ROLE OF CONTINUOUS GLUCOSE MONITORING TECHNOLOGY FOR TYPE 2 DIABETES MANAGEMENT

A thesis submitted for the fulfilment of the

Degree of Doctor of Philosophy

by

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April 2019
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Thesis Declaration

I certify 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.

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

Signed

Date: 22.4.19
Acknowledgements

There are many people who have been there for me over the course of my PhD journey, all who have provided me with suitable challenges, encouragement, words of wisdom and support. Firstly, I would like to thank my supervisors; Professor Grant Brinkworth, Professor Campbell Thompson and Professor Gary Wittert. I am grateful for your mentorship and guidance and patience during this time. Grant and Campbell, without your camaraderie, quick wit and science banter on a regular basis, PhD life would have been just about getting the job done. With this, I engaged, understood and stood up; thank you for being a great team.

In addition, I would also like to gratefully acknowledge the help from the CSIRO Health and Biosecurity Clinic staff, specifically Ms. Julia Weaver, Ms. Anne McGuffin, Ms. Therese McKinnon, Ms. Vanessa Courage and Dr Eva Pederson, for not only being there for trial support, scheduling, screening, nursing and continuous glucose monitoring device management, but for the ongoing moral support in the early mornings and late nights – lovely ladies! (and the pancakes!)

I have also benefited immensely from the statistical and data management advice and support provided by Ms Kylie Lange, University of Adelaide and Ms Julie Syrette, CSIRO Health and Biosecurity. I am amazed and inspired by their masterful approach to statistics and data-management – I have learnt a great deal from you both.

To co-authors and colleagues, Dr Natalie Luscombe-Marsh and Dr Thomas Wycherley, thank you not only for your expertise and input into the development of the clinical trial, but also
for your encouragement even before the PhD started, for pointing out the value of doing a PhD and providing the tips and pointers for getting through.

I would also like to acknowledge the behavioural expertise of co-author Dr Ian Zajac; thank you for supporting my interest in understanding the patients' experience with real-time continuous glucose monitoring (RT-CGM) and my desire to explore the hope that patients are not facing extra distress when using RT-CGM in their daily lives.

To my private practice colleagues; Dr Paul Leong, Dr Benjamin Teague, Dr Allen Gale and EvolvME staff, thank you for accepting my absence from practice to focus on this PhD work, and for realising CGM’s benefit in the real-world for the patients we see. The enthusiastic discussions have kept my thoughts grounded on application and I cannot wait to work towards applying my learning's with you to further help our patients.

Finally, getting the balance right between time spent on my private practice, PhD and family has been difficult and challenging. I would like to dedicate this thesis to the family lost, in particular Mum, Dad, my brother Peter and brother-in-law Mark, and also to the family by my side through all of this balancing, my husband Paul, my beautiful kids Skye and Mitchell as well as Bob and Lorraine Taylor and my new inspiration in life, my grandson Harrison Lucas, born during the PhD and whom has kept my focus on the good things in life.

Words can’t thank you all enough.
# Conference and Academic Presentations

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<td>2019</td>
<td>2019 Diabetes Medical Nutrition and Treatment Summit</td>
<td>29&lt;sup&gt;th&lt;/sup&gt; March, 2019</td>
<td>Shenzhen, China</td>
<td>Invited Presentation</td>
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<td>Taylor, PJ. et al. Can we use Real-Time Continuous Glucose Monitoring to Improve Effects of a Lifestyle Intervention for Diabetes Control? – Practical Considerations</td>
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<td>Diabetes Association of South Australia, Annual Food and Health Seminar</td>
<td>16&lt;sup&gt;th&lt;/sup&gt; April 2016</td>
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<td>2018</td>
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<td>Taylor, PJ. et al. Association of Glycaemic Variability and the Anti-Glycaemic Medication Effect Score in Adults with Type 2 Diabetes</td>
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<td>Abstract</td>
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<td></td>
<td>The Faculty of Health and Medical Sciences Wednesday Wrap – Research Lecture Series</td>
<td>January 2018, Adelaide, Aus.</td>
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<td>Taylor, PJ. et al. Effectiveness and Acceptability of CGM for Type 2 Diabetes Management – Findings from a Narrative Review.</td>
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2017


Taylor, PJ. et al. Effectives and Acceptability of Continuous Glucose Monitoring for Type 2 Diabetes Management – A Narrative Review.


Taylor, PJ. Eating Your Way to a Healthy Lifestyle; Low Carb Diets in Perspective.


Taylor, PJ. et al. Background of the Development for the CSIRO Low Carbohydrate Diet for Diabetes, Practical Considerations.

2016

**Diabetes Association of South Australia, Annual Food and Health Seminar, 31st March, 2016, Adelaide, Aus. (Invited Oral presentation)**

Taylor, PJ. Fats and Fads, Dietary Trends vs. Science, what’s the take home messages for T2D?

**Royal College of General Practitioners, Diabetes Seminar Series, 1st October, 2016 (Voice Recorded, Oral Presentation)**

Brinkworth, GD. & Taylor, PJ. Comparisons of long-term health effects of a very low and high carbohydrate diet in Obese adults with Type 2 diabetes – Building a Diabetes Lifestyle Program.
**Awards and Grants**

2015-2018  Australian Post Graduate Award (APA) Scholarship

2018  Medtronic and ANZMOSS combined international travel grant $3,200


2015  Joan Mary Woodhill, Young Achievers Award - Dietitians Association Australia

2012  Best Speaker Award (allied health and medical category) - Australia and New Zealand Metabolic and Obesity Surgery Society (ANZMOSS) previously (OSSANZ) 24th Annual Scientific conference, 11th - 13th April, 2012, Darwin, Aus.
Chapter 1: Introduction

1.1 Obesity and Type 2 Diabetes

The epidemic of obesity is one of the most durable public health challenges of this century. Overweight and obesity occur because of a positive energy balance and increases the risk for the development of several chronic diseases including type 2 diabetes (T2D)[1].

Overweight, defined as body mass index (BMI) of 25 to 29.9 kg/m², and obesity, as BMI > 30 kg/m², broadly reflect the risk of morbidity and mortality in overweight and obese adults. While limitations of BMI exist, recognising its limited generalisability in diverse populations and inability to distinguish between excess fat and muscle, these thresholds provide significant clinical value, and are commonly used with the understanding of these limitations [2].

Approximately 30% of the global population is considered either overweight or obese [3]. In Australia, the prevalence of adult overweight and obesity reached 63% in 2017 (11.2 million) [4, 5] and the impact of obesity has been considerable in both developed and developing countries.

Determinants of overweight and obesity are well documented [6, 7]. Despite their complex nature, the built environment (including urbanisation, food accessibility), excess energy intake and physical inactivity are well-established determinants [6-8].

Elevated body weight leads to multiple metabolic aberrations, which can increase the risk of chronic disease, including cardiovascular (CVD) and respiratory diseases, hypertension, hyperlipidaemia, diabetes mellitus and certain cancers. These diseases are associated with increased morbidity and mortality rates and contribute to the burden of disease for the
individual, resulting in poorer quality of life and productivity [3, 9]. Chronic diseases are the major cause of death and disability worldwide [3, 9]. Diabetes mellitus was the second leading cause of obesity-related deaths globally in 2015, contributing to 0.6 (CI 0.4 to 0.7) million deaths and 30.4 (CI 21.5 to 39.9) million disability adjusted life-years (DALY’s) in those with T2D and BMI > 30kg/m² [9].

In Australia, obesity-related chronic diseases contribute to 37% of hospitalisations, 87% of deaths and 61% of the total burden of disease [10]. Diabetes Mellitus (Type 1 and Type 2) accounts for 9.9% of hospitalisations and 10.4% of all deaths, with half of these due to T2D (55%; 9 000 deaths) [4]. At least 80% of disabilities and deaths associated with T2D are classed as being preventable, which can be primarily achieved through lifestyle interventions, including a healthy diet and regular physical activity [9]. Consequently, lifestyle modification remains a foundation for obesity and T2D prevention and management, with the aim of achieving energy balance for weight control in concert with medical management.

1.2 Economic Impact of Type 2 Diabetes

There is clear evidence that diabetes and its associated complications (discussed further in section 1.6) have an undesirable financial burden on both the individual and the health care environments worldwide [11, 12]. The estimated global health expenditure related to diabetes (direct and indirect costs) is USD 1.3 trillion dollars (1.8% of the global gross domestic product (GDP)) with predictions for this to increase to USD $2.1 trillion dollars (2.2% of the GDP) by 2045 [12-14]. The age group with the greatest expenditure in diabetes is those aged 60-69 years (USD $127 billion) with men realising 7% higher expenditure than
women in the same age group [14]. The top 5 countries with the greatest expenditure rates for diabetes were: the USA (International Dollar (ID) $348 billion), China (ID $110 billion), Germany (ID $42 billion), India (ID $31 billion) and Japan (ID $28 billion) [13, 14].

The major drivers of diabetes costs are attributed to direct costs, including complication treatment, which is the greatest component of overall healthcare costs that has increased over 50% in the past decade (2008-2018) [15].

The magnitude of economic burden varies between and within countries. The consistent message is that the economic burden related to diabetes remains high and those most affected live in low to middle income countries. However, 80% of this global health expenditure is projected to be in the world’s highest income countries, displaying an inequity in global health care relating to diabetes management [11, 14, 15]. These costs are not sustainable for all health systems and there is an urgent need to identify financially beneficial solutions for the prevention and management of T2D.

1.3 Diabetes Mellitus and Classifications

Diabetes Mellitus is a chronic, metabolic disease characterised by impaired glucose metabolism. It occurs as a consequence of the deficiency in the production of the hormone insulin, either through autoimmune destruction of the pancreatic β-cells (T1D) or from the chronic loss of β-cells over time in association with insulin resistance (T2D) [16]. Insulin is a peptide hormone secreted by the β-cells located in the pancreas that allows the healthy body to maintain normal glucose control by facilitating cellular glucose uptake from the blood, which is then stored in the muscle and liver for later use [17]. When glucose uptake is
disrupted, elevated blood glucose concentrations occur (hyperglycemia). As blood glucose rises over time, β-cell function deteriorates, resulting in inadequate glucose sensing and worsening hyperglycaemia [16-19]. There is often a long, pre-symptomatic phase before diabetes diagnosis [16, 19]. Duration of glycaemic burden is considered a strong predictor of diabetes related micro- and macrovascular complications. These are complications that are based upon nerve and vascular damage to parts of the body, including diabetic retinopathy (diabetic eye disease); diabetes nephropathy (diabetic kidney disease); peripheral neuropathy (loss of protective sensation, as observed in diabetes foot ulcers and infections); delayed gastric emptying (gastroparesis) and cardiovascular disease (heart disease)[16]. Delay in diagnosis of diabetes is usually a result of the symptoms not being severe enough to be detected by the patient [16, 19]. Section 1.6 further details diabetes complications and their consequences.

Traditional classifications divide diabetes into Type 1 diabetes (T1D) and T2D. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes also include other categories: gestational diabetes mellitus (GDM) and a subclass labelled "specific types of diabetes due to other causes". This latter category captures diabetes secondary to drug or chemical induced diabetes (such as with glucocorticoid use), monogenic diabetes (i.e. neonate diabetes or maturity-onset diabetes in the young) and disease induced diabetes (i.e. pancreatitis or cystic fibrosis induced) [16].

Since 1980, the global prevalence in adults with diabetes mellitus has increased from 108 million in 1980 to 422 million in 2014, with 451 million adults now living with diabetes mellitus and that figure estimated to grow to 693 million by 2045 [12, 14, 20, 21]. Currently 87-91% of adults are reported to have T2D, 7-12% to have T1D and 1-3% other types of
diabetes, including GDM [13, 14, 16, 20]. A further estimated 212 million adults aged 20-79 years are living with undiagnosed diabetes [14].

The heterogeneity of determinants for the two most commonly reported types of diabetes mellitus (T1D and T2D) result in a high variance in clinical presentation and disease progression, therefore diabetes treatment also varies, despite some similarities in the type of diabetes-related complications [16].

T1D, previously known as juvenile diabetes or insulin dependent diabetes mellitus (IDDM), can occur idiopathically, but most cases are characterised by autoimmune related β-cell destruction, leading to complete insulin deficiency [16]. Autoimmune β-cell destruction has many genetic predispositions, and although environmental factors play an additional role, these genetic factors remain poorly defined. Of note, individuals with T1D are predisposed to other autoimmune disorders including Hashimoto’s thyroiditis, Graves disease, Addison’s disease, coeliac disease, vitiligo and pernicious anaemia (vitamin B12 deficiency) [16].

Type 2 diabetes, previously known as adult onset or non-insulin dependent diabetes (NIDDM), is largely a result of the progressive loss of β-cell function and the subsequent reduced insulin secretion. As this is associated with peripheral insulin resistance, T2D is characterised by a relative rather than absolute insulin deficiency [16]. Although definitive aetiology is not known, genetic predisposition plays a role in T2D combined with factors such as excess energy intake, suboptimal nutrient intake and sedentary lifestyles. These factors promote overweight and obesity and are considered to be fuelling the rise in T2D; 45% of T2D is reported to be attributed to overweight and obesity [3, 13, 16, 20, 22].

Gestational diabetes (GDM), or hyperglycaemia in pregnancy, is commonly diagnosed between 24- and 28-weeks’ gestation. It is a form of diabetes characterised by high blood
glucose levels during pregnancy that were not evident prior to gestation [14, 16]. GDM is the most common complication of pregnancy, occurring in 11-14% of pregnancies [3]. During pregnancy, placental hormones (including lactogen and growth hormone) along with tumour necrosis factor alpha (TNFα) and other cytokines, cause insulin resistance that can lead to the onset of GDM [23]. Risk factors for GDM development include maternal age > 40 years, ethnicity, family history of diabetes, BMI > 35kg/m², polycystic ovarian syndrome or previous macrosomia (baby with birth weight > 4500g) and rapid weight gain during pregnancy [14]. Although considered a transient disorder, resolving postpartum, 50% of GDM cases are at increased risk of developing T2D within 5-10 years after delivery [14]. Since GDM confers increased risk for T2D development, those diagnosed with GDM require lifelong screening for T2D [16].

Overall, the epidemic of overweight and obesity in global communities is promoting a rise in the prevalence of T2D that is associated with major health implications. Consequently, there is a critical need to identify effective therapeutic treatment options for the management of T2D. In accordance with this need, this thesis and the related research will focus on overweight and obese individuals with T2D.

1.4 Diagnostic Criteria of Type 2 Diabetes

Diagnosis of T2D commonly proceeds once a patient has presented with classical symptoms of hyperglycaemia. These symptoms include, but are not limited to: increased urinary frequency (Polyuria); increased hunger (Polyphagia); and, increased thirst (Polydipsia). Other features suggesting the diagnosis of T2D include: random blood glucose values of ≥ 200mg/dL (>11.1mmol/L) on more than one occasion; a family history of diabetes; the
presence of overweight or obesity; and, advancing age[16]. The American Diabetes Association have well established clinical diagnostic criteria for the diagnosis of non-pregnant adults based on the following plasma glucose benchmarks: fasting plasma glucose (FPG) OR the 2-hour plasma glucose, obtained during an oral 75g glucose tolerance test, (OGTT) OR glycated haemoglobin (HbA1c%) (See Table 1) [16]. These tests, procedures and their limitations are further described below.

Table 1: Criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Range mg/dL</th>
<th>Range mmol/L</th>
</tr>
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<tbody>
<tr>
<td>Fasting Plasma Glucose (FPG)</td>
<td>&gt;126</td>
<td>&gt;7</td>
</tr>
<tr>
<td>2-hr Oral (75g) Glucose Tolerance Test</td>
<td>&gt;200</td>
<td>&gt;11.1</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>&gt;6.5%</td>
<td>&gt;48 mmol/mol</td>
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Adapted from: American Diabetes Association, Standards of Medical Care in Diabetes 2019

The Fasting Plasma Glucose (FPG) test measures blood glucose in a person who has fasted (no food or caloric based beverage) for the preceding 8-12 hours [16, 19]. The FPG assay is considered relatively easy and inexpensive to implement and it is widely available, but has limitations [19]. FPG is a relatively insensitive marker displaying within individual, within day and between subject variations of up to 12.5% due to biological variations, illness, stress, anxiety, medication usage and pre-test exercise [24]. This level of variation suggests that an individual with a FPG of 126mg/dL (7mmol/L) could experience a FPG range between 110.4 - 141.2 mg/dL (6.8 mmol/L), potentially leading to a false negative reading [24].

The oral glucose tolerance test (OGTT) measures blood glucose after the patient has fasted for the 8-10 hour pre-test period. Following the blood sample, the patient consumes a 75ml glucose solution in water (drink) followed by an assessment of blood glucose 2 hours post-
consumption – post prandial glucose (PPG) [24]. As a measure of the body’s efficiency in metabolising glucose, the OGTT is also a widely used and accepted clinical biomarker for the diagnosis of diabetes. The OGTT has greater sensitivity in detecting increased glucose concentration compared to FPG or Glycated Haemoglobin (HbA1c) [16, 24]. The OGTT also has limitations, including stringent test conditions and cost [19], and within-individual variation of up to 16.7% leading to lack of reproducibility. Consequently, the FPG is favoured as a glucose-based diagnostic test for diabetes, despite similar limitations. Today the OGTT is rarely performed in Australia outside pregnancy [16, 24].

HbA1c is formed by the non-enzymatic attachment of glucose at the N-terminal valine of the \( \beta \)-chain of haemoglobin. Its measurement is used as a clinical marker of chronic glycaemia. Compared to the blood glucose markers detailed above, HbA1c levels are strongly associated with the risk of complications associated with diabetes[19, 25]. HbA1c can be performed randomly in a non-fasted state, making this test clinically attractive [24]. For accuracy and to prevent misdiagnosis, it is recommended by the American Diabetes Association (ADA) that the HbA1c assay is performed using the Diabetes Control and Complications Trial (DCCT) standardised assay and protocol, certified by the National Glycohemoglobin Standardisation Program (NGSP) [16]. Advantages of HbA1c measurement include limited intra-individual biological variability and its high correlation with blood glucose. The test is not influenced by acute factors of stress, illness or exercise. This has also led to HbA1c becoming the reference parameter for assessing the success of therapies aimed at improving blood glucose control and reducing diabetes associated complication risk [19, 24-26].
Given the insidious onset of T2D and asymptomatic increases in blood glucose levels over months and even years, attention has been given to the prevention or delay of the development of T2D. This process begins with assessment of at-risk individuals to determine either the presence of a state of established diabetes or considerable risk of developing diabetes, called prediabetes. Prediabetes is defined as an intermediate form of impaired glucose homeostasis where blood glucose is above the normal range but below that of the clinical diabetes cut off. Prediabetes represents an increased risk of developing T2D and CVD [16, 19]. Prediabetes thresholds are outlined by the American Diabetes Association as impaired fasting glucose (IFG), defined as a fasting plasma glucose or an impaired glucose tolerance (IGT), established by a 2-hour OGTT or an elevated HbA1c (see Table 2) [16, 27]. Both IFG and IGT signify an increased risk of developing diabetes and/or CVD through several metabolic abnormalities including hypertension, hyperglycaemia, hyper-triglyceridaemia, insulin resistance, visceral adiposity and low levels of high-density lipoprotein (HDL) [28].

**Table 2: Criteria for the diagnosis of prediabetes**

<table>
<thead>
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<th>Measure</th>
<th>Range mg/dL</th>
<th>Range mmol/L</th>
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<td>Fasting Plasma Glucose (FPG)</td>
<td>100-125</td>
<td>5.6-6.9</td>
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<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>2-hr Oral (75g) Glucose Tolerance Test</td>
<td>140-199</td>
<td>7.8-11</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>HbA1c %</td>
<td>5.7-6.4%</td>
<td>39-47 mmol/mol</td>
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</table>

Adapted from: American Diabetes Association, Standards of Medical Care in Diabetes 2019
1.5 Pathophysiology of Type 2 Diabetes

Chronic prolonged hyperglycaemias, arising from the body’s inability to maintain glucose homeostasis resulting in β-cell dysfunction will, overtime, contribute to the pathophysiological defects underlying T2D [13, 27, 29].

To understand T2D progression, it is important to understand the conditions within which glycaemia is regulated. Insulin is the key hormone for blood glucose regulation and to maintain normoglycaemia. Normoglycaemia is regulated through a balanced interaction between insulin action and insulin secretion [30]. In healthy individuals, insulin is produced by pancreatic β-cells predominantly in response to nutrient ingestion that enables hepatic and muscle cells to utilise and absorb glucose for energy [29]. Insulin interacts in the liver to suppress glucose production and in the muscle and adipocytes to stimulate the uptake of glucose for optimal glucose control [31].

Progressive β-cell destruction and insulin resistance, predominantly in the liver and muscle, are the two primary pathophysiological features that not only precede and predict T2D but also are cardinal features of established T2D [27, 29, 32].

The pathophysiology of T2D has been studied extensively, with evidence reporting that by the time hyperglycaemia is present, reduction in insulin sensitivity and beta cell function already exists, with reports that patients have already lost 80% of their β-cell function requiring immediate medical intervention [32, 33]. Although genetic predisposition may lead to the onset of insulin resistance, environmental factors, including a sedentary lifestyle, excess nutrient intake and obesity, are insulin resistant states that are implicated in the progression to T2D [17, 30-32, 34]
Insulin resistance arises as a result of nutrient storage pathways developing to maximise efficient energy utilisation when exposed to long-term energy excess [34]. The state of being overweight or obese, leads to lipid (non-esterified fatty acid (NEFA)) accumulation in the liver and skeletal muscle alongside increased circulation of several adipokines. These adipokines increase visceral adiposity, impeding insulin action in these tissues and adding stress to the pancreatic β-cells to increase insulin secretion to counteract the reduction in insulin sensitivity post nutrient ingestion [30, 31, 34]. These factors link the disease progression from insulin resistance to impaired glucose tolerance (prediabetes), and if not treated, through to T2D.

As the disease process develops towards overt T2D, and β-cell dysfunction continues, insulin production and secretion continue to fail and glucose tolerance worsens, resulting in glycotoxicity or more commonly, chronic hyperglycemia. This chronic hyperglycemia further progresses the deterioration of β-cell function until the β-cells reach failure, which is not offset by β-cell proliferation or neogenesis, hence the disease progression is heightened. It is this progressive loss of β-cell function which governs the rate of T2D disease progression [27, 31, 35].

Metabolic derangements of T2D are complicated, including incretin abnormalities. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretins, which account for 90% of the incretin effect within the gastrointestinal tract. Other derangements include increased glucagon secretion from the pancreatic α-cell (hyperglucagonaemia), deranged adipocyte metabolism, resulting in increased plasma free fatty acid concentration, and increased renal glucose reabsorption. All of these factors are associated with the development of glucose intolerance in T2D [33]. To add to the
complexity, environmental and lifestyle and genetic elements play a role in the initiation of insulin resistance and contribute to disease progression. These elements include a family history of T2D, which presents a 2.4-fold increased risk for the disease, with 15-25% of first-degree relatives of patients with T2D developing prediabetes or T2D [16, 22, 30, 31, 36, 37]. The link between obesity and/or insulin resistance with diabetes is subclinical chronic inflammation and stimulation of the immune system, which results in inflammatory markers being raised in insulin resistant states of obesity [35]. Inflammatory markers, including white blood cell count, C-reactive protein (CRP), pro-inflammatory cytokines (tumour necrosis factor TNFα and Interleukin (IL-1β and IL-6)) and chemokines, are elevated in obese and individuals with T2D. These factors are strongly associated with the early development of insulin resistance, progression to prediabetes and manifestation to T2D [19, 29-31, 37]. These markers have been shown to be reduced in those with obesity and T2D who engage in lifestyle changes resulting in weight loss [18, 30, 31, 35].

1.6 Complications of Type 2 Diabetes

While T2D itself can lead to health complications, the severity of multiple comorbidities can be reduced through effective self-management and health practitioner support [16]. The fewer the complications that a patient develops, the lesser their comorbidity burden, the lower their mortality risk and the lower the health care system costs.

Diabetes complications can be commonly described by microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular complications (coronary and peripheral artery disease leading to angina, myocardial infarction or stroke) [38, 39].
It is widely acknowledged that T2D impacts macro-vasculature through persistent hyperglycaemia, which accelerates atherosclerosis through oxidative stress, thus triggering various intracellular signalling pathways that create a pro-inflammatory state [16, 39, 40]. Overtime, this leads to chronic inflammation and arterial wall injury, causing narrowing in the peripheral and coronary vascular systems [16, 39, 41]. Inflammatory mediators, in particular α-Tumour Necrosis Factor (α TNF) expedite the atherosclerotic changes and the development of macro complications [41]. As such, poorly controlled diabetes is an independent risk factor and leading cause of CVD in those with T2D, with diabetes duration also being a key factor [42]. CVD is the leading cause of mortality in individuals already living with diabetes. CVD encompasses hypertension, coronary heart disease, cerebrovascular disease, myocardial infarction, stroke, transient ischaemic attack and atherosclerotic peripheral artery disease. It is coronary heart disease and cerebrovascular disease which accounts for 52% of all deaths for T2D and 44% in T1D [41, 43, 44]. Additional risk factors for progression of CVD in diabetes include dyslipidaemia, insulin resistance, increased plasminogen, increased fibrinogen, microalbuminuria, proteinuria and nephropathy [45].

1.6.1 Chronic Kidney Disease

Diabetes-related chronic kidney disease, or diabetic kidney disease (DKD), affects approximately 20-40% of the diabetic population. DKD may be present at the time of T2D diagnosis and is the primary cause of End Stage Renal Disease (ESRD) necessitating dialysis or kidney transplantation [16]. A declining Estimated Glomerular Filtration Rate (EGFR), hypertension and unstable lipids are all signs of early stages of DKD resulting from glomerular and tubular hypertrophy induced by oxidative stress and chronic inflammation in
association with poorly controlled diabetes [40, 46]. Additional risk factors that enhance the probability of DKD and disease progression to ESRD include: persistent presence of elevated urinary albumin excretion (albuminuria); family history of renal/kidney disease; raised uric acid concentration; increased or worsening hypertension, in parallel with the presence of macrovascular disease (CVD) or other microvascular disease, including diabetic retinopathy [40, 46].

The clinical consequence of these microvascular changes is protein leakage from the kidney (hyper-filtration or increased permeability) leading to microalbuminuria (urine albumin excretion 30-300mg/g creatinine) and progressing to macroalbuminuria (>300mg/g creatinine), which occurs over an estimated 5-15 years [46]. Further decline in glomerular filtration rates can see ESRD being reached in 5-7 years without interventional treatment [46].

1.6.2 Diabetic Retinopathy

Diabetic retinopathy is another microvascular complication of T2D. Although a spectrum of diabetic eye disorders exists, including diabetic macular edema, cataracts and glaucoma, diabetic retinopathy is ranked the fifth most common cause of preventable blindness in adults, affecting one third of the diabetic population [47]. Those with duration of diabetes > 20 years are at the greatest risk of developing diabetic retinopathy [13, 47]. Diabetic retinopathy ensues when capillaries inside the retina are damaged because of poor glucose control [47]. Damage over time progresses from mild to severe to proliferative retinopathy where micro-aneurysms in retinal vessels leak fluid or blood behind the retina [48]. As the retina swells and distorts, vision is impacted and, if not managed, loss of vision and
blindness can occur [48]. Curative treatments are remote, and with diabetes retinopathy one of the leading causes of blindness in the working aged population, preventative strategies are required [47, 48]. Additional factors augmenting the risk of progression from diabetic retinopathy to blindness include prolonged hyperglycaemia, hypertension, nephropathy and dyslipidaemia [13, 47, 48].

Although no further detail has been provided in this thesis, it has been suggested that retinal vessels have similar anatomy to cerebral small vessels, raising the possibility that deleterious changes in the microvascular “at-risk” areas may be responsible for not only nephropathy and retinopathy, but also moderate cognitive changes, largely in the domains of memory, psychomotor speed and executive functioning [49].

1.6.3 Diabetic Neuropathy

Ranges of neuropathies exist as complications of diabetes that can be classified as diabetic neuropathy. This diagnosis is established by the presence of symptoms and/or signs of peripheral or autonomic nerve dysfunction and can be expressed in several different forms including peripheral, autonomic and cardiac autonomic neuropathy. Diabetic neuropathy carries a diverse range of clinical manifestations hindered by asymptomatic presentations (in up to 50% of cases) [16]. Although the mechanisms of nerve-injury from hyperglycaemia are largely still being explored, a suggestion is that prolonged hyperglycaemia damages nerve cells by impairing vasodilation. There is capillary basement membrane thickening resulting from accumulated advanced glycosylated end products (AGEs) and oxidative stress [39, 50].
There is a range of symptoms associated with diabetes neuropathy dependent on the class of motor or sensory fibres involved. Commonly, neuropathy starts with unpleasant sensations (dysaesthesia) which include pain and burning (small fibre involvement/loss) progressing to numbness and loss of protective sensations (large fibre involvement/loss (LOPS)) [16].

The presence of LOPS indicates lost distal sensorimotor polyneuropathy. This polyneuropathy is a risk factor for diabetes foot ulceration and Charcot arthropathy. The lack of sensation in the lower extremities can be compounded by concomitant peripheral vascular disease and may progress to digital or limb amputation [16, 38, 39, 50, 51].

Evidence suggests that lower limb morbidity such as foot ulcers is one of the most disabling and painful diabetes complications [51-53]. Up to 15% of the population with T2D will experience foot ulceration and 11% will progress to amputation if left poorly or untreated [16, 52, 53]. The cost of amputations attributed to sub-optimally managed diabetes and subsequent foot infections ranges between USD $35,000-$45,000 per amputation depending on the severity of the case [53].

Other neuropathic disorders include autonomic neuropathy, which can present as orthostatic hypotension, gastroparesis, bowel and bladder disorders and erectile dysfunction. Cardiac autonomic neuropathy (CAN) is associated with mortality independent of other cardiovascular risk factors [16]. Cardiac autonomic neuropathy, largely asymptomatic, is identified by decreased heart rate variability with deep breathing, and, if the disease becomes advanced, is associated with resting tachycardia and orthostatic hypotension [16].
1.6.4 Psychological Functioning

Another consequence of poorly controlled diabetes is impaired psychological functioning, usually a consequence of microvascular and macrovascular injury [54, 55]. The clinical features and potential health complications of T2D discussed above, also contribute to psychological morbidity, reflected by emotional stress, poor health-related quality of life and diabetes distress [54-56]. Disagreement in the literature exists over the role of stress and depression in the pathogenesis of T2D, however, the commonality remains that health-related quality of life (HRQOL) becomes worse when complications start to develop, or comorbidities co-exist in individuals with T2D [56]. HRQOL is a multifaceted assessment model capturing physical, social and psychological traits of health. Its assessment permits the effects of T2D (the disease) or its treatment to be measured [57]. Recently, a secondary analysis (n=5,367) measured the impact of HRQOL over 5-12 years (mean: 8.7 years) and compared individuals with T2D or incidence of diabetes (T2D not present at baseline but classified at follow up) (n=779) to those living without diabetes (n=4,588). Individuals were aged 45-74 years at baseline [58]. This study showed that the decline in HRQOL was double for individuals with T2D, or incidence of T2D, compared to those living without T2D, suggesting that time augments poorer HRQOL in those with T2D [58]. Poorly controlled T2D has been linked with mild to moderate cognitive decline, mostly in the domains of memory, psychomotor speed and executive function, and this decline can be seen early in the disease process [49]. Risk factors for the decline include presence of microvascular complications, diabetes duration and glycaemic control. Moreover, suggestions exist that T2D increases the risk of dementia in the elderly T2D population [49].
Despite the heterogeneity of diabetes-related complications, some commonalities exist. Specifically, there are modifiable risk factors, and, with modification, the number and severity of complications diminish; addressing one factor can improve prospects in a variety of complications. Onset and progression of diabetes-related micro- and macrovascular complications are primarily related to the duration and magnitude of hyperglycaemia and hypertension, presence of visceral and/or central adiposity, dyslipidaemia and obesity, which represent primary therapeutic targets. Broad treatment strategies, inclusive of multidisciplinary medical and nutritional therapies, target these risk factors. Successful therapy results in delayed onset or slower progression of diabetes-related complications with longer median survival rates and improved HRQOL [16, 50, 59]. Nonetheless, once patients reach an advanced stage of complications, their care usually may focus more upon symptom management strategies for improved quality of life and rely on using targeted pharmacological and medical nutrition therapies to achieve comfort care (i.e. pain management) [16]. Therapeutic options and treatment strategies for T2D management will be further discussed in the following section.

### 1.7 Therapeutic Interventions of Type 2 Diabetes

The risk factors for developing complications of T2D, listed in Section 1.6, have multiple and diverse, short- and long-term health consequences that are underpinned by poor glycaemic control. Poor glycaemic control underlies the symptoms and complications of diabetes and so diabetes therapies focus on the pursuit of normoglycaemia. Markers of glycaemic control are vital in routine clinical practice and clinical trials to guide treatment and to investigate the effectiveness of treatments on a patient’s/participant’s glycaemic outcomes.
As a result of landmark studies providing evidence that glycated haemoglobin (HbA1c) is linked to macrovascular complications, HbA1c has become the benchmark for diabetes management [60, 61].

HbA1c and FPG are commonly used to assess glycaemic control in clinical practice [16]. With emerging technologies being able to assess glucose levels more dynamically, new markers of glycaemic control are being considered. These new markers include inter- and intra-day glycaemia and variability. These measures incorporate not only fasting glycaemia but also postprandial glycaemia and hypo- and hyperglycaemia.

1.7.1 Conventional Measures of Glycaemic Control and Clinical Outcomes in Type 2 Diabetes

The advantage of using conventional measures of glycaemic control, FPG and HbA1c, are that they are relatively low cost and straightforward to perform, making them favourable for clinical practice and population-based studies. Moreover, landmark studies reinforce their suitability as markers for predicting diabetes risk and determining glycaemic control [61-66].

HbA1c is a measurement which reflects mean ambient fasting and postprandial glycaemia and remains the “gold standard” measure for predicting the occurrence of diabetes-related complications [16, 60]. Red blood cells (erythrocytes) contain the pigment haemoglobin and have a lifecycle of 120 days. Consequently, HbA1c is an indirect measure of average blood glucose levels in the preceding 8 to 12-weeks before the test [24]. Factors that influence
the lifespan of the erythrocyte need to be considered when assessing diagnosis or complication risk of a patient with diabetes, as they are likely to impact on the glycation of haemoglobin, providing an erroneous result. These factors include: genetics, haemolytic and iron deficiency anaemia, haemoglobinopathies, and recent blood loss or transfusion [16, 67]. In cases where these factors are present, just the FPG, or OGTT in isolation, is recommended as the only test for diagnosing diabetes [16].

Data from many large-scale randomized clinical trials (RCT’s), including the UK Prospective Diabetes Study (UKPDS); Diabetes Control and Complications Trial (DCCT); Veteran Affairs Diabetes Trail (VADT); Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) collaboration trial, provide clear association between HbA1c and the risk of diabetes-related complications. These studies have established that a 1% incremental increase in HbA1c was associated with a 10-20% increased CVD risk [61-63, 66, 68, 69].

A meta-analysis by Selvin et al., collated the outcomes of 10 observational studies involving individuals with T2D (n = 7,435) to evaluate the association between HbA1c and CVD. This meta-analysis found a pooled relative risk for CVD of 18% for every 1% increase in HbA1c [70]. This is consistent with data from the UKPDS trial which, for every 1% reduction in HbA1c in recently diagnosed individuals with T2D, identified a risk reduction of 21% for deaths related to diabetes, 16% for heart failure, 37% for microvascular complications, 14% for myocardial infarction and 12% for stroke. This analysis was reported after adjusting for traditional risk factors of CVD (age, gender, duration of diabetes, blood pressure, ethnicity, cholesterol and smoking) and was achieved typically with intensive glycaemic control [63].
10-year post UKPDS trial monitoring study observed a continued reduction in microvascular complications of 16-24%, risk reductions for myocardial infarction of 15-33% and stroke of 9-20% over time, indicating that intensive glucose control at time of diagnosis is associated with significant and sustained reduction in diabetes complication risk [63, 64]. Targets for HbA1c, used widely in clinical practice to establish glucose control, were largely determined from data relating to the decreased rates and progression of microvascular complications, and not from cardiovascular trials [61-63, 66, 68, 71].

Despite a lack of glycaemic thresholds for any category of diabetes-related complications, near normal HbA1c levels in individuals with T2D are recommended and adjusted based on the patient’s/individual’s progression of diabetes, age and risk of hypoglycaemia [16, 63]. The approach to individualisation of glycaemic targets suggests a glycaemic continuum based on an individuals’ characteristics and predicaments [16]. The general HbA1c target of < 7% (53.0 mmol/mol) is the treatment objective, however, those characterised as low risk of hypoglycaemia (newly diagnosed T2D with a long-life expectancy and no present comorbidities with highly motivated behaviour and excellent self-care capabilities and resource availability) will be targeted for more stringent control, such as HbA1c of <6% (42.1 mmol/mol) [16]. This tighter control is suggested in order to capitalise upon the associated benefit of reducing microvascular complication risk further in these subjects even though their risk of hypoglycaemia increases [61, 63]. Conversely, those with long-standing T2D, shorter life-expectancy, few to several co-morbidities, and poorer self-care behaviour with limited resources, a less stringent HbA1c is targeted (HbA1c 7-9% [53-74.9 mmol/mol]) but is also monitored [16].
Large trials including VADT, ACCORD and ADVANCE that involved individuals with early to established diabetes (mean diabetes duration >2 years), showed that tight glycaemic control reduced microvascular complications [62, 66, 71]. In those with established diabetes (mean diabetes duration > 7 years), large studies failed to demonstrate altered CVD outcomes consequent to lower HbA1C levels [61, 62, 66, 68, 71]. More recently, a 10-year follow-up of the VADT cohort demonstrated that those previously receiving intensive glucose therapy, had an 8.6% absolute risk reduction in major CVD events per 1000-person years, however, no reduction in total mortality was evident [72]. Differences in outcomes for CVD risks in these studies could be a result of population heterogeneity, in particular age and duration of diabetes. Those in the UKPDS and DCCT trials were younger and had an overall shorter diabetes duration than those in the ACCORD, VADTS and ADVANCE trials [61, 62, 66, 68, 71, 73].

These outcomes are suggestive that earlier, intensive glycaemic interventions that reduce HbA1c may be more effective in lowering CVD risk in the newly diagnosed population than in those with longer durations of T2D (2 years).

Despite its clinical utility, HbA1c measurement is not without its limitations. Individuals with T2D can have identical HbA1c levels with different mean glucose concentrations [74, 75]. One limitation of HbA1c, as a single metric for diabetes control, is that it provides limited information about glucose fluctuations within each day or across several days. Other factors must also be considered that affect the reliability and accuracy of HbA1c, including erythrocyte production, ageing and ethnicity. Despite the copious amounts of evidence supporting HbA1c as the "gold standard" measure of glycaemic control, the limitation of HbA1c have promoted investigation to consider alternative measures of glycaemic control,
including glycaemic variability which will be later described in emerging measures of glycaemic control (Section 1.7.2) [16, 74, 75].

In contrast to HbA1c, other commonly used glycaemic control markers are FPG and postprandial glucose (PPG). FPG provides an estimation of glucose over a specific time of fast, overnight (8-12 hours) or 2-4 hours postprandial (i.e. PPG) and is a measurement of glucose in individuals after a period of fast, therefore reflecting blood glucose control in the absence of nutrient (glucose) ingestion [16]. The Baltimore Longitudinal Study that assessed the relationship of FPG and 2-hour plasma glucose (PPG) to mortality, showed that risk of mortality in those with T2D did not increase until the FPG exceeded 6.1mmol/L (110mg/dL), with an estimated 40% increased risk in all-cause mortality in the range of 6.1 - 6.9mmol/L (110 -125mg/dL) and doubled when FPG ranged from 7.0 - 7.7mmol/L (126 -139mg/dL) [76]. However, solitary FPG measures provide suboptimal characteristics of diurnal glucose oscillations and post-meal hyperglycaemia and are therefore not reflective of longer-term glucose concentrations. FPG also lacks an ability to predict postprandial hyperglycaemia [76-79]. FPG is also less tightly linked to diabetes complications compared to HbA1c and only reflects glucose homeostasis at the point of time the test was conducted, and is not favoured as an independent marker to determine effectiveness of therapeutic interventions [19, 24]. Therefore, until recently, the best advice for acute glucose assessment in individuals with diabetes was derived from studies such as the Baltimore Longitudinal Study which suggests a combination of FPG and 2-hour plasma glucose (PPG) for providing a better evaluation of glucose control [76]. Together, FPG and PPG are the time course from fasting to the time to peak glucose in individuals with T2D [80]. PPG is commonly taken 2 hours post-meal ingestion and is characterised by postprandial hyperglycaemia, with
findings suggesting PPG is an independent predictor of CVD with 40% greater risk in those with a mean PPG > 10mmol/L (180mg/dL) [81, 82].

1.7.2 Emerging Measures of Glycaemic Control – Glycaemic Variability

The measurement of HbA1c has been the conventional method for assessing glycaemic control for many years, however, the inherent limitations of FPG, PPG and HbA1c may limit a clinician’s ability to assess a patient’s glycaemic variability (GV). In particular, HbA1c is unable to reflect intra- and inter-day glycaemic oscillations, potentially concealing brief, but life-threatening hypoglycaemia or post-prandial hyperglycaemic events which have been linked to macro and microvascular complications [77, 83, 84]. These frustrations have given rise to the exploration of new markers of glycaemic control [85]. Although national testing standards exist to minimise the risk of technical error with the HbA1c assay, individual variations can lead to erroneous outcomes such as a false HbA1c readings, which can impact the therapeutic management of individuals with T2D [84-86].

While definitive consensus has not been reached, a growing body of evidence suggests that acute intra- and inter-day glycaemic oscillations play a significant role in the onset of diabetes-related complications [86, 87]. These oscillations exist beyond the changes detected by a PPG. Studies demonstrate that acute glycaemic fluctuations (including hyperglycaemic spikes and the hypoglycaemic lows) are associated with endothelial and cardiovascular damage in patients with diabetes with optimal glycaemic control (HbA1c <7%) and these fluctuations result in microvascular and macrovascular complications [86-95]. Glucose fluctuations are related to oxidative stress, such as mitochondrial super-oxide anion production leading to endothelial dysfunction and raised inflammation markers, with
outcomes being macrovascular damage in diabetes (i.e. myocardial infarction, stroke) [82, 96, 97].

A few studies have also revealed that a reduction in GV fluctuations resulted in a reduction in oxidative stress markers (nitro-tyrosine and 8-hydroxydeoxyguanosine), suggesting that acute glycaemic fluctuations are more damaging to endothelial cells than chronic hyperglycaemia in the pathogenesis of macrovascular complications such as CVD [86, 88, 89, 92, 94, 98].

The role of GV (defined in section 1.7.2.1) in microvascular complications of diabetes is somewhat limited and the area remains controversial; similar to the understanding of the role of GV in predicting macrovascular complications. In brief, one study associated the single GV measure, standard deviation (SD) of blood glucose, with peripheral neuropathy but not with retinopathy or nephropathy [82]. A more recent prospective cohort study with a median follow up of 10 years identified standard deviation (SD) as an associate of nephropathy but not peripheral neuropathy and retinopathy [98]. GV was a significant predictor of diabetes retinopathy development in patients with good glycaemic control (< 7.5% [<58 mmol/mol]) but not in those with poorer controlled diabetes (> 7.5% [>58 mmol/mol]) [98]. The prognostic relevance of GV would be further clarified if more data were generated regarding the various measures of GV distinct from SD. More work is needed on all measures of GV and their relation to the incidence and progression of microvascular (i.e. retinopathy, neuropathy, nephropathy) and macrovascular (i.e. myocardial infarction, stroke, CVD) clinical endpoints in individuals with good control (HbA1c <7% [>53mmol/mol]) vs poorly controlled (HbA1c > 7% [> 53mmol/mol]) and in individuals classified by duration of diabetes.
The recognition of GV as a clinically relevant maker of glycaemic control has recently expanded. Recent publications have recommended that diabetes control should not be expressed by HbA1c alone, but in conjunction with measures of glycaemic variability (GV) [16, 85, 97, 99]. The use of GV remains the subject of debate. GV has not yet been definitively confirmed as an independent risk factor for diabetes-related complications. There remains a large and increasing number of metrics for which GV can be determined, but no accepted standard of GV measure exists. This heterogeneity confounds the interpretation of the literature and limits our understanding of factors that influence GV [96, 97, 100-102].

1.7.2.1 Measures of Glycaemic Variability

Glycaemic variability (GV) is a term used to refer to one or more of a set of markers developed in order to define glycaemic control. GV can be defined by the scale and rate (including time intervals) of intra-day daily blood glucose fluctuations as well as fluctuations in blood glucose occurring at the same time on different days, inclusive of postprandial hyperglycaemic peaks and hypoglycaemic lows [26, 82, 86, 88].

Table 3 below provides a summary of the commonly used GV measures and their calculations with key advantages and disadvantages associated with the measure.
Table 3: Common Measures for Assessing Glycaemic Variability (GV)

<table>
<thead>
<tr>
<th>Measure of GV</th>
<th>Definition</th>
<th>Calculation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Deviation (SD) of glucose</td>
<td>Rate of variation of dispersion from average glycaemia</td>
<td>[\sqrt{\frac{\sum (x_i - \bar{x})^2}{k-1}}]</td>
<td>Within-day and between-day glucose variability (dependant on &gt; 24hrs of measures); easy to determine; marker of metabolic stability over time; extensively used.</td>
<td>Does not consider frequency of glucose oscillations. Underestimation can occur (high and low glycaemic excursions are not weighted)</td>
</tr>
<tr>
<td>Coefficient of variation (CV) for glucose</td>
<td>Describes the spread of blood glucose independent from its unit of measure</td>
<td>[SD \div \bar{x}]</td>
<td>Within-day glucose variability; good measure of between group comparisons; easily calculated from SD and mean</td>
<td>Does not consider frequency of glucose oscillations; difficulty in determining a meaningful threshold.</td>
</tr>
<tr>
<td>Mean amplitude of glycaemic excursions (MAGE)</td>
<td>Mean differences of glucose fluctuations, from high to low levels with magnitude &gt; 1 SD</td>
<td>[\frac{\sum \lambda}{n} \text{If} \lambda &gt; v]</td>
<td>Correlates well with oxidative stress in T2D; extensively used; measure of within day variability; reflects glucose fluctuations (weights high and low fluctuations)</td>
<td>Not valid if there is only one hyper or hypo excursion during the observation period; excludes minor fluctuations (&lt; 1 SD) of mean glucose; CGM (simple calculation) and SMBG only with 7 measures daily</td>
</tr>
<tr>
<td>Mean of daily differences (MODD)</td>
<td>Mean of absolute differences between glucose values obtained at exactly the same time of day on two consecutive days under standardized conditions</td>
<td>[\frac{\sum_{t=1}^{k^<em>} (GR_t - GR_t - 1440)}{k^</em>}]</td>
<td>Intra-day variability; high MODD score is indicative of large glucose fluctuations.</td>
<td>Not directly reported by CGM; needs additional calculation</td>
</tr>
<tr>
<td>Continues overall net glycaemic action (CONGA)</td>
<td>Integrates duration and scale of glucose excursions</td>
<td>[\sqrt{\frac{\sum_{t=1}^{k^<em>} (GR_t - G_{t-1})^2}{k^</em>-1}}]</td>
<td>High level of accuracy of within-day variability and if &gt;24hrs good accuracy for between-day variability; includes progressive variability that coincides with observations lasting (n1, n2, n4 and n8 hrs) most commonly used are CONGA-1; CONGA-2 and CONGA-4.</td>
<td>Complex calculation (higher the CONGA value the greater the glycaemic excursion) Specifically developed for continuous glucose monitoring devices.</td>
</tr>
</tbody>
</table>

SMBG = self-monitoring blood glucose. CGM=continuous glucose monitoring. CV=coefficient of variation. MAGE=mean amplitude of glycaemic excursions. MODD=mean of daily differences. CONGA=continuous overall net glycaemic action

* Table adapted from Ceriello et al 2018; Nusca 2018; Tay et al 2015; Smith-Palmer et al 2014 and Frontoni et al 2013
Currently, a systematic approach to self-monitoring blood glucose levels (SMBG) can be used to determine the two main elements of GV; within-day and between-day variability [96]. This can be achieved by patients using personal glucometers to measure capillary blood samples (finger-stick) frequently (7-8 times) during the day or on a day-to-day basis [80, 93, 103]. With these multiple glucose levels, the estimated mean within-day daily glycaemic variability over the measured time, the standard deviation (SD) or the derived coefficient of variation (CV), can be determined [96]. It is suggested that a short SMBG profile (over 1-3 days) be performed once a month in those with T2D treated with lifestyle intervention alone, and such an approach will improve glycaemic control [16]. For insulin-treated T2D, SMBG should, at a minimum, be taken twice daily (one morning fasting and one post-prandial measure) together with one bedtime measure a week [16]. In these individuals, these data should be used to guide treatment decisions, however, limitations with adherence exist due to time and cost but also due to the low relative importance patients place on their self-care [16, 103, 104]. The computation of GV from SMBG requires there to be enough capillary blood glucose samples to achieve an acceptable interpretation of a typical diurnal pattern, with the onerous collection being placed on the patient; consequently, regular compliance with SMBG to meet this need is sub-optimal [103, 105]. The usefulness of the GV data received by traditional SMBG levels is further limited by the lack of nocturnal glycaemic patterns, and this increases the likelihood of missing night-time hypoglycaemic episodes [93]. The recent use of continuous glucose monitoring systems (CGM) to obtain continuous daily glucose data, without relying on the patient to initiate the sampling, has increased the accuracy and opportunity to streamline GV metrics to investigate more precise individual characteristics that may influence GV.
CGM continuously measures interstitial glucose levels at 5-minute intervals over 24 hours across several days (7-10 days) via a glucose sensor inserted into subcutaneous tissue, which not only alleviates the patient burden of traditional finger stick tests, but also provides additional measures for GV which otherwise would not be measured [93, 96, 97].

As previously discussed, although limited studies exist demonstrating a reduction in GV is directly or indirectly related to a reduction T2D-related complications, there is growing evidence demonstrating acute glucose fluctuations as emerging risk factors for CVD outcomes, which have been shown to induce greater vascular damage, mediated by oxidative stress [86, 91, 92, 99, 106].

Studies have investigated the effect of GV (MAGE, CONGA) on surrogate measures of diabetic-related complications, including markers of oxidative stress (urinary excretion rate of fre-8-isoprostaglandine F2 and F2α (8-iso-PGF2)), ventricular mass, advanced glycated end products and flow-mediated dilatation [88, 89, 107, 108]. These studies demonstrated that 8-iso-PGF2 was highly correlated to GV (MAGE) [89] and left-ventricular mass was significantly associated with CONGA2, in adults with T2D [88].

More recently, a study investigating the prognostic value of GV (using SD Glucose) identified that the event-free survival rate for freedom from Midterm Major Cardiovascular Events (MACE), in patients with diabetes and Acute Coronary Syndrome (ACS), to be significantly lower in patients with a GV >2.70mmol/L (p<0.0001) who demonstrated a 2.21 times increased risk of developing MACE than those with GV < 2.70mmol/L [106]. The population of 327 presented with a baseline GV of 2.5 mmol/L and HbA1c of 7.6% (no difference between groups) [106]. Overall the study suggests the GV cut-off value of >2.70mmol/L to be a strong independent predictor of MACE for this clinical cohort [106].
Although research mounts, mechanisms in the pathogenesis of GV mediated diabetes complications are still largely undetermined. Figure 1 provides a view of the proposed mechanisms related to the pathogenesis of GV-medicated diabetes complications [86].

**Figure 1:** Potential Mechanisms in the pathogenesis of GV-mediated complications: Adapted from Nusca et al 2018

The increasing interest in understanding the role of GV as an independent risk factor for diabetes complications, has seen a number of measures emerge for the assessment of GV in the attempt to understand an optimum method for characterising GV, these include; the Mean Amplitude of Glycaemic Excursions (MAGE); Mean of Daily Differences (MODD); High Blood Glucose Index (HBGI); Low Blood Glucose Index (LBGI); Glycaemic Risk Assessment Diabetes Equation (GRADE); and, Continuous Overall Net Glycaemic Action (CONGA) (see Table 3) [90, 93, 96, 102, 109-111]. Despite the many measures available, the lack of an agreed single gold standard measure of GV prevents this area of research reaching application of GV to clinical practice. Agreement between each GV measure is not clear and
cannot be assumed to be equivalent. However, since different measurements of GV are based on measuring different components of the time-dependent glucose profile, it is possible that different GV metrics are advantageous in different clinical situations.

Future studies should evaluate the most common measures of GV simultaneously to establish GV as an independent risk factor for diabetes complications, and to confirm whether lowering GV reduces incidence or progressions of diabetes complications. Furthermore, to obtain reliable, consistent and stable estimates of GV, CGM data, used to determine SD glucose, MAGE and CONGAn, is recommended over a period 14 days minimum to detect reproducible changes in GV patterns [97].

Caution also needs to be exercised when interpreting GV data, as parameters such as MAGE (reflected as mean) and CONGAn (reflected as within 1 SD) require consistent and frequent glucose data captured across the day and over several days for their estimations to be meaningful. Although both reflect intra-day variability, MAGE is reported to be more intuitive for the clinician, reflecting change with CONGAn being more statistically robust [97, 112]. Missing data can weaken the calculation and hinder both the interpretation and clinical application of the outcomes, suggesting studies with >14 days of continuous glucose data capture are needed to explore clinical application of these measures of GV.

This is also limited understanding and characterisation of individual and modifiable risk factors that may influence GV. Chapter 2 describes the associations between various measures of GV (MAGE, CONGA2 and CONGA4) and individual characteristics such as age, gender, weight, diabetes duration, physical activity and antglycaemic medication (MES) use, which can help to inform targets in diabetes care therapies to manage GV and optimise
glycaemic control. These findings emphasise the importance of considering lifestyle factors beyond diet and exercise in diabetes and GV management.

### 1.7.3 Lifestyle Management Strategies for Type 2 Diabetes

The multiple symptoms and complications of T2D have short and long-term health consequences, subsequently, there are several lifestyle strategies targeting improvements in blood glucose control and metabolic health outcomes in those individuals with T2D. These strategies include therapies towards optimising dietary intake and physical activity levels to achieve and/or maintain a healthy body weight and improve blood glucose control [16].

The broad treatment goals for the management of T2D is to firstly, secure a quality of life and lifespan comparable to those without T2D, and secondly, to prevent or delay progression of microvascular and macrovascular complications by targeting optimal blood glucose control (refer to Section 1.7) [16]. Lifestyle modification strategies are recognised as the cornerstone of diabetes care and serve as adjunctive therapies to pharmacotherapy and metabolic (bariatric) surgery interventions [16, 113-115].

Understanding the role and efficacy of lifestyle therapies to improve glycaemic control is pivotal to the research conducted in this thesis and will be outlined further in the following section.
1.7.3.1 Weight Loss

The prevalence of overweight and obesity amongst the T2D population is reported to have reached 60-90% [116, 117]. Obesity has a strong relationship in the progression of insulin resistance and diabetes, with obesity considered to increase the risk of diabetes by 25% in those with abdominal obesity, which is known to worsen clinical features of T2D [1]. Weight loss through manipulation of energy balance (caloric reduction and/or increased physical activity to increase energy expenditure) is considered the preferred first line treatment in overweight or obese individuals with T2D, with the primary goal to normalise blood glucose control [1, 16, 114]. Recommendations further suggest a reduction of at least 5% (to >15% as BMI increases) of total body weight is required to achieve improvements in glycaemic control as well as a reducing CVD risk-factors, blood pressure, and obesity-related comorbidities, with recommendations made based on BMI category (see Table 4 below) [16].

Table 4: American Diabetes Association’s (ADA) Treatment options for overweight & obesity in T2D:

<table>
<thead>
<tr>
<th>BMI Category (Kg/m²)</th>
<th>25.0–26.9 (or 23.0–26.9*)</th>
<th>27.0–29.9 (or 27.5–32.4*)</th>
<th>30.0–34.9 (or 27.5–32.4*)</th>
<th>35.0–39.9 (or 32.5–37.4*)</th>
<th>&gt;40 (or &gt;37.5*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Diet, physical activity and behavioural therapy</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Metabolic Surgery</td>
<td>√ with comorbidities</td>
<td>√ without comorbidities</td>
<td>√ without comorbidities</td>
<td>√ without comorbidities</td>
<td>√</td>
</tr>
</tbody>
</table>

* Cut-off points for Asian American individuals. √ Treatment may be indicated for selected motivated patients. Adapted from American Diabetes Association Standards of medical care in diabetes 2019
An early review of 10 clinical trials with a meta-analysis of 192 individuals with T2D and obesity, demonstrated a 50% reduction in FPG levels after 6 weeks with a 10% reduction in total body weight, achieved through caloric restriction (~800-1200 Kcal per day) [117]. The meta-analysis further investigated the association between weight loss and CVD risk factors, identifying weight loss was significantly associated with reductions in total cholesterol (TC), low density lipoprotein (LDL), triglycerides and blood pressure (BP) [117].

More recently, a similar systematic review and meta-analysis, exploring the effects of intensive lifestyle interventions of 12-months or over on weight loss achieved through caloric restriction and increased physical activity in 6,754 obese individuals with T2D, reported a <5% weight reduction of initial weight, with an overall, non-significant reduction in HbA1c of 0.2% (95% CI: -0.6 -0.2). Furthermore, investigations of the data revealed further non-significant but clinical beneficial effects on lipids and blood pressure [114].

However, a further sub-analysis in this review discovered two weight loss intervention studies reporting > 5% weight loss at 12-months, which showed significant reductions in HbA1c of 0.6-1.2% at 12-months, improvements in systolic blood pressure and HDL cholesterol [114]. These studies were calorie restricted and presented as a Mediterranean-style diet in newly diagnosed individuals with mean HbA1c of 7.8% at baseline, and the other study, an intensive diet and exercise program, the Look AHEAD Trial, including participants with a 5 year mean duration of diabetes and HbA1c of 7.3% [114, 118-121].

The Look AHEAD trial, sought to observe the effects of an intensive lifestyle intervention in 5,145 overweight and obese individuals with T2D, to assess if this intervention, based on caloric restriction and increased physical activity, would reduce CVD mortality and morbidity [119-121]. Despite this intervention group reducing 8.6% of total body weight by year 1,
with a 6% overall loss at the end of the 2-years vs. 3.5% for the control group, the study did not demonstrate reduction in CVD morbidity or mortality [120, 121]. However, results from Look AHEAD Trial, over a median follow up of 9.6-years, has established feasibility in achieving clinically meaningful weight loss of >5%, with sustainable long-term weight loss maintenance in 50% of participants at 8-years post-intervention compared to the control group, reaching 3.5% reduction in weight with lesser improvements in HbA1c or CVD risk factors [120].

The recommendation for at least a 5% weight reduction in individuals with obesity and T2D is predominantly based on short-term studies of up to 24-months, with successful longer-term studies (> 24-months) being few and reporting only modest benefits [114, 120-122]. These results suggest that lifestyle interventions may have limited effect on diabetes macrovascular-related complications that take years to manifest [64]. Furthermore, individuals in these trials also received intense counselling by dietitians or active support from health care professionals on a 2-4 weekly basis, suggesting the weight loss benefits are augmented by intense health professional contact, and it is unclear whether provision of a step-by-step guide providing detailed information on how to implement and monitor lifestyle changes over time, without intensive support, could affect markers of diabetes control and weight loss outcomes differently [114, 117, 122].

The evidence consistently reports that for every 1kg of mean weight loss, there is an association with a mean 0.1% reduction in HbA1c percentage points [114, 122] and 0.2mmol/L in FPG [123], with additional reports highlighting that HbA1C lowering is greater in populations with poorer glycaemic control compared to those with good glycaemic.
control with the same degree of weight loss, independent of method for weight loss (i.e. weight loss surgery, caloric restriction or pharmacotherapy) [122].

Furthermore, a recent meta-analysis collated 12-year data to develop a linear model to quantify the effect of weight loss on HbA1c at a group level. The linear modelling demonstrated that weight loss beyond 15% to 20% does not produce further HbA1c reductions. This plateau reflected the natural limit in HbA1c reduction [122].

Collectively, data from these trials consistently demonstrates that caloric restriction and weight loss markedly improved blood glucose control, demonstrated by reductions in HbA1c and FPG, and identify and deliver cost-effective weight loss strategies for individuals with T2D that have become the foundation of T2D management.

1.7.3.2. Dietary Patterns and Composition

In addition to the beneficial effects of caloric restriction and weight loss, a separate body of evidence has examined the effects of different dietary patterns, composition and strategies that target improved glycemic control [124-132]. Although a one-size-fits-all approach to dietary intake has not yet been determined, recommendations are to refer individuals with T2D to a registered or accredited dietitian skilled in providing diabetes-specific medical nutrition therapy [16]. The role of the dietitian is to provide macronutrient distribution recommendations based on current evidence in collaboration with the individual’s assessment of current dietary intake, food preferences and metabolic goals [16]. Recently, evidence suggests dietary therapies provided by a credentialed dietitian was associated with a reduction in HbA1c of 0.3 – 2.0% in T2D [133].
In regard to current evidence examining the effect of dietary patterns on glycemic control, a systematic review with meta-analysis assessing the effect of various dietary patterns lasting ≥ 6-months on glycemic control, identified 4 distinctive dietary patterns to be effective in improving HbA1c [130]. These dietary patterns are: low glycemic-index (low GI); Mediterranean; low carbohydrate; and, higher protein, reducing HbA1c by -0.14%, -0.47%, -0.12% and -0.28% respectively compared with their respective control diets, with all except higher protein also increasing HDL cholesterol [130].

A meta-analysis that evaluated 10 years of research on the effects dietary glycaemic index on glycaemia in T2D, identified 6 articles comparing low glycaemic index diets higher in wholegrains and mixed fibre (low GI) to higher GI diets or controls (lower fibre and mixed grains), for use in the meta-analysis [134]. The duration of the studies ranged between 2 weeks to 22 months and concluded the low-GI diet resulted in significant improvements in HbA1c and FPG compared to the higher-GI diet [134].

In addition, the Mediterranean diet, which includes a large focus on vegetables, fruits, wholegrains and monounsaturated fat has been extensively evaluated [125, 131]. Within a systematic review of 8 meta-analysis’ and 5 RCTs published from 2011 to 2014, a sub-analysis on 3 long-term (≥ 6-months) studies comparing the effects of the Mediterranean diet vs. control on HbA1c in individuals with T2D, favoured the Mediterranean diet, with a greater HbA1c reduction between -0.3 to -0.47% compared to the control diet described as usual care or a low-fat diet [131]. These findings were supported in a later meta-analysis also reporting that compared to controlled diets, Mediterranean dietary patterns led to greater reductions in HbA1c (mean difference, − 0.30; 95% CI, − 0.46 to − 0.14), with greater CVD benefits and reduction in the concentrations of total cholesterol and
triglycerides (−0.14 mmol/l; CI, −0.19 to −0.09 and −0.29 mmol/l; CI, −0.47 to −0.10, respectively), increased HDL cholesterol (0.06 mmol/l; CI, 0.02 to 0.10) and an associated decline in blood pressure of 1.45mmHg (CI, −1.97 to −0.94) for systolic blood pressure and 1.41mmHg (CI, −1.84 to −0.97) for diastolic blood pressure [125]. The evidence from the Mediterranean diet research has led the nutritional guidelines to recognise the benefits of this eating strategy for individuals with T2D [16].

With regard to higher protein diets, an updated meta-analysis of 18 RCTs (2002 to 2018) involving 1,099 adults with T2D over 4 weeks to 24 months, demonstrated that the change in HbA1c after following a high protein vs low protein diet were similar (mean difference -0.07, 95% CI=−0.20 to 0.06, P = .27), suggesting the ratio of energy from protein in these diets did not significantly affect glycaemic control [135], opposing the views highlighted in earlier studies [130]. In contrast, a reduction in carbohydrate intake reduces glycaemic load (GL) and has been shown to improve glycaemic control independent of weight loss during energy balance with early research demonstrating an absolute reduction in mean HbA1c by 2.2% (from 9.8% to 7.6%) [136]. Later research presented in a Cochrane review comparing the effects of low GI compared to low GL also further reported HbA1c reductions of -0.2% to -0.5% with lower glycaemic load diets [137]. The relative importance of lowering carbohydrate on glycaemic control has raised significant interest around the role of low carbohydrate diets for the management of blood glucose control and T2D. In a review of the literature comparing low carbohydrate diets (LCD < 130g total carbohydrate/day or < 26% of daily energy from carbohydrate) to normal or higher carbohydrate diets (HCD > 130g total carbohydrate/day or >26% of daily energy from carbohydrate), reporting on the outcomes from 9 trials including a total of 734 participants with study durations of 3 to 24- months, indicated in their meta-analysis that HbA1c significantly decreased by -0.44% in the LCD
when compared to the HCD (p = 0.00) [128]. Furthermore, a recently published meta-analysis of 36-years of low carbohydrate research (January 1980 to August 2016) examined the effects of carbohydrate restricted diets (≤45% of total energy from carbohydrates) compared to high carbohydrate diets (≥45% of total energy from carbohydrates) on the weighted mean difference in HbA1c change in individuals with diabetes, further revealed a greater mean HbA1c reduction of -0.19% at 3 months on the carbohydrate restricted diets overall [132]. In a sub-group analysis, the authors tested the effect of different levels of carbohydrate restriction on HbA1c, showing that a carbohydrate restriction of ≤ 26% of total energy produced greater reduction in HbA1c at 3-months of -0.47% and at 6-months -0.36% with no significant difference at 12 and 24-months. No significant difference between moderate (26-45% carbohydrate) and high carbohydrate diets (> 45% carbohydrate) were reported [132].

A limitation of these systematic reviews is that they commonly do not report on the effects of dietary patterns on day-to-day glycaemic variability, an important factor in reducing the risk of diabetes-related complications, nor do they systematically assess changes in diabetes-related medication changes that can alter the HbA1c response. Conversely, a RCT of 115 individuals with T2D were placed on a prescriptive very-low carbohydrate diet (50g total carbohydrate, < 15% of carbohydrate from total energy) compared to an isocaloric higher carbohydrate intake (> 200 g total carbohydrate, 53% of carbohydrate from total energy), demonstrating that the LCD produced greater reduction in HbA1c among participants with baseline HbA1c > 7.8%, with no diet effect in those with baseline HbA1c ≤ 7.8%. This study further reported that the LCD produced greater reductions in markers of GV (CONGA1, CONGA4 and MAGE) and diabetes-related medication, which are outcomes not often described in the literature due to lack of these data being collected or reported [138].
Further follow-up of the patients showed that the outcomes and differences between the diet groups were sustained after 1 and 2 years [110, 139]. Based on the currently available evidence, it is well demonstrated that caloric restriction and weight loss is an effective strategy to improve blood glucose control, reduce hyperglycaemia and improve diabetes control. Furthermore, there is no one-size-fits-all approach and a range of dietary strategies that deliver an energy deficit can be used to achieve these outcomes, however, emerging evidence suggests that lowering carbohydrates, independent of caloric restriction, may be effective to further optimise and magnify the improvement of weight loss due to the lower glycaemic load. Therefore, realising that energy restriction initiates effective weight loss and carbohydrate restricted diets demonstrated not only improved glycaemic control but superior benefits for medication and GV reduction, an energy restricted, low carbohydrate dietary pattern was selected for implementation into the clinical trial described in Chapter 4 and Chapter 5.

1.7.3.3 Exercise Management

Exercise has long been recognised as an essential therapy for the management of T2D [140-142] and is often used in combination with dietary modifications and frequent health professional contact [143, 144] to improve health outcomes and in particular glucose control (HbA1c) [16, 145]. An abundance of evidence has confirmed beneficial improvements of physical exercise training in improving insulin sensitivity, bodyweight, cardiovascular risk factors, blood lipid levels, blood pressure, physical fitness and overall general wellbeing and reductions in the risk of CVD morbidity and mortality [146-148]. Although several factors associated with physical activity contribute to these beneficial
effects (i.e. enhanced mitochondrial oxidative enzyme capacity, muscular hypertrophy, improved blood flow and perfusion to capillary bends and muscle), for glycaemic control the increased expression of GLUT4 receptors (Glucose transporter type 4), the transporter of glucose in skeletal muscle, stimulates activity of adenosine monophosphate activated protein kinase (AMPK) within the muscle [149]. In individuals with T2D and obesity that have impaired glucose metabolism, exercise-induced stimulation of AMPK activates the glucose transport system, accelerating muscular glucose disposal and fatty acid oxidation [145, 150], enhancing glucose uptake by up to 50-fold during physical activity and improving insulin sensitivity for up to 48-72 hours post exercise [149].

Intensity and duration of exercise are determinants of glucose uptake by skeletal muscle, and both aerobic and resistance exercise activates different pathways in a synergistic manner to improve glucose control [16, 142, 148].

Resistance/strength training stimulates isolated muscular contraction to improve muscle density and hypertrophy, increasing blood glucose uptake, whereas aerobic activity (repeated and continuous movement of large muscle groups) stimulates whole body insulin action and glucose uptake, independent from AMPK’s action, as previously discussed [142, 148, 149].

Current physical activity guidelines recommend that for adults with T2D, >150 minutes of moderate-vigorous aerobic activity at 50-70% of maximum heart rate (MHR) to be spread over at least 3 days a week, with no more than 2 consecutive days without activity [16].

Furthermore, recommendations have accounted for the younger and more active individual, suggesting a shorter duration (minimum 75 minutes a week) of vigorous intensity or interval training to be sufficient (70-80% MHR), with either option including 2 days a week of
resistance training using compound exercises [16, 142]. However, the overall message to start to reduce the amount of time spent in daily sedentary behaviour, such as prolonged sitting, by interrupting this behaviour every 30 minutes, is a simple message to combat the critical problem facing many individuals with T2D, that is the lack of adherence to longer-term physical activity recommendations [142, 148].

Generally, exercise independent of modality has repeatedly shown to improve glycaemic control, assessed as changes in HbA1c in T2D. This is supported by a meta-analysis investigating the short-term (8-weeks) effects of structured exercise that showed, in the absence of weight loss, individuals with T2D and obesity reduced HbA1c by 0.66% [151]. A subsequent meta-analysis exploring resistance training dose, showed a high intensity dose of resistance exercise had greater reduction in HbA1c compared to a low to moderate dose of resistance exercise (-0.61% vs -0.23%) over 6-weeks to 12-months [152]. Whist interests in the effect of high intensity interval training (HITT) on glycaemic control in T2D have peaked, a systematic review revealed limited evidence to demonstrate the effectiveness of HITT in this population, citing limited studies and poor methodological quality [153].

Furthermore, when exploring the effect of different exercise modalities on glycaemic control, Pan and colleagues confirmed that supervised aerobic and supervised resistant training demonstrated a significant 0.33% reduction in HbA1c, compared to those in the no-exercise group, however, when the exercise modalities of aerobic and resistance training were combined, there was a further 17% reduction in HbA1c for the combined group when compared to the independently supervised aerobic and resistance training groups in < 6 months [154].
With respect to the impact of exercise on GV, research is still evolving, with study methods inconsistently calculating and reporting on measures of GV [155, 156]. With the interest in using CGM to capture rigorous glucose data to evaluate GV response to exercise, it is prudent that future randomised control trials are conducted to determine the individual variability in glycaemic control caused by various exercise modalities (dose, frequency, time and type) in individuals with T2D, using a range of GV markers.

Overall, these reviews consistently report that increasing time spent undertaking physical activity, independent of exercise modality, produces a significant improvement in blood glucose control in individuals with obesity and T2D, yielding an average improvement in HbA1c of between -0.23 to -0.66% percentage points over 3-days to 52-weeks.

### 1.8 Role of Technology in Diabetes Care

Despite strong efficacy of lifestyle modification programs, effectiveness is often underpinned by intensive techniques requiring close monitoring and health professionals’ support to achieve desired health outcomes [157, 158]. In the real-world scenario, adherence and engagement in these self-management strategies has often been difficult to achieve and/or maintain as the practice models often proposed in research programs are resource intensive and cost-prohibitive, which can limit their accessibility and widespread availability [114, 115, 158, 159]. Furthermore, self-regulation that enables a patient to exert confidence and control over their diet and exercise behaviours, is a key component to effective lifestyle intervention adherence [160, 161]. Therefore, there is a strong need to identify and develop a cost-effective health delivery strategy that can be used to support
and enhance the application of lifestyle programs, including treatment therapies targeting optimal glycaemic management in T2D, and patient self-monitoring.

Traditional wearable systems and medical devices are commonly used in practice to measure key health indicators including heart rate (i.e. halter monitor), blood pressure monitors, blood oxygen saturation, body temperature and activity [162]. Over time these wearable systems and medical devices have become supported by advanced information technology software systems. Recent advancements in technology and the rise in availability of smart mobile phones, roaming internet accessibility and mobile hand-held and wearable devices, has attracted the interest of healthcare research and professionals of how best to utilise these technologies to enhance health care communication to optimise patient outcomes and self-monitoring practices beyond telemedicine [162, 163].

Self-monitoring of health markers and behaviours beyond the research setting, using these technologies (wearable devices and/or health applications/software interfaces), have shown to be effective in monitoring treatment response and adherence for a variety of health outcomes including body weight, blood pressure and physical activity, with mixed outcomes [162, 164-168].

A systematic review of the current barriers associated with the clinical adoption of wearable health devices used in acute clinical and community settings for management of chronic conditions, including T2D, revealed that despite barriers to early adoption, there is clear appeal in the literature that technologies could potentially facilitate efficiency in managed care by improving outcomes amongst users, and may also facilitate greater engagement in diabetes self-care [97, 162, 169, 170].
The ADA recently incorporated diabetes technology into their standards of medical care in diabetes, defining diabetes technology as the hardware, devices and software, patients and health professionals can use as adjunctive tools to assist in the management of blood glucose control [16]. Technologies for diabetes have traditionally been referred to as either insulin administering (insulin pens or pumps) or blood glucose monitoring (glucometers or Continuous Glucose Monitoring (CGM)). More recently, diabetes technologies have advanced, resulting in a mixture of technologies that can monitor glucose and administer insulin, whilst combining with software algorithms to provide diabetes self-management support [16]. Such technologies include the CGM or intermittent/flash glucose monitoring devices, which will be described below.

1.8.1 Continuous Glucose Monitoring Technology

Self-monitoring of blood glucose (SMBG) is an essential part of the diabetes self-care regime, enabling individuals living with T2D to evaluate if their glucose targets are being met and to help not only with self-management of diet and lifestyle but also medication adjustment [16]. However, traditional SMBG methods place considerable burden on the patient and is a process impeded by several limitations previously described [103, 104, 171]. Advances in CGM technology since 1999, has seen not only increased accuracy in detecting interstitial blood glucose levels, from ± 20% measurement error to ± 10%, resulting in more robust glycaemic variability computation, but also the evolution of real-time visual feedback of blood glucose readings, having the potential to overcome the limitations of traditional SMBG practices [103, 104, 171-173].
The most recent continuous glucose monitoring systems are wearable health devices usually involving three main components:

1. A wearable glucose sensor
2. A glucose transmitter that sends out the glucose data readings to a device
3. The device, being a receiver or glucose monitor (usually hand-held device) with inbuilt software to receive and convert the glucose transmission into visual displays for the user to interpret their glucose pattern.

For the purposes of this thesis, description of the CGM system selected and used in the clinical trials for the associated thesis research is the Medtronic™ Guardian Connect© device with the Harmony® sensor released 2016 in the USA.

The glucose sensor is a minimally invasive sensor that is inserted into the subcutaneous tissue (see Figure 2) on the body (usually arm or abdomen) and continuously and automatically measures interstitial glucose levels at 5 minutes intervals, 24 hours a day during the sensor wear period of up to 10-days [97, 164]. Interstitial fluid is extracellular fluid which is looked upon favourably as a potential diagnostic as it possesses a similar composition to a number of clinically important biomarkers of metabolic health as blood (such as glucose) [173, 174]. However, the limitation of using CGM and interstitial fluid vs blood measures, is the lag time of several minutes in detecting change in glucose, which has more important clinical implications for those requiring insulin, warranting traditional SMBG and adjunctive CGM monitoring in these cases [16].
The CGM device is an integrated system with built in software, which provides the user with alerts and alarms informing of hyper and hypoglycaemic events. Although still requiring finger-stick (capillary blood) calibration at 12-hourly intervals, the system provides a “biofeedback” display of comprehensive glucose profiles received from the transmitter attached to the glucose sensor via an easy-to-interpret visual display, represented as a mean blood glucose from the previous 5 minutes (see Figure 3). This continual biofeedback enables the user (patient, health care provider or both) to view the individual’s biological response to therapeutic interventions on daily or between-day glucose levels, including the effects of meal type and dose, exercise, medications, stress and sleep [97, 172, 175, 176].
Figure 3: Visual (Real-Time) display of daily glucose readings received from glucose transmitter:

With the additional accuracy and ability to capture 288 interstitial glucose readings within a day, continuing across several days within a real-world environment, the RT-CGM moves towards addressing the limitations inherent of HbA1c testing and traditional self-monitoring, to improve glycaemic control through prompt remedial action [85, 97, 164, 171, 176].
1.8.1.1 Continual Emergence of Glucose Monitoring Technologies

Although not considered for within the body of the thesis, it is important to recognise the evolving landscape of glucose monitoring technologies.

The most recent extension in continuous glucose monitoring technology is the flash glucose monitoring system (FGM), released in 2017 [172, 177]. At present, the FGM is vastly different to the RT-CGM described above. Flash glucose monitoring continuously measures interstitial glucose every minute, however, the user is required to scan the transmitter at least every 8-hours, if not, the glucose data from the previous 8 hours is overwritten and will not be available for data downloads or to assist in therapeutic decisions [177]. The FGM provides retrospective glucose readings for the preceding 8-hour time period displayed in 15-minute intervals, only on scanning the hand-held device over the glucose sensor which is implanted for up to 14 days in the arm [172]. Although no finger-stick calibration is needed (factory calibrated), it is limited by the lack of alerts or alarms to indicate to the user when their glucose levels are out of range [171-173]. Furthermore, accuracy of the FGM in comparison to RT-CGM is still evolving, with reports identifying that although FGM and RT-CGM show similar concurrence within a range of > 80-200mg/dL (> 4.4-11.1 mmol/L), the concern is with the lower ranges, such as if the FGM reads 60mg/dL (2.2 mmol/L) there is a 40% chance that it is actually between > 80-200mg/dL (> 4.4-11.1 mmol/L), prompting the user to supplement glucose therapeutically, potentiating hyperglycaemia, an important consideration when interpreting results comparing RT-CGM and FGM systems, as studies that show equivalence may be inaccurate [177]. The evolution of the FGM is considered to be a hybrid between standard glucometers and CGM, with the benefit of an overall lower cost (AUD) compared to CGM (FGM $95 device and $95 per disposable 14-day sensor vs RT-
CGM ~$3000 hardware and software and $65 per disposable 10-day sensor). As accuracy continues to improve over time, FGM may precede RT-CGM and may increase utility of CGM in clinical practice, independent of type of system [172, 177].

1.8.2 The Role of CGM to improve blood glucose control in diabetes

Although previous studies have used older CGM systems, results from a systematic review and meta-analysis exploring the effectiveness of CGM on glucose control in diabetes compared to traditional SMBG, revealed that blinded or retrospective use of CGM was no more effective than SMBG in reducing HbA1c (-0.13% [95% CI -0.38% to 0.11%]) [178]. However, results were contrasting for RT-CGM which achieved greater reductions in HbA1c compared to SMBG (-0.18% [CI 95%-0.35% to -0.02%]) [178]. Although these studies included T1D, the authors produced a sub-analysis on the T2D population showing that the effect of CGM use in reducing HbA1c was superior to SMBG (-0.31% [CI 95%-0.6% to -0.02%]), however, these finding were limited to 4 RCT’s of 116 individuals with T2D of short study duration with outcomes of HbA1c and did not assess the effect on diet, exercise or behavioural change [178].

For a more detailed summary of the effects of CGM use on improving blood glucose control in T2D, Chapter 3 provides a detailed narrative review, conducted using systematic review protocols, exploring clinical trials evaluating the effectiveness of CGM (real time and/or flash and/or blinded) to improve HbA1c, body weight and lifestyle behaviour in adults with T2D.

In brief, the narrative review identified a total of 5,542 individuals with T2D recruited into 8 RCTs and 3 observational trials, with study durations of 3 days to 52 weeks. With high
heterogeneity between studies, a meta-analysis was precluded. However, the available evidence showed that CGM promoted greater, absolute reductions in HbA1c (-0.4 to -0.9%), body weight and caloric intake and increases in physical activity compared to the controls. The findings suggest that these independent benefits may be further enhanced when CGM is integrated with lifestyle prescription, but attributes of such interventions remain unclear. Subsequently, two further systematic reviews and meta-analyses to explore the effectiveness of CGM in adults with T2D were conducted in late 2018 [179] and early 2019 [180] that showed CGM (real-time and flash glucose monitoring) are effective in improving HbA1c. However, study heterogeneity continued to be identified as a limitation of the existing literature suggesting further RCT's are required [179-181].

Together with recent evidence suggesting that a lower carbohydrate diet promotes greater improvements in glycaemic control, that includes attenuating daily glycaemic fluctuations and reducing diabetes-medication requirements, the benefit of combining a lower carbohydrate diet with an exercise prescription, delivered as a lifestyle modification program, combined with the use of a RT-CGM device for improving glycaemic control in individuals with T2D, was explored. In Chapter 4, the results of an original experimental study to examine the effects of RT-CGM compared to Blinded-CGM on blood glucose control, assessed by HbA1c, GV and CVD risk markers, when undertaking a prescriptive lifestyle modification program with minimal health practitioner involvement, is reported.

### 1.8.3 Usability of RT-CGM in Clinical Practice

As the prevalence of T2D grows, therapeutic treatment options are extending into self-monitoring and mobile-health device delivered therapies to support patients to achieve better control of their disease, including the use of real-time continuous glucose monitoring
systems (RT-CGM) [97, 162, 164, 182]. Self-monitoring makes up to 95% of diabetes self-care [183], in particular traditional SMBG, which is considered paramount to the self-care process [16]. Compliance with this behaviour is generally poor, not only due to the issues including time requirements and perceived pain caused by the lancet device, but the overwhelming complexity of self-care regimes and the relatively low importance patients place on their diabetes self-care [103]. A study examining the impact on beliefs and patient experiences of using SMBG with instruction (training on interpretation and application of the results to enhance lifestyle (diet and exercise) adherence vs without instruction in individuals with non-insulin treated T2D, showed that those who were self-monitoring their blood glucose, with instructions experienced no change in beliefs about their personal control over diabetes or perceived effectiveness of diabetes lifestyle therapies [184]. In a sub-analysis, the authors found that those with more intensive SMBG behaviours experienced significantly lower quality of life (-0.72 [95% CI -0.12 to -0.02]) compared to the control, which correlated to greater levels of anxiety and depression at 12-months [184].

The goal of effective self-management, in practice, requires considerable patient-clinician interaction to be effective. In comparison, it seems intuitive that having more data available via RT-CGM may change clinical practice, improve patient-clinician interaction aid in the management of T2D.

A retrospective blinded evaluation, examining the application of blinded-CGM in clinical practice, evaluated the change in baseline HbA1 data at 6-months following CGM-guided management of 296 individuals with T2D receiving various management therapies (exercise, diet, medication), with a secondary aim to determine if outcomes were different in therapy management, compared to a matched control group receiving usual clinical practice [185]. The study showed a significant reduction in HbA1c at 6 months in the CGM-guided group.
(baseline 7.5 ± 1.4% vs. baseline 7.0 ± 0.9%; p < 0.0001), compared to the control group (baseline 7.7 ± 1.1% vs. baseline 7.4 ± 1.0%; p = 0.0593). It was also reported that 99% (n=291) of the CGM-guided treatment group demonstrated improvements in all baseline treatment therapies [185] including medication adjustments by dose or overall regime and dietary changes and 96% received exercise recommendations guided by CGM readings, compared to 94% of control patients who received medication adjustments, 64% received dietary changes and 67% received exercise recommendations. Although no details were provided outlining the type of advice implemented, the practice-team showed the CGM-guided advice included a professionally trained CGM team consisting of diabetologists, dietitians, nurses, pharmacist and a device technician, who prepared guidelines and treatment recommendations through a combination of clinical experience and the results of the CGM data [185].

Furthermore, a review of the evidence provided a narrative and qualitative summation of clinician’s experience and preference for use of CGM in practice. Reporting clinicians felt a blinded period of CGM use is helpful to record the patient’s usual habit, referring to diet and exercise behaviours and identifies patient use of medication. Further recommendations included a follow-up period of 14-days using either RT-CGM or flash CGM, stating the visualisation of the glucose trends was a critical education and learning tool to help to drive treatment changes and aided the clinician in providing education to the patient on how to modify diet and exercise to improve self-management skills [176].

Together these studies show, that relative to SMBG, CGM can promote and enhance diabetes self-management and is considered to be an effective interventional tool in
assisting patients and health professionals to tailor their diet and exercise behaviours to achieve better glycaemic control, in a time efficient manner [97, 176, 178-181].

From the patient’s perspective, a psychological sub-study of the PRECISE trial was conducted by Barnard and colleagues in 2018, who delivered a psychological questionnaire to determine acceptability and impact of the implantable CGM sensor in 102 individuals with diabetes (T2D n=5; T1D n=41) and found that participants reported the usability of the CGM system as ‘high’ on ease of use, convenience and comfort with 92% reporting no experience of pain or discomfort with sensor wear, 93% of participants indicating that CGM minimised their burden of diabetes identified by reports of improvements on all domains in the diabetes distress scale [186]. However, these findings are limited, as a high proportion of the population were T1D (90%) and most participants were previous CGM users (86%) who are likely to be more motivated and engaged than the T2D population [186, 187].

It is estimated that one quarter of those with T2D may have an affective disorder as a result of their disease [188] and others may adhere less closely to treatment advice due to the stress induced by the diagnosis and the consequent requirements for treatment monitoring [187]. Any negative effects of RT-CGM technology on acceptance, tolerance, stress levels and behaviour may limit its usefulness as a strategy for T2D, and greater examination of these effects will assist understanding of the use for RT-CGM in clinical practice [189, 190].

Therefore, despite the promising efficacy of CGM, independent of type, to promote behaviour change and improve glycaemic control, there appears to be no studies that have examined the effect of these devices on outcomes including patient acceptance, tolerance and overall stress or perceived diabetes self-management behaviours.
In response, Chapter 5 details the outcomes of an original study that examines the effects of RT-CGM compared to blinded CGM, on tolerance and acceptability of device wear, stress and diabetes management and motivation to change.

1.9 Summary

Type 2 Diabetes is characterised as a progressive loss of β-cell insulin secretion, resulting in hyperglycaemic events, commonly preceded by insulin resistance and is associated with increased prevalence of overweight, obesity, cardiovascular disease (CVD) risk factors and psychological complications including distress. The incidence of T2D continues to rise globally, and the burden associated with the direct and indirect costs of diabetes management warrants concern. Lifestyle modification (diet and exercise) is the first line treatment of T2D, however, adherence to lifestyle modification is low, complicated by the lack of explicit biological symptomology.

Interventions targeting management and prevention of T2D focus on achieving optimal blood glucose control and prevention or management of diabetes related complications. Self-monitoring of blood glucose to achieve improved blood glucose control, usually requires using finger stick tests or reliance on the routine clinical measurement of glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG), requiring a specialist clinical visit every 3-6 months. Although relevant for diagnostic or clinical monitoring purposes, these tests are limited to only providing the patient with a single measure in time, restricting the patient from seeing the influence of their lifestyle choices on daily blood glucose levels.

However, the emergence of new technologies such as RT-CGM devices that capture glucose at 5-minute intervals, provides the user with a visual display of continuous glucose reading...
and the ability to measure and monitor within-day and intra-day GV. Growing interest in measures of GV have emerged with evidence suggesting that large fluctuations in GV is an independent risk factor for T2D complications, although individual characteristics that potentially influence GV remains unclear.

This aim of this thesis is to provide original analyses and experiments that will assist to advance the understanding of factors that influence GV and to investigate the role of Real-Time Continuous Glucose Monitoring (RT-CGM) as a self-monitoring behaviour change tool to enhance glycaemic control of individuals with T2D. Therefore, the body of research provided includes:

**Chapter 2** describes the outcomes of a retrospective, secondary analysis of an existing dataset of patients with T2D exploring associations between measures of GV and factors such as age, gender, weight, diabetes duration, physical activity and antglycaemic medication use.

**Chapter 3** represents a narrative review, exploring clinical trials evaluating the effectiveness of CGM (real time and/or blinded) to improve glycated haemoglobin (HbA1c), body weight and lifestyle behaviour adherence in adults with T2D, with a secondary aim to understand CGM user acceptance and potential implications from primary care use.

With recent evidence suggesting lower carbohydrate diets result in greater improvements in glycaemic control and attenuate daily glycaemic fluctuations, it was proposed that combining a lifestyle modification program with a real-time continuous glucose monitoring
device (RT-CGM) would offer benefits for improving glycaemic control in patients with T2D, which has not been previously studied.

**Chapter 4** provides the outcomes of an experimental study testing the hypothesis that the use of RT-CGM will assist in adherence to a prescribed low carbohydrate diet in overweight and obese individuals with T2D, thereby inducing greater glycaemic control (HbA1c and glycaemic variability) compared with a conventional finger prick test for self-monitoring blood glucose levels. This research focuses on the metabolic effects of T2D, measuring HbA1c, lipids, body weight, body composition, fasting insulin and fasting glucose, with a unique focus on observing various indices of glycaemic variability. This study provides preliminary evidence that RT-CGM may be an effective strategy in optimising glucose control whilst following a low-carbohydrate lifestyle program with minimal professional support.

The literature exploring the tolerance and acceptance of CGM device wear on diabetes management is limited. With the premise that wearing and self-managing a RT-CGM could pose a burden to the user, potentially having a negative effect and limiting the usefulness of RT-CGM technology in practice, a greater examination of these effects was deemed warranted.

**Chapter 5**, presents the results of a supplementary investigation of the experimental study to examine the effects of RT-CGM vs. Blinded-CGM on tolerance and acceptability of device wear, stress and diabetes management and motivation to change in a bid to improve our understanding of how individuals respond to wearing a device.
Chapter 6 summarises the overall findings of the research topic and the strengths and limitations of the current work, combined with recommendations for future research in this priority area to advance clinical practice of T2D management.
Introduction References


82. Cavalot, F. Do Data in the literature Indicate that Glycaemic Variability is a Clinical Problem? Glycaemic Variability and Vascular Complications of Diabetes - A Review, Diabetes Obesity Metabolism, 2013. 15 Suppl1: p.3-8


Chapter 2: Manuscript 1

Association of glycemic variability and the anti-glycemic medication effect score in adults with Type 2 Diabetes

Publication:
Diabetes Management. 2018; 8(5), 117-121
Statement of Authorship

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<td>Published</td>
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Principal Author

| Name of Principal Author (Candidate) | Pennie (Penelope) Taylor |
| Contribution to the Paper | Conceived paper concept, generated hypothesis for assessment and determined characteristics for analysis, performed analysis, interpreted the data, reviewed relevant journal articles, prepared manuscript and acted as corresponding author and prepared rebuttals. |
| 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. |

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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 | Kylie Lange |
| Contribution to the Paper | Supervised statistical analysis, helped with data interpretation and contributed to manuscript methodology. |

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<tr>
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<tr>
<td>Grant Brinkworth</td>
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<td>16.4.19</td>
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Please cut and paste additional co-author panels here as required.
SHORT COMMUNICATION

Association of glycemic variability and the anti-glycemic medication effect score in adults with type 2 diabetes

Pennie J Taylor\textsuperscript{1,2,3}, Kylie Lange\textsuperscript{4}, Campbell H Thompson\textsuperscript{1}, Wittert Gary\textsuperscript{2,3} & Grant D Brinkworth\textsuperscript{4}

ABSTRACT

While evidence implicates glycemic variability (GV) as an independent risk factor for type 2 diabetes (T2D) complications, individual characteristics and factors that determine and influence GV remain unclear. This study explored associations between GV and individual characteristics including age, body fat, diabetes duration, physical activity, gender, glycated haemoglobin (HbA1c) with a focus on anti-glycemic medication use. An observational, cross-sectional investigation was conducted as a secondary analysis on baseline data of 95 participants (age: 35-65 y; Body Mass Index (BMI): 26-45 kg/m\textsuperscript{2}) with T2D (HbA1c > 7.0\% and/or using diabetes medication) who participated in a Randomised Control Trial. Three glycemic variability indices were calculated using interstitial glucose level readings (mean of 5 mins) over a 48 h period, collected by continuous blood glucose monitoring. Multiple linear regressions were used to examine the association between the participant characteristics of interest and the GV indices. There were significant positive associations between all GV indices and anti-glycemic medication use (all $P<0.004$). Similarly, significant positive associations between all GV indices and HbA1c (all $P<0.001$) were observed. However, associations between HbA1c and all GV indices plateaued above an HbA1c of 8%. Finally, there were no observable associations between the GV indices and any other characteristics. From a range of patient characteristics, only the characteristic of a greater anti-glycemic medication score was significantly associated with greater GV in overweight or obese individuals with T2D. These data suggest clinical targets for optimal glycemic management may require greater consideration of the impact of pharmacotherapy on GV.

Introduction

Glycemic variability (GV), the amplitude, frequency and duration of glycemic fluctuations around mean blood glucose (1,2) is emerging as an independent risk factor of type 2 diabetes related macro- and microvascular complications (3-9). Consequently, strategies to reduce GV are becoming recognised as an important treatment target in T2D management. These strategies involve lifestyle adjustment and often medication as well (2,10-12). However, there is limited understanding and characterisation of individual and modifiable factors that may influence GV. This limits the development of effective targeted therapeutic strategies that consider all the factors that influence GV in individuals with T2D. The aim of this study was to explore associations between characteristics of overweight or obese individuals with T2D, most importantly their pharmacotherapy, and their GV.

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Diabetes Manag (2018) 8(5), 117-121
ISSN 1758-1907

95
Methods

Study outline

This was an observational, cross-sectional study conducted as a secondary analysis of the baseline data of 95 participants who participated in a diet and lifestyle intervention trial (ACTRN1261000369820) [13]. Participants with established type 2 diabetes under the care of a general practitioner and/or endocrinologist were recruited from the community in Adelaide, Australia. Participants were aged between 35-68yrs with T2D (HbA1c > 7.0% and/or using diabetes medication), and with a body mass index (BMI) of 26 to 45 kg/m². Exclusion criteria included smoking, type 1 diabetes, renal, hepatic, respiratory gastrointestinal or cardiovascular disease; history of malignancy or any significant endocrinopathy (other than stable treated thyroid disease); pregnancy/ lactation; history of or current eating disorder [13]. All study participants provided written informed consent and the study was approved by the CSIRO Human Research Ethics Committee.

Covariates and medication effect score

The participant characteristics identified to have an established and/or potential influence upon GV and to be included in the analysis models based on cohort size were: 1. age; 2. duration of diabetes; 3. HbA1c measured by a certified laboratory (SA Pathology; Adelaide, Australia); 4. percentage of body fat determined by whole-body dual-energy X-ray absorptiometry (DEXA; Lunar Prodigy General Electric Corporation; Madison, Wisconsin); 5. time spent in sedentary and moderate/vigorous activity assessed using data from seven consecutive days of triaxial accelerometry (GT3X+ model; ActiGraph, Pensacola, Florida), with pre-defined validity cutoffs [14] and 6. diabetes medication as measured by the anti-glycemic medication effect score (MeS). The MeS provides an overall assessment of the utilization of anti-glycemic agents based on type and dose of agent, with a higher score corresponding to higher anti-glycemic medication use [13,15]. The calculation includes determining the prescribed dose of each anti-glycemic drug for each patient as a percentage of the maximum recommended daily dose of that drug. If the maximum daily dose of metformin is 3000 mg and the daily dose utilised is 500 mg, the percentage of maximum daily dose is 16.7%. This percentage, for each medication, is then multiplied by an adjustment factor for metformin (biguanides) and sulfonylureas the adjustment factor is 1.5; for insulin 2.5. In this example, the subject on this dose of metformin alone has a MeS of 0.25. For a patient taking more than one anti-glycemic medication, each medication’s prescribed maximum daily dose is multiplied by the respective adjustment factor and the outcomes summed to generate the final MeS [15].

Glycemic variability assessment

Blood glucose profiles were collected at 5-minute intervals over a 48 h period, using an interstitial glucose sensor and the iPro 2 continuous glucose monitoring device (Medtronic, North Ryde, Australia). Glycemic variability measures were computed and included the mean amplitude of glycemic excursions (MAGE, average of blood glucose excursions exceeding 1 SD of the mean blood glucose value), and continuous overall net glycemic action (CONGA-2 and CONGA-4, SD of differences between observed blood glucose reading and an observed blood glucose level (n) hours prior (i.e. 2 or 4 hours apart, respectively)) [16].

Data analysis

Multiple linear regressions were used to examine the association between the participant characteristics including age, duration of diabetes, HbA1c, percentage of body fat, time spent in sedentary and moderate/vigorous activity and diabetes medication and each GV outcome. All GV outcomes were compared by automated algorithm and log transformed (ln) prior to analysis [17]. Covariates to be included were specified a priori, based on clinical justifications. A quadratic term for HbA1c was also included to account for non-linearity. Normality, heteroscedasticity and collinearity assumptions were assessed for each model and were met. Statistical significance was assessed at P<0.05. Analyses were conducted using SPSS Statistics 25 (IBM Corp, 2017).

Results

A total of 95 participants were included in the multiple regression analysis for this study. An additional 20 participants had been recruited for participation in the initial lifestyle intervention but were excluded from this analysis due to the unavailability of diabetes duration data. Participants’ characteristics are presented in Table 1. Table 2 presents relationships between GV outcomes and patient characteristics. There were significant positive
Table 1. Baseline characteristics of participants (n=95)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.3 ± 6.8</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>95 (55 Male, 40 Female)</td>
</tr>
<tr>
<td>Duration of T2D (years)</td>
<td>6.7 ± 5.9</td>
</tr>
<tr>
<td><strong>Diabetes Medication</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes Medication Effect Score (MeS)</td>
<td>1.2 ± 1.1</td>
</tr>
<tr>
<td>Sulfonylureas (n [%])</td>
<td>28 [30]</td>
</tr>
<tr>
<td>Metformin (n [%])</td>
<td>40 [42]</td>
</tr>
<tr>
<td>GLP1 agonists (n [%])</td>
<td>2 [2]</td>
</tr>
<tr>
<td>DPP4 inhibitors (n [%])</td>
<td>2 [2]</td>
</tr>
<tr>
<td>Thiazolidinedione (n [%])</td>
<td>6 [5]</td>
</tr>
<tr>
<td>insulin (n [%])</td>
<td>10 [11]</td>
</tr>
<tr>
<td>Other (n [%])</td>
<td>3 [4]</td>
</tr>
<tr>
<td>**Anti-hypertensive Medication (n [%])</td>
<td>88 (92%)</td>
</tr>
<tr>
<td><strong>Body Composition</strong></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>101.8 ± 15.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.5 ± 4.4</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>112.0 ± 10.8</td>
</tr>
<tr>
<td>Total Body Fat (%)</td>
<td>39.8 ± 7.4</td>
</tr>
<tr>
<td><strong>Glycemic Control</strong></td>
<td></td>
</tr>
<tr>
<td>Glycated Hemoglobin (% HbA1c)</td>
<td>7.3 ± 1.1</td>
</tr>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td>8.1 ± 2.1</td>
</tr>
<tr>
<td>MAGE (mmol/L)</td>
<td>5.1 ± 1.7</td>
</tr>
<tr>
<td>CONGA-2 (mmol/L)</td>
<td>2.4 ± 0.8</td>
</tr>
<tr>
<td>CONGA-4 (mmol/L)</td>
<td>2.9 ± 1.0</td>
</tr>
<tr>
<td><strong>Physical Activity</strong></td>
<td></td>
</tr>
<tr>
<td>Time spent in Sedentary behavior (%)</td>
<td>87.5 ± 3.7</td>
</tr>
<tr>
<td>Time Spent in Moderate to vigorous intensity activity (%)</td>
<td>3.5 ± 1.4</td>
</tr>
</tbody>
</table>

**Standard Deviation.** Data is mean ± SD; unless otherwise stated Abbreviations: MeS: anti-glycemic Medication effect Score; GLP-1 agonists; GLP-1 agonist; DPP-4 inhibitors; Dipeptidyl-peptidase-4 inhibitors; BMI: Body Mass Index; SD: MAGE: Mean Amplitude of Glycemic Excursions; CONGA-2: Continuous Overall Net Glycemic Action of observations 2 hour apart; CONGA-4: Continuous Overall Net Glycemic Action of observations 4 hour apart.

Table 2. Adjusted Multiple Regression Output (unstandardized regression coefficients)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Glycemic Variability Indices</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAGE (ln mmol/L)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>b= 0.006 (P=0.230)</td>
</tr>
<tr>
<td>Female gender</td>
<td>b= 0.061 (P=0.494)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>b= -0.006 (P=0.344)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>b= -2.018 (P&lt;0.001)</td>
</tr>
<tr>
<td>HbA1c squared</td>
<td>b= -0.119 (P&lt;0.001)</td>
</tr>
<tr>
<td>MeS (arbitrary units)</td>
<td>b= -0.113 (P=0.003)</td>
</tr>
<tr>
<td>Diabetes Duration (yrs)</td>
<td>b= -0.002 (P=0.756)</td>
</tr>
<tr>
<td>Time Spent Sedentary Activity (%)</td>
<td>b= -0.019 (P=0.169)</td>
</tr>
<tr>
<td>Time Spent Mod/High Activity (%)</td>
<td>b= -0.032 (P=0.398)</td>
</tr>
</tbody>
</table>

**Significance p<0.05**

**Abbreviations.** HbA1c: Glycated Hemoglobin; MeS: anti-Glycemic Medication Effect Score; MAGE: Mean Amplitude of Glycemic Excursions; CONGA 2: Continuous Overall Net Glycemic Action 2-Standard Deviations of the difference in blood glucose readings 2 hours apart (Score); CONGA 4: Continuous Overall Net Glycemic Action 3-Standard Deviations of the difference in blood glucose readings 3 hours apart (Score).
associations between HbA1c and all GV indices (all \( P<0.001 \)), which plateaued above an HbA1c of 8% and between MeS and all GV indices (all \( P<0.004 \)). There were no statistically significant associations between GV indices and any of the other characteristics in the model.

Discussion

After controlling for individual characteristics, results revealed a significant, independent positive association between GV and the anti-glycemic MeS. Beyond the expected, positive associations between HbA1c and all GV indices [18], there were no observable associations of GV indices with any of the other characteristics included in the model. Hyperglycemia (as measured by HbA1c) is an important contributor to the incidence of microvascular and macrovascular complications in T2D [4,18]. In contrast, a growing body of evidence suggests that high GV is an important determinant of vascular damage and reflects sub-optimal diabetes control [4,5,19-23]. The positive associations between GV and the anti-glycemic MeS suggests that a higher use of anti-glycemic medication is not associated with any decrease in GV. Similarly, a previous study, conducted in T2D patients on mixed insulin with concomitant anti-glycemic medication, observed short and occasional prolonged episodes of hypoglycemia in individuals with low mean blood glucose levels and wide fluctuations in blood glucose values in patients taking higher insulin doses [7]. This study also reported no correlation between HbA1c and time spent in hypoglycemia. This suggests that a glycemic profile with smaller GV should be a target when designing an intervention to optimise glycemic control over and above lowering HbA1c concentrations [7]. These findings have important clinical implications, suggesting close attention should be considered when prescribing anti-glycemic medication and dosing regimes. These drugs may affect GV in addition to any effect they have on HbA1c. In a separate line of evidence, a recent cross-over study demonstrated that participation in moderate intensity exercise over a 3-day period reduced GV in individuals with T2D [24]. No association between GV and either time spent in sedentary activity or in moderate/vigorous activity was observed in the present study. The exact reason for this discrepancy remains unclear. It is possible that medication use has a stronger association with GV than any of the other variables considered in the model, at least in patients with T2D.

Study limitations

This is the first study investigating associations between GV and individual characteristics in T2D that includes diabetes medication usage yet several limitations exist. Firstly, this was a secondary analysis of baseline data that consisted of a heterogeneous population treated with a variety of treatment strategies for diabetes management. These strategies included oral anti-glycemic medications and insulin in addition to concomitant medications including anti-hypertensives. This limits the ability to explore specific associations by medication type. Secondly, whilst the anti-glycemic MeS is useful in clinical research to assess global changes in medication over time, it has not yet been established in clinical practice. At this point it is impossible to decipher the relationship between GV and specific medication types and dosages. Finally, the study sample examined was relatively small, with well controlled diabetes. Inclusion of potential confounding variables was limited. Consequently, the present findings may not be generalizable to the wider population and larger studies examining more diverse populations considering the confounding effects of diet, caloric intake, kidney and renal disease should be conducted to describe these relationships more comprehensively. It is also important to acknowledge that the cross-sectional design of this study does not provide evidence of cause-and-effect. Future interventional studies should be conducted to understand the direct effect of changing medication dosage and type on GV, including HbA1c. It will also be necessary to conduct longitudinal studies in controlled vs poorly controlled individuals investigating the effects on GV of differing types and changes of dose of medication over time on. This will inform clinical practice guidelines and appropriate prescription of medications with greater consideration of GV control.

Conclusion

From a range of patient characteristics, only the characteristic of a greater anti-glycemic medication score was significantly associated with greater GV in overweight or obese individuals with T2D. These findings suggest that clinical targets for optimal glycemic management should consider the impact of pharmacotherapy upon GV because more medication may not translate.
Association of glycemic variability and the anti-glycemic medication effect score in adults with type 2 diabetes


Chapter 3: Manuscript 2

Effectiveness and acceptability of continuous glucose monitoring for type 2 diabetes management – A narrative review

Publication:
Journal of Diabetes Investigation. 2018; 8, 713-725
## Statement of Authorship

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### Principal Author

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<td>Contribution to the Paper</td>
<td>Co-designed the review question, planned the approach and performed literature search, reviewed literature and screened trials for inclusion, interpreted findings, prepared manuscript and rebuttals, acted as corresponding author</td>
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<td>Overall percentage (%)</td>
<td>85%</td>
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<td>Certification:</td>
<td>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.</td>
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| Signature | Date | 16.4.19 |

### Co-Author Contributions

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

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

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

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

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<th>Campbell Thompson</th>
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<td>Co-designed review question, reviewed the studies for quality for inclusion, contributed to reviewer and approving final manuscript for inclusion</td>
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Effectiveness and acceptability of continuous glucose monitoring for type 2 diabetes management: A narrative review

Pennie J Taylor1,2, Campbell H Thompson3, Grant D Brinkworth4

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Keywords
Glycemic control, Lifestyle, Technology

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J Diabetes Investig. 2018
doi: 10.1111/jdi.12807

ABSTRACT
The present narrative review discusses the role of continuous glucose monitoring (CGM) in glycemic and weight control, and lifestyle behavior adherence in adults with type 2 diabetes. A literature search from January 2001 to November 2017 was carried out (MEDLINE, CINAHL, Web of Science, and Scopus). Eligible studies were trials evaluating the use of CGM with the aim of achieving glucose control or lifestyle-related treatment adherence over a period of 28 weeks in adults with type 2 diabetes compared with usual care or another comparison intervention, or observational trials reporting CGM user experience. A total of 5,542 participants were recruited into 11 studies (eight randomized controlled trials \( n = 5,346 \)) and three observational studies \( n = 196 \). The sample size ranged 6-4,678 participants, the mean age was 51.7-60.0 years and diabetes duration was 21-192 years, with high heterogeneity between studies. Overall, the available evidence showed, compared with traditional self-monitoring of blood glucose levels, CGM promoted greater reductions in glycated hemoglobin, body weight, and caloric intake; higher adherence rating to a personal eating plan; and increases in physical activity. High compliance to CGM wear and device calibration was reported (≥90%). The addition of lifestyle and/or behavioral counseling to CGM appeared to further potentiate these improvements. Preliminary evidence suggests that CGM use promotes glycemic and weight control, and lifestyle behavior adherence in adults with type 2 diabetes. These benefits might be further enhanced with integration of diet, exercise, and glucose excision education and counseling. However, specific attributes of effective interventions and the application of CGM information for promoting improved outcomes and healthier choices remain unclear.

INTRODUCTION
Approximately 422 million adults worldwide have diabetes, with ~90% of cases having type 2 diabetes. With a disproportionately greater increase in type 2 diabetes in the Asian region, the burden of type 2 diabetes is fast being realized, with <25% reaching good glycemic control. Hence, effective evidence-based strategies are urgently required. Poor blood glucose control underpins diabetes-related vascular complications, and its increased risk of cardiovascular disease and premature death. Although diet and lifestyle interventions remain the cornerstones of type 2 diabetes management, alone these are often insufficient to achieve sustained glycemic control and adjucyce therapies are required for effective management. Furthermore, current approaches to implementing lifestyle strategies are often laborious, costly and resource intensive, requiring close health professional supervision to provide feedback to blood glucose response changes. This creates challenges for long-term adherence to lifestyle strategies, and the need for alternative effective and acceptable treatment strategies for sustained therapy.

Self-monitoring of blood glucose levels (SMBGL) is widely accepted as being beneficial for long-term glycemic control in type 2 diabetes, both with or without insulin therapy.
However, limitations and poor adherence to regular SMBG exist due to inconvenience, costs of disposables, and erroneous and reduced measurement frequency resulting in suboptimal glycemic control.3,4 Alternatively, continuous glucose monitoring systems (CGM) have emerged that utilize sensor technology inserted subcutaneously to measure interstitial glucose levels across the day that could enhance behavior change adherence and glycemic control. CGM enables an individual to observe blood glucose levels, and understand interactions and impact between diet, physical activity and medication choices with greater qualitative and quantitative feedback, providing health practitioners with a unique education tool.1,2,5,6 In 2013, a meta-analysis including four randomized control trials (RCTs) of 116 individuals with type 2 diabetes, reported CGM improves glycated hemoglobin (HbA1c) in type 2 diabetes over 8–12 weeks. However, this meta-analysis limited reporting to HbA1c outcomes, and did not assess lifestyle or behavioral change adherence, which are critical for effective diabetes management.7,8 The authors also identified only two of the four RCTs were high quality. More recently, less invasive technology and real-time CGM (RT-CGM) technologies have emerged that offer greater potential for combining CGM with lifestyle strategies to enhance type 2 diabetes management. CGM use and sensor wear time have been associated with treatment adherence and improved glycemic control.10 The aim of the present article was to provide a narrative review of trials (identified using a systematic search strategy) investigating the effectiveness of CGM interventions to improve HbA1c, body weight status and lifestyle behavior adherence in adults with type 2 diabetes. Where possible, a further aim was to understand CGM user acceptance and potential implications for primary care use. A systematic approach with a narrative analysis was used due to insufficient availability of high-quality published studies and data reporting on the outcomes of interest in the target population to carry out a meta-analysis.

METHODS

Search strategy

Conduct and reporting of the present review was based on guidelines outlined by the Joanna Briggs Institute peer reviewed protocol for scoping reviews.11 To identify appropriate keywords, an initial limited search of MEDLINE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) was carried out, and the title, abstract and index terms to describe the articles were accepted. Search terms were continuous glucose monitoring OR CGM, diabetes NOT type 1 diabetes AND obese* OR overweight AND lifestyle OR blood glucose control AND/management OR glycemic control AND/OR physical activity AND/OR nutrition OR diet, effectiveness and self-monitoring OR acceptability.

Key terms were used in the second search phase using MEDLINE, CINAHL, Web of Science and SCOPUS electronic databases to include published and unpublished articles, and limited to adults (aged >18 years) and English language publications.
and intervention specifications are presented in Figure 1 and Table 1, respectively.

Participants
A total of 5,542 participants were recruited into eight RCT's (n = 5,342) and three observational trials (n = 196), with 60% men24,27,30,31, and 9% (n = 487) receiving multiple daily insulin injections24,30,32,33. Nine studies assessed baseline body mass index (BMI)24,28,30,33,35 with the majority of participants classified as overweight or obese (BMI >25 kg/m2; n = 5,432). The RCT sample size ranged between 29 and 4,678 participants, with a mean age range of 52-60 years and diabetes duration of 5.2-19.2 years30,31,33,35; one RCT (n = 40) did not report diabetes duration31. The observational trials examined 6 to 181 participants with a mean age range of 54-77 years and diabetes duration of 2.1-14.6 years44,31,35. Of the 11 studies, a total of 159 of 5,542 participants (3%) were reported as dropouts; one trial (n = 6) did not report attrition rates33.

All studies except Cox et al.33 reported participant recruitment strategies including military healthcare beneficiaries (n = 100)24,28,30,31, community health services (n = 278)30,33, and general hospitals (n = 65)27. Studies were carried out in the USA30,31,33,34,35, Canada24, India44, Europe24, South Korea27, and across multiple sites throughout the USA and Canada10.

Study aims and Intervention description
The aims of the studies were to determine whether CGM use elicits changes in glycemic control24,27,30,33,35 and physical activity28,29 and to investigate CGM in relation to self-efficacy and self-monitoring behavior24,28,33,35 and acceptability, satisfaction and tolerance to CGM wear and use24,27,30,33,35. Across the studies, different intervention protocols were used and five distinct research themes identified (Table 1). These research themes included: (i) four RCT's determining the effects of RT-CGM (user can view visual feedback of blood glucose responses instantaneously) compared with SMBG (control)24,27,30,31; (ii) one RCT determining the effects of using retrospective CGM data with diabetes education combined with self-efficacy counseling compared with diabetes education with SMBG (control)28; (iii) three RCT's determining the effects of retrospective CGM with problem-solving counseling compared with retrospective CGM with standard diabetes education (control)24,27,30,31; (iv) two observational studies describing the effect of retrospective CGM data (requiring researchers/health professionals to download "blinded" CGM data into a graphical format to share with participants for counseling purposes)30,31, with one including accelerometer data32; and (v) one observational study describing the effects of RT-CGM combined with a lifestyle program to improve patient outcomes33. Intervention durations for observational studies were 3 days30 and 12 weeks24,31, and for RCT's the range was 8-22 weeks24,31.

Effectiveness of CGM interventions on outcomes
HbA1c changes
All RCT's reported HbA1c changes (Table 2)24-33. Of the four studies comparing RT-CGM with conventional SMBG combined with standard diabetes education over 26 weeks (n = 363) where 43% (n = 158) were on multiple daily insulin injections, three studies reported RT-CGM achieved significant greater HbA1c reductions by a magnitude of 1% (absolute)24,27,30,31. A 40-week follow up from one of these studies assessing the residual effects without wearing RT-CGM showed the greater HbA1c lowering with RT-CGM use was maintained compared with SMBG control after 52 weeks (0.8 vs 0.2%; P < 0.001)24,32,33. RT-CGM compared with an internet-based SMBG protocol after 26 weeks showed no difference between treatments (-0.3 vs -1.07%; P = 0.312)24,33.

Greater HbA1c reduction was observed after 8 weeks of retrospective CGM with self-efficacy counseling compared with SMBG with standard education (-1.16 vs 0.32%; P < 0.05)24,33.
Table 1 | Protocol summary of continuous glucose monitoring intervention studies in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population (years)</th>
<th>Mean age (years)</th>
<th>Duration of type 2 diabetes (years)</th>
<th>Study duration (weeks)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies</td>
<td>Nine adults community health clinic (USA)</td>
<td>57.0 ± 15 (SD)</td>
<td>8.6 ± 6 (SD)</td>
<td>3 days</td>
<td>Phase 1: Retrospective CGM + education Phase 2: Focus group interview</td>
</tr>
<tr>
<td>Gu et al. (2019)19</td>
<td>91 adults (Canada)</td>
<td>55.3 (mean)</td>
<td>2.1 years (mean)</td>
<td>12</td>
<td>RT-CGM + lifestyle program</td>
</tr>
<tr>
<td>Mohan et al. (2016)20</td>
<td>181 Adults (India)</td>
<td>51.1 ± 10 (SD)</td>
<td>14.6 ± 3.1 (SD)</td>
<td>12</td>
<td>Retrospective CGM + education and profession support</td>
</tr>
<tr>
<td>RCT - RT-CGM vs SMBG</td>
<td>Bedi et al. (2017)21</td>
<td>158 Adults receiving multi-dose insulin</td>
<td>SMGCL 60 ± 9 (SD)</td>
<td>SMGCL 18 (range 12-23)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 Endocrine clinics (USA and Canada)</td>
<td>RT-CGM 60 ± 11 (SD)</td>
<td>RT-CGM 17 (range 11-23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infanraj et al. (2011)22</td>
<td>100 Adults military healthcare beneficiaries (USA)</td>
<td>SMGCL 60 ± 11.3 (SD)</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&amp; Vignay &amp; Vinh (2012)23</td>
<td></td>
<td>RT-CGM 25.5 ± 6.8 (SD)</td>
<td>NR</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Tang et al. (2016)24</td>
<td>40 adults</td>
<td>RT-CGM 59.3 ± 8.7 (SD)</td>
<td>RT-CGM 192 ± 74 (SD)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrinology clinic (Canada)</td>
<td>IGMS 65.2 ± 10.9 (SD)</td>
<td>IGMS 174 ± 156 (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yoo et al. (2008)25</td>
<td>64 adults</td>
<td>RT-CGM 54.6 ± 4.8 (SD)</td>
<td>RT-CGM 117 ± 58 (SD)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Hospital based Korea (Seoul)</td>
<td>SMGCL 57.5 ± 9.3 (SD)</td>
<td>SMGCL 13.3 ± 6.9 (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT - Retrospective CGM55 feedback vs control</td>
<td>Allen et al. (2009)26</td>
<td>12 adults</td>
<td>Community Health Service (USA)</td>
<td>Intervention 50 ± 12.4 (SD)</td>
<td>Intervention 0.2 ± 0.7 (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control 50.0 ± 15.6 (SD)</td>
<td>Control 85 ± 23.3 (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anjali et al. (2017)27</td>
<td>6578 Adults (8% Male)</td>
<td>Intervention 57.3 ± 12.1 (SD)</td>
<td>Intervention 157 ± 83 (SD)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Seven public health diabetes clinics (India)</td>
<td>Control 57.1 ± 12.2 (SD)</td>
<td>Control 135 ± 82 (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hasik et al. (2019)28</td>
<td>224 Adults</td>
<td>Intervention 39.0 ± 19.9 (SD)</td>
<td>Intervention 17 ± 8.2 (SD)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>140 Intervention</td>
<td>Control 59.5 ± 9.9 (SD)</td>
<td>Control 18 ± 8 (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 Control receiving multi-dose insulin</td>
<td></td>
<td></td>
<td></td>
<td>Retrospective flash-CGM +</td>
</tr>
<tr>
<td></td>
<td>76 public diabetes clinics</td>
<td></td>
<td></td>
<td></td>
<td>to adjust insulin</td>
</tr>
<tr>
<td>RCT - CGM with counseling vs CGM without counseling</td>
<td>Allen et al. (2011)29</td>
<td>59 Women</td>
<td>Community health service (USA)</td>
<td>Retrospective CGM + problem solving counseling 52 ± 6.5 (SD)</td>
<td>Retrospective CGM + problem solving counseling 67 ± 6.6 (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Community health service (USA)</td>
<td>Retrospective CGM + usual care 51.7 ± 8.0 (SD)</td>
<td>Retrospective CGM + diabetes education 67 ± 6.6 (SD)</td>
</tr>
</tbody>
</table>

1 Usual care consisting of diabetes education/physical activity is defined as per the diabetes management guidelines of the country where the study was carried out. 2 Unable to separate type 1 diabetes data from type 2 diabetes data for this outcome. CGM, continuous glucose monitoring; IEGM, internet blood glucose monitoring; NA, not applicable; NR, not reported; RCT, randomized control trial; RT-CGM, real-time continuous glucose monitoring; SD, standard deviation; SMGCL, Self-Monitoring Blood Glucose Levels.

Two studies compared retrospective CGM using flash CGM with visual charts and counseling to SMGCL.33,34 Greater HbA1c reductions were observed following CGM after 12 weeks (~0.9 vs ~0.7%, P < 0.001) in 4,678 individuals, but not after 24 weeks (~0.28 vs −0.21%, P = 0.823) of 224 individuals taking multiple daily insulin injections.35 After 12 weeks, HbA1c reduction with retrospective CGM was similar when combined with either problem-solving counseling or standard diabetes education (no counseling −0.7 vs −0.5; P = 0.69).36

A 12-week lifestyle program combined with RT-CGM produced an average 1.1% HbA1c reduction in six participants.37 The authors compared these data with findings from a separate, independent 12-week intervention (n = 47) that used the same lifestyle program with SMBG and reported similar HbA1c reductions (1%).38,39 However, population size heterogeneity
<table>
<thead>
<tr>
<th>Control</th>
<th>CGM system type</th>
<th>CGM wear time protocol</th>
<th>Calibration protocol</th>
<th>Total CGM Wear</th>
<th>Reported CGM acceptability/subject satisfaction</th>
<th>Compliance to CGM protocol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Medtronic MiniMed</td>
<td>3 days</td>
<td>NR</td>
<td>3 days</td>
<td>/</td>
<td>NR</td>
</tr>
<tr>
<td>NA</td>
<td>DexCom™ G4 Platinum</td>
<td>NR</td>
<td>Undecid</td>
<td>NR</td>
<td>/</td>
<td>NR</td>
</tr>
<tr>
<td>NA</td>
<td>Medtronic Pro™</td>
<td>NR</td>
<td>Undecid</td>
<td>NR</td>
<td>/</td>
<td>NR</td>
</tr>
<tr>
<td>SMBGL + usual care*</td>
<td>DexCom™ G4 Platinum</td>
<td>Daily wear (160 days)</td>
<td>Calibrate 2x daily and glucose testing 2x daily</td>
<td>1995 of 1885 days NR</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>SMBGL + usual care*</td>
<td>DexCom™ Seven™</td>
<td>12 weeks of intermittent CGM followed by SMBGL only 8 weeks</td>
<td>As per manufacturer's instructions</td>
<td>56 days per protocol/68 days minimum</td>
<td>68%</td>
<td>68-88 days</td>
</tr>
<tr>
<td>SMBGL + usual care*</td>
<td>Guardian IT-CGM Medtronic Minimed</td>
<td>Undecid</td>
<td>Undecid</td>
<td>Undecid</td>
<td>/</td>
<td>NR</td>
</tr>
<tr>
<td>SMBGL + usual care*</td>
<td>Guardian IT-CGM Medtronic Minimed</td>
<td>3 days per month for study duration</td>
<td>3x daily</td>
<td>9 days</td>
<td>x</td>
<td>NR</td>
</tr>
<tr>
<td>Usual care*</td>
<td>Medtronic MiniMed</td>
<td>3 days continuous at baseline and post</td>
<td>NR</td>
<td>6 days</td>
<td>x</td>
<td>NR</td>
</tr>
<tr>
<td>Usual care*</td>
<td>Abbotts Freestyle Libre™ Flash Glucose Monitoring</td>
<td>14 day continuous wear time</td>
<td>NR</td>
<td>14 days continuous wear time</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>SMBGL + usual care*</td>
<td>Abbotts Freestyle Libre™ Flash Glucose Monitoring</td>
<td>14 day continuous wear time</td>
<td>Intervention: Scan the flash sensor every 6 h</td>
<td>Both groups: Received blood glucose levels daily</td>
<td>/</td>
<td>NR</td>
</tr>
<tr>
<td>SMBGL + usual care*</td>
<td>Abbotts Freestyle Libre™ Flash Glucose Monitoring</td>
<td>14 day continuous wear time</td>
<td>Intervention: Scan the flash sensor every 6 h</td>
<td>Both groups: Received blood glucose levels daily</td>
<td>/</td>
<td>NR</td>
</tr>
</tbody>
</table>

between the two datasets carried out over different time periods, limits the ability to draw effective comparisons.

**Bodyweight changes**

For bodyweight changes, BMI (kg/m²) is reported in the instance where weight (kg) data is not reported. Eight studies reported bodyweight changes (Table 2)**20-22**. Three intervention studies compared RT-CGM combined with education including RT-CGM output interpretation to SMBG1 combined with standard diabetes education (control)**24,25,27,28**. Two studies showed a trend for greater weight loss with RT-CGM after 12 weeks (range -1.8 to -2.2 kg RT-CGM vs -1.4 to 0.4 kg control)**24,25,27**, A further study reported 1.3-kg weight gain with RT-CGM vs -0.2 kg control (P-value not reported), and was the only trial to include individuals taking insulin (Table 2)**20**. Another intervention showed a non-significant greater BMI
reduction in the RT-CGM group compared with control participants over 26 weeks (-1.44 vs -0.35 kg/m²). A 40-week follow-up from a previous 12-week CGM study showed a sustained, non-significant greater weight reduction in the RT-CGM group compared with control participants (-1.9 vs -0.9 kg; P = 0.22). The specific details of counseling and education provided were unclear, although contact frequency was reduced from every 3 weeks during the initial 12-week intervention to 3 monthly during 40-week follow-up.

A 12-week intervention using retrospective CGM with problem-solving counseling produced a non-significant greater weight loss compared with retrospective CGM with standard diabetes education (-6.2 vs -2.4 kg; P = 0.05). Furthermore, retrospective CGM plus behavior change counseling for 8 weeks produced significantly greater BMI reduction compared with SMBG and standard diabetes education (-0.53 vs -0.12 kg/m²; P < 0.05). A 12-week lifestyle program combined with counseling and RT-CGM achieved a 7.3-kg weight loss. This was greater than the weight loss reported in a previous study using the same lifestyle program combined with counseling and SMBG (-2.5 kg).

Change in behavior, physical activity and diet
Eight of the 11 studies reported at least one of the three lifestyle behavior domains of physical activity, dietary and behavioral outcomes (Table 2).

Behavioral change
Six studies (five observational and five RCTs) reported behavioral changes with CGM, noting a generally minimal effect. Two studies comparing RT-CGM vs SMBG with standard diabetes education over 12 weeks and a 40-week follow-up without RT-CGM reported no differences between groups for changes in diabetes distress. Meanwhile, greater diabetes treatment satisfaction was observed in a control group utilizing SMBG combined with an internet-based monitoring protocol and standard diabetes education compared with a RT-CGM intervention group. Conversely, greater improvements in diabetes treatment satisfaction were observed after an intervention using retrospective flash CGM with clinician interaction to adjust insulin compared with SMBG combined with usual care control. A further study reported retrospective CGM with problem-solving counseling achieved greater improvements in diabetes problem-solving compared with retrospective CGM with standard education (1.05 vs 0.43 arbitrary units; P = 0.02).

An 8-week intervention of retrospective CGM achieved greater increases in the stidling to it domain of the Self-Efficacy for Exercise Behavior Survey compared with SMBG with standard diabetes education (0.52 vs -0.11; P = 0.05). A 12-week lifestyle program combined with RT-CGM lowered the diabetes distress score. However, similar improvements were achieved with the same lifestyle program combined with SMBG.

Physical activity outcomes
Four studies (one observational trial, three RCTs) reported physical activity outcomes after CGM intervention with differing assessment methodologies and results. RT-CGM with standard diabetes education produced greater increases in total exercise minutes compared with SMBG with standard diabetes education (+1584 vs +43.3 min/week; P = 0.02). Similarly, 8 weeks after retrospective CGM with education relating to exercise-associated blood glucose response produced greater increases in mean activity counts/day compared with SMBG with standard exercise guideline education (31,144 vs 9,281 counts; P ≤ 0.05). Another study investigating retrospective CGM with counseling and problem-solving or with standard education showed no differences in changes in physical activity levels after 12 weeks, although the group that received retrospective CGM with problem-solving skills showed a non-significant greater increase in activity counts (+15,000/ day vs -4000/day; P = 0.48) and levels of moderate activity (5 min/day vs -3 min/day; P = 0.11). An increase in absolute step counts (8,400-13,000 steps/per day) occurred after a 12-week lifestyle intervention combined with RT-CGM. A similar magnitude of change was reported in a separate study carried out in a different cohort following the same lifestyle program combined with SMBG.

Dietary outcomes
Three studies (one observational and two RCTs) assessed dietary outcomes. There were greater reductions in caloric intake after 12 weeks of RT-CGM compared with SMBG and standard diabetes education (-168.7 vs -113.9 kcal/day; P = 0.05). It was found that 12 weeks of retrospective CGM with problem-solving counseling achieved higher ratings of adherence to a personal eating plan compared with retrospective CGM and standard diabetes education (7/7 vs 6.7 arbitrary units; P = 0.01), with no difference between the groups for domains of healthful eating, fruits and vegetables, and high-fat foods.

A 12-week observational study showed a lifestyle intervention combined with RT-CGM reduced total energy intake (pre: 2,860 Kcal, post: 1,796 Kcal [difference = -894 Kcal]) and total carbohydrate intake (pre: 243.3 g, post: 150.5 g [difference = 92.8 g]).

Device acceptability, usability and wear time
Total CGM sensor wear time and compliance is described in Table 1. One study showed no change in CGM wear acceptance using a system usability scale score before and after 12 weeks of RT-CGM wear, indicating moderate-to-good usability. Another study (n = 181) reported a high CGM wear comfort (6.1/7) and improved diabetes awareness (6.2/7). Three studies (n = 287) recorded compliance with CGM protocols defined as attendance at CGM counseling sessions and compliance with CGM wear protocol. One study (n = 29) comparing CGM with problem-solving counseling...
with CGM without counseling showed high levels of compliance to the intervention protocol based onession attendance (>90%)27. Two studies compared RT-CGM with SMBGL with no counseling; a 12-week intervention used a wear time protocol of 2 weeks of continuous device wear separated by 1 week of no wear (i.e., 56 days total wear time required), and showed 32% of participants (n = 16) used the CGM device <48 days, and 68% (n = 34) for >48 days24,25; whereas a 24-week intervention using a continuous daily wear protocol for 168 days reported 97% compliance with mean wear time of 159 days26.

A follow-up interview of participants prescribed to wear a blinded CGM device for 72 h with limited support reported just 57% of participants remembered to use event buttons on the monitor to enter medication, and meal and physical activity times, and reported many other problems in contrast to using manual logs27. Issues with wearing appropriate clothes to attach the monitor at night were also reported28. Post-study themes included visual CGM graphs reinforcing the need for behavior change, and the role of diet, exercise and stress on glucose levels24.

DISCUSSION
Continuous glucose monitoring has a potential role in limiting the frequency and/or onset of hypoglycemia in type 2 diabetes patients, particularly for those receiving insulin therapy, who have a history of severe hypoglycemia or with irregular routines (skipping meals, vigorous exercise and poor sleep patterns)27,29-31. The present narrative review evaluated the evidence of the acceptance and effectiveness of CGM use on improving glycemic control, weight status and behavior change in adults with type 2 diabetes. Published observational and randomized controlled studies over the past decade were included, and revealed a relatively small number of studies with high heterogeneity in intervention design and outcomes reported. Of the studies available, a high level of CGM technology acceptance was reported and, compared with standard SMBGL combined with diabetes education, CGM use promoted greater HbA1c lowering and weight loss. The addition of lifestyle and/or behavioral counseling to CGM promoted higher diabetes treatment satisfaction and reduced diabetes-related distress. However, specific counseling or lifestyle attributes that were most effective could not be ascertained. Although visual glucose outputs from CGMs were repeatedly reported as beneficial for educational purposes, communication specifics surrounding effective delivery strategies were not provided24,26,30,31,33,34.

Compared with standard SMBGL with standard education, RT-CGM achieved a 0.4-0.7% (absolute) greater HbA1c reduction over 12-24 weeks in non-insulin (n = 168) and insulin-dependent (n = 158) individuals with type 2 diabetes, respectively24,25,29,30 in non-insulin-dependent individuals, a 40-week follow-up period without continued RT-CGM use showed these differential changes between the groups were maintained24. Similarly, provision of retrospective CGM feedback delivered with diabetes education plus self-efficacy counseling achieved a 0.9% (absolute) greater reduction in HbA1c compared with standard diabetes education alone over 8 weeks30. More recently, a 12-week study of 4,678 individuals showed the use of retrospective flash CGM, delivered with professional support at weeks 0, 4 and 12 using visual glucose charts to address medication management, achieved greater HbA1c reduction compared with SMBGL with standard education (−0.2% absolute; P < 0.001)28. These data suggest that access to CGM information can promote greater HbA1c reductions compared with standard care, and that these effects are sustained over the longer term. Furthermore, the addition of self-efficacy counseling and not problem solving counseling has been shown to further magnify the CGM treatment effects without medication intensification27,28. The exact reason for the variation of HbA1c change observed between the studies (6.4-0.9%) is not clear, but might arise because the study showing the greatest absolute change provided a walking and exercise plan as part of the standard education30, compared with exercise information and monitoring24,27. A meta-analysis has shown that supervised walking achieved greater HbA1c reduction compared with non-walking controls (−0.5%)24,30. This suggests an additive benefit of prescriptive exercise instruction in conjunction with CGM for intensifying glycemic control.

The current study results concur with a previous meta-analysis that reported a group mean −0.31% greater HbA1c reduction over an 8-12-week period of CGM use compared with SMBGL in adults with type 2 diabetes30. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study for the use of CGM in type 1 diabetes management in children and adults also showed a −0.53% greater reduction in HbA1c compared with SMBGL over 26 weeks for individuals aged ≥2.5 years26. This smaller HbA1c change in the Juvenile Diabetes Research Foundation cohort compared with studies reported in the current analysis could be explained by the tighter glycemic control at baseline (HbA1c < 8 vs. >8%). By way of comparison of magnitude, lifestyle-based weight loss interventions lasting between 16 weeks and 9 years produced a smaller non-significant greater reduction in HbA1c of −0.29% compared with usual diabetes care and education in type 2 diabetes patients32. A 1% HbA1c reduction is estimated to reduce the risk of diabetes-related death by 21%, myocardial infarction by 14% and microvascular complications by 37%33. Hence, the additional −0.3% reduction achieved by RT-CGM use could translate to significant further reductions in diabetes complication risk.

Interestingly, no differences in HbA1c changes were observed between RT-CGM and SMBGL when delivered through an internet protocol with endocrinologist feedback. The reason for this lack of additional effect of RT-CGM is difficult to explain. However, these data suggest using an internet platform to monitor blood glucose readings throughout the day and/or close professional support might engender similar effects to RT-CGM.
Table 2 | Changes in glycemic control, bodyweight, physical activity, diet and behavioral outcomes from continuous glucose monitoring studies in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Study population</th>
<th>Mean age (years)</th>
<th>Duration of type 2 diabetes (years)</th>
<th>Intervention duration (weeks)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Allen et al. (2009)</td>
<td>Nine adults community health clinic (AUS)</td>
<td>57.0 ± 15.5 (SD)</td>
<td>8.6 ± 6.0 (SD)</td>
<td>3 days</td>
</tr>
<tr>
<td>Cox et al. (2016)</td>
<td>56 adults (Canada)</td>
<td>55.3 (mean)</td>
<td>2.1 years (mean)</td>
<td>12</td>
</tr>
<tr>
<td><strong>RCTs vs. SMGBL</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beck et al. (2017)</td>
<td>65 adults</td>
<td>59.1 ± 10.0 (SD)</td>
<td>16.4 ± 4.8 (SD)</td>
<td>12</td>
</tr>
<tr>
<td>Elliott et al. (2017)</td>
<td>Adults receiving multidose insulin</td>
<td>60.1 ± 11 (SD)</td>
<td>RT-GCM 60 ± 11 (SD)</td>
<td>24</td>
</tr>
<tr>
<td>Sibbald et al. (2017)</td>
<td>100 adults</td>
<td>60.1 ± 11.9 (SD)</td>
<td>RT-GCM 55.5 ± 9.6 (SD)</td>
<td>12</td>
</tr>
<tr>
<td>Tang et al. (2017)</td>
<td>46 adults</td>
<td>60.1 ± 11.7 (SD)</td>
<td>RT-GCM 60.6 ± 10.9 (SD)</td>
<td>20</td>
</tr>
<tr>
<td>Yon et al. (2017)</td>
<td>65 adults</td>
<td>56.6 ± 6.8 (SD)</td>
<td>RT-GCM 57.5 ± 0.0 (SD)</td>
<td>12</td>
</tr>
<tr>
<td><strong>RCTs vs. SMGBL</strong></td>
<td></td>
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<tr>
<td>Allen et al. (2008)</td>
<td>52 adults</td>
<td>57.3 ± 14.7 (SD)</td>
<td>Control 57.3 ± 14.7 (SD)</td>
<td>8</td>
</tr>
<tr>
<td>Arjena et al. (2017)</td>
<td>4670 adults</td>
<td>57.1 ± 12.1 (SD)</td>
<td>Control 57.1 ± 12.1 (SD)</td>
<td>12</td>
</tr>
<tr>
<td>Pask et al. (2017)</td>
<td>204 adults</td>
<td>59.5 ± 9.0 (SD)</td>
<td>Control 59.5 ± 9.0 (SD)</td>
<td>24</td>
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<tr>
<td><strong>RCTs vs. CGM without counseling</strong></td>
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<tr>
<td>Allen et al. (2017)</td>
<td>79 women</td>
<td>Retrospective CGM + problem-solving counseling</td>
<td>52.2 ± 6.6 (SD)</td>
<td>12</td>
</tr>
</tbody>
</table>

*Usual care consisting of diabetes education/physical activity is defined as per the diabetes management guidelines of the country where the study was carried out. Significant between-group differences identified as P < 0.05. CGM: continuous glucose monitoring; HbA1c, glycated hemoglobin; IGBM: internet blood glucose monitoring; NA: not applicable; NR: not reported; PAD: Problem Areas in Diabetes; RCT, randomized control trial; RT-GCM, real-time continuous glucose monitoring; SD: standard deviation; SMGBL, Self-Monitoring Blood Glucose Levels.
<table>
<thead>
<tr>
<th>Study</th>
<th>Dietary Intervention vs Control (P-value)</th>
<th>Physical Activity Intervention vs Control (P-value)</th>
<th>Diet Intervention vs Control (P-value)</th>
<th>Behavioral Intervention vs Control (P-value)</th>
</tr>
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<tbody>
<tr>
<td>NR</td>
<td>NR</td>
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<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>Weight (kg) or BMI (kg/m²)</td>
<td>Change in weight (kg) 12 weeks -10 vs -5 (P = 0.02)</td>
<td>BMI kg/m² 1.41 vs 1.35 (P = 0.01)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>Pedometer (steps) P = 0.005</td>
<td>Total energy intake -88 Kcal (P = 0.3)</td>
<td>Total energy intake 86 Kcal (P = 0.3)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>12 weeks Change weight (kg) -15 vs -4 (P = 0.02)</td>
<td>PAD score 12 weeks -10 vs -6 (P = 0.01)</td>
<td>Change in total energy intake -88 Kcal (P = 0.3)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>Change in BMI kg/m² 1.41 vs 1.35 (P = 0.01)</td>
<td>Self-Efficacy for Exercise Behavioural Survey (b) 12 weeks 6.5 vs 6.5 (P = 0.02)</td>
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<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>Change in BMI kg/m² 1.41 vs 1.35 (P = 0.01)</td>
<td>Diabetes Treatment Satisfaction Questionnaire score (a) 12 weeks 111 vs 50 (P = 0.005)</td>
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<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>Change in BMI kg/m² 1.41 vs 1.35 (P = 0.01)</td>
<td>Subscale of diabetes self-care score Healthy eating plan 77 vs 67 (P = 0.03)</td>
<td>Heathy eating plan 77 vs 67 (P = 0.03)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;0.1 (change) (P-value &lt; 0.05)</td>
<td>Change in BMI kg/m² 1.41 vs 1.35 (P = 0.01)</td>
<td>Sleepiness level 12 vs 12 (P = 0.03)</td>
<td>Sleepiness level 12 vs 12 (P = 0.03)</td>
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References:
Excess weight is a strong predictor of type 2 diabetes and HbA1c. Approximately 80% of people with type 2 diabetes are overweight or obese. Studies comparing SMBG with RT-CGM showed no statistically significant differences in weight loss or BMI changes between treatments. Nevertheless, three of the four studies using RT-CGM consistently achieved a 4 kg greater weight loss reduction compared with standard SMBG over 12-26 weeks, an effect that was sustained 40 weeks after the cessation of RT-CGM treatment. It is possible the relatively small sample sizes used in previous studies precluded realization of the relatively modest effect sizes as statistically significant. Previous studies have shown as little as a 1-kg or 1% weight loss can have a substantial benefit for glycemic control, morbidity and mortality. It is therefore possible that RT-CGM could offer modest, yet clinically relevant, weight loss benefits.

Interestingly, a 24-week RT-CGM intervention in patients with type 2 diabetes on multiple daily injections of insulin showed a 1.3-kg weight gain compared with a -0.2-kg weight loss for the control. This was despite significant greater HbA1c reductions with RT-CGM, suggesting that, although HbA1c and weight are closely linked, for those requiring insulin, weight gain might be acceptable. However, more research documenting insulin titration strategies for weight management using RT-CGM is required.

The studies identified in the present review further suggest the possibility that CGM data could be used to potentiate the weight loss effects of other intervention initiatives to provide a comprehensive weight loss strategy. CGM information combined with self-efficacy and/or problem-solving counseling (the latter which incorporates individualized counseling based on blood glucose response) provided an additional 2-kg greater loss compared with CGM with standard diabetes education. However, only few, small studies have examined the effects of diet and lifestyle advice combined with CGM use on weight, and more research is needed to establish these effects. Nevertheless, personalization achieved through feedback or tailored information received during counseling support has been established as a critical component of successful weight loss interventions. The Action for Health in Diabetes study (Look AHEAD) showed a 5-10% weight loss in individuals with type 2 diabetes effectively reduces HbA1c, and diabetes and lipid-lowering medication requirements. Hence, the potential role for CGM technology as an adjunctive therapy for sustainable weight loss management warrants further investigation.

Diet, physical activity and behavioral therapy are the cornerstones of type 2 diabetes management. It is well established that dietary habits, food choices and physical inactivity profoundly affect blood glucose response and control and self-monitoring is a key driver for behavior change. However, therapeutic strategies are often required for optimal glycemic control. Recent availability of real-time and ambulatory CGM technology provides the opportunity to use this monitoring information to educate patients on blood glucose response to lifestyle choices (diet and exercise), with the objective of modifying choices and augmenting adherence to effective behaviors, in the absence of medication intensification. Preliminary data suggest short-term use of RT-CGM that incorporates graph interpretation and hypoglycemic alarms without counseling can promote greater physical activity levels and reductions in caloric intake. Yeo et al. (2014) successfully instructed participants to increase exercise and reduce food portions in response to RT-CGM-generated hypoglycemic event alarms (>50 mg/dL). Similarly, provision of retrospective CGM data with feedback on physical activity responses using self-efficacy counseling was shown to increase physical activity levels and confidence in engaging with a physical activity routine. These early data suggest that access to CGM information might promote favorable changes, and adherence to diet and exercise behaviors. However, the ease and significance of data interpretation for the user is an important consideration. Future lifestyle and behavior change studies need to investigate the integrated role between CGM and the quality and quantity of information provided to the user with type 2 diabetes to identify practices that facilitate adherence to lifestyle modification changes. The few studies reporting user acceptance and/or compliance to CGM wear suggest a high-level device wear compliance confidence with using RT-CGM devices and moderate-to-good useability. Secondary analysis of 7,916 individuals with type 1 diabetes and type 2 diabetes using glucose sensors for >15 days during any 6-month period over 2 years reported that compliance with sensor use in the first month of therapy predicted longer-term compliance and self-management adherence. High satisfaction and perceived value ratings have also been reported in interventions using CGM combined with either problem-solving and/or self-efficacy counseling or standard diabetes education. Some evidence exists suggesting greater CGM satisfaction when combined with problem-solving and targeted feedback directly linked to diet and exercise behaviors. These data suggest the relative ease of use and high short-term acceptance of CGM systems among type 2 diabetes patients. This concurs with reported responses in type 1 diabetes that could assist to promote long-term compliance and acceptance of this device technology. The reported high acceptance of CGM as a useful therapeutic and educational tool should be considered in the context of the relatively limited feedback alternatives provided by standard diabetes self-management strategies that rely on 3- to 6-monthly HbA1c measures and SMBG. The latter only provides a snapshot of current glucose levels and lacks the sensitivity to detect small changes or specify glucose responses to food or activity. The limited ability of these established tools to provide individualized insight into glucose response might therefore contribute to the reported frustration and poor compliance with current diabetes self-management and attend medical poor glycemic control. Overall, the present review suggests a potential role for CGM to improve awareness.
of the effectiveness for diet and exercise in diabetes treatment, and enhance adherence to behavioral strategies in primary care. Therefore, it is disappointing that because of the limited evidence available to date, current consensus on the optimal frequency and duration of CGM use in primary care remains unclear. The role and the type of counseling to accompany CGM, and a clear strategy for use of CGM in insulin management in this milieu is even more unclear. To promote effective use of CGM in clinical practice, research must consider and report on the type of complementary advice provided for medication management and counseling style used in order to determine its full benefits and overall effects.

The relatively small number of studies available and small sample sizes associated with some of the studies have resulted in the high heterogeneity of outcomes assessed and study design features used. This suggests results should be interpreted with some caution. This also has precluded the ability to carry out a meta-analysis at this time, and to draw specific and reliable conclusions regarding the effectiveness and acceptability of CGM use for type 2 diabetes. Additionally, the quality, quantity and diversity of adjacent counseling, education techniques and clinical involvement further confound interpretation of these studies for optimization of clinical type 2 diabetes management. With the view of using CGM in primary care, there is an urgent need to provide evidence to identify individual risk and the frequency of hypoglycemia for the effective development of risk management strategies for clinical practice. More, larger, longer-term studies that detail intervention methods and delivery protocols will provide better understanding of the chronic effects and durability of CGM, its acceptance and the appropriate balance of its application with clinical involvement. Additionally, given the greater disproportionate burden of type 2 diabetes in Asians, future studies should also focus on these populations. As more rigorous evidence emerges from larger studies using homogenous study designs, a meta-analysis is warranted. The current review was also unable to directly compare and differentiate responses to CGM use between insulin-dependent and non-insulin-dependent individuals with type 2 diabetes, or the effects of medication types and doses in these populations. Individuals requiring insulin for glycemic control might experience greater risk of hypoglycemia using CGM when compared with their non-insulin-taking counterparts. Therefore, larger, controlled studies that consider these factors and examine diverse population subgroups are required to better understand the wider benefits and application of CGM use in primary care. The paucity of detail regarding specific education and counseling protocols used within the reported studies also precludes description or the comparison of the type and frequency of education and support provided within the lifestyle interventions. The American Association of Clinical Endocrinologists and American College of Endocrinology have identified the necessity for users and administrators in primary care to be well informed of the benefits and potential issues associated with CGM device use, and the appropriate translation of such information into lifestyle strategies to optimize glycemic control and diabetes care. It is imperative therefore, when reporting study protocols in future studies, that counseling, education and feedback strategies are clearly described. If these strategies potentiate the benefits of CGM wear, this will assist the translation of these new clinical practices into established diabetes management strategies. It is long overdue that CGM devices with lifestyle interventions are compared with usual clinical care in both depth and detail.

In conclusion, the present narrative review suggests that CGM promotes improvements in glycemic and weight control, and lifestyle behaviour change in adults with type 2 diabetes, and that these benefits might be enhanced when CGM is integrated with diet, exercise, and glucose excursion education and counseling. However, the limited number of highly heterogeneous studies available makes it difficult to identify specific attributes of effective interventions and to draw cohesive robust evidence for multidisciplinary clinical practice that promotes healthier choices for the type 2 diabetes patient population. As new evidence begins to emerge, there is a considerable need for a meta-analysis to inform a greater understanding of the application of CGM for practice. In particular, its integration with pre-existing and established monitoring and education tools should facilitate user engagement and device acceptability in type 2 diabetes and lifestyle management.

ACKNOWLEDGMENTS

The authors thank Darren Jones, Information Officer in Information Management & Technology for the Commonwealth Scientific and Industrial Organisation (CSIRO), for assistance in determining the search protocol for the review.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES


Chapter 4: Manuscript 3

Efficacy of real-time continuous glucose monitoring to improve effects of a prescriptive lifestyle intervention in type 2 diabetes: A pilot study

Publication:
Diabetes Therapy: 2019; 10; 509-522
# Statement of Authorship

## Title of Paper

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<th>Published</th>
<th>Accepted for Publication</th>
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## Publication Details


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| Name of Principal Author (Candidate) | Pennie (Penelope) Taylor |

**Contribution to the Paper**

Co-designed original protocol, responsible for ethics preparation, submission and adoptions, responsible for trial conduct, monitored adverse events of trial participants, managed data, analysed data, prepared manuscript and corresponding author.

**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 16.4.19

## 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.

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**Contribution to the Paper**

Co-designed original protocol, contributed to ethics preparation, screened medical suitability of participant inclusion, monitored adverse events of trial participants, supervised and supported data analysis and interpretation, critically reviewed and edited original and revised manuscript.

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<tr>
<td>Natalie Luscombe-Marsh</td>
<td>Co-designed original protocol, contributed to ethics preparation, provided trial support, critically reviewed original and revised manuscript.</td>
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<td>Grant Brinkworth</td>
<td>Co-designed original protocol, contributed to ethics preparation, supervised and supported data analysis and interpretation, critically reviewed and edited original and revised manuscript</td>
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Efficacy of Real-Time Continuous Glucose Monitoring to Improve Effects of a Prescriptive Lifestyle Intervention in Type 2 Diabetes: A Pilot Study

Penelope J. Taylor, Campbell H. Thompson, Natalie D. Luscombe-Marshal, Thomas F. Wycherley, Gary Wittert, Grant D. Brinkworth

Received: December 4, 2018 © The Author(s) 2019

ABSTRACT

Introduction: Optimising patient adherence to prescribed lifestyle interventions to achieve improved blood glucose control remains a challenge. Combined use of real-time continuous glucose monitoring systems (RT-CGM) may promote improved glycaemic control. This pilot study examines the effects of a prescriptive lifestyle modification programme when combined with RT-CGM on blood glucose control and cardiovascular disease risk markers.

Methods: Twenty adults (10 men, 10 women) with obesity and type-2 diabetes (T2D) (age 60.55 ± 8.38 years, BMI 34.22 ± 4.67 kg/m²) were randomised to a prescriptive low-carbohydrate diet and lifestyle plan whilst continuously wearing either an RT-CGM or an ‘offline-blinded’ monitor (control) for 12 weeks. Outcomes were glycaemic control (HbA1c, fasting glucose, glycaemic variability [GV]), diabetes medication (MeS), weight, blood pressure and lipids assessed pre- and post-intervention.

Results: Both groups experienced reductions in body weight (RT-CGM − 7.4 ± 4.5 kg vs. control − 5.5 ± 4.0 kg), HbA1c (− 0.67 ± 0.82% vs. − 0.68 ± 0.74%), fasting blood glucose (− 1.2 ± 1.9 mmol/L vs. − 1.0 ± 2.2 mmol/L), LDL-C (− 0.07 ± 0.34 mmol/L vs. − 0.26 ± 0.42 mmol/L) and triglycerides (− 0.32 ± 0.46 mmol/L vs. − 0.36 ± 0.53 mmol/L); with no differential effect between groups (P > 0.10). At week 12, GV indices were consistently lower by at least

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Published online: 31 January 2019
sixfold in RT-CGM compared to control (CONGA-1 = 0.27 ± 0.36 mmol/L vs. 0.06 ± 0.19 mmol/L; CONGA-2 = 0.36 ± 0.54 mmol/L vs. 0.05 ± 2.88 mmol/L; CONGA-4 = 0.44 ± 0.67 mmol/L vs. 0.02 ± 0.42 mmol/L; CONGA-8 = 0.36 ± 0.61 vs. 0.02 ± 0.52 mmol/L; MAGE = 0.69 ± 1.14 vs. 0.09 ± 0.08 mmol/L, although there was insufficient power to achieve statistical significance ($p \geq 0.11$). Overall, there was an approximately 40% greater reduction in blood glucose-lowering medication (MeS) in RT-CGM ($-0.30 \pm 0.59$) compared to control ($0.02 \pm 0.23$).

**Conclusion:** This study provides preliminary evidence that RT-CGM may be an effective strategy to optimise glucose control whilst following a low-carbohydrate lifestyle programme that targets improved glycaemic control, with minimal professional support.

**Trial Registration:** Australian New Zealand Clinical Trials Registry Identifier, ANZTR:372898.

**Funding:** Grant funding was received for the delivery of the clinical trial only, by the Diabetes Australia Research Trust (DART).

**Keywords:** Glycemic variability; Real-time continuous glucose monitoring; Type 2 diabetes

**INTRODUCTION**

Type 2 diabetes (T2D) poses an enormous socioeconomic burden [1]. It is associated with numerous vascular complications and a three-to sixfold increase in cardiovascular disease (CVD) risk. Optimising blood glucose levels remains a primary therapeutic target [2]. Despite modest effects, lifestyle modification incorporating diet and exercise remains the cornerstone of T2D management [2-6]. Lifestyle modification and particularly a low-carbohydrate diet can improve glycaemic control [7, 8] including reducing a patient’s glycaemic variability (GV), i.e. the oscillations in blood glucose levels throughout the day [9]. GV has been identified as an independent risk factor for diabetes complications including CVD [1, 10-14]. Despite strong efficacy of lifestyle modification programmes, their effectiveness is often underpinned by intensive techniques requiring close monitoring and health professionals’ support to achieve adherence and desired health outcomes [15]. These practice models are therefore resource-intensive and cost-prohibitive, limiting their widespread availability.

Self-regulation that enables a patient to exert confidence and control over their diet and exercise behaviours is a key component to effective lifestyle intervention adherence [16, 17]. One approach to enhance patient self-regulation is to provide them with immediate feedback based on the results of their behaviours [18]. Self-monitoring of health markers and behaviours beyond the clinical setting has been used as an effective tool to monitor treatment response and improve adherence for a variety of health outcomes including body weight, blood pressure and physical activity [18]. This suggests that self-monitoring of blood glucose (SMBG) in T2D could serve as an immediate feedback function to provide patients with evidence of the biological effect of lifestyle choices on blood glucose levels that may improve adherence to lifestyle prescription and improve glycaemic outcomes [19-21]. Real-time continuous glucose monitoring (RT-CGM), which provides an ongoing display of glucose levels over an extended period (i.e. days/weeks), allows an individual to self-monitor how their blood glucose level responds to various lifestyle factors including diet and exercise, with direct and continuous dynamic feedback. It is therefore possible that RT-CGM might motivate and guide patients to adapt their lifestyle patterns in an appropriate manner to reduce GV and improve glycaemic control. Previous studies have shown that RT-CGM can promote an approximately 0.5% (absolute) greater reduction in HbA1c compared to conventional SMBG using the finger-prick method in T2D [20, 22-25]. However, these studies did not comprehensively assess the effects of RT-CGM on GV or combine this therapeutic strategy within a comprehensive and structured diet and lifestyle programme that targets minimisation of wide glucose fluctuations. Consequently, previous studies have required patients to make changes to diet and exercise in response to SMBG in the absence of advice on those changes that will be most effective to optimise glycaemic control. The purpose of this feasibility study was
to examine the effects of RT-CGM compared to blinded CGM on blood glucose control as assessed by HbA1c, GV and CVD risk markers when undertaking a prescriptive lifestyle modification programme that has minimal healthcare practitioner involvement.

METHODS

Study Participants

Twenty adults who were overweight or obese (BMI 26-45 kg/m², age 20-75 years) with T2D [HbA1c 5.9–6.9% (41.0–51.9 mmol/mol)] were recruited via public advertisement to participate in a randomised controlled study, conducted between June and September 2017 at the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Health and Nutrition Research Unit (Adelaide Australia), Table 1, Fig. 1 (participant flow). Exclusion criteria were type 1 diabetes; proteinuria (urinary albumin-to-creatinine ratio ≥ 30 mg/mmol), abnormal liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST) or gamma-glutamyl transferase (GGT) ≥ 2.5 times the normal upper limit], impaired renal function (eGFR < 60 ml/min), any abnormal or significant clinical history including current malignancy, liver, respiratory, gastrointestinal, cardiovascular disease or pregnancy/lactation, eating disorder or clinical depression; any significant endocrinopathy (other than stable treated thyroid disease); have taken/or taking glucocorticoids (oral/inhaled or topical) within last 3 months, psychotropics other than a stable dose of a selective serotonin reuptake inhibitor; illicit drugs, medications which affect gastrointestinal motility or hunger/appetite (e.g. metoclopramide, domperidone and cisapride, anticholinergic drugs (e.g. atropine), erythromycin) or past history of gastrointestinal surgery which may affect study outcomes. All participants provided written informed consent prior to participation. The study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR 372898) and approved by the Human Research Ethics Committees of the CSIRO and the University of Adelaide.

Study Design and Intervention

This was a feasibility pilot study, i.e., a small-scale investigation that was conducted and published to inform researchers of important parameters and sample size requirements required for an adequately powered randomised control trial. In a parallel design, participants were matched for age and gender and randomised using a computer-generated randomisation procedure (www.randomisation.com) to undertake a 12-week lifestyle (diet and exercise) intervention with either (1) real-time continuous glucose monitoring (RT-CGM) with access to visual display or (2) continuous glucose monitoring (blinded CGM; control), with no access to visual display. Randomisation (sequence generation) was performed by the clinical trials manager, who was blinded for the purpose of providing device and technology support, including technical troubleshooting for device connectivity and the administration of sensor kits to the participants. All other research associates responsible for data collection, processing and analysis were blinded until data analysis was complete. Participants received a once-off honorarium ($200 AUD) for trial participation.

At week 0 (after the completion of baseline assessments), participants in both groups received a prescriptive low-carbohydrate, high-protein and unsaturated fat diet (LC diet) and exercise plan, incorporating moderate intensity aerobic/resistance exercises in the form of a commercial publication; at this point randomisation was revealed to participants and to primary staff responsible for administration of glucose sensors and downloads [26]. The dietary prescription had a planned macronutrient profile of 14% of total energy as carbohydrate, 28% protein and 58% total fat (35% monounsaturated fat), individualised for energy level based on achieving a 30% energy restriction. This dietary profile and lifestyle programme have been previously demonstrated to promote weight loss and enhance glycaemic control and cardiovascular disease risk markers [7, 8]. At week 3, participants were provided with education on food exchanges and provided lists of alternative foods, based on similar nutrient and
<table>
<thead>
<tr>
<th>Variable</th>
<th>RT-CGM ($n = 10$)</th>
<th>Blinded CGM ($n = 10$)</th>
<th>$P$ value (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
<td>Change</td>
</tr>
<tr>
<td>Glycemic control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.60 ± 0.86</td>
<td>5.90 ± 0.57</td>
<td>-0.67 ± 0.82</td>
</tr>
<tr>
<td>MeS&lt;sup&gt;+&lt;/sup&gt;</td>
<td>1.01 ± 1.08</td>
<td>0.71 ± 0.72</td>
<td>-0.30 ± 0.59</td>
</tr>
<tr>
<td>Body weight and composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>101.26 ± 15.03</td>
<td>93.85 ± 15.59</td>
<td>-7.41 ± 4.50</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>33.36 ± 6.07</td>
<td>32.79 ± 6.34</td>
<td>-0.58 ± 0.95</td>
</tr>
<tr>
<td>Body fat (kg)</td>
<td>41.75 ± 11.29</td>
<td>35.18 ± 11.34</td>
<td>-6.57 ± 4.05</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>40.80 ± 7.60</td>
<td>37.00 ± 8.58</td>
<td>-3.80 ± 3.16</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>59.5 ± 10.24</td>
<td>58.67 ± 10.65</td>
<td>-0.84 ± 1.55</td>
</tr>
<tr>
<td>Lean trunk mass (kg)</td>
<td>28.07 ± 4.41</td>
<td>26.97 ± 4.78</td>
<td>-1.10 ± 1.16</td>
</tr>
<tr>
<td>Fat trunk mass (kg)</td>
<td>21.50 ± 4.33</td>
<td>18.40 ± 5.23</td>
<td>-3.10 ± 2.43</td>
</tr>
<tr>
<td>Cardiovascular risk markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>7.44 ± 1.35</td>
<td>6.27 ± 1.42</td>
<td>-1.17 ± 1.94</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)</td>
<td>19.19 ± 8.65</td>
<td>14.93 ± 9.12</td>
<td>-4.26 ± 5.91</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>132.26 ± 60.04</td>
<td>103.68 ± 63.37</td>
<td>-29.58 ± 41.08</td>
</tr>
<tr>
<td>Serum TC (mmol/L)</td>
<td>4.33 ± 1.32</td>
<td>4.29 ± 1.25</td>
<td>-0.04 ± 0.38</td>
</tr>
<tr>
<td>Serum LDL-C&lt;sup&gt;+&lt;/sup&gt; (mmol/L)</td>
<td>2.53 ± 1.08</td>
<td>2.46 ± 1.02</td>
<td>-0.07 ± 0.34</td>
</tr>
<tr>
<td>Serum HDL-C (mmol/L)</td>
<td>1.34 ± 0.16</td>
<td>1.41 ± 0.19</td>
<td>0.07 ± 0.26</td>
</tr>
<tr>
<td>Serum TAG (mmol/L)</td>
<td>1.62 ± 0.65</td>
<td>1.30 ± 0.76</td>
<td>-0.32 ± 0.46</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (mg/Hg)</td>
<td>76.70 ± 9.76</td>
<td>75.53 ± 8.00</td>
<td>-1.67 ± 7.24</td>
</tr>
<tr>
<td>Mean systolic blood pressure (mg/Hg)</td>
<td>133.40 ± 22.50</td>
<td>130.03 ± 12.79</td>
<td>-3.37 ± 17.71</td>
</tr>
<tr>
<td>Variable</td>
<td>RT-CGM (n = 10)</td>
<td></td>
<td>Blinded CGM (n = 10)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
<td>Change</td>
</tr>
<tr>
<td>Physical activity (accelerometry) (9 intervention, 10 control)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (Mean daily) time spent in sedentary behaviour</td>
<td>87.4 ± 4.9</td>
<td>84.2 ± 5.8</td>
<td>−3.2 ± 2.2</td>
</tr>
<tr>
<td>% (Mean daily) time spent in moderate/vigorous activity</td>
<td>3.9 ± 2.2</td>
<td>5.4 ± 3.4</td>
<td>1.5 ± 1.8</td>
</tr>
</tbody>
</table>

All values are mean ± SD unless otherwise stated. ANCOVA analysis was used to compare the change in each of the outcome measures at week 12, between the 2 groups using baseline measures as covariates.

Total analysed n = 20 (RT-CGM 10, blinded CGM 10) unless otherwise stated.

RT-CGM real-time continuous glucose monitoring, Blinded CGM blinded continuous glucose monitoring, HbA1c% glycated haemoglobin, MeS medication effect score, IQR interquartile range (median), TC total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TAG triacylglycerol.

a Analyses were performed on natural log (MeS + 0.1) (P values), raw data reported.
b Analyses were performed on natural log transformed data (P values), raw data reported.
energy density of foods within the dietary benchmarks, to assist participants with making suitable food substitutions to improve their dietary flexibility. Use of the materials was self-regulated. Participants received no further formal lifestyle counselling regarding the diet and exercise plan.

Both groups were instructed to perform usual SMBG readings before and after each meal and at bedtime, as per standard practice. Blood glucose monitoring logs were kept and participants were provided with glucometers and testing strips to promote compliance. To facilitate compliance with CGM device wear, at commencement of the study, participants met with a research nurse and dietitian who provided training with practice demonstrations on how insert, initiate, calibrate and change the glucose sensor every 10 days over the 12-week period. Contact details for the research nurse were provided to participants for remote device support and to answer any queries on insertion, initiation and changing of the sensor during the intervention. Participants visited the clinic every 3 weeks for the research nurse to download sensor glucose data, check on glucose sensor insertion and initiation technique, review morning fasting glucose logs, and to replenish devices supplies.

**Outcome Measures**

Outcomes were assessed at baseline (week 0) and end of intervention (week 12). The primary outcomes were HbA1c (Clinpath, Adelaide, Australia), diurnal GV [7, 27] and diabetes-related medication changes assessed by the anti-glycaemic medication effect score (MeS) [7, 28, 29]. The anti-glycaemic medication effect score is an overall assessment of the total use of anti-glycaemic agents, based on type and dose of agents, with the high scores corresponding to higher anti-glycaemic medication usage. This calculation takes into consideration each prescribed drug by daily patient dose and is
expressed as a percentage of maximum recommended daily dose of that drug. This percentage is then multiplied by an adjustment factor, e.g. 1.5 for sulfonylureas and biguanides and 2.5 for insulin. For individuals prescribed more than one anti-glycaemic agent, each agent’s daily dose is multiplied by the respective adjustment factor and outcomes aggregated to generate the final MeS [28-30]. For example, at baseline one participant was prescribed 1000 mg and 500 mg of an oral hypoglycaemic agent, metformin, in the morning and night, respectively, for a total daily dose of 1500 mg. Maximum daily dose for this medication is 3000 mg, and therefore the participant’s dose for this medication was 50%. This value is then multiplied by the relevant drug’s adjustment factor, 1.5 in this example, providing an overall baseline MeS of 0.75. At trial completion (week 12), this participant had experienced a dose reduction in metformin to 500 mg twice daily resulting in a total daily dose of 1000 mg (33% of the drugs maximum daily dose) and a MeS of 0.50. To determine the change in the MeS (and medication intensity), the post-study MeS (0.50) is subtracted from baseline MeS (0.75) to provide an overall absolute reduction in MeS and medication intensity of 0.25.

Secondary outcomes included weight and body composition assessed by bioelectrical impedance (InBody 230, InBody Co. Ltd. South Korea), fasting blood lipids (total cholesterol, triglycerides and HLDL-cholesterol), glucose and insulin (Circlaph, Adelaide, Australia) with LDL-cholesterol calculated using the modified Friedewald equation [31] and blood pressure was measured using an automated sphygmomanometer (SureSigns VS3, Phillips Medical Systems, MA, USA); and physical activity levels assessed using seven consecutive days of ambulatory accelerometer monitoring (GT3X+; ActiGraph, Pensacola, FLA).

Continuous Glucose Monitoring, Glycaemic Variability and Medication Effect Score

Participants wore the Medtronic™ Guardian Connect® device with the Harmony® glucose sensor (Medtronic, Los Angeles, CA, USA) continuously for 13 weeks. All participants were blinded CGM for 1 week prior to commencement of the lifestyle intervention for baseline data collection, then randomisation revealed at baseline (week 0) for 12 weeks whilst following the lifestyle intervention. Devices were calibrated according to the manufacturer’s recommendations with a sensor change every 10 days. Participants in the RT-CGM group received an iPod device (Apple iPod Nano, portable media player, Cupertino, CA) which was Bluetooth connected to the CGM to provide real-time blood glucose level displays throughout the 12-week intervention period. All participants were asked to perform SMBG first thing in the morning before breakfast (fasting) and before each meal. Participants were provided with AccuChek™ glucometers (Roche Diagnostics, Sydney Australia) and testing strips, to replicate standard care.

Diurnal glucose profiles, derived from interstitial fluid readings performed every 5 min over back-to-back 10-day cycles for 91 days (i.e. 13 weeks), were collected using the CGM device; CGM data for the 7 days prior to intervention commencement and the final 7 days of the intervention were used as the pre- and post-study outcomes respectively to compute GV measures including mean, maximum and minimum glucose levels; standard deviation of glucose (SDtray); mean amplitude of glycaemic excursions (MAGE); continuous overall net glycaemic action (CONGA-1, 2, 4 and 8); overall percentage of total time spent in euglycaemia (3.9–10 mmol/L), hyperglycaemia (> 10.0 mmol/L) and hypoglycaemia (< 3.9 mmol/L) were calculated as per glycaemic control targets described by the American Diabetes Association (ADA) [2].

At baseline and throughout the study, blood sugar-lowering medication type, dosage and changes were monitored and documented. The anti-glycaemic MeS was calculated to assess overall utilisation of blood sugar-lowering medication, with higher MeS corresponding to higher usage of blood sugar-lowering medication [28, 29].
Statistical Analysis

Statistical analysis was conducted using SPSS Statistics 25 (IBM Corp, 2017). Analysis of covariance (ANCOVA) was used to test between-group differences at 12 weeks, using baseline measures as covariates [32]. The model residuals were examined for normality and constant variance. Where these assumptions were not met, transformations of the variables were considered. Log (natural) transformation improved the distributional assumptions for serum LDL-C, GV indices and MeS, and P values from the transformed analyses are reported. Statistical significance was determined at P < 0.05. Data are presented as mean ± SD.

RESULTS

Twenty participants commenced and completed the study (Fig. 1). Baseline characteristics were similar between groups (mean ± SD; RT-CGM vs blinded CGM): age 60.2 ± 8.8 years vs. 60.9 ± 8.4 years, diabetes duration 10.5 ± 7.3 years vs. 11.0 ± 4.1 years, HbA1c 6.6 ± 0.9% vs. 7.1 ± 0.8% (49 ± 2 mmol/mol vs. 54 ± 2 mmol/mol) with an even gender distribution (5 men/5 women in both groups) (see Table S1 in the supplementary material).

Changes from baseline (mean ± SD) are reported in Table 1 (see supplementary material and Tables 1, 2 and 3 for changes in primary and secondary outcome profiles during the study and comparisons between treatments). After week 12, body weight, body fat, HbA1c, fasting glucose, insulin, blood lipids (total cholesterol, LDL-C, triglycerides and HDL-C) and blood pressure were not statistically different between groups (P ≥ 0.10).

Participants wore the CGM device for 84 consecutive days, with wear-time adherence at 100% for all but one participant who removed the device for aquatic activities for 3 days only. GV was assessed in 15 participants (RT-CGM, n = 9; blinded CGM, n = 6). Sufficient data, at week 12, were not collected for n = 5 participants secondary to reduced connectivity between glucose sensor and glucose recorder. No statistically significant differences between the groups at week 12 occurred for markers of GV including MAGE, CONGA-1, CONGA-8 and SD or anti-glycaemic MeS (P ≥ 0.11). Despite the lack of statistical significance, at week 12, GV indices were consistently 20–25% lower in the RT-CGM group compared with the blinded CGM group. Post hoc power analysis determined that a minimum of 35 participants per group would have been needed to achieve statistical significance. This was based on determining, for a parallel group superiority trial, the number of participants required in two randomised groups to have an 80% chance of detecting as significant at the 5% level the minimum difference between the groups means observed for the GV outcomes in the present study.

The level of diabetes medication, as reflected by the anti-glycaemic MeS, was 40% lower in the RT-CGM compared to the blinded CGM group at week 12. Thirteen participants had no change in anti-glycaemic MeS (RT-CGM, n = 7; blinded CGM, n = 6). In the RT-CGM group, three participants experienced a reduction in MeS with no participants experiencing an increase. In the blinded CGM group, two participants experienced a decrease in MeS and two participants experienced an increase.

Percentage time spent in sedentary behaviour and percentage time spent in moderate/vigorous activity were similar in both groups (P ≥ 0.11) at 12 weeks.

DISCUSSION

This pilot study examined the effects of RT-CGM with visual feedback compared to blinded CGM, with no visual feedback in individuals with T2D when undertaking a low-intensity, prescriptive low-carbohydrate diet and lifestyle plan. Despite the apparent lack of statistical power, this study provides preliminary evidence that access to RT-CGM feedback is an effective approach to reinforce the effects of lifestyle modification strategies to improve diabetes control by reducing GV and diabetes medication requirements. The high level of device wear-time adherence also suggests a good tolerability to the device usage.
Table 2: Changes in glycemic variability profiles during the study and comparisons between treatments

<table>
<thead>
<tr>
<th>Variable</th>
<th>RT-CGM (n = 8)</th>
<th>Blinded CGM (n = 5)</th>
<th>P value (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
<td>Change</td>
</tr>
<tr>
<td>Mean glucose minimum (mmol/L)</td>
<td>4.24 ± 0.33</td>
<td>4.37 ± 0.90</td>
<td>0.13 ± 0.79</td>
</tr>
<tr>
<td>Mean glucose maximum (mmol/L)</td>
<td>11.70 ± 1.78</td>
<td>11.25 ± 2.60</td>
<td>-0.45 ± 2.55</td>
</tr>
<tr>
<td>Overall mean total glucose (mmol/L)</td>
<td>7.00 ± 0.79</td>
<td>6.75 ± 1.21</td>
<td>-0.24 ± 0.87</td>
</tr>
<tr>
<td>Standard deviation glucose (mmol/L)</td>
<td>1.38 ± 0.52</td>
<td>1.29 ± 0.52</td>
<td>-0.07 ± 0.40</td>
</tr>
<tr>
<td>Overall % time spent in Hypoglycemia (&lt; 3.9 mmol/L)</td>
<td>0.01 ± 0.018</td>
<td>0.26 ± 0.61</td>
<td>0.25 ± 0.61</td>
</tr>
<tr>
<td>Overall % time spent in hyperglycemia (&gt; 10 mmol/L) (mmol/L)</td>
<td>6.58 ± 8.68</td>
<td>7.09 ± 11.08</td>
<td>0.51 ± 7.86</td>
</tr>
<tr>
<td>Overall % time spent in euglycemia (3.9–10 mmol/L) (mmol/L)</td>
<td>93.41 ± 8.67</td>
<td>92.62 ± 11.15</td>
<td>-0.75 ± 7.49</td>
</tr>
</tbody>
</table>

Total analysed n = 13 (RT-CGM 8, blinded CGM 5). Missing glucose data due to device error or poor recording compliance. All values are mean ± SD unless otherwise stated.

RT-CGM real-time continuous glucose monitoring, Blinded CGM blinded continuous glucose monitoring.
Table 3 Changes in glycaemic variability profiles for MAGE, CONGA-1, 2, 4 and 8 during the study and comparisons between treatments

<table>
<thead>
<tr>
<th>Variable</th>
<th>RT-CGM (n = 9)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>Change</th>
<th>Blind CGM (n = 6)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>Change</th>
<th>P value (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONGA-1</td>
<td>(mmol/L)</td>
<td>1.30 ± 0.36</td>
<td>1.03 ± 0.36</td>
<td>−0.27 ± 0.36</td>
<td>1.24 ± 0.41</td>
<td>1.30 ± 0.48</td>
<td>0.06 ± 0.19</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>CONGA-2</td>
<td>(mmol/L)</td>
<td>1.72 ± 0.51</td>
<td>1.36 ± 0.55</td>
<td>−0.36 ± 0.54</td>
<td>1.79 ± 0.63</td>
<td>1.84 ± 0.77</td>
<td>0.05 ± 2.88</td>
<td>0.110</td>
<td></td>
</tr>
<tr>
<td>CONGA-4</td>
<td>(mmol/L)</td>
<td>2.02 ± 0.68</td>
<td>1.58 ± 0.75</td>
<td>−0.44 ± 0.67</td>
<td>2.18 ± 0.74</td>
<td>2.16 ± 0.93</td>
<td>−0.02 ± 0.42</td>
<td>0.186</td>
<td></td>
</tr>
<tr>
<td>CONGA-8</td>
<td>(mmol/L)</td>
<td>2.09 ± 0.68</td>
<td>1.73 ± 0.83</td>
<td>−0.36 ± 0.61</td>
<td>2.25 ± 0.73</td>
<td>2.22 ± 0.95</td>
<td>−0.02 ± 0.52</td>
<td>0.298</td>
<td></td>
</tr>
<tr>
<td>MAGE</td>
<td>(mmol/L)</td>
<td>3.69 ± 1.08</td>
<td>3.01 ± 1.44</td>
<td>−0.69 ± 1.14</td>
<td>4.06 ± 1.23</td>
<td>4.05 ± 1.61</td>
<td>−0.09 ± 0.80</td>
<td>0.250</td>
<td></td>
</tr>
</tbody>
</table>

Total analysed n = 15 (RT-CGM 9, blinded CGM 6). Missing glucose data due to device recording or sensor insertion error. All values are mean ± SD unless otherwise stated.

RT-CGM real-time continuous glucose monitoring, Blinded CGM blinded continuous glucose monitoring, CONGA-1 continuous overall net glycemic action of observations 1 h apart, CONGA-2 continuous overall net glycemic action of observations 2-h apart, CONGA-4 continuous overall net glycemic action of observations 4 h apart, CONGA-8 continuous overall net glycemic action of observations 8 h apart, MAGE mean amplitude of glycemic excursions.

Overall, both groups achieved approximately 6% weight loss which is considered clinically relevant and comparable to most structured weight loss programmes that typically involve intensive counselling compared to this study that provided limited professional support [4, 33]. The lifestyle intervention in the present study used a low-carbohydrate-based prescriptive meal plan combined with a prescriptive aerobic/resistance-based exercise programme presented in a book format. This demonstrates that provision of a highly structured, prescriptive lifestyle plan can be an effective strategy to promote weight loss without the necessity of intensive professional support.

Together with weight loss, both groups experienced an average 0.7% HbA1c reduction. This is consistent with other weight loss studies in T2D of similar study duration [20, 23, 34]. A recent meta-analysis demonstrated an estimated mean HbA1c reduction of 0.1% for each 1 kg of reduced body weight in this population [35]. For every 1% reduction in HbA1c there is an expected 37% reduced risk for microvascular complications and 21% reduction in the risk of premature death related to T2D [33]. This highlights the clinical significance of the changes observed in the present study.

Beyond HbA1c, which reflects average blood glucose levels over approximately 3 months, GV relates to fluctuations in blood glucose levels across the day or between days [36, 37]. GV has been identified as an independent risk factor of T2D-related micro- and macrovascular complications. Intermittent high blood glucose spikes, as opposed to constant exposure to high blood glucose, has been shown to promote damaging effects [10, 12, 38]. Daily glucose fluctuations are incompletely expressed by HbA1c alone, particularly in patients considered to have good metabolic control or with prediabetes [9, 13, 36, 39, 40]. To date, few studies have examined the effects of RT-CGM on GV. Yoo et al. demonstrated a 22% reduction in GV as measured by MAGE following the use of RT-CGM (worn for 3 days a month for 3 months) in 65 individuals with poorly controlled T2D (HbA1c >8%) [20]. In this study no control
group comparison was made. Similarly, in the present study, GV was approximately 20–25% lower in the RT-CGM compared to the blinded-CGM control after the intervention. However, as a result of the small sample size and lack of statistical significance, these data need to be interpreted with caution.

Nonetheless, these data suggest that RT-CGM may assist individuals to minimise blood glucose fluctuations and, given the emerging clinical importance of GV for promoting diabetes-related complications, larger studies are required to confirm these effects. A larger study could also investigate differences in the trajectories in the GV response over the intervention period. Additionally, since the individuals studied were in reasonable glycaemic control at baseline (mean HbA1c < 7% and a high proportion of time spent in the euglycaemic range) this may have moderated the degree of improvement observed. Hence, further investigation of poorly controlled individuals that may experience more amplified improvements warrants further investigation. Larger future trials could use an intention to treat design and appropriate analysis to mitigate completer bias.

Despite commencing with a lower MeS, the RT-CGM group experienced a greater reduction in MeS compared to the blinded CGM group such that MeS was 40% lower in RT-CGM at week 12. However, it is important to note that these differential group changes were driven by medication changes in only a few individuals. Hence, these observations need to be treated with great caution. Nonetheless, despite the clinical benefits of intensive hypoglycaemic medication prescription for reducing macrovascular and microvascular disease risk through HbA1c reduction [2], a recent report suggests that HbA1c reduction alone may not reduce macrovascular endpoints [41, 42] and the side effects of pharmacotherapy are well known [43, 44]. Thus it is necessary to examine the potential of RT-CGM to alter medication prescription in larger populations, particularly in highly medicated individuals.

It is well known that lifestyle therapies are effective in T2D management but adherence is difficult and that negatively impacts effectiveness [15, 40, 45]. The preliminary data from the current study suggest that instant access to feedback regarding their daily glucose levels may improve patients’ adherence and sustainability of lifestyle changes to optimise glucose control [40, 46]. This is supported by a recent systematic review providing robust evidence suggesting that engagement in self-management education had a most favourable effect on glycaemic control [45]. However, debate exists on the duration and frequency of CGM data exposure that are required to modify behaviour and achieve clinically relevant improvements. Further studies should also examine the dose–response effect of exposure to RT-CGM data for the improvement of diabetes control.

The present study had several limitations. Firstly, this was a pilot study and, despite the promising magnitude of the differences observed between groups, results should be treated with caution and these promising results warrant further investigation with larger trials. The study also examined individuals with relatively good glycaemic control and future studies examining larger populations with wider levels of glucose control would allow a better understanding of the applicability of RT-CGM for T2D management. Additionally, evaluation of various drug types on markers of GV or MeS was not performed. Previous studies have demonstrated that an increase in oral hypoglycaemic medications may sometimes result in a drop in MAGE [40]. To better understand the clinical implications of RT-CGM on GV, future trials should closely monitor and consider medication types, doses and changes in dose over the time course of the intervention. Some difficulties with device connectivity between sensor and recorder in the blinded CGM group were also experienced and future studies should specifically examine whether this is related to the blinded use of the CGM device. Finally, our retention rate was high, and it cannot be ruled out that provision of an honorarium, which is not reflective of current clinical practice, could have potentially influenced participant compliance to the intervention.
CONCLUSION

This study provides preliminary evidence that RT-CGM may enhance the benefits of a prescriptive low-carbohydrate diet and exercise plan delivered with minimal professional support, improving glycaemic control by reducing daily GV. These pilot findings provide a rationale for more comprehensive, larger-scale randomised controlled trials to be conducted. Trials should also consider the duration and frequency of sensor-wear time, medication types and changes in medication over longer-term interventions in order to better assess this therapeutic technology.

ACKNOWLEDGEMENTS

The authors would like to thank all study participants and their families for their participation in the study.

Funding. Grant funding was received for the delivery of the clinical trial only, by the Diabetes Australia Research Trust (DART). No funding was received for preparation or publication of this article, these were funded by the authors.

Additional Assistance. The authors wish to thank Julia Weaver, Anne McGuffin, Vanessa Conrage, Dr Eva Pederson and Theresa McKinnon for their support during the study and to Julie Syrette for supporting the preparation of the glucose data for this analysis. A heartfelt thank you is extended to the Taylor family, Paul, Mitchell, Skye and Harry for their patience during this year, and for the support you have provided.

Authorship. All authors meet the International Committee of Medical Journal Editors authorship guidelines (ICMJE) for this article, all had access to the data obtained in this study and take responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures. All authors, Pennie Taylor, Campbell Thompson, Grant Brinkworth, Natalie Luscombe-Marsh, Thomas Wycherley and Gary Wittert state that they have no conflict of interest to declare.

Compliance with Ethics Guidelines. Ethics approval for the conduct of this clinical trial was provided by The Adelaide University Human Research Ethics Committee and the study has conformed to the Helsinki Declaration 1964, as reviewed by 2013, concerning human rights. Springers policy concerning informed consent has been followed. All procedures performed in this study were in accordance with the ethics standards of the Adelaide University Human Ethics and Research Committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Chapter 5: Manuscript 4

Tolerability and acceptability of real-time continuous glucose monitoring and its impact on diabetes management behaviours in individuals with type 2 diabetes – A pilot study

Submitted for publication in peer review journal:

Journal of Diabetes Research and Clinical Practice 14th April 2019 (Under Review)
# Statement of Authorship

<table>
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## Principal Author

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<th>Pomia (Ponelopya) Taylor</th>
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<tr>
<td>Contribution to the Paper</td>
<td>Co-designed original protocol, responsible for ethics preparation, submission and adaptations, responsible for trial conduct, monitored adverse events of trial participants, managed data, analysed metabolic data, Co-designed behavioural questionnaires, prepared manuscript and corresponding author.</td>
</tr>
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<td>Overall percentage (%)</td>
<td>75%</td>
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<tr>
<td>Certification</td>
<td>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.</td>
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**Signature**

**Date** 13.4.19

## Co-Author Contributions

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

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

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

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

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<th>Campbell Thompson</th>
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<td>Contribution to the Paper</td>
<td>Co-designed original trial protocol, contributed to ethics preparation, screened medical suitability of participant inclusion, monitored adverse events of trial participants, supervised and supported data analysis and interpretation, critically reviewed original and revised manuscript</td>
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<td>Co-designed behavioural questionnaire and contributed to trial protocol and ethics preparation, analysed and interpreted behavioural data, critically reviewed and edited original and revised manuscript</td>
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Please cut and paste additional co-author panels here as required.
Title: Tolerability and Acceptability of Real-Time Continuous Glucose Monitoring and its impact on diabetes management behaviours in individuals with Type 2 Diabetes - A Pilot Study

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Conflict of interest

Nothing to disclose
Abstract

Introduction
Therapeutic options are now involving real-time continuous glucose monitoring systems (RT-CGM) for self-monitoring, however the impact of these on patients’ stress levels and behaviour is poorly understood. This study examined the effects of RT-CGM on tolerance and acceptability of device wear, stress, diabetes management and motivation to change.

Methods
20 adults (10 Male) with T2D (aged 60.6±8.4 years, BMI 34.2±4.7 kg/m2), were randomised to a low-carbohydrate lifestyle plan whilst wearing a RT-CGM or an ‘offline-blinded’ (Blinded-CGM) monitoring system continuously for 12-weeks. Outcomes include glycaemic control, weight, perceived stress scale (PSS), CGM-device intolerance, acceptability, motivation to change and diabetes management behaviour questionnaires.

Results
Both groups experienced significant reductions in body-weight (RT-CGM -7.4±4.5kg vs. Blinded-CGM -5.5±4.0kg) and HbA1c (-0.67±0.82% vs. -0.68 ±0.74%). There were no differences between groups for PSS (P=0.47) or device-intolerance at week-6 or 12 (both P>0.30). There was evidence of greater acceptance of CGM in the RT-CGM group at week-12 (P=0.03), improved blood glucose monitoring behaviour in the RT-CGM group at week-6 and week-12 (P≤0.01), and a significant time x group interaction (P=0.03) demonstrating improved diabetes self-management behaviours in RT-CGM.
Conclusion

This study provides preliminary evidence of improved behaviours that accompany RT-CGM use in the context of diabetes management and glucose self-monitoring, without resulting in increased disease distress.

Key Words

Continuous Glucose Monitoring, Type 2 Diabetes, Acceptability, Tolerance
1. Introduction

As the prevalence of Type 2 Diabetes (T2D) grows, therapeutic treatment options are extending into self-monitoring and mobile-health device delivered therapies to support patients to achieve better control of their disease [1]. This includes real-time continuous glucose monitoring systems (RT-CGM) that provide users with immediate feedback by enabling them observe their current glucose levels every 1-5 minutes [2, 3]. Traditional methods of self-monitoring glucose levels (SMG) use finger stick glucometer readings that only provide a snapshot of daily fasting and postprandial blood glucose concentrations as 1-3 ‘isolated’ measures at best, and compliance with this behaviour is generally poor due to issues including perceived pain caused by the lancet device, insufficient or contaminated blood droplet onto the test strip, or low relative importance patients place of their diabetes self-care [4]. In comparison, RT-CGM provides advantages of greater ease and frequency of measurement throughout the day and prompt feedback. This may enable the user to better understand the impact of a particular behaviour on blood glucose response and could subsequently result in timely remedial action and improved glycaemic control [4-12].

Emerging data suggests the use of RT-CGM can promote and enhance diabetes self-management [6, 13-15] and is an effective interventional tool in assisting patients and health professionals in tailoring diet and exercise behaviours in a timely manner to achieve better glycaemic control. However, despite the promising efficacy of RT-CGM to promote behaviour change and improve glycaemic control, there appears to be no studies that have examined the effect of these devices on outcomes including patient acceptance, tolerance and overall stress or perceived diabetes self-management behaviours. Many people with chronic disease have to adjust emotionally, often grieving about the changes they face related to management of their disease [16]. One quarter of those with T2D may have an affective disorder as a result of their disease [16] and others may adhere less closely to
treatment regimens due to the stress induced by the diagnosis and the subsequent requirements for treatment monitoring [17]. Any negative effects of RT-CGM technology on acceptance, tolerance, stress levels and behaviour may limit its usefulness as a strategy for T2D. Consequently, greater examination of these effects will assist understanding of the use for RT-CGM in clinical practice [18, 19]. Therefore, the purpose of this study was to examine the efficacy of RT-CGM compared to blinded CGM, on tolerance and acceptability of device wear, stress and diabetes management and motivation to change.

2. Methods

2.1 Study Participants

Recruitment criteria, study design and the primary study outcomes have been previously described [20]. In brief, 20 overweight/obese adults (BMI 26-45 kg/m², age range 20-75 yrs) with T2D (HbA1c: 5.9-6.9% [41.0 – 51.9 mmol/mol], Diabetes Duration mean 10.8 ± 5.4 yrs) were recruited through public advertisement at the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Health and Nutrition Research Unit (Adelaide Australia), Figure 1(Participant Flow). Exclusion criteria included type 1 and gestational diabetes and any poorly controlled endocrinopathies. The study was registered with the Australian New Zealand Clinical Trials Registry (ANZTR: 372898) and approved by the Human Research Ethics committees of the CSIRO and the University of Adelaide. Participants provided written informed consent before trial commencement.

In a parallel study design, participants were matched for age and gender and randomised (www.randomisation.com) to one of two, 12-week lifestyle intervention groups: (i) Real Time Continuous Glucose Monitoring group (RT-CGM; n = 10) with use of a real-time continuous glucose monitor and access to real-time data, or (ii) Blinded-CGM Group
(Blinded; n = 10), with use of a non-display, continuous glucose monitor without access to real-time data. All participants wore the Medtronic™ Guardian Connect® device with the Harmony® glucose sensor (Medtronic, Los Angeles, CA).
2.2 Intervention

One week prior to baseline in preparation for the intervention, all participants were instructed by the research nurse and dietitian on daily self-monitoring of blood glucose levels (SMBG), including daily fasting and 2hr postprandial readings, as per standard practice, and how to perform CGM glucose sensor insertion, calibration and hygiene requirements, which were performed every 10 days. Additional education to the RT-CGM group was provided by the clinical trial manager that included how to activate the CGM glucose sensor and initiate connectivity to the proprietary Guardian Connect® Application (Medtronic, Los Angeles, CA) for translating the glucose feedback into readable glucose curves and identification of acceptable glucose ranges. To facilitate compliance with CGM device wear, all participants were provided adequate supplies free of charge to enable self-care and hygiene regimes. Every 3 weeks participants returned to the clinic for a body weight check and for the research nurse to review glucose sensor insertion and initiation techniques and to re-stock supplies.

In addition to wearing the glucose monitors all participants were provided a prescriptive low carbohydrate, high protein and unsaturated fat diet (LC diet) and exercise plan incorporating moderate intensity aerobic and resistance exercises in the form of a commercial publication [21]. This dietary profile and program components have been previously demonstrated to optimise glycaemic control, including diurnal blood glucose stability and reduce CVD risk markers and to facilitate dietary compliance [22-24].

At week 3, participants were provided a 30-minute group-based education session on food exchanges, which informed the participant of food groups and proportions of foods that are
matched for the benchmark food (i.e. 1 slice of bread can be exchanged for 3 regular sized crispbreads). A food exchange booklet, to assist participants in making informed food exchanges, to maintain the prescribed energy level and macronutrient profile was provided at visit 2. Participants received no further formal lifestyle counselling or support regarding the diet and exercise plan, or clinical counselling to provide individual strategies that would assist them to achieve their blood glucose goals.

2.3 Outcomes

2.3.1 Glycated Haemoglobin (HbA1c) and Weight

Outcomes were assessed at baseline (wk 0) and end of study (wk 12). HbA1c was measured by a certified pathology laboratory (Clinpath Adelaide, Australia). Weight (kg) was assessed using bioelectrical impedance scales (InBody 230, InBody Co. Ltd. South Korea) [20].

2.3.2 Perceived Stress Scale

At baseline and Week 12, the Perceived Stress Scale (PSS-14), a 14-item (7 positive and 7 negative) self-report measure, was used to assess the degree to which participants perceive the impact of CGMS wear on levels of chronic stress. Responses range from “never” (0) to “very often” (4) on a 5-point Likert scale. A higher score indicates higher perceived stress, with a total score ranging between 0-40. The PSS-14 is a well validated measure that has been shown to correlate well with stressful life events measures and social anxiety [25].

2.3.3 CGM Device Tolerance and Acceptability questionnaire

To assess participant’s acceptance or intolerance of the CGM device, a purpose-designed questionnaire was developed because of the apparent absence of any other validated measures pertaining to this technology. The questionnaire consisted of 16 items, each scored using a 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree. A
total of 9-items measured intolerance of the device (e.g., “The sensor and recorder caused me problems with regards to showering”, “Installation of the sensor caused me pain”, “It was difficult to be intimate with others whilst wearing the sensor and recorder” etc), and 7-items measured acceptability (e.g., “Installing the sensor was easy for me”, “I was easily able to calibrate the sensor using my finger-prick lancet”, “I was satisfied with the look and feel of the sensor and recorder” etc). Participants completed the questionnaire at Week 6 and Week 12. Scores were summed across items measuring the intolerance and acceptability domains, and internal consistency of the questionnaire—assessed using Chronbach’s alpha—was high at each time point (Week 6: intolerance $\alpha_r=0.96$, acceptability $\alpha_r=0.85$. Week 12: intolerance $\alpha_r=0.89$, acceptability $\alpha_r=0.81$). Higher scores were associated with higher acceptance, or greater intolerance as per their respective domains.

2.3.4 CGM Motivation to Change questionnaire

The extent to which the CGM device directly motivated behavioural change was assessed using a purpose-designed CGM motivation questionnaire. This measure included 20-items assessing four broad behavioural areas (diet, exercise, blood glucose, and social). Each item was answered in response to the phrase: “Wearing the Continuous Glucose Monitor motivated me to ...”. A total of 5-items were used for diet behaviours (e.g., “... reduce my meal portions”, “... modify my diet to better suit my diabetes” etc), 6-items assessed exercise behaviour (e.g., “... increase my exercise frequency”, “... increase the duration of my exercise sessions” etc), 6-items assessed blood glucose related behaviours (e.g., “... understand the impact of difference foods on my blood glucose levels”, “... monitor and take note of my blood glucose levels” etc), and 3-items assessed social behaviour (e.g., “... educate my friends about my health needs”, “... interact with my Doctor about my diabetes management” etc). The questionnaire was administered at Week 6 and Week 12. Scores
were summed across items measuring the same domain, and internal consistency of the questionnaire—assessed using Chronbach’s alpha—was high at each time point (Week 6: diet $\alpha_r=0.86$, exercise $\alpha_r=0.84$, blood glucose $\alpha_r=0.90$, social $\alpha_r=0.82$. Week 12: diet $\alpha_r=0.63$, exercise $\alpha_r=0.83$, blood glucose $\alpha_r=0.88$, social $\alpha_r=0.72$). Higher scores on each domain were associated with improved behaviours in relation to managing diabetes.

2.3.5 Diabetes Management Questionnaire

Change in diabetes management behaviours was assessed using a purpose-designed questionnaire. This questionnaire consisted of 18-items assessing a range of behavioural domains (e.g., “I set goals for managing my diabetes”, “I feel in control of my diabetes”, “I often binge on food” etc). Each item is answered using a 5-point Likert scale (ranging from 1=strongly disagree to 5=strongly agree). The questionnaire was administered at Week 6 and Week 12 and obtained estimates of diabetes self-management behaviours at each time point. In addition, following the retrospective pre-test methodology [26], participants provided retrospective ratings of their diabetes-related behaviours before commencing the study (both at Week 6 and again at Week 12). This approach overcomes the phenomenon of response-shift which occurs as a result of interventions, and controls for the effect of participants overestimating their behaviours at baseline, which often occurs in traditional pre-then-post designs [27]. Distributions of reverse-coded items were reflected, and scores were summed across items to produce a total diabetes self-management score. Internal reliability of the scale was strong at Week 6 (baseline $\alpha_r=.082$, current $\alpha_r=0.85$) and Week 12 (baseline $\alpha_r=0.71$, current $\alpha_r=0.88$). Higher scores on this measure signify better behavioural management of diabetes.
2.4 Statistical Analysis

Statistical analysis was conducted using SPSS Statistics 25 (IBM Corp, 2017) and data were examined for normality (no violations were noted). Analysis of covariance (ANCOVA) was used to test between group differences at Week 12, using baseline measures as covariates for Weight (kg) and HbA1c [28]. The model residuals were assessed for normality and constant variance, assumptions were met.

For the Diabetes Management Questionnaire, retrospective pre-study estimates of behaviour provided at Week 6 and Week 12 were not significantly different (p>.05) and were strongly correlated (r=0.65, p=0.002), demonstrating participants’ ability to retrospectively rate their baseline self-management behaviours. The baseline score for this measure was therefore generated by averaging the retrospective responses provided at each time point. Linear mixed effects models were used to examine change over time for the Diabetes Management Questionnaire and the Perceived Stress Scale. Time was modelled as a continuous variable to enable a comparison of difference in slopes of change through the study. Parameter estimates (using time as a fixed factor) were used to interpret significant interaction effects if present. For measures that did not obtain baseline data (Device Tolerance and Acceptability Questionnaire and the Motivation to Change Questionnaire), independent samples t-tests were used to compare scores across groups within each of the data collection time points. All models were two-tailed and used a threshold of $p \leq 0.05$ for statistical significance. Cohen’s $d$ is reported to reflect the magnitude of the effects observed between groups.
3. Results

A total of 20 participants completed the study. For the duration of the intervention (12 weeks, 84 days) all participants achieved 100% compliance to wear time; the only exception being one participant from the RT-CGM group who did not wear the glucose sensor and recorder for 3 non-consecutive days secondary to participation in aquatic activities.

Over the 12 weeks, reduction in weight (RT-CGM – 7.41±4.5kg vs. Blinded CGM -5.45±4.03) and HbA1c (RT-CGM; -0.67±0.82 kg vs. Blinded CGM -0.68±0.74) were not statistically different between groups (p>0.30).

Descriptive statistics for all behavioural measures are provided in Table 1. Over the course of the study, there was no differential change in PSS scores between groups. CGM intolerance scores were not different between groups at either Week 6 or Week 12. CGM acceptance scores were similar between groups at Week 6, but there was a significantly higher score in the RT-CGM group at Week 12 (Cohen’s d=1.04).
Table 1: Means (±SD) for behavioural measures throughout the study for each treatment group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Condition</th>
<th>Baseline</th>
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<th>12 weeks</th>
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<tr>
<td>Perceived Stress Survey*</td>
<td>Blind CGM</td>
<td>35.5 ± 3.5</td>
<td>-</td>
<td>35.2 ± 2.53</td>
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<tr>
<td></td>
<td>RT-CGM</td>
<td>33.2 ± 5.1</td>
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<td>33.7 ± 4.67</td>
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<tr>
<td>Diabetes Management Behaviours</td>
<td>Blind CGM</td>
<td>53.3 ± 6.4</td>
<td>62.9 *a± 8.87</td>
<td>58.9 ± 6.06</td>
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<td></td>
<td>RT-CGM</td>
<td>51.5 ± 8.90</td>
<td>67.3 *a± 9.36</td>
<td>66.3 *a± 8.45</td>
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<tr>
<td>Acceptance of CGMS</td>
<td>Blind CGM</td>
<td>-</td>
<td>27.2 ± 5.31</td>
<td>27.5 ± 3.38</td>
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<tr>
<td></td>
<td>RT-CGM</td>
<td>-</td>
<td>30.2 ± 3.79</td>
<td>31.2 *a± 3.73</td>
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<tr>
<td>Intolerance of CGMS</td>
<td>Blind CGM</td>
<td>-</td>
<td>18.4 ± 11.55</td>
<td>16.3 ± 6.60</td>
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<td>RT-CGM</td>
<td>-</td>
<td>14.9 ± 4.51</td>
<td>13.4 ± 5.44</td>
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<td>Social Behaviours</td>
<td>Blind CGM</td>
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<td>9.8 ± 2.97</td>
<td>10.4 ± 1.58</td>
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<td>RT-CGM</td>
<td>-</td>
<td>10.0 ± 2.82</td>
<td>11.2 ± 2.49</td>
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<tr>
<td>Exercise Behaviour</td>
<td>Blind CGM</td>
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<td>22.9 ± 4.09</td>
<td>21.4 ± 3.09</td>
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<td>RT-CGM</td>
<td>-</td>
<td>20.3 ± 5.48</td>
<td>23.0 ± 4.62</td>
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<td>Diet Behaviour</td>
<td>Blind CGM</td>
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<td>20.1 ± 4.12</td>
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<td></td>
<td>RT-CGM</td>
<td>-</td>
<td>20.7 ± 2.98</td>
<td>21.5 *b± 2.76</td>
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<td>Blood Glucose Monitoring</td>
<td>Blind CGM</td>
<td>-</td>
<td>21.8 ± 4.07</td>
<td>24.2 ± 2.57</td>
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<td>Behaviour</td>
<td>RT-CGM</td>
<td>-</td>
<td>26.4 **b± 3.31</td>
<td>28.7 **b± 1.70</td>
</tr>
</tbody>
</table>

Blind CGM, n=10; RT-CGM, n=10; RT-CGM = Real Time Continuous Glucose Monitoring; *Within group comparison to baseline; †Between group comparison for respective time point; ‡p=.08, *p<.05, **p<.01. Perceived Stress Scores: 0-13 = low perceived stress; 14-26 = moderate perceived stress; 27-40 = high perceived stress. Possible range of scores were: Acceptance of CGMS (0-to-35); Intolerance of CGMS (0-to-45); Social Behaviours (0-to-15); Exercise Behaviours (0-to-30); Diet Behaviours (0-to-25); Blood Glucose Monitoring Behaviours (0-to-30); Higher scores on these measures signify better behavioural management of diabetes.
For the motivated behaviour change scales, social and exercise behaviour scores did not differ between groups at either Week 6 or Week 12. For diet behaviour, there was no difference between groups at Week 6, but a trend for a higher score in the RT-CGM group at Week 12 was noted ($d=0.81$). For blood glucose monitoring behaviour, scores were significantly higher in the RT-CGM group compared to the Blinded group at both Week 6 ($d=1.24$) and Week 12 ($d=2.06$).

For the total diabetes self-management behaviour assessment, there was a significant effect between treatments ($p=0.03$ time x group interaction), such that there was a greater overall increase and maintained improvement in behaviour throughout the trial in the RT-CGM group compared to the Blinded group. Post-hoc, within group analysis revealed that scores for the Blinded group had increased significantly from baseline to Week 6 ($p=0.03$, $d=1.24$) but were reduced at Week 12 such that scores were not different from baseline ($p>0.05$, $d=0.90$). In contrast, scores in the RT-CGM group were significantly higher compared to baseline at Week 6 ($p<0.001$, $d=1.68$) and remained higher at Week 12 ($p<0.001$, $d=1.71$).

4. Discussion

This study demonstrates that individuals with T2D who were prescribed to follow a self-directed lifestyle modification program expressed good tolerance and compliance to wearing a CGM for 12 weeks as demonstrated by the high level of wear time achieved. Furthermore, compared to wearing a blinded device, access to glucose data in real time was linked with greater device acceptance and improvements in diabetes self-management behaviours over a 12-week period. Interestingly, both groups experienced similar reductions in HbA1c suggesting that possibility that the potency of the prescriptive lifestyle plan that was administered to both groups may have overridden additional benefits of the RT-CGM
over this short time period. Future longer studies (>12 weeks) are required to better understand the chronic effects of RT-CGM when used in conjunction with prescriptive lifestyle interventions.

Previous reports suggest that monitoring of blood glucose in patients with diabetes is associated with general stress and/or anxiety which can impact quality of life [29, 30] and promote poorer diabetes self-management and glycaemic control [17, 31]. In contrast, the present study showed no evidence of changes in stress levels over time or between groups, suggesting that exposure to real-time blood glucose data did not adversely affect stress. The specific reason for discrepant findings between this and previous studies is not clear. However, previous studies reporting high stress levels associated with blood glucose monitoring have included newly diagnosed participants who may have had insufficient time to adjust to their diabetes diagnosis. These studies also examined the 7-point method of blood glucose self-monitoring (7 or more finger sticks daily), a method that results in pain from multiple finger sticks and requires greater patient effort could explain the reported negative effects on stress [29, 30]. It is possible that differences between studies in device wear and support protocols could influence the effects of RT-CGM use on stress levels and that differences in the type and frequency of technical and clinical professional support also could contribute to differences between the current findings and others’ and therefore future studies to explore the effects of RT-CGM compared to traditional SMBG on diabetes management and stress are warranted [32-34]. In this study, the device was administered with a prescriptive lifestyle plan that engendered improvements in clinical outcomes such as weight and HbA1c. These positive clinical effects, some of which were obvious to participants, may have countered any possible negative effects of stress that were associated with glucose monitoring.
In the present study, there was no significant difference in tolerance of the device between groups but there was evidence of higher acceptance in the RT-CGM group at Week 12 compared to the blinded condition. Changes in acceptance and tolerance of RT-CGM device wear with time are rarely reported in the literature [15]. Overall, on the basis of compliance reports, a consistently high level of device acceptance and tolerance has usually been observed [33-35]. Studies that examined acceptance and tolerance to RT-CGM use by applying a system usability score [33] or a purpose designed acceptability and utility survey [36] also reported no change in either acceptance or tolerance following 12 week interventions [33, 36]. Therefore, there is novelty to the present finding that RT-CGM produced a greater level of acceptance by study endpoint. This is highly likely due to the perceived value and positive reinforcement of the visual display of real-time blood glucose data for participants in this condition compared to those who could not access their glucose data in real time.

Current diabetes management guidelines promote patient engagement in self-management behaviours. If patients have increased engagement in their own health, this should increase their motivation towards adapting appropriate diet and lifestyle strategies [37]. The present study showed that access to RT-CGM did not change diet, exercise and social behaviour domains compared to blinded-CGM, although there was some preliminary evidence of improved diet behaviour in RT-CGM at Week 12. However, direct measures of dietary and physical activity compliance were not measured. It is also important to note, that both groups were provided a lifestyle intervention consisting of diet and exercise changes, thus precluding our ability to explore specifically the impact of RT-CGM on diet and exercise behaviour in individuals who are otherwise not asked to modify such behaviours.
Access to RT-CGM did appear to have a positive influence on other behaviours, blood glucose monitoring and overall self-management behaviour. Self-monitoring blood glucose is considered an integral part of diabetes self-management that can optimise glycaemic control to prevent the onset of diabetes related complications [4, 38-40]. Traditional SMBG in people with diabetes presents compliance challenges that are well documented and include high levels of avoidance (a desire not to think about blood glucose levels and diabetes), perceived pointlessness (the belief that self-monitoring is not of personal value), and low engagement with health professionals including limited sharing of glucose data with their health care provider [12]. The current data provide preliminary evidence that RT-CGM may offer a solution to overcome difficulties with compliance and improve diabetes self-management leading to improvements in diabetes-related outcomes. Larger, longer-term studies are required to understand the effects of prolonged RT-CGM use upon self-management behaviour and diabetes control.

Although this experiment provides early insights into the effects of RT-CGM on diabetes management and self-monitoring glucose behaviour, there are several study limitations. The study had a small sample size and was conducted in a well-controlled and possibly highly-motivated population of individuals with T2D that limit generalisability of the findings. Future larger studies conducted in diverse populations including individuals newly diagnosed with either T2D, T1D, Gestational Diabetes or have poorer glycaemic control should be conducted. The study duration was also relatively short and longer-term studies are needed to better understand the durability and tolerability of this intervention approach before the practical applications can be fully realised. Both groups wore a CGM device making it difficult to understand the effects of general device wear on the study’s outcomes, however this was not the purpose of this study. Provision of RT-CGM compared to usual
control (SMBG) is likely to have more profound effects, and should be incorporated in
designs of future studies. It is also important to acknowledge that health professionals,
although providing lifestyle information, were not actively involved in reinforcing the
lifestyle intervention and patient management protocols, only providing device support
(calibration, insertions and hygiene management). Health professionals play an important
role in the management of patients with T2D [38] and further research should examine the
effects of RT-CGM administered with a structured lifestyle program that includes close
professional support and interaction. RT-CGM should help health professionals to
understand the educational needs of patients and enable integration of this technology with
other management paradigms to enhance patient practice and glucose management advice
and support.

5. Conclusion

In summary, this pilot study showed a high degree of tolerability and acceptance of an RT-
CGM device continuously-worn over a 12-week period. There were accompanying
improvements in diabetes self-management behaviour in those with real time visual access
to frequent BGL data, suggesting CGM offers an alternative approach to glucose
management that may effectively support some individuals with T2D without promoting
disease distress. Moreover, the use of RT-CGM systems opens the prospect for more
insightful patient interaction relative to current practice. RT-CGM could overcome negative
barriers associated with traditional glucose monitoring methods. Focussed device education
and technical support for participants may explain differences between these findings and
others’. RT-CGM should be evaluated further for its use as a lifestyle management tool
because it encourages patient engagement with diabetes self-management behaviours.
6. Paper Acknowledgements

6.1 Thank you participants and families. The authors would like to thank all study participants for their participation in the study.

6.2 Funding

Grant funding was received for the delivery of the clinical trial only, by the Diabetes Australia Research Trust (DART). No funding was received for preparation or publication of this article.

6.3 Additional Assistance:

The authors wish to thank Julia Weaver, Anne McGuffin, Vanessa Courage, Dr Eva Pederson and Theresa McKinnon for their trial support during the study.

6.4 Compliances with Ethics Guidelines

Ethics approval for the conduct of this clinical trial was provided by The Adelaide University, Human Research Ethics Committee and the study has conformed to the Helsinki Declaration 1964, as reviewed by 2013, concerning human rights. Springer's policy concerning informed consent has been followed. All procedures performed in this study, were in accordance with the ethics standards of the Adelaide University Human Ethics and Research Committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.
7. References


Chapter 6: Thesis Summary

1. Summary of the Research and Key Findings

In this thesis, the effect of RT-CGM compared to blinded-CGM for improving glycaemic control and reducing CVD risk makers when combined with the prescription of a low carbohydrate (50g total carbohydrate) diet and exercise program in overweight and obese individuals with T2D was examined.

In addition, the potential beneficial effects of an individual’s acceptance, tolerance experiences of wearing and interacting with the real-time continuous glucose monitoring device and how it impacts on diabetes self-care was also explored.

In this final Chapter, the main findings will be summarised and discussed with the emphasis on the implications for clinical practice and future research direction.

2. General Discussion Summary

The epidemic of T2D is one of the most durable public health challenges of the 21st century, with prevalence likely to continue to increase into the future. Due to the various associated cardio-metabolic, psychological and cost implications, T2D represents a major public health concern and there is a high importance to identify effective therapies to alleviate or minimise complications associated with the disease.

The beneficial effects of lifestyle modification (diet and exercise) on these outcomes, in particular glycaemic control in overweight and obese individuals with T2D, are well documented. However, for several reasons, difficulties in optimising patient engagement in self-care regimes for improved glycaemic control have been problematic, including patient
perception of disease risk and effect of treatments, accessibility, and cost and time
associated with therapy implementation for both the practitioner and patient. Historically,
patient education and adherence to diabetes management strategies have represented the
cornerstone for prevention or reducing the progression of diabetes-related complications,
but in more recent times, technology has provided additional therapeutic approaches,
including the increased accuracy in measuring and providing feedback on acute blood
-glucose responses and inter and intra-day glycaemic variability. This has led to the
exploration of the inclusion of RT-CGM technology to assist in optimising glycaemic control
-and the hypothesis that use of RT-CGM combined with a prescriptive lifestyle modification
-program might be associated with improved glycaemic control compared with current
practice. However, to date there has been limited research evaluating the effects of RT-CGM
combined with prescriptive dietary and lifestyle modification strategies that has limited the
ability to understand the effectiveness and patient acceptance of this approach. There is
also limited knowledge regarding the effect of RT-CGM use on psychological well being in
overweight and obese individuals living with T2D, which needs exploration as a negative
effect could be detrimental for in-patient care.

The studies reported in this thesis extended the current knowledge with a primary focus to
determine the overall effectiveness of RT-CGM when combined with a prescriptive diet and
exercise modification on glycaemic control in overweight and obese individuals with T2D.
2.1 Measures of glycaemic variability and clinical intervention development

There is growing interest in measures of GV and understanding that large fluctuations in GV are an independent risk factor in the development of T2D-related complications, however, individual characteristics that potentially influence GV have remained largely unclear. To address this gap in the literature, the aim of the research presented in Chapter 2 was to understand factors that influenced GV by performing a retrospective, secondary analysis of an existing dataset of patients with T2D that examined the associations between measures of GV and factors such as age, gender, weight, diabetes duration, physical activity and anti-glycaemic medication use. The analysis showed that increased use of anti-hyperglycaemic medication is significantly associated with greater GV, with no observable association on GV indices with any other characteristics included in the model. The positive associations between measures of GV and use of anti-glycaemic medication suggests that closer attention to the impact of prescription of anti-glycaemic medication, dosing regimens and patient education on acute glycaemic responses are needed, as greater medication levels may not necessarily translate to greater reductions in GV or diabetes complications. Future studies need to monitor medication including all adjustments such as types of medications, dosages and usage, throughout the trial.

Chapter 3 presents the findings from a narrative review exploring clinical trials evaluating the effectiveness of CGM (real time and/or blinded) to improve glycated haemoglobin (HbA1c), body weight and lifestyle behaviour adherence in adults with T2D. This analysis demonstrated that lifestyle counselling with CGM use promotes glycaemic and weight control in adults with T2D, with the benefits potentially being augmented by integration of CGM with a prescriptive lifestyle plan. These effects may be due to the intensive nature of
the support provided by researchers and/or health professionals during the study periods, which are not necessarily reflective of real-world scenarios. This review also identified that current studies displayed a relatively high degree of heterogeneity limiting the ability of a meta-analysis to be performed. The lack of studies considering the use of real-time CGM or providing detailed attributes of the interventions and study designs, identified a clear gap in the literature with the need to consider interventions which utilises RT-CGM in conjunction with prescriptive lifestyle information but with limited health professional support. The original experimental study described in Chapter 4 and 5 contributes to addressing this knowledge gap and to provide this understanding.

2.2 Effects of RT-CGM to Improve Effects of a Prescriptive Lifestyle Intervention

Chapter 4 provides preliminary evidence that access to RT-CGM feedback compared to wearing a blinded CGM device is an effective approach to reinforce the effects of a lifestyle modification program (i.e. low carbohydrate diet and exercise program) to improve diabetes control by reducing GV and diabetes medication requirements in overweight or obese individuals with T2D, with minimal professional support. Chapter 4 was able to demonstrate that although both groups achieved clinically relevant weight loss (6% weight loss overall) and an average 0.7% reduction in HbA1c, which is comparable to most structured weight loss interventions with intensive support, individuals using RT-CGM experienced 20-25\% lower GV and 40\% low anti-glycaemic medication use compared to the control (‘blinded’) group. Although these findings are limited by the lack of statistical power and significance, they demonstrated clinical significance with a post-hoc power analysis, suggesting a minimum of 35 participants would be required to achieve statistical significance.
Whilst demonstrating that RT-CGM may enhance the benefits of a prescribed low carbohydrate diet and exercise program on glycaemic control, limited data exploring the tolerance and acceptance of CGM device wear on diabetes management was identified. Traditional self-monitoring of blood glucose levels were reported to be associated with general stress and/or anxiety which can impact on the quality of life of individuals with T2D. This has raised the possibility of negative effects on acceptance and tolerance of RT-CGM wear, including undue stress or poor device wear-time that could potentially limit the usefulness of RT-CGM technology. However, a lack of research systematically evaluating these effects was identified. Greater examination of these effects will assist to increase the understanding of the feasibility of using RT-CGM in clinical practice.

### 2.3 Tolerability and Acceptability of RT-CGM and its Impact on Diabetes Self-Management

To further the understanding of the user experience of RT-CGM in overweight and obese individuals with T2D, a quantitative adjunct study to the original experimental reported in Chapter 4 was conducted and reported in Chapter 5. In response to noticeable lack of validated measures relating to RT-CGM technology in this target population, a purpose-designed questionnaire was developed using the Likert-scale scoring system that measured device acceptability and intolerance (16-questions), motivation to change (20-questions) and impact on diabetes management (18-questions). This analysis demonstrated that positive experiences with RT-CGM device use outweighed any negative experiences, with questionnaire results showing no evidence of change in stress levels overtime or between groups (RT-CGM vs ‘blinded CGM’), suggesting that the use of RT-CGM did not adversely
affect stress. Furthermore, those using the RT-CGM demonstrated a higher degree of device tolerance, acceptance and improvements in diabetes self-management behaviours over the 12-week period, compared to blinded-CGM. This greater engagement could be related to the perceived value and positive reinforcement of the visual display associated with the RT-CGM device. These findings suggest that access to RT-CGM may have a positive influence of overall diabetes self-management behaviours, and assist to overcome the difficulties with compliance, however, larger clinical trials are required to confirm these results.

2.4 Implications of Findings for Clinical Practice

The findings shown in this thesis advance the evidence in support of RT-CGM use in clinical practice in conjunction with a low carbohydrate lifestyle plan in patients with T2D and obesity. The findings support the usability of RT-CGM as an educational tool to create awareness of the effects of diet and exercise on glucose levels, to enhance the benefits of lifestyle intervention in practice, and assist to improve effectiveness of lifestyle interventions being delivered by health professionals that enable them to act in a prompt and meaningful way to adjust therapeutic lifestyle advice rather than responding to chronic 3 or 6-monthly HbA1c measurements.

Health professionals such as dietitians have not traditionally utilised health devices in mainstream practice, however, the inclusion of RT-GCM in routine practices for providing T2D therapeutic interventions is a natural progression, potentially improving primary care. Therefore, the impact includes health professional re-training for upskilling of device implementation into practice, but also for regulatory health professional bodies and/or associated universities to consider providing accredited training to ensure safe and effective implementation and assessment using RT-CGM in future health care environments. Based
on the current findings, it is not implied that health professionals should treat all patients with T2D with RT-CGM. Given the prevalence of T2D in Australia, and the current lack of financial reimbursement for RT-CGM use in T2D, treatment of all individuals with T2D with RT-CGM would represent an insurmountable cost burden. Therefore, an efficacy and benefit to treat those with poorly controlled T2D or newly diagnosed T2D for shorter (7-10 days) periods is warranted.

In addition to other recent advice, the current findings could also provide supporting evidence to potentially advocate for device re-imbursement (full or partial) either via private health insurers (PHI) or the national diabetes services scheme (NDSS) for use of RT-CGM in therapeutic management of T2D.

3. Future Research Areas for RT-CGM, GV and Type 2 Diabetes

This body of work has established several future avenues for research listed throughout the chapters within. Broadly, however, at present RT-CGM and GV do not predict glycaemic control per se, though the use of RT-CGM to evaluate the effect of therapeutic intervention proves valuable. Therefore, a common theme emerged from the pilot data identifying future, greater powered and longer-term studies are required to continue investigating the benefits of RT-CGM and GV if they were to have a role in diagnostics.

Chapter 3 highlighted a need for future studies to examine the measures of GV simultaneously (i.e. using CGM to determine SD glucose, mean amplitude of glycaemic excursions (MAGE) and continuous overall net glycaemic action (CONGA_n)), to establish GV as an independent risk factor for diabetes complications, and to confirm whether lowering
GV reduces incidence or progression of diabetes-related complications (including rate of change and stratification of the population by weight and/or medication change).

Furthermore, to obtain reliable, consistent and stable estimates of GV, it is recommended that future studies increase CGM wear to over a period 14 days minimum to detect reproducible changes in GV patterns.

With regard to future studies examining exercise and CGM, Chapter 3 similarly states that there is a need to capture rigorous glucose data to evaluate GV response to exercise. It is prudent that future randomised control trials are conducted to determine the individual variability in glycaemic control caused by various exercise modalities (dose, frequency, time and type) in individuals with T2D, using a range of GV markers. Similarly, with dietary interventions, the timing and frequency of dietary intake along with dietary composition and duration of meal times, in concert with CGM data is needed to further understand the effects of meal timing on markers of GV and if timing and composition of meals can improve diabetes related outcomes.

Chapter 4 and 5 also highlighted the need for larger, longer duration interventions, and for future research to consider T2D populations with wider levels of glucose control, to enable a greater understanding of the applicability of RT-CGM for the wider management of T2D. Additionally, to better understand the clinical implications of RT-CGM on GV, closer monitoring of all medication types, doses and changes over the course of the intervention are warranted and needed to appropriately assess the variable measures of GV.

Chapter 5 emphasized that larger trials of longer duration comparing RT-CGM, self-monitoring blood glucose and blinded-CGM are needed to improve the understanding of the durability and tolerability of this type of intervention before practical application can be
fully realised. Studies are needed to evaluate how attitudes and coping styles influence self-management behaviour during the use of RT-CGM but also a follow up study of 6-months post-device intervention is required to look at the longer-term effects on self-management behaviour.

Finally, with the growing diversity in CGM devices (Flash, Real-Time, Blinded) there is limited evaluation of cost and time implications to the individual, practitioner or society. Therefore, an economic evaluation would be prudent and beneficial in assisting the health-care environment to understand cost and time savings that could be realised by utilising the device in practice.
Appendix 1: SAMPLE – Acceptance and Tolerance Questionnaire (RT-CGM)

CSIRO Diabetes Study Questionnaire

This questionnaire will measure perceptions and experiences in regards to the Continuous Glucose Monitoring device. It will also explore your feelings around your diabetes in general.

There are no right or wrong answers in this questionnaire. Don’t spend too long on any individual question. Just answer based on your first instinct.

For each question, simply mark the appropriate response box as shown below:

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Installing the sensor was easy for me</td>
<td></td>
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</tbody>
</table>

PARTICIPANT ID: GM_______

VISIT DATE: Visit 9_______
### SECTION 1
When answering these questions, think about the Continuous Glucose Monitor that you have been asked to wear as part of this study

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Installing the sensor was easy for me</td>
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<tr>
<td>The sensor and recorder impacted my sleep quality</td>
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<tr>
<td>Wearing the sensor and recorder for 10-weeks was excessive</td>
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<tr>
<td>The Sensor and Recorder caused me difficulties when driving</td>
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<tr>
<td>The sensor and recorder caused me problems with regards to showering</td>
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<tr>
<td>I found it easy to understand the Glucose Variation Curves provided by the iPod</td>
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<td>It was difficult to be intimate with others whilst wearing the sensor and recorder</td>
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<td>I was easily able to calibrate the sensor using my finger-prick lancet</td>
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<td>Installation of the sensor caused me pain</td>
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<td>In order to accommodate the sensor and recorder I had to adapt my usual clothing</td>
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<td>Changing the sensor every 10 days was inconvenient</td>
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<tr>
<td>Wearing the sensor and recorder continuously for 10-weeks was acceptable to me</td>
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<td>I was satisfied with the look and feel of the sensor and recorder</td>
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<td>I had no difficulty pairing the recorder with the iPod</td>
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<td>Removing the sensor was easy for me</td>
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<tr>
<td>Accessing the Continuing Glucose Monitoring visuals on the iPod was straight forward</td>
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<tr>
<td>Wearing the sensor and recorder was inconvenient</td>
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<tr>
<td>I found it easy to attach the recorder</td>
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<tr>
<td>Changing the sensor every 10 days was acceptable to me</td>
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</table>
**SECTION 2**

When answering these questions, think about the Continuous Glucose Monitor that you have been asked to wear as part of this study.

<table>
<thead>
<tr>
<th>Wearing the <strong>CONTINUOUS GLUCOSE MONITOR</strong> motivated me to:</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>...... reduce my meal portions</td>
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<tr>
<td>...... monitor and take note of my blood glucose levels</td>
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<td>...... increase my exercise frequency</td>
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<td>...... reduce my snacking occasions</td>
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<td>...... increase my intake of healthy fats</td>
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<td>...... increase the intensity of my exercise</td>
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<td>...... reduce my intake of carbohydrates</td>
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<tr>
<td>...... read the nutrition labels on food packaging</td>
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<td>...... increase the duration of my exercise sessions</td>
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<td>...... interact with my Doctor about my diabetes management</td>
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<tr>
<td>...... modify my diet to better suit my diabetes</td>
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</table>

*Continued over page...*
### SECTION 3

When answering these questions, think about the Continuous Glucose Monitor that you have been asked to wear as part of this study.

<table>
<thead>
<tr>
<th>Using the CONTINUOUS GLUCOSE MONITOR helped me to:</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>...understand the impact of difference foods on my blood glucose levels</td>
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<td>...understand the importance of exercise for managing my diabetes</td>
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<td>...understand the impact of sugar on my blood glucose levels</td>
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<td>...understand the impact of protein and healthy-fats on my blood glucose levels</td>
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<td>...actively manage and control my blood glucose levels</td>
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<td>...exercise regularly</td>
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<tr>
<td>...educate my friends about my health needs</td>
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<tr>
<td>...understand how carbohydrates impact on my blood glucose levels</td>
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<tr>
<td>...educate my family about my health needs</td>
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</table>

*Continued over page...*
**SECTION 4**

When answering these questions, think about your participation in this study and your diabetes management in general

<table>
<thead>
<tr>
<th>Since starting this program I:</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>...set goals for managing my diabetes</td>
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<td></td>
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<tr>
<td>...take poor care of my diabetes</td>
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<td>...am effectively managing my diet</td>
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<td>...often make unhealthy dietary choices</td>
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<td>...set goals in regards to my body weight</td>
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<tr>
<td>...understand how exercise affects my blood glucose levels</td>
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<td>...check my blood sugar levels regularly</td>
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<td>...feel in control of my diabetes</td>
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<td>...feel successful with regards to managing my diabetes</td>
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<tr>
<td>...often skip exercising</td>
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<td>...I often feel my blood sugars were unacceptably high.</td>
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<tr>
<td>...use physical activity to help manage my blood glucose levels</td>
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<td>...am satisfied with my exercise level</td>
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<td>...actively choose foods that are good for my blood glucose levels</td>
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<td>...often eat foods rich in sugar and/or carbohydrates</td>
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<td>...often forget to take my diabetes medication (insulin, tablets)</td>
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<td>...often binge on food</td>
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SECTION 5
When answering these questions, think about your participation in this study and your diabetes management in general

<table>
<thead>
<tr>
<th>Before starting this program I:</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
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<tr>
<td>...often ate foods rich in sugar and/or carbohydrates</td>
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<td>...understood how exercise affected my blood glucose levels</td>
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<td>...took poor care of my diabetes</td>
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</table>
Appendix 2: List of peer-reviewed journal article publications, public reports (Outside Candidature), commercial publications and affiliations.

In Submission:


Published


4) Welma Stonehouse¹⁺, Thomas Wycherley², Natalie Luscombe-Marsh¹, Pennie Taylor¹, Grant Brinkworth¹ and Malcolm Riley¹ Dairy intake enhances body weight and composition
changes during energy restriction in 18-50 year old adults – a meta-analysis of randomized controlled trials, Nutrients, 2016;8 (7).

5) Brindal E, Hendrie GA, Taylor P, Freyne J, Noakes M Cohort Analysis of a 24-Week Randomized Controlled Trial to Assess the Efficacy of a Novel, Partial Meal Replacement Program Targeting Weight Loss and Risk Factor Reduction in Overweight/Obese Adults., Nutrients, May 2016 4;8(5).

6) Duncan, M; Vandelanotte, C, M; Kolt, G; ; Rosenkranz, R; Caperchione, C; George, E; Ding, H; Hooker, C; Karunanithi, M; Maeder, A; Noakes, M; Tague, R; Taylor, P; Viljoen, P; Mummery, K. Effectiveness of a Web and Mobile Phone Based Intervention to Promote Physical Activity and Healthy Eating in Middle-Aged Males: Randomized Control Trial of the ManUp study. Journal of medical internet research. 12th June 2014 16(6):e136


12) Duncan, M; Vandelanotte, C; Rosenkranz, R; Caperchione, C; Ding, H; Ellison, M; George, e; Hooker, C; Karunanithi, M; Kolt, G; Maeder, A; Noakes, M; Taylor, P; Tague, R; Viljoen, P; Mummery, K. Effectiveness of a website and mobile phone based physical activity and nutrition intervention for middle-aged males: Trial protocol and baseline findings of the ManUp Study BMC Public Health, 2012, 12;656.

14) George, ES, Kolt, GS, Duncan, M J, Caperchione, C M, Mummery, WK; Vandelanotte, C, Taylor, PJ and Noakes, MJ. A Review of the Effectiveness of Physical Activity Interventions for Adult Males Sports Medicine, February 2012


INDUSTRY REPORTS


Commercial Publications


  Significant Contributions: Part 1, 2 & 3: including assessing and development of the healthy eating plan and menus; recipe analysis; shopping tips, food labels, Low GI Foods
<table>
<thead>
<tr>
<th>Date Range</th>
<th>Professional Affiliation</th>
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<tr>
<td>Jan 2015 – Current</td>
<td>Member of the Dietitian Association Australia – Bariatric Surgery Short Course Working Group (Course development and implementation)</td>
</tr>
<tr>
<td>March 2014 – Current</td>
<td>Member for the Obesity Society (TOS) and American Society of Metabolic and Bariatric Surgery (ASMBS)</td>
</tr>
<tr>
<td>Feb 2010 – Current</td>
<td>University Nutrition and Dietetics Strategic Planning committee member, Flinders University Nutrition and Dietetics</td>
</tr>
<tr>
<td>Feb 2009- Current</td>
<td>Allied Health Member for Australia and New Zealand Metabolic and Obesity Surgery Society (ANZMOSS) Previously OSSANZ</td>
</tr>
<tr>
<td>Dec 2005 - Current</td>
<td>Accredited Practising Dietitian (APD) - Dietitians Association Australia (DAA)</td>
</tr>
<tr>
<td>Jan 2015 – 2017</td>
<td>Member of the Australia and New Zealand Metabolic and Obesity Surgery Society (ANZMOSS) Conference and workshop planning committee</td>
</tr>
<tr>
<td>Oct 2012 – Nov 2016</td>
<td>Committee Member (non-voting) for Obesity Surgery Society of Australia and New Zealand (Ossanz)</td>
</tr>
<tr>
<td>Jan 2010- 2016</td>
<td>DAA-SA Exec Committee Member, (2016) Vice -Chair and Chair</td>
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