, vol. 29, no. 8, Aug, pp. 2609-2613.

Toro, JP, Lin, E, Patel, AD, Davis, SS, Jr., Sanni, A, Urrego, HD, Sweeney, JF, Srinivasan, JK, Small, W, Mittal, P, Sekhar, A & Moreno, CC 2014, 'Association of radiographic morphology with early gastroesophageal reflux disease and satiety control after sleeve gastrectomy', *Journal of the American College of Surgeons*, vol. 219, no. 3, Sep, pp. 430-438.

Torres, JC, Oca, CF & Garrison, RN 1983, 'Gastric bypass: Roux-en-Y gastrojejunostomy from the lesser curvature', *Southern Medical Journal*, vol. 76, no. 10, Oct, pp. 1217-1221.

Trung, VN, Yamamoto, H, Furukawa, A, Yamaguchi, T, Murata, S, Yoshimura, M, Murakami, Y, Sato, S, Otani, H, Ugi, S, Morino, K, Maegawa, H & Tani, T 2013, 'Enhanced Intestinal Motility during Oral Glucose Tolerance Test after Laparoscopic Sleeve Gastrectomy: Preliminary Results Using Cine Magnetic Resonance Imaging', *PloS One*, vol. 8, no. 6, pp. e65739-e65739.

Tschop, M, Weyer, C, Tataranni, PA, Devanarayan, V, Ravussin, E & Heiman, ML 2001, 'Circulating ghrelin levels are decreased in human obesity', *Diabetes*, vol. 50, no. 4, Apr, pp. 707-709.

Tulchinsky, M, Ciak, BW, Delbeke, D, Hilson, A, Holes-Lewis, KA, Stabin, MG & Ziessman, HA 2010, 'SNM practice guideline for hepatobiliary scintigraphy 4.0', *Journal of Nuclear Medicine Technology*, vol. 38, no. 4, Dec, pp. 210-218.

United Nations Scientific Committee on the Effects of Atomic Radiation 2008, *Sources and effects of ionizing radiation*, United Nations, Viewed: 4/1/21, <http://www.unscear.org/unscear/en/publications/2008_1.html>.

Vaezi, MF, Lacamera, RG & Richter, JE 1994, 'Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system', *American Journal of Physiology*, vol. 267, no. 6 Pt 1, Dec, pp. G1050-1057.

Vakil, N, van Zanten, SV, Kahrilas, P, Dent, J & Jones, R 2006, 'The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus', *American Journal of Gastroenterology*, vol. 101, no. 8, Aug, pp. 1900-1920; quiz 1943.

Valezi, AC, Herbella, FA, Junior, JM & de Almeida Menezes, M 2012, 'Esophageal motility after laparoscopic Roux-en-Y gastric bypass: the manometry should be preoperative examination routine?', *Obesity Surgery*, vol. 22, no. 7, Jul, pp. 1050-1054.

Vella, E, Hovorka, Z, Yarbrough, DE & McQuitty, E 2017, 'Bile reflux of the remnant stomach following Roux-en-Y gastric bypass: an etiology of chronic abdominal pain treated with remnant gastrectomy', *Surgery for Obesity and Related Diseases*, vol. 13, no. 8, Aug, pp. 1278-1283.

Verbeek, RE, Leenders, M, Ten Kate, FJ, van Hillegersberg, R, Vleggaar, FP, van Baal, JW, van Oijen, MG & Siersema, PD 2014, 'Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study', *American Journal of Gastroenterology*, vol. 109, no. 8, Aug, pp. 1215-1222.

Vere, CC, Cazacu, S, Comanescu, V, Mogoanta, L, Rogoveanu, I & Ciurea, T 2005, 'Endoscopical and histological features in bile reflux gastritis', *Romanian Journal of Morphology and Embryology*, vol. 46, no. 4, pp. 269-274.

Vigneshwaran, B, Wahal, A, Aggarwal, S, Priyadarshini, P, Bhattacharjee, H, Khadgawat, R & Yadav, R 2016, 'Impact of Sleeve Gastrectomy on Type 2 Diabetes Mellitus, Gastric Emptying Time, Glucagon-Like Peptide 1 (GLP-1), Ghrelin and Leptin in Non-morbidly Obese Subjects with BMI 30-35.0 kg/m(2): a Prospective Study', *Obesity Surgery*, vol. 26, no. 12, Dec, pp. 2817-2823.

Vissapragada, R, Bulamu, NB, Brumfitt, C, Karnon, J, Yazbeck, R & Watson, DI 2021, 'Improving cost-effectiveness of endoscopic surveillance for Barrett's esophagus by reducing low-value care: a review of economic evaluations', *Surgical Endoscopy*, vol. 35, no. 11, Nov, pp. 5905-5917.

Wang, DH 2017, 'The Esophageal Squamous Epithelial Cell-Still a Reasonable Candidate for the Barrett's Esophagus Cell of Origin?', *Cellular and Molecular Gastroenterology and Hepatology*, vol. 4, no. 1, Jul, pp. 157-160.

Wang, FG, Yu, ZP, Yan, WM, Yan, M & Song, MM 2017, 'Comparison of safety and effectiveness between laparoscopic mini-gastric bypass and laparoscopic sleeve gastrectomy: A meta-analysis and systematic review', *Medicine (Baltimore)*, vol. 96, no. 50, Dec, p. e8924.

Wang, G, Agenor, K, Pizot, J, Kotler, DP, Harel, Y, Van Der Schueren, BJ, Quercia, I, McGinty, J & Laferrère, B 2012, 'Accelerated gastric emptying but no carbohydrate malabsorption 1 year after gastric bypass surgery (GBP)', *Obesity Surgery*, vol. 22, no. 8, Aug, pp. 1263-1267.

Wang, JH, Luo, JY, Dong, L, Gong, J & Zuo, AL 2004, 'Composite score of reflux symptoms in diagnosis of gastroesophageal reflux disease', *World Journal of Gastroenterology*, vol. 10, no. 22, Nov 15, pp. 3332-3335.

Wang, W, Wei, PL, Lee, YC, Huang, MT, Chiu, CC & Lee, WJ 2005, 'Short-term results of laparoscopic mini-gastric bypass', *Obesity Surgery*, vol. 15, no. 5, May, pp. 648-654.

Wang, X, Ouyang, H, Yamamoto, Y, Kumar, PA, Wei, TS, Dagher, R, Vincent, M, Lu, X, Bellizzi, AM, Ho, KY, Crum, CP, Xian, W & McKeon, F 2011, 'Residual embryonic cells as precursors of a Barrett's-like metaplasia', *Cell*, vol. 145, no. 7, Jun 24, pp. 1023-1035.

Wang, Y, Yi, XY, Gong, LL, Li, QF, Zhang, J & Wang, ZH 2018, 'The effectiveness and safety of laparoscopic sleeve gastrectomy with different sizes of bougie calibration: A systematic review and meta-analysis', *International Journal of Surgery*, vol. 49, Jan, pp. 32-38.

Wang, Z, Dai, X, Xie, H, Feng, J, Li, Z & Lu, Q 2016, 'The efficacy of staple line reinforcement during laparoscopic sleeve gastrectomy: A meta-analysis of randomized controlled trials', *International Journal of Surgery*, vol. 25, Jan, pp. 145-152.

Warren, JR & Marshall, B 1983, 'Unidentified curved bacilli on gastric epithelium in active chronic gastritis', *Lancet*, vol. 1, no. 8336, Jun 4, pp. 1273-1275.

Watson, DI, Smythe, A, Mangnall, YF & Johnson, AG 1996, 'Detection of duodenal fluid in the oesophagus with a sodium ion selective electrode', *Journal of Gastroenterology and Hepatology*, vol. 11, no. 5, May, pp. 486-490.

Wei, M, Shao, Y, Liu, QR, Wu, QZ, Zhang, X, Zhong, MW, Liu, SZ, Zhang, GY & Hu, SY 2018, 'Bile acid profiles within the enterohepatic circulation in a diabetic rat model after bariatric surgeries', *American Journal of Physiology: Gastrointestinal and Liver Physiology*, vol. 314, no. 5, May 1, pp. G537-g546.

Wenner, J, Johnsson, F, Johansson, J & Oberg, S 2007, 'Wireless esophageal pH monitoring is better tolerated than the catheter-based technique: results from a randomized cross-over trial', *American Journal of Gastroenterology*, vol. 102, no. 2, Feb, pp. 239-245.

Weusten, B, Bisschops, R, Coron, E, Dinis-Ribeiro, M, Dumonceau, JM, Esteban, JM, Hassan, C, Pech, O, Repici, A, Bergman, J & di Pietro, M 2017, 'Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement', *Endoscopy*, vol. 49, no. 2, Feb, pp. 191-198.

Whiteman, DC, Appleyard, M, Bahin, FF, Bobryshev, YV, Bourke, MJ, Brown, I, Chung, A, Clouston, A, Dickins, E, Emery, J, Eslick, GD, Gordon, LG, Grimpen, F, Hebbard, G, Holliday, L, Hourigan, LF, Kendall, BJ, Lee, EY, Levert-Mignon, A, Lord, RV, Lord, SJ, Maule, D, Moss, A, Norton, I, Olver, I, Pavey, D, Raftopoulos, S, Rajendra, S, Schoeman, M, Singh, R, Sitas, F, Smithers, BM, Taylor, AC, Thomas, ML, Thomson, I, To, H, von Dincklage, J, Vuletich, C, Watson, DI & Yusoff, IF 2015, 'Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma', *Journal of Gastroenterology and Hepatology*, vol. 30, no. 5, May, pp. 804-820.

Wilkinson, LH & Peloso, OA 1981, 'Gastric (reservoir) reduction for morbid obesity', *Archives of Surgery*, vol. 116, no. 5, May, pp. 602-605.

Wolf, E, Utech, M, Stehle, P, Busing, M, Stoffel-Wagner, B & Ellinger, S 2015, 'Preoperative micronutrient status in morbidly obese patients before undergoing bariatric surgery: results of a cross-sectional study', *Surgery for Obesity and Related Diseases*, vol. 11, no. 5, Sep-Oct, pp. 1157-1163.

Wölnerhanssen, BK, Peterli, R, Hurme, S, Bueter, M, Helmiö, M, Juuti, A, Meyer-Gerspach, AC, Slawik, M, Peromaa-Haavisto, P, Nuutila, P & Salminen, P 2021, 'Laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy: 5-year outcomes of merged data from two randomized clinical trials (SLEEVEPASS and SM-BOSS)', *British Journal of Surgery*, vol. 108, no. 1, Jan 27, pp. 49-57.

Wong, WM, Bautista, J, Dekel, R, Malagon, IB, Tuchinsky, I, Green, C, Dickman, R, Esquivel, R & Fass, R 2005, 'Feasibility and tolerability of transnasal/per-oral placement of the wireless pH capsule vs. traditional 24-h oesophageal pH monitoring--a randomized trial', *Alimentary Pharmacology and Therapeutics*, vol. 21, no. 2, Jan 15, pp. 155-163.

World Health Organisation 2017, *Obesity*, Accessed 4/9/19, <https://www.who.int/health-topics/obesity>.

Wormsley, KG 1972, 'Aspects of duodeno-gastric reflux in man', *Gut*, vol. 13, no. 4, Apr, pp. 243-250.

Wu, JC, Mui, LM, Cheung, CM, Chan, Y & Sung, JJ 2007, 'Obesity is associated with increased transient lower esophageal sphincter relaxation', *Gastroenterology*, vol. 132, no. 3, Mar, pp. 883-889.

Xu, HC, Pang, YC, Chen, JW, Cao, JY, Sheng, Z, Yuan, JH, Wang, R, Zhang, CS, Wang, LX & Dong, J 2019, 'Systematic Review and Meta-analysis of the Change in Ghrelin Levels After Roux-en-Y Gastric Bypass', *Obesity Surgery*, vol. 29, no. 4, Apr, pp. 1343-1351.

Yang, J, Gao, Z, Williams, DB, Wang, C, Lee, S, Zhou, X & Qiu, P 2018, 'Effect of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy on fasting gastrointestinal and pancreatic peptide hormones: A prospective nonrandomized trial', *Surgery for Obesity and Related Diseases*, vol. 14, no. 10, Oct, pp. 1521-1529.

Yeung, KTD, Penney, N, Ashrafian, L, Darzi, A & Ashrafian, H 2020, 'Does Sleeve Gastrectomy Expose the Distal Esophagus to Severe Reflux?: A Systematic Review and Meta-analysis', *Annals of Surgery*, vol. 271, no. 2, Feb, pp. 257-265.

Zaika, S, Paliy, I, Chernobrovyi, V & Ksenchyn, OO 2020, 'The study and comparative analysis of GerdQ and GSRS Questionnaires on gastroesophageal reflux disease diagnostics', *Przegląd Gastroenterologiczny*, vol. 15, no. 4, pp. 323-329.

Zerbib, F, Roman, S, Ropert, A, des Varannes, SB, Pouderoux, P, Chaput, U, Mion, F, Verin, E, Galmiche, JP & Sifrim, D 2006, 'Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy', *American Journal of Gastroenterology*, vol. 101, no. 9, Sep, pp. 1956-1963.

Zhang, C, Rigbolt, K, Petersen, SL, Biehl Rudkjær, LC, Schwahn, U, Fernandez-Cachon, ML, Bossart, M, Falkenhahn, M, Theis, S, Hübschle, T, Schmidt, T, Just Larsen, P, Vrang, N & Jelsing, J 2019, 'The preprohormone expression profile of enteroendocrine cells following Roux-en-Y gastric bypass in rats', *Peptides*, vol. 118, Aug, p. 170100.

Zhang, C, Zhang, J & Zhou, Z 2021, 'Changes in fasting bile acid profiles after Roux-en-Y gastric bypass and sleeve gastrectomy', *Medicine (Baltimore)*, vol. 100, no. 3, Jan 22, p. e23939.

Zhang, L, Sun, B, Zhou, X, Wei, Q, Liang, S, Luo, G, Li, T & Lü, M 2021, 'Barrett's Esophagus and Intestinal Metaplasia', *Frontiers in Oncology*, vol. 11, p. 630837.