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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Thesis Declaration

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

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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 29.9kg/m^2, and obesity, as BMI $\geq$ 30kg/m^2, 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 in ability 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/m^2 [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 Hashimotos 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 $\geq$ 35kg/m^2, 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 $\geq$ 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

Measure	Range mg/dL	Range mmol/L
Fasting Plasma Glucose (FPG)	>126	>7
2-hr Oral (75g) Glucose Tolerance Test	>200	>11.1
HbA1c %	>6.5%	>48 mmol/mol

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 8-12hours [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 β-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 Glyco-hemoglobin 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

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

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 though 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 meditators, 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 5-15years [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 $\geq$ 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 un-treated [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]. A

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)

Measure of GV	Definition	Calculation	Advantages	Disadvantages
Standard Deviation (SD) of glucose	Rate of variation of dispersion from average glycaemia	$\sqrt{\frac{\sum(x_i - x^{-2})}{k-1}}$ x_i : glucose reading (individual) x-: mean glucose k: number of observations	Within-day and between-day glucose variability (dependant on > 24hrs of measures); easy to determine; marker of metabolic stability over time; extensively used.	Does not consider frequency of glucose oscillations. Underestimation can occur (high and low glycaemic excursions are not weighted)
Coefficient of variation (CV) for glucose	Describes the spread of blood glucose independent from its unit of measure	$\frac{SD}{x-}$ $x-$: mean glucose SD = standard deviation	Within-day glucose variability; good measure of between group comparisons; easily calculated from SD and mean	Does not consider frequency of glucose oscillations; difficulty in determining a meaningful threshold.
Mean amplitude of glycaemic excursions (MAGE)	Mean differences of glucose fluctuations, from high to low levels with magnitude > 1 SD	$\frac{\sum \lambda}{n}$ If $\lambda > v$ λ *:* magnitude of each blood glucose excursion from highest to lowest point (or lowest to highest point) *n:* number of valid observations v*:* 1 SD of the mean glucose for a 24hr period	Correlates well with oxidative stress in T2D; extensively used; measure of within day variability; reflects glucose fluctuations (weights high and low fluctuations)	Not valid if there is only one hyper or hypo excursion during the observation period; excludes minor fluctuations (< 1 SD) of mean glucose; CGM (simple calculation) and SMBG only with 7 measures daily
Mean of daily differences (MODD)	Mean of absolute differences between glucose values obtained at exactly the same time of day on two consecutive days under standardized conditions	$\frac{\sum_{t=t1}^{tk*}(GR_t - GR_t - 1440)}{k^*}$ $k*$ = number of observations where there is an observation 1,440 minutes (24 hours) ago $GRt - GRt{-}1440$ = difference between glucose readings at time *t* and 1,440 minutes (24 hours) ago	Intra-day variability; high MODD score is indicative of large glucose fluctuations.	Not directly reported by CGM; needs additional calculation
Continues overall net glycaemic action (CONGA $_n$)	Integrates duration and scale of glucose excursions	$\sqrt{\frac{\sum_{t=t1}^{tk*}(D_t - D^{-2})}{K^*-1}}$ $Dt = GRt - GRt - m$ $D^- = \frac{\sum_{t=t1}^{tk*}(Dt)}{k^*}$ k = number of observations in which there is a value (observation) n x 60 min before = n x 60 mins G = Glucose	High level of accuracy of within-day variability and if >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.	Complex calculation (higher the CONGA value the greater the glycaemic excursion) Specifically developed for continuous glucose monitoring devices.
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-n=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].

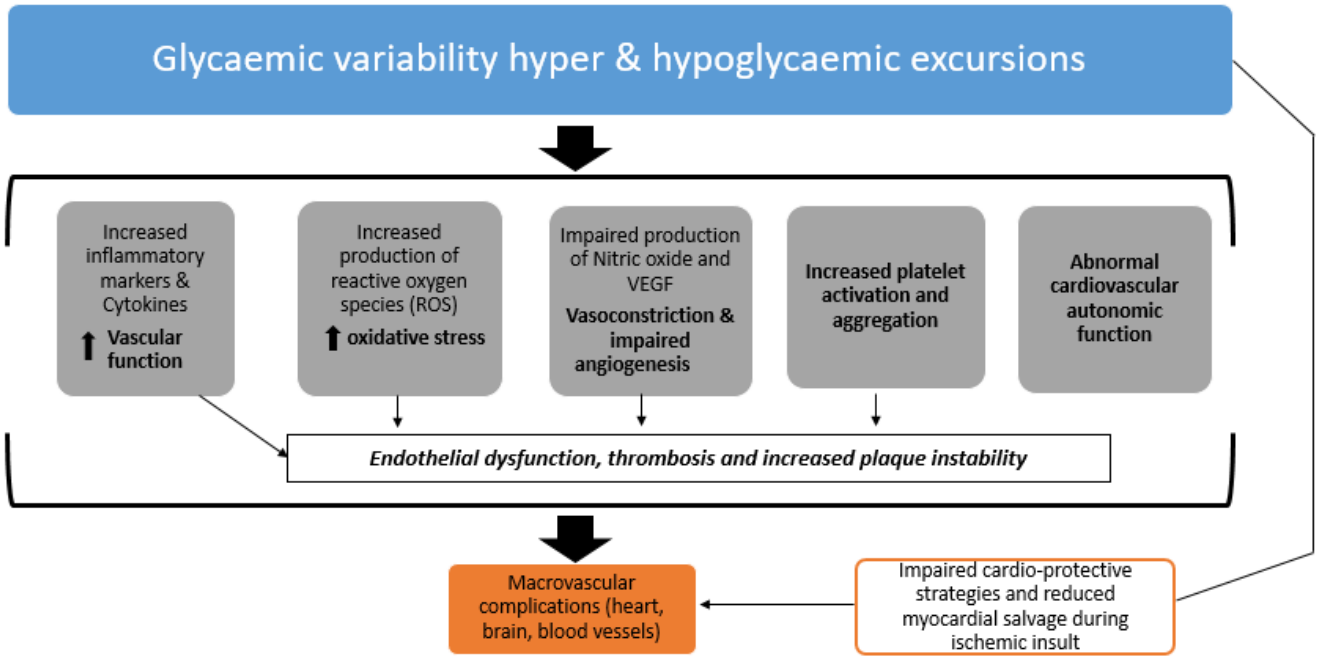
As previously discussed, although limited studies exist demonstrating a reduction in GV is directly or indirectly related to a reduction T2D-related complications, there is growing evidence demonstrating acute glucose fluctuations as emerging risk factors for CVD outcomes, which have been shown to induce 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 $CONGA_2$, 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 $\geq$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. Figure1 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 CONGA*n*, 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 $CONGA_n$ (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 $CONGA_n$ 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 $\geq$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, $CONGA_2$ and $CONGA_4$) and individual characteristics such as age, gender, weight, diabetes duration, physical activity and antiglycaemic 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:

	BMI Category (Kg/m^2)				
	25.0-26.9 (or 23.0-26.9*)	27.0–29.9	30.0–34.9 (or 27.5–32.4*)	35.0–39.9 (or 32.5–37.4*)	≥40 (or ≥ 37.5*)
Treatment					
Diet, physical activity and behavioural therapy	√	√	√	√	√
Pharmacotherapy		√	√	√	√
Metabolic Surgery			√ with comorbidities	√ without comorbidities	√ without comorbidities

** 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 $\geq$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 ($CONGA_1$, $CONGA_4$ 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, $\geq$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 $\pm$ 20% measurement error to $\pm$ 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].

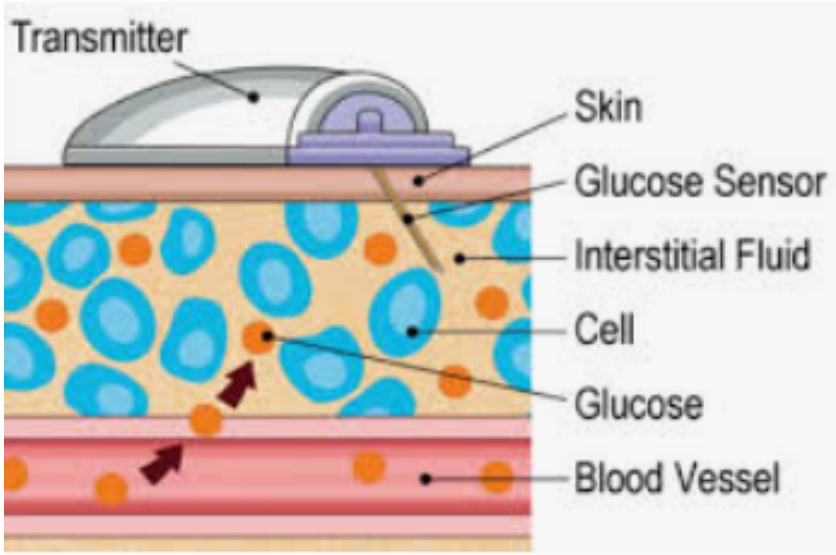
The most recent continuous glucose monitoring systems are wearable health devices usually involving three main components:

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].

Figure 2: Example of sensor placement



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 antiglycaemic 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

1. Han, S.J. and E.J. Boyko, *The Evidence for an Obesity Paradox in Type 2 Diabetes Mellitus.* Diabetes Metab J, 2018. 42(3): p. 179-187.
2. Okorodudu, D.O., Jumean, M.F., Montori, V.M. et al., *Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis.* Int J Obes (Lond), 2010. 34(5): p. 791-9.
3. Loring, B. and A. Robertson, *Obesity and Inequities; Guidance for addressing inequities in overweight and obesity*. 2014, World Health Organisation Europe. p. 1-29.
4. Australian Institure of Health and Welfare, *Australias health 2018: Australias Health Series*. 2018, Australian Government: Australia p. 1-9.
5. Australian Institure of Health and Welfare, *A picture of overweight and obesity in Australia 2017*. 2017, AIHW: Australia. p. 1-49.
6. Hruby, A., Manson, J.E., Qi, L. et al., *Determinants and Consequences of Obesity.* Am J Public Health, 2016. 106(9): p. 1656-62.
7. Lakerveld, J. and J. Mackenbach, *The Upstream Determinants of Adult Obesity.* Obes Facts, 2017. 10(3): p. 216-222.
8. Avsar, G., R. Ham, and W.K. Tannous, *Factors Influencing the Incidence of Obesity in Australia: A Generalized Ordered Probit Model.* Int J Environ Res Public Health, 2017. 14(2).
9. The Global Burden of Disease (GBD) 2015 Obesity Collaborators . et al., *Health Effects of Overweight and Obesity in 195 Countries over 25 Years.* N Engl J Med, 2017. 377(1): p. 13-27.

10. Australian Institure of Health and Welfare, *Deaths among people with diabetes in Australia, 2009-2014*. 2017, AIHW: Australia p. 1-76.

11. Seuring, T., Archangelidi, and M. Suhrcke, *The Economic Costs of Type 2 Diabetes: A Global Systematic Review.* Pharmacoeconomics, 2015. 33(8): p. 811-31.

12. Bommer, C., Sagalova, V., Heesemann, E. et al., *Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030.* Diabetes Care, 2018. 41(5): p. 963-970.

13. Cho, N.H., Shaw, J.E., Karuranga, S. et al., *IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045.* Diabetes Res Clin Pract, 2018. 138: p. 271-281.

14. International Diabetes Federation (IDF), *Diabetes Atlas Eighth Edition 2017*. 2017, IDF: United Kingdom. p. 1-147.

15. Ramzan, S., Timmins, P., Hasan, S.S. et al., *Cost analysis of type 2 diabetes mellitus treatment in economically developed countries.* Expert Rev Pharmacoecon Outcomes Res, 2019. 19(1): p. 5-14.

16. American Diabetes Association (ADA), *ADA Standards of Medical Care in Diabetes - 2019.* Diabetes Care, 2019. 42(Suppl 1): p. S4-S182.

17. Wilcox, G., *Insulin and Insulin Resistance.* Clin Biochem Review, 2005. 25: p. 19-39.

18. Dandona, P., Aljada, A. and Bandyopadhya, A., *Inflammation: the link between insulin resistance, obesity and diabetes.* Trends in Immunology, 2004. 25(1): p. 1-3.

19. Keller, U., *Diagnosing diabetes and prediabetes seems to be trivial but is often delayed.* Swiss Med Wkly, 2015. 145: p. w14232.

20. Einarson, T.R., Acs, A., Ludwig, C. et al., *Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017.* Cardiovasc Diabetol, 2018. 17(1): p. 83.

21. NCD Risk Factor Collaboration (NCD RisC)., *Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants.* The Lancet, 2016. 387(10027): p. 1513-1530.

22. Kolb, H. and S. Martin, *Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes.* BMC Med, 2017. 15(1): p. 131.

23. Barbour, L.A., McCurdy, C.E., Hernandez, T.L. et al., *Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes.* Diabetes Care, 2007. 30 Suppl 2: p. S112-9.

24. Sacks, D.B., *A1C versus Glucose Testing: A Comparison.* Diabetes Care, 2011. 32(4): p. 518.

25. Lim, W.Y., Ma, S., Heng, D. et al., *Screening for diabetes with HbA1c: Test performance of HbA1c compared to fasting plasma glucose among Chinese, Malay and Indian community residents in Singapore.* Sci Rep, 2018. 8(1): p. 12419.

26. Suh, S. and J.H. Kim, *Glycemic Variability: How Do We Measure It and Why Is It Important?* Diabetes Metab J, 2015. 39(4): p. 273-82.

27. Shah, M. and A. Vella, *What is type 2 diabetes?* Medicine, 2014. 42(12): p. 687-691.

28. Abraham, T.M. and C.S. Fox, *Implications of rising prediabetes prevalence.* Diabetes Care, 2013. 36(8): p. 2139-41.

29. Kahn, S.E., Cooper, M.E. and Del Prato, S., *Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future.* The Lancet, 2014. 383(9922): p. 1068-1083.

30. Stumvoll, M., Goldstein, B.J. and van Haeften, T.W., *Type 2 diabetes: principles of pathogenesis and therapy.* The Lancet, 2005. 365(9467): p. 1333-1346.

31. Kaku, K., *Pathophysiology of Type 2 Diabetes and Its Treatment Policy.* Japan Medical Assoc. Journal, 2010. 138(1): p. 28-32.

32. Kahn, S.E., *The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes.* Diabetologia, 2003. 46(1): p. 3-19.

33. Defronzo, R.A., *Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus.* Diabetes, 2009. 58(4): p. 773-95.

34. Samuel, V.T. and G.I. Shulman, *The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux.* J Clin Invest, 2016. 126(1): p. 12-22.

35. Esser, N., Legrand-Poels, S., Piette, J, et al., *Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes.* Diabetes Res Clin Pract, 2014. 105(2): p. 141-50.

36. Edelstein, S.L., Knowler, W.C., Bain, R.P., et al., *Predictors of Progression From Impaired Glucose Tolerance to NIDDM: An Analysis of Six Prospective Studies.* Diabetes, 1997. 46(4): p. 701-710.

37. Tuomi, T., Santoro, N., Caprio, S., et al., *The many faces of diabetes: a disease with increasing heterogeneity.* The Lancet, 2014. 383(9922): p. 1084-1094.

38. Chawla, A., Chawla, R. and Jaggi, S., *Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum?* Indian J Endocrinol Metab., 2016. 20(4): p. 546-551.

39. Fowler, M.J., *Microvascular and Macrovascular Complications of Diabetes.* Clinical Diabetes, 2008. 26(2): p. 77-82.

40. Ahlqvist, E., van Zuydam, N.R., Groop, L.C., et al., *The genetics of diabetic complications.* Nat Rev Nephrol, 2015. 11(5): p. 277-87.

41. Huang, D., Refaar, M., Mohammedi, K., et al., *Macrovascular Complications in Patients with Diabetes and Prediabetes.* Biomed Res Int, 2017. 2017: p. 7839101.

42. Mannucci, E., Dicembrini, I., Lauria, A., et al., *Is glucose control important for prevention of cardiovascular disease in diabetes?* Diabetes Care, 2013. 36 Suppl 2: p. S259-63.

43. Fox, C.S., Golden, S.H., Anderson, C., et al., *Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association.* Diabetes Care, 2015. 38(9): p. 1777-803.

44. Morrish, N.J., Wnag, S.L., Stevens, L.K., et al., *Mortality and causes of death in the WHO multinational study of vascular disease in diabetes.* Diabetologia, 2001. 44(S2): p. S14-21.

45. Valabhji, J. and Elkeles, R.S., *Macrovascular Disease in Diabetes.* Medicine, 2002. 30(2): p. 47-50.

46. Rossing, P., Persson, F. and Frimodt-Moller, M., *Prognosis and treatment of diabetic nephropathy: Recent advances and perspectives.* Nephrol Ther, 2018. 14 Suppl 1: p. S31-S37.

47. Lee, R., Wong, T.Y. and Sabanayagam, C., *Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss.* Eye Vis (Lond), 2015. 2: p. 17.

48. Tarr, J.M., Kaul, K., Chopra, M., et al., *Pathophysiology of diabetic retinopathy.* ISRN Ophthalmol, 2013. 2013: p. 343560.

49. Moheet, A., Mangia, S. and Seaquist, E.R., *Impact of diabetes on cognitive function and brain structure.* Ann N Y Acad Sci, 2015. 1353: p. 60-71.

50. Barrett, E.J., Liu, Z., Khamaisi, M., et al., *Diabetic Microvascular Disease: An Endocrine Society Scientific Statement.* J Clin Endocrinol Metab, 2017. 102(12): p. 4343-4410.

51. Deli, G., Bosnyak, E., Pusch, G., et al., *Diabetic neuropathies: diagnosis and management.* Neuroendocrinology, 2013. 98(4): p. 267-80.

52. West, M., Chuter, V., Munteanu, S., et al., *Defining the gap: a systematic review of the difference in rates of diabetes-related foot complications in Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians.* J Foot Ankle Res, 2017. 10: p. 48.

53. Petrakis, I., Kyriopoulos, I.J., Ginis, A., et al., *Losing a foot versus losing a dollar; a systematic review of cost studies in diabetic foot complications.* Expert Rev Pharmacoecon Outcomes Res, 2017. 17(2): p. 165-180.

54. Perrin, N.E., Davies, M.J., Robertson, N., et al., *The prevalence of diabetes-specific emotional distress in people with Type 2 diabetes: a systematic review and meta-analysis.* Diabet Med, 2017. 34(11): p. 1508-1520.

55. Joseph, J.J. and Golden, S.H., *Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus.* Ann N Y Acad Sci, 2017. 1391(1): p. 20-34.

56. Trikkalinou, A., Papazafiropoulou, A.K., and Melidonis, A., *Type 2 Diabetes and Quality of Life.* World Journal of Diabetes, 2017. 8(4): p. 120-171.

57. Glasziou, P., Alexander, J., Beller, E., et al., *Which health-related quality of life score? A comparison of alternative utility measures in patients with Type 2 diabetes in the ADVANCE trial.* Health Qual Life Outcomes, 2007. 5: p. 21.

58. Schunk, M., Reitmeir, P., Ruckert-Eheberg, I.M., et al., *Longitudinal change in health-related quality of life in people with prevalent and incident type 2 diabetes compared to diabetes-free controls.* PLoS One, 2017. 12(5): p. e0176895.

59. Andresdottir, G., Jensen, M.L., Carstensen, B., et al., *Improved Survival and Renal Prognosis of Patients With Type 2 Diabetes and Nephropathy With Improved Control of Risk Factors.* Diabetes Care, 2014.

60. Nathan, D.M., McGee, P., Steffes, M.W., et al., *Relationship of Glycated Albumin to Blood Glucose and HbA1c Values and to Retinopathy, Nephropathy, and Cardiovascular Outcomes in the DCCT/EDIC Study.* Diabetes, 2014. 63: p. 282-290.

61. The Diabetes Control and Complications Research Group (DCCT)., *The effect of intensive treatment on diabetes on the development and progression of long-term complications in insulin dependant diabetes mellitus.* N Engl J Med, 1993. 329(14): p. 977-986.

62. Duckworth, W., Abraria, C., Moritz, T. et al., *Glucose control and vascular cmplications Veterans with type 2 diabetes, (VADT trial)* , N Engl J Med, 209. 360: p. 129-39

63. Stratton, I.M., Adler, A.I., Andrew, H., et al., *Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study.* British Medical Journal, 2000. 321: p. 405-412.

64. Holman, R.R., Sanjoy, K.P., Bethel, A.M., et al., *10-year follow-up of intensive glucose control in type 2 diabetes.* N359, 2008(1577-1589).

65. Ismail-Beigi, F., Craven, T., Banerji, M-A., et al., *Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial.* The Lancet, 2010. 376(9739): p. 419-430.

66. The ADVANCE collaboration Group. *Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes.* N Engl. J. Med, 2008. 358: p2560-72

67. Wright, L.A. and Hirsch, I.B., *Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters.* Diabetes Technol Ther, 2017. 19(S2): p. S16-S26.

68. Gerstein, H.C., Miller, M.E., Ismail-Neigi, F., et al., *Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial.* The Lancet, 2014. 384(9958): p. 1936-1941.

69. Elley, C.R., Kenealy, T., Robinson, E., et al., *Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study.* Diabet Med, 2008. 25(11): p. 1295-301.

70. Selvin, E., Marinopoulos, S., Berkenblit, G., et al., *Meta-Analysis: Glycosolated Hemaglobin and Cardiovascular Disease in Diabetes Mellitus.* Annals of Internal Medicine, 2004. 141(6): p. 421-431.

71. Ginsberg, H.N., *The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial: what we learn from subgroup analyses.* Diabetes Care, 2011. 34 Suppl 2: p. S107-8.

72. Hayward, R.A., Reaven, P.D., Witala, W.L., et al., *Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes.* N Engl J Med, 2015. 372(23): p. 2197-206.

73. The ACCORD Study Group., *Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods.* Am J Cardiol, 2007. 99(12A): p. 21i-33i.

74. Service, J.F. and O'Brien, P.C., *Influences of Glycemic Variables on Hemaglobin A1c.* Endocrine Practice, 2007. 13(4): p. 350-354.

75. Kohnert, K.D., Vogt, L., Augstein, P., et al., *Relationships Between Glucose Variability and Conventional Measures of Glycemic Control in Continuously Moniotored Pateints with Type 2 Diabetes.* Horm Metab Res, 2009. 41: p. 137-141.

76. Sorkin, J.D., Muller, D.C., FLeg, J.I., et al., *The Relation of Fasting and 2-h Postchallenge Plasma Glucose Concentrations to Mortality: Data from the Baltimore Longitudinal Study of Aging with a critical review of the literature.* Diabetes Care, 2005. 28: p. 2626-2632.

77. Bonora, E. and Tuomilehto, J., *The pros and cons of diagnosing diabetes with A1C.* Diabetes Care, 2011. 34 Suppl 2: p. S184-90.

78. Borg, R., Kuenen, J.C., Carstensen, B., et al., *Associations between features of glucose exposure and A1C: the A1C-Derived Average Glucose (ADAG) study.* Diabetes, 2010. 59(7): p. 1585-90.

79. Rohlfing, C.L., Weidmayer, B.H-M.,, Little, R.R., et al., *Defining the Relationship Between Plasma Glucose and HbA1c: Analysis of glucose profiles and HbA1c in the Diabetes Control and Complications Trial.* Diabetes Care, 2002. 25(2): p. 275-278.

80. Monnier, L. and Colette, C., *Target for glycemic control: concentrating on glucose.* Diabetes Care, 2009. 32 Suppl 2: p. S199-204.

81. Standl, E., Schnell, O. and Ceriello, A., *Postprandial hyperglycemia and glycemic variability: should we care?* Diabetes Care, 2011. 34 Suppl 2: p. S120-7.

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

83. Beck, R.W., Connor, C.G., Mullen, D.M., et al., *The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading.* Diabetes Care, 2017. 40(8): p. 994-999.

84. Fayyaz, B., Rehman, H.J. and Minn, H., *Interpretation of hemoglobin A1C in primary care setting.* J Community Hosp Intern Med Perspect, 2019. 9(1): p. 18-21.

85. Danne, T., Nimri, R., Battelino, T., et al., *International Consensus on Use of Continuous Glucose Monitoring.* Diabetes Care, 2017. 40(12): p. 1631-1640.

86. Nusca, A., Tuccinardi, D., Albano, M., et al., *Glycemic variability in the development of cardiovascular complications in diabetes.* Diabetes Metab Res Rev, 2018. 34(8): p. e3047.

87. Dandona, P., *Minimizing Glycemic Fluctuations in Patients with Type 2 Diabetes: Approaches and Importance.* Diabetes Technol Ther, 2017. 19(9): p. 498-506.

88. Di Flaviani, A., Picconi, F., Di Stefano, P., et al., *Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients.* Diabetes Care, 2011. 34(7): p. 1605-9.

89. Monnier, L., Mas, E., Ginet, C., et al., *Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes.* JAMA, 2006. 12(14): p. 1681-1687.

90. Monnier, L., Colette, C., Wojtusciszyn, A., et al., *Toward Defining the Threshold Between Low and High Glucose Variability in Diabetes.* Diabetes Care, 2017. 40(7): p. 832-838.

91. Nalysnyk, L., Hernandez-Medina, M. and Krishnarajah, G., *Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature.* Diabetes Obes Metab, 2010. 12(4): p. 288-98.

92. Ceriello, A., Esposito, K., Piconi, L., et al., *Glucose "peak" and glucose "spike": Impact on endothelial function and oxidative stress.* Diabetes Res Clin Pract, 2008. 82(2): p. 262-7.

93. Smith-Palmer, J., Brandle, M., Trevisan, R., et al., *Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes.* Diabetes Res Clin Pract, 2014. 105(3): p. 273-84.

94. Picconi, F., Di Flaviani, A., Malandrucco, I., et al., *Impact of glycemic variability on cardiovascular outcomes beyond glycated hemoglobin. Evidence and clinical perspectives.* Nutr Metab Cardiovasc Dis, 2012. 22(9): p. 691-6.

95. Tsai, C.J., Hsieh, C.J., Tung, S.C., et al., *Acute blood glucose fluctuations can decrease blood glutathione and adiponectin levels in patients with type 2 diabetes.* Diabetes Res Clin Pract, 2012. 98(2): p. 257-63.

96. Ceriello, A., Monnier, L. and Owens, D., *Glycaemic variability in diabetes: clinical and therapeutic implications.* The Lancet Diabetes & Endocrinology, 2019. 7(3): p. 221-230.

97. Rodbard, D., *Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes.* Diabetes Technol Ther, 2017. 19(S3): p. S25-S37.

98. Cardoso, C.R.L., Leite, N.C., Moram, C.B.M., et al., *Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study.* Cardiovasc Diabetol, 2018. 17(1): p. 33.

99. Hirsch, I.B., *Glycemic Variability and Diabetes Complications: Does It Matter? Of Course It Does!* Diabetes Care, 2015. 38(8): p. 1610-4.

100. Munoz, O.M., Gomez, A.M., Garcia-Jaramillo, M., et al., *The different methods of assessing glycemic variability, quality of glycemic control and glycemic risk cannot be interpreted as equivalent in clinical practice.* Diabetes Metab Syndr, 2018. 12(4): p. 555-561.

101. Sakamoto, M., *Type 2 Diabetes and Glycemic Variability: Various Parameters in Clinical Practice.* J Clin Med Res, 2018. 10(10): p. 737-742.

102. Peyser, T.A., Balo, A.K,m Buckingham, B.A., et al., *Glycemic Variability Percentage: A Novel Method for Assessing Glycemic Variability from Continuous Glucose Monitor Data.* Diabetes Technol Ther, 2018. 20(1): p. 6-16.

103. Czupryniak, L., Barkai, L., Bolgarska, S., et al., *Self-monitoring of blood glucose in diabetes: from evidence to clinical reality in Central and Eastern Europe--recommendations from the international Central-Eastern European expert group.* Diabetes Technol Ther, 2014. 16(7): p. 460-75.

104. Hu, Z.D., Zhang, K.P., Huang, Y., et al., *Compliance to self-monitoring of blood glucose among patients with type 2 diabetes mellitus and its influential factors: a real-world cross-sectional study based on the Tencent TDF-I blood glucose monitoring platform.* Mhealth, 2017. 3: p. 25.

105. Schnell, O., Alawi, H., Battelino, T., et al., *Self-Monitoring of Blood Glucose in Type 2 Diabetes: Recent Studies.* Journal of Diabetes Science and Technology, 2013. 7(2).

106. Gerbaud, E., Darier, R., Montaudon, M., et al., *Glycemic Variability Is a Powerful Independent Predictive Factor of Midterm Major Adverse Cardiac Events in Patients With Diabetes With Acute Coronary Syndrome.* Diabetes Care, 2019. 42(4): p. 674-681.

107. Chow, E., Bernjak, A., Wiliams, S., et al., *Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk.* Diabetes, 2014. 63(5): p. 1738-47.

108. Saisho, Y., *Glycemic variability and oxidative stress: a link between diabetes and cardiovascular disease?* Int J Mol Sci, 2014. 15(10): p. 18381-406.

109. Garcia, A., Balo, A.K., Buckingham, B.A., et al., *Application of Glycemic Variability Percentage: Implications for Continuous Glucose Monitor Utilization and Analysis of Artificial Pancreas Data.* Diabetes Technol Ther, 2017. 19(12): p. 699-706.

110. Tay, J., Luscomber-Marhs, N.D., Thompson, C.H., et al., *Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial.* Am J Clin Nutr, 2015. 102(4): p. 780-90.

111. Frontoni, S., Di Bartolo, P., Avodaro, A., et al., *Glucose variability: An emerging target for the treatment of diabetes mellitus.* Diabetes Res Clin Pract, 2013. 102(2): p. 86-95.

112. Joshi, A., Mitra, A., Anjum, N., et al., *Patterns of Glycemic Variability During a Diabetes Self-Management Educational Program.* Med Sci (Basel), 2019. 7(3).

113. Davies, M.J., D'Alessio, D.A., Fradkin, J., et al., *Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).* Diabetes Care, 2018. 41(12): p. 2669-2701.

114. Franz, M.J., Boucher, J.L., Rutten-Ramos, S., et al., *Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials.* J Acad Nutr Diet, 2015. 115(9): p. 1447-63.

115. Terranova, C.O., Brakenridge, C.L., Lawler, S.P. et al., *Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis.* Diabetes Obes Metab, 2015. 17: p. 371-378.

116. Daousi, C., Casson, I.F., Gill, G.V., et al., *Prevalence of obesity in type 2 diabetes in secondary care: association with cardiovascular risk factors.* Postgrad Med J, 2006. 82(966): p. 280-4.

117. Anderson, J.W., Kendall, C.W.C. and Jenkins, D.J.A., *Importance of Weight Management in Type 2 Diabetes: Review with Meta-analysis of Clinical Studies.* Journal of the American College of Nutrition, 2003. 22(5): p. 331-339.

118. Esposito, K., Maiorina, M.I., Ciotola, M., et al., *Effects of a Mediterranean-Style Diet on the Need for Antihyperglycemic Drug Therapy in Patients With Newly Diagnosed Type 2 Diabetes: A Randomized Trial* Annals of Internal Medicine, 2009. 151(5): p. 306-314.

119. The Look AHEAD Research Group., *Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial.* Arch Intern Med, 2010. 170(17): p. 1566-75.

120. Pi-Sunyer, X., *The Look AHEAD Trial: A Review and Discussion Of Its Outcomes.* Curr Nutr Rep, 2014. 3(4): p. 387-391.

121. The Look AHEAD Research Group., *Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes.* N Engl J Med, 2013. 369(2): p. 145-54.

122. Gummesson, A.,Nyman, E., Knutsson, M., et al., *Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes.* Diabetes Obes Metab, 2017. 19(9): p. 1295-1305.

123. Anderson, J.W. and Konz, E.Z., *Obesity and Disease Management: effects of weight loss on comorbid conditions,* Obesity Research, 2001. 9, Suppl 4: p. 326S-334.

124. Steven, S. and Taylor, R., *Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes.* Diabet Med, 2015. 32(9): p. 1149-55.

125. Huo, R., Du. T., Xu, Y., et al., *Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis.* Eur J Clin Nutr, 2015. 69(11): p. 1200-8.

126. Guldbrand, H., Lindstrom, T., Dizdar, D., et al., *Randomization to a low-carbohydrate diet advice improves health related quality of life compared with a low-fat diet at similar weight-loss in Type 2 diabetes mellitus.* Diabetes Res Clin Pract, 2014. 106(2): p. 221-7.

127. Myette-Cote, E., Durrer, C., Neudorf, H., et al., *The effect of a short-term low-carbohydrate, high-fat diet with or without postmeal walks on glycemic control and inflammation in type 2 diabetes: a randomized trial.* Am J Physiol Regul Integr Comp Physiol, 2018. 315(6): p. R1210-R1219.

128. Meng, Y., Bai, H., Wang, S., et al., *Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials.* Diabetes Res Clin Pract, 2017. 131: p. 124-131.

129. Sami, W., Butt, N.S., Ansari, M., et al., *ffect of diet on type 2 diabetes mellitus: A review.* International Journal of Health Science, 2017. 11(2).

130. Ajala, O., English, P., and Pinkney, J., *Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes.* Am J Clin Nutr, 2013. 97(3): p. 505-16.

131. Esposito, K., Maiorina, M.I., Ciotola, M., et al., *A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses.* BMJ Open, 2015. 5(8): p. e008222.

132. Sainsbury, E., Kizirian, V., Partridge, S.R., et al., *Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis.* Diabetes Res Clin Pract, 2018. 139: p. 239-252.

133. MacLeod, J., Franz, M.J., Handu, D>, et al., *Academy of Nutrition and Dietetics Nutrition Practice Guideline for Type 1 and Type 2 Diabetes in Adults: Nutrition Intervention Evidence Reviews and Recommendations.* J Acad Nutr Diet, 2017. 117(10): p. 1637-1658.

134. Ojo, O., Ojo, O.O., Adebowale, F., et al., *The Effect of Dietary Glycaemic Index on Glycaemia in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.* Nutrients, 2018. 10(3).

135. Zhao, W.T., Luo, Y., Zhang, Y., et al., *High protein diet is of benefit for patients with type 2 diabetes: An updated meta-analysis.* Medicine (Baltimore), 2018. 97(46): p. e13149.

136. Gannon, M.C. and Nuttall, F.Q., *Effect of a High-Protein, Low-Carbohydrate Diet on Blood Glucose Control in People With Type 2 Diabetes* Diabetes, 2004. 53: p. 2375-2382.

137. Thomas, D. and Elliott, E.J., *Low glycaemic index, or low glycaemic load, diets for diabetes mellitus.* Cochrane Database Syst Rev, 2009(1): p. CD006296.

138. Tay, J., Luscombe-Marsh, N.D., Thomposon, C.H., et al., *A Very Low-Carbohydrate, Low–Saturated Fat Diet for Type 2 Diabetes Management: A Randomized Trial.* Diabetes Care, 2014. 37: p. 2909-2913.

139. Tay, J., Thomposon, C.H., Luscombe-Marsh, N.D., et al., *Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial.* Diabetes Obes Metab, 2018. 20(4): p. 858-871.

140. Avery, A., Flynn, D., Van Wersh, A., et al., *Changin Physcial Activity Behavior in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Behavioral Interventions,* Diabetes Care, 2012. 35: p.2681-2689.

141. Boule, N.G., Weinsnagel, J.S., Lakka, T.A., et al., *Effects of Exercise training on Glucoses Homeostasi: The HERITAGE family study,* Diabetes Care, 2005. 28 (1). p. 108-114.

142. Van Dijk, J.W., Venema, M., Van Mechelen, W., et al., *Effect of Moderate-Intensity Exercise Versus Activities of Daily Living on 24-Hour Blood Glucose Homeostasis in Male Patients With Type 2Diabetes.* Diabetes Care, 2013. 36: p. 3448-3453.

143. Brand, T., Pischke, C.R., Steebock, B., et al., *What works in community-based interventions promoting physical activity and healthy eating? A review of reviews.* Int J Environ Res Public Health, 2014. 11(6): p. 5866-88.

144. Barreira, E., Novo, A., Vaz, J.A., et al., *Dietary program and physical activity impact on biochemical markers in patients with type 2 diabetes: A systematic review.* Aten Primaria, 2018. 50(10): p. 590-610.

145. Zenari, L. and Maragoni, A., *What are the preferred strategies for control of glycaemic variability in patients with type 2 diabetes mellitus? - A review.* Diabetes Obes Metab, 2013. 15(S2): p. 17-25.

146. Reiner, M., Niermann, C., Jekauc, D., et al., *Long-term health benefits of physical activity – a systematic review of longitudinal studies.* BMC Public Health, 2013. 13: p. 813-821.

147. Raveendran, A.V., Chacko, E. and Pappachan, J.M., *Non-pharmacological Treatment Options in the Management of Diabetes Mellitus.* Eur Endocrinol, 2018. 14(2): p. 31-39.

148. Solomon, T.P.J., *Sources of Inter-individual Variability in the Therapeutic Response of Blood Glucose Control to Exercise in Type 2 Diabetes: Going Beyond Exercise Dose.* Front Physiol, 2018. 9: p. 896.

149. Sylow, L., Kleinert, M., Richter, E.A., et al., *Exercise-stimulated glucose uptake - regulation and implications for glycaemic control.* Nat Rev Endocrinol, 2017. 13(3): p. 133-148.

150. Kahn, B.B., Alquier, T., Carling, D., et al., *AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism.* Cell Metab, 2005. 1(1): p. 15-25.

151. Boulé, N.G., Normand, G., Haddad, E., et al., *Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes MellitusA Meta-analysis of Controlled Clinical Trials.* JAMA, 2001. 286(10): p. 1218-1227.

152. Liu, Y., Ye, W., Chen, Q., et al., *Resistance Exercise Intensity is Correlated with Attenuation of HbA1c and Insulin in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis.* Int J Environ Res Public Health, 2019. 16(1).

153. da Silva, D.E., Grande, A.J., Roever, L., et al., *High-Intensity Interval Training in Patients with Type 2 Diabetes Mellitus: a Systematic Review.* Curr Atheroscler Rep, 2019. 21(2): p. 8.

154. Pan, B., Ge. L., Xun, Y.Q., et al., *Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis.* Int J Behav Nutr Phys Act, 2018. 15(1): p. 72.

155. Figueira, F.R., Umpierre, D., Casali, K.R., et al., *Aerobic and combined exercise sessions reduce glucose variability in type 2 diabetes: crossover randomized trial.* PLoS One, 2013. 8(3): p. e57733.

156. Terada, T., Friesen, A., Chahal, B.S., et al., *Exploring the variability in acute glycemic responses to exercise in type 2 diabetes.* J Diabetes Res, 2013. 2013: p. 591574.

157. Wens, J., Vermeire, E., Royen, P.V., et al., *GPs' perspectives of type 2 diabetes patients' adherence to treatment: A qualitative analysis of barriers and solutions.* BMC Fam Pract, 2005. 6(1): p. 20.

158. Nagelkerk, J., Reick, K. andMeengs,L., *Perceived barriers and effective strategies to diabetes self-management.* Journal of Advanced Nursing, 2006. 54(2): p. 151-158.

159. Dunkley, A.J., Charles, K., Gray, L.J., et al., *Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis.* Diabetes Obes Metab, 2012. 14(7): p. 616-25.

160. Samdal, G.B., Eide, G.E., Barth, T., et al., *Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses.* Int J Behav Nutr Phys Act, 2017. 14(1): p. 42.

161. Guerci, B., Drouin, P., Grange, V., et al., *Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study.* Diabetes & Metabolism, 2003. 29(6): p. 587-594.

162. Baig, M.M., GholamHosseini, H., Moqeem, A.A., et al., *A Systematic Review of Wearable Patient Monitoring Systems - Current Challenges and Opportunities for Clinical Adoption.* J Med Syst, 2017. 41(7): p. 115.

163. Yang, H., Yu, J., ZO, H., et al., *User acceptance of wearable devices: An extended perspective of perceived value.* Telematics and Informatics, 2016. 33(2): p. 256-269.

164. Klonoff, D.C., Ahn, D. and Drincic, A., *Continuous glucose monitoring: A review of the technology and clinical use.* Diabetes Res Clin Pract, 2017. 133: p. 178-192.

165. Flores Mateo, G., Granado-Font, E., Ferre-Grau, C., et al., *Mobile Phone Apps to Promote Weight Loss and Increase Physical Activity: A Systematic Review and Meta-Analysis.* J Med Internet Res, 2015. 17(11): p. e253.

166. Semper, H.M., Povey, R., and Clark-Carter, D., *A systematic review of the effectiveness of smartphone applications that encourage dietary self-regulatory strategies for weight loss in overweight and obese adults.* Obes Rev, 2016. 17(9): p. 895-906.

167. Schoeppe, S., Alley, S., Van Lippevelde, W., et al., *Efficacy of interventions that use apps to improve diet, physical activity and sedentary behaviour: a systematic review.* Int J Behav Nutr Phys Act, 2016. 13(1): p. 127.

168. Lo, A.,. Jenkins, P.H. andChoobineh, J., *Patient's Acceptance of IT-Assisted Self-Monitoring: A Multiple-Case Study.* Journal of Computer Information Systems, 2017: p. 1-15.

169. Osborn, C.Y., van Ginkel, J., Rodbard, D., et al., *One Drop | Mobile: An Evaluation of Hemoglobin A1c Improvement Linked to App Engagement.* JMIR Diabetes, 2017. 2(2): p. e21.

170. Rodbard, D., *Clinical interpretation of indices of quality of glycemic control and glycemic variability.* Postgrad Med, 2011. 123(4): p. 107-18.

171. Price, D. and Walker, T., *The Rationale for Continuous Glucose Monitoring-based Diabetes Treatment Decisions and Non-adjunctive Continuous Glucose Monitoring Use.* Eur Endocrinol, 2016. 12(1): p. 24-30.

172. Klimek, M. and Tulwin, T., *Continuous glucose monitoring: review of promising technologies.* MATEC Web of Conferences, 2019. 252. p. 1-5.

173. Olczuk, D. and Priefer, R., *A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus.* Diabetes Metab Syndr, 2018. 12(2): p. 181-187.

174. Bruen, D., Delaney, C., Florea, L., et al., *Glucose Sensing for Diabetes Monitoring: Recent Developments.* Sensors (Basel), 2017. 17(8).

175. Hoeks, L.B., Greven, W.L., and de Valk, H.W., *Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review.* Diabet Med, 2011. 28(4): p. 386-94.

176. Carlson, A.L., Mullen, D.M. and Bergenstal, R.M., *Clinical Use of Continuous Glucose Monitoring in Adults with Type 2 Diabetes.* Diabetes Technol Ther, 2017. 19(S2): p. S4-S11.

177. Adolfsson, P., Pakrin, C.G., Thomas, A., et al., *Selecting the Appropriate Continuous Glucose Monitoring System - a Practical Approach.* Eur Endocrinol, 2018. 14(1): p. 24-29.

178. Poolsup, N., Suksomboon, N. and Kyaw, A.M., *Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes.* Diabetology & Metabolic Syndrome, 2013. 5(39): p. 1-14.

179. Park, C. and Le, Q.A., *The Effectiveness of Continuous Glucose Monitoring in Patients with Type 2 Diabetes: A Systematic Review of Literature and Meta-analysis.* Diabetes Technol Ther, 2018. 20(9): p. 613-621.

180. Ida, S., Kaneko, R. and Murata, K., *Utility of Real-Time and Retrospective Continuous Glucose Monitoring in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials.* J Diabetes Res, 2019. 2019: p. 4684815.

181. Taylor, P.J., Thompson, C.H. and. Brinkworth, G.D*., Effectiveness and acceptability of continuous glucose monitoring for type 2 diabetes management: A narrative review.* J Diabetes Investig, 2018. 9(4): p. 713-725.

182. Tougas, M.E., Hayde, J.A., McGarth, P.J., et al., *A Systematic Review Exploring the Social Cognitive Theory of Self-Regulation as a Framework for Chronic Health Condition Interventions.* PLoS One, 2015. 10(8): p. e0134977.

183. Funnell, M.M. and. Anderson, R.M., *Working Toward the Next Generation of Diabetes Self-Management Education.* Am J Prev Med, 2002. 22(4S).

184. Farmer, A.J., Wade, A.N., French, D.P., et al., *Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.* Health Technol Assess, 2009. 13(15): p. iii-iv, ix-xi, 1-50.

185. Kesavadev, J., Vigersky, R., Shin, J., et al., *Assessing the Therapeutic Utility of Professional Continuous Glucose Monitoring in Type 2 Diabetes Across Various Therapies: A Retrospective Evaluation.* Adv Ther, 2017. 34(8): p. 1918-1927.

186. Barnard, K.D., Kropff, J.,Choudhary, P., et al., *Acceptability of Implantable Continuous Glucose Monitoring Sensor.* J Diabetes Sci Technol, 2018. 12(3): p. 634-638.

187. Fisher, L., Gonzalez, J.S., and Polonsky, W.H., *The confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision.* Diabet Med, 2014. 31(7): p. 764-72.

188. Turner, J., *Emotional dimensions of chronic disease.* West J Med, 2000. 172: p. 124-128.

189. Petrie, J.R., Peters, A.L., Bergenstal, R.M., et al., *Improving the clinical value and utility of CGM systems: issues and recommendations : A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group.* Diabetologia, 2017. 60(12): p. 2319-2328.

190. Vigersky, R. and Shrivastav, M., *Role of continuous glucose monitoring for type 2 in diabetes management and research.* J Diabetes Complications, 2017. 31(1): p. 280-287.

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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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SHORT COMMUNICATION

Diabetes Management

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

Pennie J Taylor*[1,2,3], Kylie Lange[2], Campbell H Thompson[2], Wittert Gary[2,3] & Grant D Brinkworth[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^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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KEYWORDS

- type 2 diabetes
- glycemic variability
- risk factor
- medication

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 (ACTRN12612000369820) [13]. Participants with established T2D 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/m^2. 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 utilisation 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 computed 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)	
Characteristics	**Mean (± SD)**
Demographics	
Age (years)	58.3 ± 6.8
Gender (n)	95 (55 Male, 40 Female)
Duration of T2D (years)	6.7 ± 5.9
Diabetes Medication	
Diabetes Medication Effect Score (MeS)	1.2 ± 1.1
Sulfonylureas (n [%])	28 [30]
Metformin (n [%])	40 [42]
GLP 1 agonists (n [%])	2 [2]
DPP4 inhibitors (n [%])	2 [2]
Thiazolidinedione's (n [%])	6 [6]
Insulin (n [%])	10 [11]
Other (n [%])	3 [4]
Nil Medication (Lifestyle Control Only) (n [%])	1 [1]
Anti-hypertensive Medication [n (%)]	88 (92%)
Body Composition	
Weight (kg)	101.8 ± 15.7
BMI (kg/m²)	34.5 ± 4.4
Waist Circumference (cm)	112.0 ± 10.8
Total Body Fat (%)	39.8 ± 7.4
Glycemic Control	
Glycated Hemoglobin (% HbA1c)	7.3 ± 1.1 (n27>8%)
Fasting Glucose (mmol/L)	8.1 ± 2.1
MAGE (mmol/L)	5.1 ± 1.7
CONGA –2 (mmol/L)	2.4 ± 0.8
CONGA-4 (mmol/L)	2.9 ± 1.0
Physical Activity	
Time Spent in Sedentary behavior (%)	87.5 ± 3.7
Time Spent in Moderate to vigorous intensity activity (%)	3.5 ± 1.4

Standard Deviation. Data is mean ± SD, unless otherwise stated Abbreviations: MeS: anti-glycemic Medication Effect Score; GLP-1 agonists, Glucagon-like peptite-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)			
	Glycemic Variability Indices		
Characteristics	**MAGE (ln (mmol/L))**	**CONGA 2 (ln (mmol/L))**	**CONGA 4 (ln (mmol/L))**
Age (yrs)	b= 0.006 (P=0.230)	b= 0.001 (P=0.820)	b= 0.003 (P=0.536)
Female gender	b= 0.061 (P=0.494)	b= 0.115 (P=0.153)	b= -0.091 (P=0335)
Body fat (%)	b= -0.006 (P=0.344)	b= -0.009 (P=0.111)	b= -0.009 (P=0.192)
HbA1c (%)	b= 2.018 (P <0.001)	b= 2.157 (P<0.001)	b= 2.069 (P<0.001)
HbA1c squared	b= -0.119 (P <0.001)	b= -0.130 (P<0.001)	b= -0.123(P<0.001)
MeS (arbitrary units)	b= 0.113 (P=0.003)	b= 0.115 (P=0.001)	b= 0.115(P=0.004)
Diabetes Duration (yrs)	b = -0.002 (P=0.756)	b= -0.003 (P=0.646)	b= -0.004 (P=0.596)
Time Spent Sedentary Activity (%)	b= -0.019 (P=0.169)	b= -0.021 (P=0.088)	b= -0.019 (P=0.196)
Time Spent Mod/Vig Activity (%)	b= -0.032 (P=0.398)	b= -0.021 (P=0.525)	b= -0.023 (P=0.558)

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. Hyperglycaemia (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. Those stategies 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 cofounding 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 comprehesively. 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

to lower GV.

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References

1. Tay J, Thompson C, Brinkworth G. Glycemic variability: Assessing glycemia differently and the implications for dietary management of diabetes. *Annu. Rev. Nutr.* 35, 389–424 (2015).
2. Danne T, Nimri R, Battelino T, *et al.* International consensus on use of continuous glucose monitoring. *Diabetes. Care.* 40(12), 1631–1640 (2017).
3. Suh S, Kim J. Glycemic variability: How do we measure it and why is it important? *Diabetes. Metab. J.* 39(4), 273–282 (2015).
4. Smith P, Brandle M, Trevisan R, *et al.* Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. *Diabetes. Res. Clin. Pract.* 105(3), 273–284 (2014).
5. Hirsch I. Glycemic variability and diabetes complications: Does it matter? Of course it does! *Diabetes. Care.* 38(8), 1610–1614 (2015).
6. Carlson A, Mullen D, Bergenstal R. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes. Technol. Ther.* 19(2), 4–11 (2017).
7. Uemura F, Okada Y, Tirimoto K, *et al.* Relation between hypoglycemia and glycemic variability in type 2 diabetes patients with insulin therapy: A study based on continuous glucose monitoring. *Diabetes. Technol. Ther.* 20(2), 140–146 (2018).
8. Di Flaviani A, Picconi F, Di Stefano P, *et al.* Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes. Care.* 34(7),1605–1609 (2011).
9. American Diabetes Association (ADA) - Standards of Medical Care in Diabetes. The Journal of Clincal and Applied Research and Education. 40(1), 1–134(2017).
10. Wright L, Hirsch I. Metrics beyond hemoglobin A1C in diabetes management: Time in range, hypoglycemia, and other parameters. *Diabetes. Technol. Ther.* 19(2), S16–S26 (2017).
11. Riddle M, Gerstein H, Cefalu W. Maturation of CGM and glycemic measurements beyond HbA1c-A turning point in research and clinical decisions. *Diabetes. Care.* 40(12), 1611–1613 (2017).
12. Tay J, Luscombe-Marsh N, Thompson C, *et al.* A very low-carbohydrate low-saturated fat diet for type 2 diabetes management: A randomized control trial. *Diabetes. Care.* 37(11), 2909–2918 (2014).
13. Mayer S, Jeffreys A, Olsen M, *et al.* Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. *Diabetes. Obes. Metab.* 16(1), 90–93 (2014).
14. Tudor-Locke C, Camhi S, Troiano R. A catalog of rules, variables, and definitions applied to accelerometer data in the National Health and Nutrition Examination Survey, 2003–2006. *Prev. Chronic. Dis.* 9,E113 (2012).
15. Tay J, Thompson C, Luscombe-Marsh N, *et al.* Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes. Obes. Metab.* 20(4), 858–871 (2018).
16. Baghurst P. Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm. *Diabetes. Technol. Ther.* 13(3), 296–302 (2011).
17. Kuenen J, Borg R, Kuik D, *et al.* Does glucose variability influence the relationship between mean plasma glucose and HbA1c levels in type 1 and type 2 diabetic patients? *Diabetes. Care.* 34(8), 1843–1847 (2011).
18. Frontoni S, Di Bartolo P, Avogaro A, *et al.* Glucose variability: An emerging target for the treatment of diabetes mellitus. *Diabetes. Res. Clin. Pract.* 102, 86–95 (2013).
19. Peyser T, Balo A, Buckingham B, *et al.* Glycemic variability percentage: A novel method for assessing glycemic variability from continuous glucose monitor data. *Diabetes. Technol. Ther.* 20(1), 6–16 (2018).
20. Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. *Diabetes. Obes. Metab.* 15(2), 3–8 (2013).
21. Desouza C, Salazar H, Cheong B. Association of hypoglycemia and cardiac ischemia: A study based on continuous glucose monitoring. *Diabetes. Care.* 26(5), 1485–1489 (2003).
22. Rodbard D. Continuous glucose monitoring: A review of recent studies demonstrating improved glycemic outcomes. *Diabetes. Technol. Ther.* 19(3), 25–37 (2017).
23. Van Dijk J, Manders R, Canfora E, *et al.* Exercise and 24-h glycemic control: Equal effects for all type 2 diabetes patients? *Med. Sci. Sports. Exerc.* 45(4), 628–635 (2013).

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

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Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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ii. permission is granted for the candidate in include the publication in the thesis; and

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REVIEW ARTICLE

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

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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 ≥8 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 2.1–19.2 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, bodyweight and caloric intake; higher adherence rating to a personal eating plan; and increases in physical activity. High compliance to CGM wear-time 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 excursion 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[1]. 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[2–6]. Hence, effective evidenced-based strategies are urgently required. Poor blood glucose control underpins diabetes-related vascular complications, and its increased risk of cardiovascular disease and premature death[1,4,7]. Although diet and lifestyle interventions remain the cornerstones of type 2 diabetes management, alone these are often insufficient to achieve sustained glycemic control and adjunctive therapies are required for effective management.[8,9] 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[8,10,11], 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[12].

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However, limitations and poor adherence to regular SMBGL exist due to inconvenience, costs of disposables, and erroneous and reduced measurement frequency resulting in suboptimal glycemic control[13,14]. 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[15,16]. 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[16]. 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[8,17]. The authors also identified only two of the four RCTs were high quality[16]. More recently, less intrusive device 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[18]. 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, bodyweight 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[19]. To identify appropriate key words, 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*/overweight AND lifestyle OR blood glucose control/management OR glycemic control AND/OR physical activity AND/OR nutr* 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. Publication dates were January 2001 (coinciding with Food and Drug Administration approval for commercial CGM use) to November 2017 to capture studies utilizing CGM technology to reflect modern day practice[20,21]. Reference lists of retrieved articles and relevant systematic reviews were hand-searched for other relevant studies[16,21–23]. The present study represents a scoping review underpinned by a systematic process[19].

Study selection criteria

Duplications were removed using Endnote (EndNote, Version X7.7; Clarivate Analytics, Boston, Massachusetts, USA). Title and abstracts were manually screened for relevant articles based on selection criteria by the primary reviewer (PT). Full text of potential articles was retrieved for further assessment. Studies were selected if: (i) they were RCTs with a reported intervention utilizing CGM with the aim of achieving glycemic control and/or intervention adherence, or observational studies reporting on CGM user experience; (ii) they were carried out in adults (aged ≥18 years) with clinically diagnosed type 2 diabetes; (iii) they were RCTs that included diet and exercise interventions as one of the intervention groups targeting glycemic control; or (iv) they consisted of a usual care or control group. Studies were excluded if: (i) participants had type 1 diabetes, gestational diabetes or were aged <18 years; (ii) intervention or control was pharmacological/surgical; (iii) participants with prediabetes or type 1 and 2 diabetes were examined, but data for type 2 diabetes could not be separately extracted; or (iv) participants were critically ill or had post-surgical interventions. Retrieved studies were independently assessed for relevance by all authors and discussed for final selection.

Data extraction

Data required for analysis were extracted from included articles into data extraction tables. Data relating to study methodology/design, CGM protocols, intervention outcomes including CGM wear-time and use, sample size, attrition rates, age, sex, and outcomes associated with glycemic control were captured. One reviewer (PT) extracted the data from all included articles, while secondary reviewers (CT and GB) independently cross-checked data extraction reliability. Inconsistencies were resolved through discussion and consensus. Meta-analysis was not carried out due to high heterogeneity of interventions and outcomes. A narrative analysis summarizing the results was used.

RESULTS

Search outcomes

A total of 277 articles were identified. After removal of duplications, and excluding articles based on title and abstracts, 12 articles, reporting 11 separate studies (one article reporting long-term follow up[24] of a previously reported short-term intervention[25]) met the inclusion criteria. Nine articles (eight studies) were RCTs[24–32], and three were observational trials[33–35]. Included studies were rated as being of acceptable quality[19]. The article selection process summary, and the study protocols

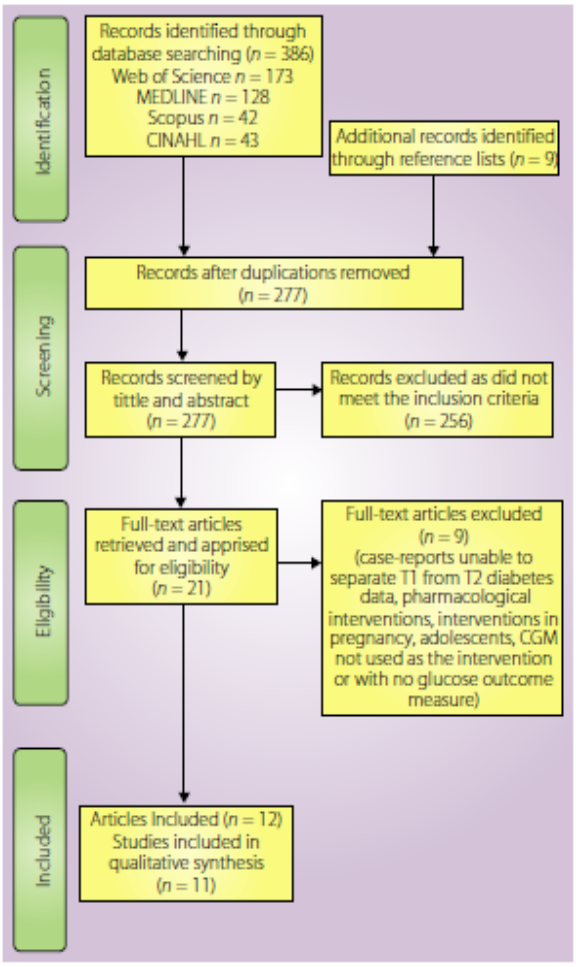

Figure 1 | Article selection process. CGM, continuous glucose monitoring; T1, type 1; T2, type 2.

and intervention specifications are presented in Figure 1 and Table 1, respectively.

Participants

A total of 5,542 participants were recruited into eight RCTs (n = 5,342) and three observational trials (n = 196), with 60% men[26,34], and ~9% (n = 487) receiving multiple daily insulin injections[30,32]. 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/m^2; 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 6.2–19.2 years[24–32,35]; one RCT (n = 40) did not report diabetes duration[29]. The observational trials examined 6 to 181 participants with a mean age range of 54–57 years and diabetes duration of 2.1–14.6 years[33–35]. 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 rates[33].

All studies, except Cox *et al*[33], reported participant recruitment strategies including military healthcare beneficiaries (n = 100)[24,25], public endocrinology clinic and/or cardiac unit (n = 5,100)[26,30–32], community health services (n = 271)[29,34,35] and general hospitals (n = 65)[27]. Studies were carried out in the USA[24,25,28,29,33,34], Canada[26], India[31,35], Europe[32], South Korea[27], and across multiple sites throughout the USA and Canada[30].

Study aims and Intervention description

The aims of the studies were to determine whether CGM use elicits changes in glycemic control[24–27,30–33,35], weight[24,25,27,29,32,33] and physical activity[28,29] to investigate CGM in relation to self-efficacy and self-monitoring behavior[26,28,32], and acceptability, satisfaction and tolerance to CGM wear and use[26,29,34,35]. Across the studies, different intervention protocols were used and five distinct research themes identified (Table 1). These research themes included: (i) four RCTs determining the effects of RT-CGM (user can view visual feedback of blood glucose responses instantaneously) compared with SMBGL (control)[24–27,30]; (ii) one RCT determining the effects of using retrospective CGM data with diabetes education combined with self-efficacy counseling compared with diabetes education with SMBGL (control)[28]; (iii) three RCTs determining the effects of retrospective CGM with problem-solving counseling compared with retrospective CGM with standard diabetes education (control)[29,31,32]; (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)[34,35], with one including accelerometer data[34]; and (v) one observational study describing the effects of RT-CGM combined with a lifestyle program to improve patient outcomes[33]. Intervention durations for observational studies were 3 days[34] and 12 weeks[33,35], and for RCTs the range was 8–52 weeks[24–32].

Effectiveness of CGM interventions on outcomes

HbA1c changes

All RCTs reported HbA1c changes (Table 2)[24–33]. Of the four studies comparing RT-CGM with conventional SMBGL 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)[25,27,30]. 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 SMBGL control after 52 weeks (0.8 vs 0.2%; $P < 0.001$)[24,25]. RT-CGM compared with an internet-based SMBGL protocol after 26 weeks showed no difference between treatments (−0.9 vs −1.07%; $P = 0.312$)[26].

Greater HbA1c reduction was observed after 8 weeks of retrospective CGM with self-efficacy counseling compared with SMBGL with standard education (−1.16 vs 0.32%, $P < 0.05$)[28].

Table 1 | Protocol summary of continuous glucose monitoring intervention studies in adults with type 2 diabetes

Author, year, reference	Study population	Mean age (years)	Duration of type 2 diabetes (years)	Study duration (weeks)	Intervention
Observational studies					
Allen et al. (2009)[34]	Nine adults community health clinic (USA)	57.0 ± 15 (SD)	8.6 ± 6 (SD)	3 days	Phase 1: Retrospective CGM + education Phase 2: Focus group interview
Cox et al. (2016)[33]	Six adults (Canada)	55.3 (mean)	2.1 years (mean)	12	RT-CGM + lifestyle program
Mohan et al. (2016)[35]	181 Adults 11 Health clinics (India)	54.1 ± 10 (SD)	14.6 ± 8.1 (SD)	12	Retrospective CGM + education and profession support
RCT – RT-CGM vs SMBGL					
Beck et al. (2017)[30]	158 Adults receiving multi-dose insulin 25 Endocrine clinics. (USA and Canada)	SMBGL 60 ± 9 (SD) RT-CGM 60 ± 11 (SD)	SMBGL 18 (range 12–23) RT-CGM 17 (range 11–23)	24	RT-CGM + health usual care†
Ehrhardt et al. (2011)[25] & Vigersky et al. (2012)[24]	100 Adults military healthcare beneficiaries (USA)	SMBGL 60 ± 11.9 (SD) RT-CGM 55.5 ± 9.6 (SD) SMBGL 60 ± 11.9 (SD) RT-CGM 55.5 ± 9.6 (SD)	NR NR	12 52	RT-CGM + usual care† 40-week follow up with SMBGL
Tang et al. (2014)[26]	40 Adults Endocrinology clinic (Canada)	RT-CGM 59.13 ± 8.70 (SD) IBGM 60.65 ± 10.19 (SD)	RT-CGM 19.2 ± 7.4 (SD) IBGM 17.24 ± 5.96 (SD)	26	RT-CGM + BGL + fortnightly health professional feedback
Yoo et al. (2008)[27]	65 adults Hospital based Korea (Seoul)	RT-CGM 54.6 ± 6.8 (SD) SMBGL 57.5 ± 9 (SD)	RT-CGM 11.7 ± 5.8 (SD) SMBGL 13.3 ± 4.9 (SD)	12	RT-CGM + usual care†
RCT – Retrospective CGMS feedback vs control					
Allen et al. (2008)[28]	52 adults Community health Service (USA)	Intervention 57.0 ± 12.47 (SD) Control 57.0 ± 14.56 (SD)	Intervention 8.3 ± 6.31 (SD) Control 8.5 ± 6.23 (SD)	8	Retrospective CGM + usual care† + self-efficacy counseling
Anjana et al. (2017)[31]	4,678 Adults (61% Male) Seven public health diabetes clinics (India)	Intervention 57.3 ± 12.1 (SD) Control 57.1 ± 12/2 (SD)	Intervention 15.7 ± 8.5 (SD) Control 13.6 ± 8.1 (SD)	12	Retrospective flash-CGM + visual charts used by clinician to adjust diabetes medication
Haak et al. (2017)[32]	224 Adults 140 Intervention 75 Control receiving multi-dose insulin 26 public diabetes clinics (European)	Intervention 59.0 ± 9.9 (SD) Control 59.5 ± 9.9 (SD)	Intervention 17 ± 8 (SD) Control 18 ± 8 (SD)	24	Retrospective flash-CGM + clinician to adjust insulin
RCT – CGM with counseling vs CGM without counseling					
Allen et al. (2011)[29]	29 Women Community health service (USA)	Retrospective CGM + problem-solving counseling 52.2 ± 6.5 (SD) Retrospective CGM + usual care† 51.7 ± 8.0 (SD)	Retrospective CGM + problem-solving counseling 6.7 ± 6.0 (SD) Retrospective CGM + diabetes education 6.7 ± 4.6 (SD)	12	Retrospective CGM + problem-solving counseling

†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. ‡Unable to separate type 1 diabetes data from type 2 diabetes data for this outcome. CGM, continuous glucose monitoring; IBGM, internet blood glucose monitoring; NA, not applicable; NR, not reported; RCT, randomized control trial; RT-CGM, real-time continuous glucose monitoring; SD, standard deviation; SMBGL, Self-Monitoring Blood Glucose Levels.

Two studies compared retrospective CGM using flash CGM with visual charts and counseling to SMBGL[31,32]. Greater HbA1c reductions were observed following CGM after 12 weeks (−0.9 vs −0.7%, $P < 0.001$) in 4,678 individuals[31], but not after 24 weeks (−0.28 vs −0.21%, $P = 0.822$) of 224 individuals taking multiple daily insulin injections[32]. 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; $P = 0.69$)[29].

A 12-week lifestyle program combined with RT-CGM produced an average 1.1% HbA1c reduction in six participants[33]. The authors compared these data with findings from a separate, independent 12-week intervention ($n = 47$) that used the same lifestyle program with SMBGL and reported similar HbA1c reductions (1%)[23,33]. However, population size heterogeneity

Control	CGM system type	CGM wear time protocol	Calibration protocol	Total CGM Wear	Reported CGM acceptance/ satisfaction/ usability	Compliance to CGM protocol (%)
NA	Medtronic Minimed.	3 days	NR	3 days	√	NR
NA	DexCom™ G4 Platinum	NR	Unclear	NR	×	NR
NA	Medtronic iPro™	Unclear	NR	Unclear	√	NR
SMBGL + usual care†	DexCom™ G4 Platinum	Daily wear (168 days)	Calibrate 2× daily and glucometer testing 2× daily	159.5 of 168 days (Mean)	NR	95%
SMBGL + usual care† 40-week follow up with SMBGL	DexCom™ Seven©	12 weeks of intermittent CGM followed by SMBGL only 40 weeks	As per manufacturer's instructions	56 days per protocol‡ 48 days accepted minimum	√	68% ≥48 days 32% ≤48 days
IBGM + BGL + fortnightly health professional feedback	Guardian RT-CGM Medtronic Minimed	Unclear	Unclear	Unclear	√	NR
SMBGL + usual care†	Guardian RT-CGM Medtronic Minimed	3 days per month for study duration	3× daily	9 days	×	NR
Usual care†	Medtronic Minimed.	3 days continuous at baseline and post	NR	6 days	×	NR
Usual care†	Abbotts FreeStyle LibrePro™ Flash Glucose Monitoring	14-day continuous wear time	NR	14 days continuous wear time	NR‡	NR
SMBGL + usual care†	Abbotts FreeStyle LibrePro™ Flash Glucose Monitoring	14-day continuous wear time	Intervention: Scan the flash sensor every 8 h Both groups: Recorded blood glucose levels daily	14 days	√	NR
Retrospective CGM + usual care†	NR	3 days continuous at baseline and post-intervention	NR	6 days	×	96% compliance (28/29) completed

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

Bodyweight changes

For bodyweight changes, BMI (kg/m^2) is reported in the instance where weight (kg) data is not reported. Eight studies reported bodyweight changes (Table 2)[24–30,32,33]. Three intervention studies compared RT-CGM combined with education including RT-CGM output interpretation to SMBGL combined with standard diabetes education (control)[24,25,27,30]. 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)[30]. 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/m^2)[26]. 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; $P = 0.2$)[24]. 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[24].

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; $P = 0.09$)[29]. Furthermore, retrospective CGM plus behavior change counseling for 8 weeks produced significantly greater BMI reduction compared with SMBGL and standard diabetes education (−0.53 vs −0.12 kg/m^2; $P < 0.05$)[28].

A 12-week lifestyle program combined with counseling and RT-CGM achieved a 7.3-kg weight loss[33]. This was greater than the weight loss reported in a previous study using the same lifestyle program combined with counseling and SMBGL (−2.5 kg)[33].

Change in behavior, physical activity and diet

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

Behavioral change

Six studies – one observational[33] and five RCTs[24–26,28,29,32] – reported behavioral changes with CGM, noting a generally minimal effect. Two studies comparing RT-CGM vs SMBGL with standard diabetes education over 12 weeks[25] and a 40-week follow up without RT-CGM[24] reported no differences between groups for changes in diabetes distress[24,25]. Meanwhile, greater diabetes treatment satisfaction was observed in a control group utilizing SMBGL combined with an internet-based monitoring protocol and standard diabetes education compared with a RT-CGM intervention group[26]. Conversely, greater improvements in diabetes treatment satisfaction were observed after an intervention using retrospective, flash CGM with clinician interaction to adjust insulin compared with SMBGL combined with usual care control[32]. A further study reported retrospective CGM with problem-solving counseling achieved greater improvements in diabetes problem-solving compared with retrospective CGM with standard education (1.06 vs 0.43 arbitrary units; $P = 0.02$)[29].

An 8-week intervention of retrospective CGM achieved greater increases in the 'sticking to it' domain of the Self-Efficacy for Exercise Behavior Survey compared to SMBGL with standard diabetes education (0.52 vs −0.11; $P = 0.05$)[28]. A 12-week lifestyle program combined with RT-CGM lowered the diabetes distress score[33]. However, similar improvements were achieved with the same lifestyle program combined with SMBGL[23].

Physical activity outcomes

Four studies (one observational trial,[33] three RCTs[27–29]) 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 SMBGL with standard diabetes education (+158.4 vs +43.5 min/week; $P = 0.02$)[27]. 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 SMBGL with standard exercise guideline education (31,144 vs −9,281 counts; $P \leq 0.05$)[28]. 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 −4,000/day; $P = 0.48$) and levels of moderate activity (5 min/day vs −3 min/day; $P = 0.11$)[29]. An increase in absolute step counts (8,400–13,000 steps/per day) occurred after a 12-week lifestyle intervention combined with RT-CGM[33]. A similar magnitude of change was reported in a separate study carried out in a different cohort following the same lifestyle program combined with SMBGL[23].

Dietary outcomes

Three studies (one observational[33] and two RCTs[27,29]) assessed dietary outcomes. There were greater reductions in caloric intake after 12 weeks of RT-CGM compared with SMBGL and standard diabetes education (−168.7 vs −113.9 kcal/day; $P = 0.05$)[27]. 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 (2.7 vs 0.7 arbitrary units; $P = 0.01$), with no difference between the groups for domains of healthful eating, fruits and vegetables, and high-fat foods[29].

A 12-week observational study showed a lifestyle intervention combined with RT-CGM reduced total energy intake (pre: 2,680 Kcal, post: 1,796 Kcal [difference −884 Kcal]) and total carbohydrate intake (pre: 243.3 g, post: 150.5 g (difference −92.8 g)[33].

Device acceptability, useability 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 useability scale score before and after 12 weeks of RT-CGM wear, indicating moderate-to-good useability[25]. Another study ($n = 181$) reported a high CGM wear comfort (6.1/7) and improved diabetes awareness (6.2/7)[35]. Three studies ($n = 287$) recorded compliance with CGM protocols defined as attendance at CGM counseling sessions and compliance with CGM wear protocol[24,25,29,30]. One study ($n = 29$) comparing CGM with problem-solving counseling

with CGM without counseling showed high levels of compliance to the intervention protocol based on session attendance (>90%)[29]. Two studies compared RT-CGM with SMBGL without 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 days[24,25]; whereas a 24-week intervention using a continuous daily wear protocol for 168 days reported 95% compliance with mean wear time of 159 days[30].

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 logs[34]. Issues with wearing appropriate clothes to attach the monitor at night were also reported[34]. Positive emerging themes included visual CGM graphs reinforcing the need for behavior change, and the role of diet, exercise and stress on glucose levels[34].

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)[8,21,36–38]. 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 provided[26,29,31,32,35].

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 = 165) and insulin-dependent (n = 158) individuals with type 2 diabetes, respectively[25,27,30]. In non-insulin-dependent individuals, a 40-week follow-up period without continued RT-CGM use showed these differential changes between the groups were maintained[24]. 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 weeks[28]. 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; $P < 0.001$)[31]. 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 intensification[28,29]. The exact reason for the variation of HbA1c change observed between the studies (0.4–0.9%) 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 education[28], compared with exercise information and monitoring[25,27]. A meta-analysis has shown that supervised walking achieved greater HbA1c reduction compared with non-walking controls (−0.5%)[39,40]. 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 grouped mean −0.31% greater HbA1c reduction over an 8–12-week period of CGM use compared with SMBGL in adults with type 2 diabetes[16]. 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 ≥25 years[41]. 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 patients[42]. 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%[43]. Hence, the additional ~0.5% 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

Author, year reference	Study population	Mean age (years)	Duration of type 2 diabetes (years)	Study duration (weeks)	Intervention	Control
Observational studies						
Allen et al. (2009)[34]	Nine adults community health clinic (USA)	57.0 ± 15 (SD)	8.6 ± 6 (SD)	3 days	Phase 1: retrospective CGM + education Phase 2: Focus group interview	NA
Cox et al. (2016)[33]	Six adults (Canada)	55.3 (mean)	2.1 years (mean)	12	RT-CGM + lifestyle program	NA
Mohan et al. (2016)[35]	181 Adults 11 Health clinics (India)	54.1 ± 10 (SD)	14.6 ± 8.1 (SD)	12	Retrospective CGM + education and professional support	NA
RCT – RT-CGM vs SMBGL						
Beck et al. (2017)[30]	158 Adults receiving multi-dose insulin 25 Endocrine clinics. (USA and Canada)	SMBGL 60 ± 9 (SD) RT-CGM 60 ± 11 (SD)	SMBGL 18 (range 12–23) RT-CGM 17 (range 11–23)	24	RT-CGM + health professional support (0, 4,12 and 24 weeks)	SMBGL + usual care† (0, 4, 12 and 24 weeks)
Ehrhardt et al. (2011)[25])& Vigersky et al. (2012)[24]	100 Adults military healthcare beneficiaries (USA)	SMBGL 60 ± 11.9 (SD) RT-CGM 55.5 ± 9.6 (SD) SMBGL 60 ± 11.9 (SD) RT-CGM55.5 ± 9.6 (SD)	NR NR	12 52	RT-CGM + usual care† 40-week follow up with SMBGL	SMBGL + usual care† 40-week follow up with SMBGL
Tang et al. (2014)[26]	40 Adults endocrinology clinic (Canada)	RT-CGM 59.13 ± 8.70 (SD) IBGM 60.65 ± 10.19 (SD)	RT-CGM 19.2 ± 7.4 (SD) IBGM 17.24 ± 5.96 (SD)	26	RT-CGM + BGL + fortnightly health professional feedback	IBGM + BGL + fortnightly health professional feedback
Yoo et al. (2008)[27]	65 Adults With poorly controlled type 2 diabetes (HbA1c 8–10%) Hospital based Korea (Seoul)	RT-CGM 54.6 ± 6.8 (SD) SMBGL 57.5 ± 9 (SD)	RT-CGM 11.7 ± 5.8 (SD) SMBGL 13.3 ± 4.9 (SD)	12	RT-CGM - with hyperglycemia counseling	SMBGL + usual care†
RCT – Retrospective CGM feedback vs control						
Allen et al. (2008)[28]	52 Adults Community health service (USA)	Intervention 57.0 ± 12.47 (SD) Control 57.0 ± 14.56 (SD)	Intervention 8.3 ± 6.31 (SD) Control 8.5 ± 6.23 (SD)	8	Usual care† + self-efficacy counseling	Usual care†
Anjana et al. (2017)[31]	4,678 Adults (61% male) Seven public diabetes clinics (India)	Intervention 57.3 ± 12.1 (SD) Control 57.1 ± 12.2 (SD)	Intervention 15.7 ± 8.5 (SD) Control 13.6 ± 8.1 (SD)	12	Retrospective flash-CGM + visual charts used by clinician to adjust diabetes medication	SMBGL and usual care†
Haak et al. (2017)[32]	224 Adults *149 Intervention* *75 Control* multi-dose insulin therapy 26 public diabetes clinics (European)	Intervention 59.0 ± 9.9 (SD) Control 59.5 ± 9.9 (SD)	Intervention 17 ± 8 (SD) Control 18 ± 8 (SD)	24	Retrospective flash-CGM + clinician to adjust insulin	SMBGL + usual care†
RCT – CGM with counseling vs CGM without counseling						
Allen et al. (2011)[29]	29 Women Community health service (USA)	Retrospective CGM + problem-solving counseling 52.2 ± 6.5 (SD) Retrospective CGM + usual care† 51.7 ± 8.0 (SD)	Retrospective CGM + problem-solving counseling 6.7 ± 6.0 (SD) Retrospective CGM + usual care† 6.7 ± 4.6 (SD)	12	Retrospective CGM + problem-Solving counseling	Retrospective CGM + usual care†

†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 difference identified as $P < 0.05$. CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; IBGM, internet blood glucose monitoring; NA, not applicable; NR, not reported; PAID, Problem Areas in Diabetes; RCT, randomized control trial; RT-CGM, real-time continuous glucose monitoring; SD, standard deviation; SMBGL, Self-Monitoring Blood Glucose Levels.

Glycemic control intervention vs control (*P*-value)	Weight (kg) or BMI (kg/m^2): Intervention vs Control (*P*-value)	Physical activity intervention vs control (*P*-value)	Diet intervention vs control (*P*-value)	Behavioral intervention vs control (*P*-value)
NR	NA	Accelerometer Activity counts 313,726 vs no control (NA) Activity level 1,403 min per day (light/sedentary)	NR	NR
HbA1c (%) −1.1 (change) (*P*-value - NR)	Weight (kg) −7.3 (change) (*P*-value - NR)	Pedometer (step counts) Pre: 8,400 Post: 13,000	Total energy intake −884 Kcal (change) Total carbohydrate −92.8 g (change)	PAID score Pre: 6.5 Post: 3.3
HbA1c (%) −0.6 ± 1.11 (SD) ($P < 0.001$)	NR	NR	NR	NR
HbA1c (%): 12 weeks−1.0 vs −0.6 ($P = 0.005$) 24 weeks−0.8 vs −0.5 ($P = 0.022$)	Change weight (kg) 24 weeks 1.3 vs −0.2 (*P*-value - NR)	NR	NR	NR
12 weeks Change HbA1c (%)−1.0 vs −0.5 ($P = 0.006$) 52 weeks Change HbA1c (%)−0.8 vs −0.2 ($P < 0.001$)	12 weeks *Change weight (kg)* −1.8 vs −0.4 ($P = 0.42$) 52 weeks *Change weight (kg)*:−1.9 vs −0.9 ($P = 0.2$)	NR	NR	12 weeks Change PAID score−6.2 vs −6.8 (*P*-value - NR) 52 weeks Change PAID score (week 12–52) −0.3 vs +1.3 (*P*-value - NR) Change PAID score (week 0–52) ($P = 0.96$)
HbA1c (%): −0.9 vs −1.07 ($P = 0.312$)	BMI (kg/m^2): 1.44 vs 0.35 ($P = 0.48$)	NR	NR	Diabetes treatment satisfaction Questionnaire scores (arbitrary units) Overall rating 24.8 vs 33.4 ($P < 0.001$) Convenience 3.8 vs 5.25 ($P = 0.004$) Flexibility 4.0 vs 5.41 ($P = 0.004$) Likelihood to recommend treatment to others 3.4 vs 5.94 ($P = 0.001$) Willingness to continue treatment 3.4 vs 5.71 ($P = 0.000$)
HbA1c (%):−1.1 vs −0.4 ($P = 0.004$)	Change Weight (kg): −2.2 vs −1.4 ($P = 0.43$)	Exercise time (total min/week) 158.4 vs 43.5 ($P = 0.02$)	Change in total energy intake (kcal/day) −168.7 vs −114.0 ($P = 0.05$) Post 12 weeks 1,859 vs 1,690 ($P = 0.002$)	NR
HbA1c (%):−1.2 vs −0.3 ($P < 0.05$)	BMI (kg/m^2): −0.53 vs −0.12 ($P = 0.05$)	Accelerometer (step counts) 31,144 vs −9,281 ($P < 0.05$)	NR	Self-Efficacy for Exercise Behaviour Survey ('sticking to it' domain) 0.52 vs −0.11 ($P < 0.05$)
HbA1c (%):−0.9 vs −0.7 ($P < 0.001$)	NR	NR	NR	NR
HbA1c (%):−0.28 vs −0.21 ($P = 0.822$)	Change weight (kg) (change values - NR) ($P = 0.250$) Change BMI (kg/m^2): (change values - NR) ($P = 0.267$)	NR	NR	Diabetes Treatment Satisfaction Questionnaire scores (arbitrary units) Overall rating 13.1 vs 9.0 ($P < 0.001$)
HbA1c (%):−0.7 vs −0.5 ($P = 0.69$)	Weight (kg):−6.2 vs +2.4 ($P = 0.09$)	Accelerometer Activity counts 1,500 vs −400 ($P = 0.48$) Level of activity (mins/day) 40 vs 2 (sedentary) ($P = 0.43$) 1 vs 6 (light) ($P = 0.78$) 5 vs −3 (moderate) ($P = 0.11$)	Subscale of diabetes self-care score Healthy eating plan 2.7 vs 0.7 ($P = 0.01$) Healthful eating plan 2.7 vs 1.2 ($P = 0.17$) Fruits and vegetables 1.5 vs 1.2 (P = NR) High-fat foods −1.6 vs −1.2 ($P = 0.55$)	Diabetes Problem-Solving Inventory score 1.06 vs 0.43 ($P = 0.02$)

Excess weight is a strong predictor of type 2 diabetes and HbA1c[44–46]. Approximately 80% of people with type 2 diabetes are overweight or obese[1,46]. Studies comparing SMBGL with RT-CGM showed no statistically significant differences in weight loss or BMI changes between treatments[24–27,30]. Nevertheless, three of the four studies using RT-CGM consistently achieved ~1 kg greater weight loss reduction compared with standard SMBGL over 12–26 weeks[24,26,27]; an effect that was sustained 40 weeks after the cessation of RT-CGM treatment[24]. 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[47,48]. It is therefore possible that RT-CGM could offer modest, yet clinically relevant, weight loss benefits[24].

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[30]. 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[30]. 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 responses) provided an additional ~2-kg greater loss compared with CGM with standard diabetes education[28,29]. However, only few, small studies have examined the effects of diet and lifestyle advice combined with CGM use on bodyweight, and more research is required 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[49,50]. 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[49,50]. 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[8,9,37,51,52], and self-monitoring is a key driver for behavior change[53]. However, therapeutic strategies are often required for optimal glycemic control[5]. 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 hyperglycemic alarms without counseling can promote greater physical activity levels and reductions in caloric intake[9–11,54]. Yoo *et al.*[27] successfully instructed participants to increase exercise and reduce food portions in response to RT-CGM-generated hyperglycemic event alarms (>300 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[28]. These early data suggest that access to CGM information might promote favorable changes, and adherence to diet and exercise behaviours. 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[25–27,29,30,34,35] suggest a high-level device wear compliance, confidence with using RT-CGM devices[27,30] and moderate-to-good useability[25]. 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[18] reported that compliance with sensor use in the first month of therapy predicted longer-term compliance and self-management adherence[18]. 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[29,34,35,54]. Some evidence exists suggesting greater CGM satisfaction when combined with problem-solving and targeted feedback directly linked to diet and exercise behaviors[29,34]. 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[55,56] 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[15,18,38,54,57,58] should be considered in the context of the relatively limited feedback alternatives provided by standard diabetes self-management strategies that rely on 3- or 6-monthly HbA1c measures and SMBGL[5,37]. The latter only provides a snapshot of current glucose levels and lacks the sensitivity to detect small changes or specific 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 attendant poor glycemic control[11,12,59]. 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[11,54,57,59]. 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[8,60].

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 adjunctive 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 hypoglycaemia 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[4], 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 counseling provided within the lifestyle interventions. The American Association of Clinical Endocrinologists and American College of Endocrinology[37] 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.

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DISCLOSURE

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REFERENCES

1. World Health Organisation (WHO). Global Report on Diabetes. Geneva: World Health Organisation, 2016. Available from http://www.who.int. Accessed June 7, 2017.
2. Herman WH, Zimmet P. Type 2 diabetes: an epidemic requiring global attention and urgent action. *Diabetes Care* 2012; 35: 943–944.
3. Nanditha A, Ma RC, Ramachandran A, *et al.* Diabetes in Asia and the Pacific: implications for the global epidemic. *Diabetes Care* 2016; 39: 472–485.
4. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus[mdash]present and future perspectives. *Nat Rev Endocrinol* 2012; 8: 228–236.
5. Ahmad NS, Islahudin F, Paraidathathu T. Factors associated with good glycemic control among patients with type 2 diabetes mellitus. *J Diabetes Investig* 2014; 5: 563–569.
6. Anoop M, Lokesh K, Sumit I, *et al.* South Asian diets and insulin resistance. *Br J Nutr* 2009; 101: 465–473.

7. Ogurtsova K, da Rocha Fernandes JD, Huang Y, *et al.* IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; 128: 40–50.
8. American Diabetes Association (ADA). Standards of Medical Care in Diabetes - 2017. *J Clin Appl Res Educat* 2017; 41 (Suppl. 1): 1–156.
9. Hu FB, Manson J, Stampfer M, *et al.* Diet, lifestyle and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001; 345: 790–797.
10. Franz MJ, Boucher JL, Rutten-Ramos S, *et al.* Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *J Acad Nutr Diet* 2015; 115: 1447–1463.
11. Wens J, Vermeire E, Royen PV, *et al.* GPs' perspectives of type 2 diabetes patients' adherence to treatment: a qualitative analysis of barriers and solutions. *BMC Fam Pract* 2005; 6: 20.
12. Schnell OAH, Battelini T, Ceriello A, *et al.* Self-monitoring of blood glucose in type 2 diabetes: recent studies. *J Diabetes Sci Technol* 2013; 7: 479–488.
13. Erbach M, Freckmann G, Hinzmann R, *et al.* Interferences and limitations in blood glucose self-testing: an overview of the current knowledge. *J Diabetes Sci Technol* 2016; 10: 1161–1168.
14. Czupryniak L, Barkai L, Bolgarska S, *et al.* Self-monitoring of blood glucose in diabetes: from evidence to clinical reality in Central and Eastern Europe–recommendations from the international Central-Eastern European expert group. *Diabetes Technol Ther* 2014; 16: 460–475.
15. Allen NA, Fain JA, Braun B, *et al.* Continuous glucose monitoring in non-insulin-using individuals with type 2 diabetes: acceptability, feasibility, and teaching opportunities. *Diabetes Technol Ther* 2009; 11: 151–158.
16. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetol Metab Syndr* 2013; 5: 39.
17. Dunkley AJ, Charles K, Gray LJ, *et al.* Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. *Diabetes Obes Metab* 2012; 14: 616–625.
18. Battelino T, Liabat S, Veeze HJ, *et al.* Routine use of continuous glucose monitoring in 10 501 people with diabetes mellitus. *Diab Med* 2015; 32: 1568–1574.
19. Joanna Briggs Institute (JBI). "The Joanna Briggs Institute Reviewer' Manual: 2015 edition / Supplement." Available from: http://joannabriggs.org/assets/docs/sumari/Reviewers-Manual_Methodology-for-JBI-Scoping-Reviews_2015_v2.pdf Accessed February 12, 2017.
20. Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. *Diabetes Metab Syndr: Clin Res Rev* 2017. https://doi.org/10.1016/j.dsx.2017.09.005
21. Rodbard D. Continuous glucose monitoring: a review of recent studies demonstrating improved glycemic outcomes. *Diabetes Technol Ther* 2017; 19: S25–S37.
22. Hoeks L, Greven WL, de Valk HW. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. *Diab Med* 2011; 28: 386–394.
23. Cox DJ, Taylor AG, Singh H, *et al.* Glycemic load, exercise, and monitoring blood glucose (GEM): a paradigm shift in the treatment of type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2016; 111: 28–35.
24. Vigersky RA, Fonda SJ, Chellappa M, *et al.* Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care* 2012; 35: 32–38.
25. Ehrhardt NM, Chellappa M, Walker MS, *et al.* The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. *J Diabetes Sci Technol* 2011; 5: 668–675.
26. Tang TS, Digby EM, Wright AM, *et al.* Real-time continuous glucose monitoring versus internet-based blood glucose monitoring in adults with type 2 diabetes: a study of treatment satisfaction. *Diabetes Res Clin Pract* 2014; 106: 481–486.
27. Yoo HJ, An HG, Park SY, *et al.* Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract* 2008; 82: 73–79.
28. Allen NA, Fain JA, Braun B, *et al.* Continuous glucose monitoring counseling improves physical activity behaviors of individuals with type 2 diabetes: a randomized clinical trial. *Diabetes Res Clin Pract* 2008; 80: 371–379.
29. Allen N, Whittemore R, Melkus G. A continuous glucose monitoring and problem-solving intervention to change physical activity behavior in women with type 2 diabetes: a pilot study. *Diabetes Technol Ther* 2011; 13: 1091–1099.
30. Beck RW, Riddlesworth TD, Ruedy K, *et al.* Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections. *Annals Intern Med* 2017; 167: 365–374.
31. Anjana RM, Kesavadev J, Neeta D, *et al.* A multicenter real-life study on the effect of flash glucose monitoring on glycemic control in patients with type 1 and type 2 diabetes. *Diabetes Technol Ther* 2017; 19: 533–540.
32. Haak T, Hanaire H, Ajjan R, *et al.* Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017; 8: 55–73.
33. Cox DJ, Taylor AG, Moncrief M, *et al.* Continuous glucose monitoring in the self-management of type 2 diabetes: a paradigm shift. *Diabetes Care* 2016; 39: E71–E73.

34. Allen NA, Jacelon CS, Chipkin SR. Feasibility and acceptability of continuous glucose monitoring and accelerometer technology in exercising individuals with type 2 diabetes. *J Clin Nurs* 2009; 18: 373–383.
35. Mohan V, Jain S, Kesavadev J, *et al.* Use of retrospective continuous glucose monitoring for optimizing management of type 2 diabetes in India. *J Assoc Phys India* 2016; 64: 16–21.
36. Klonoff DC, Buckingham B, Christiansen JS, *et al.* Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2011; 96: 2968–2979.
37. Bailey TS, Grunberger G, Bode BW, *et al.* American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement. *Endocr Pract* 2016; 22: 231–261.
38. Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes Technol Ther* 2017; 19: S4–S11.
39. Qiu S, Cai X, Schumann U, *et al.* Impact of walking on glycemic control and other cardiovascular risk factors in type 2 diabetes: a meta-analysis. *PLoS One* 2014; 9: e109767.
40. Figueira FR, Umpierre D, Casali KR, *et al.* Aerobic and combined exercise sessions reduce glucose variability in type 2 diabetes: crossover randomized trial. *PLoS One* 2013; 8: e57733.
41. The Juvenile Diabetes Research Foundation CGM monitoring Study Group. Continuous glucose monitoring and intenstive treatment of type 1 diabetes. *N Engl J Med* 2008; 359: 1464–1476.
42. Terranova CO, Brakenridge CL, Lawler SP, *et al.* Effectivenss of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2015; 17: 371–378.
43. Stratton IMA, Neil HA, Matthews DR, *et al.* Association of glycaemia with macrovascular and mictrovasular complications of type 2 diabetes (UKPD 35): prospective observational study. *BMJ* 2000; 321: 405–412.
44. Lorenzo C, Okoloise M, Williams K, *et al.* The metabolic syndrome as predictor of type 2 diabetes - The San Antonio Heart Study. *Diabetes Care* 2003; 26: 3153–3159.
45. Wander PL, Boyko EJ, Leonetti DL, *et al.* Change in visceral adiposity independently predicts a greater risk of developing type 2 diabetes over 10 years in Japanese Americans. *Diabetes Care* 2013; 36: 289–293.
46. Gomez-Ambrosi J, Silva C, Galofre JC, *et al.* Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity (Silver Spring)* 2011; 19: 1439–1444.
47. Ross SA, Dzida G, Vora J, *et al.* Impact of weight gain on outcomes in type 2 diabetes. *Curr Med Res Opin* 2011; 27: 1431–1438.
48. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia* 2010; 53: 1270–1287.
49. Wing RR, Look Ahead Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010; 170: 1566–1575.
50. Wing RR, Lang W, Wadden TA, *et al.* The Look AHEAD research group benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011; 34: 181.
51. Ardisson Korat AV, Willett WC, Hu FB. Diet, lifestyle, and genetic risk factors for type 2 diabetes: a review from the Nurses' Health Study, Nurses' Health Study 2, and Health Professionals' Follow-up Study. *Curr Nutr Rep* 2014; 3: 345–354.
52. Karstoft K, Winding K, Knudsen SH, *et al.* The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2013; 36: 228–236.
53. Baker RC, Kirshenbaum DS. Self-monitoring may be necessary for successful weight control. *Behav Ther* 1993; 24: 377–394.
54. Bailey KJ, Little JP, Jung ME. Self-monitoring using continuous glucose monitors with real-time feedback improves exercise adherence in individuals with impaired blood glucose: a pilot study. *Diabetes Technol Ther* 2016; 18: 185–193.
55. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther* 2016; 18(Suppl 2): S3–S13.
56. Borges U Jr, Kubiak T. Continuous glucose monitoring in type 1 diabetes. *J Diabetes Sci Technol* 2016; 10: 633–639.
57. Joubert M, Reznik Y. Personal continuous glucose monitoring (CGM) in diabetes management: review of the literature and implementation for practical use. *Diabetes Res Clin Pract* 2012; 96: 294–305.
58. Blumer I. The contemporary role of masked continuous glucose monitoring in a real-time world. *J Diabetes Sci Technol* 2016; 10: 790–792.
59. Wagner J, Tennen H, Wolpert H. Continuous glucose monitoring: a review for behavioral researchers. *Psychosom Med* 2012; 74: 356–365.
60. Rodbard D. Clinical interpretation of indices of quality of glycemic control and glycemic variability. *Postgrad Med* 2011; 123: 107–118.

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

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Contribution to the Paper	Co-designed original protocol, responsible for ethics preparation, submission and adaptions, responsible for trial conduct, monitored adverse events of trail participants, managed data, analysed data, prepared manuscript and corresponding author.		
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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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ORIGINAL RESEARCH

Efficacy of Real-Time Continuous Glucose Monitoring to Improve Effects of a Prescriptive Lifestyle Intervention in Type 2 Diabetes: A Pilot Study

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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/m^2) 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 ($P \geq 0.10$). At week 12, GV indices were consistently lower by at least

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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 ± 0.59) compared to control (0.02 ± 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/m^2, 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 $\geq$ 30 mg/mmol), abnormal liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST) or gamma-glutamyl transferase (GGT) $\geq$ 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 (ANZTR 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 unblinded 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 1 Changes in primary and secondary outcome profiles during the study and comparisons between treatments

Variable	RT-CGM (n = 10)			Blinded CGM (n = 10)			P value (ANCOVA)
	Baseline	12 weeks	Change	Baseline	12 weeks	Change	
Glycaemic control							
HbA1c (%)	6.60 ± 0.86	5.90 ± 0.57	− 0.67 ± 0.82	7.11 ± 0.80	6.43 ± 0.92	− 0.68 ± 0.74	0.43
MeS[a]	1.01 ± 1.08	0.71 ± 0.72	− 0.30 ± 0.59	1.19 ± 1.02	1.21 ± 0.98	0.02 ± 0.23	0.110
Body weight and composition							
Weight (kg)	101.26 ± 15.03	93.85 ± 15.59	− 7.41 ± 4.50	92.94 ± 15.51	87.49 ± 16.75	− 5.45 ± 4.03	0.307
Muscle mass (kg)	33.36 ± 6.07	32.79 ± 6.34	− 0.58 ± 0.95	32.43 ± 7.16	31.88 ± 7.44	− 0.55 ± 0.86	0.881
Body fat (kg)	41.75 ± 11.29	35.18 ± 11.34	− 6.57 ± 4.05	35.11 ± 6.21	30.51 ± 5.79	− 4.60 ± 3.27	0.455
Body fat (%)	40.80 ± 7.60	37.00 ± 8.58	− 3.80 ± 3.16	38.5 ± 5.46	35.1 ± 3.90	− 3.40 ± 2.95	0.904
Fat free mass (kg)	59.5 ± 10.24	58.67 ± 10.65	− 0.84 ± 1.55	57.83 ± 11.90	56.98 ± 12.29	− 0.85 ± 1.38	0.956
Lean trunk mass (kg)	28.07 ± 4.41	26.97 ± 4.78	− 1.10 ± 1.16	27.33 ± 5.14	26.49 ± 5.43	− 0.84 ± 0.89	0.533
Fat trunk mass (kg)	21.50 ± 4.53	18.40 ± 5.23	− 3.10 ± 2.43	18.93 ± 3.45	16.59 ± 3.38	− 2.34 ± 1.71	0.524
Cardiovascular risk markers							
Fasting glucose (mmol/L)	7.44 ± 1.35	6.27 ± 1.42	− 1.17 ± 1.94	8.74 ± 1.92	7.77 ± 1.86	− 0.97 ± 2.20	0.146
Fasting insulin (mU/L)	19.19 ± 8.65	14.93 ± 9.12	− 4.26 ± 5.91	20.23 ± 7.37	17.77 ± 6.76	− 2.46 ± 5.73	0.419
Fasting insulin (pmol/L)	132.26 ± 60.04	103.68 ± 63.37	− 29.58 ± 41.08	140.49 ± 51.16	123.40 ± 46.93	− 17.08 ± 39.82	0.419
Serum TC (mmol/L)	4.33 ± 1.32	4.29 ± 1.25	− 0.04 ± 0.38	3.67 ± 0.49	3.41 ± 0.40	− 0.26 ± 0.52	0.123
Serum LDL-C[b] (mmol/L)	2.53 ± 1.08	2.46 ± 1.02	− 0.07 ± 0.34	2.15 ± 0.41	1.89 ± 0.38	− 0.26 ± 0.42	0.152
Serum HDL-C (mmol/L)	1.34 ± 0.16	1.41 ± 0.19	0.07 ± 0.26	1.10 ± 0.34	1.17 ± 0.36	0.07 ± 0.09	0.619
Serum TAG (mmol/L)	1.62 ± 0.65	1.30 ± 0.76	− 0.32 ± 0.46	1.65 ± 0.72	1.29 ± 0.45	− 0.36 ± 0.53	0.884
Mean diastolic blood pressure (mg/Hg)	76.70 ± 9.76	75.53 ± 8.00	− 1.67 ± 7.24	76.87 ± 8.70	71.80 ± 7.42	− 5.07 ± 6.28	0.152
Mean systolic blood pressure (mg/Hg)	133.40 ± 22.50	130.03 ± 12.79	− 3.37 ± 17.71	130.93 ± 8.38	120.70 ± 11.10	− 10.23 ± 12.96	0.099

Table 1 continued

Variable	RT-CGM (n = 10)			Blinded CGM (n = 10)			P value (ANCOVA)
	Baseline	12 weeks	Change	Baseline	12 weeks	Change	
Physical activity (accelerometry) (9 intervention, 10 control)							
% (Mean daily) time spent in sedentary behaviour	87.4 ± 4.9	84.2 ± 5.8	− 3.2 ± 2.2	88.4 ± 4.6	86.5 ± 4.7	− 2.0 ± 1.7	0.329
% (Mean daily) time spent in moderate/vigorous activity	3.9 ± 2.2	5.4 ± 3.4	1.5 ± 1.8	3.3 ± 2.1	3.8 ± 2.3	0.5 ± 0.5	0.114

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

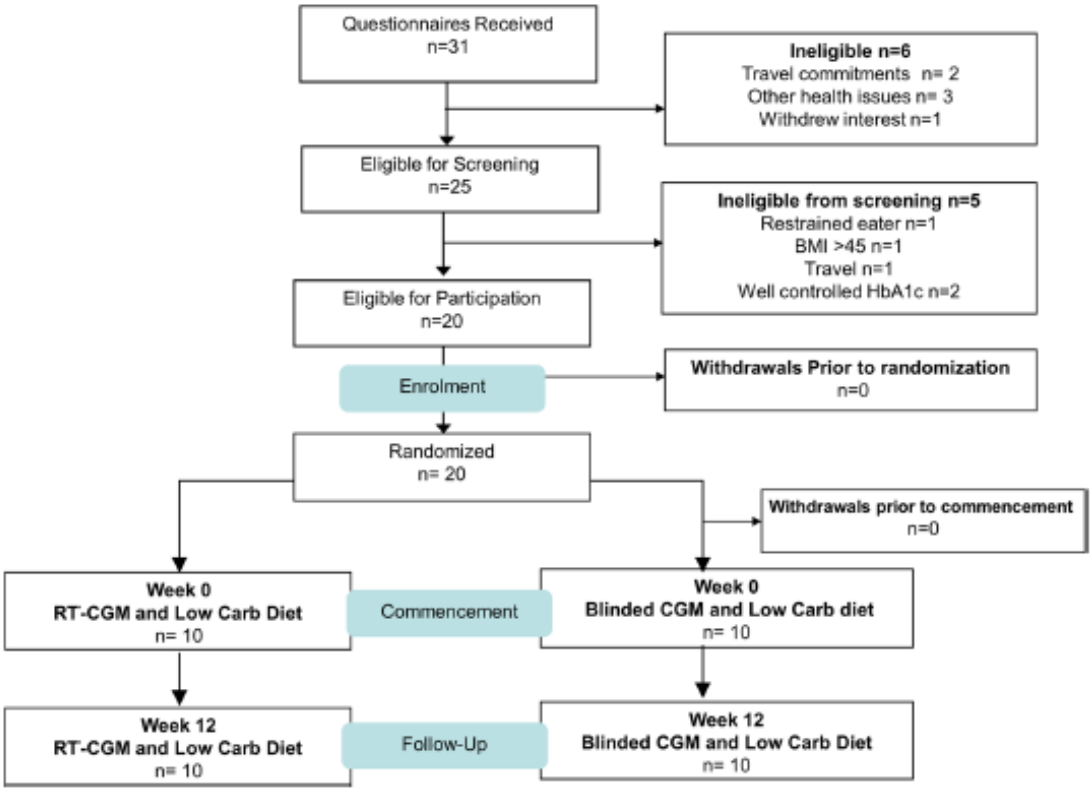

Fig. 1 Participant flow

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 HDL-cholesterol), glucose and insulin (Clinpath, 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 medial 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 ($SD_{intraday}$); 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 ($P \geq 0.10$).

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 ($P \geq 0.11$). 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 ($P \geq 0.11$) 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 glycaemic variability profiles during the study and comparisons between treatments

Variable	RT-CGM (n = 8)			Blinded CGM (n = 5)			P value (ANCOVA)
	Baseline	12 weeks	Change	Baseline	12 weeks	Change	
Mean glucose minimum (mmol/L)	4.24 ± 0.33	4.37 ± 0.90	0.13 ± 0.79	5.55 ± 0.43	4.388 ± 0.77	− 1.17 ± 0.93	0.509
Mean glucose maximum (mmol/L)	11.70 ± 1.78	11.25 ± 2.60	− 0.45 ± 2.55	13.49 ± 2.17	11.50 ± 2.09	− 1.99 ± 2.00	0.632
Overall mean total glucose (mmol/L)	7.00 ± 0.79	6.75 ± 1.21	− 0.24 ± 0.87	8.70 ± 0.86	7.48 ± 1.45	− 1.22 ± 1.37	0.413
Standard deviation glucose (mmol/L)	1.38 ± 0.52	1.29 ± 0.52	− 0.07 ± 0.40	1.42 ± 0.36	1.47 ± 0.48	− 0.06 ± 0.31	0.880
Overall % time spent in Hypoglycemia (< 3.9 mmol/L)	0.01 ± 0.018	0.26 ± 0.61	0.25 ± 0.61	0.00 ± 0.00	0.14 ± 0.311	0.14 ± 0.31	0.630
Overall % time spent in hyperglycemia (> 10 mmol/L) (mmol/L)	6.58 ± 8.68	7.09 ± 11.08	0.51 ± 7.86	19.27 ± 13.71	11.71 ± 18.29	− 7.56 ± 14.15	0.139
Overall % time spent in euglycaemia (3.9–10 mmol/L) (mmol/L)	93.41 ± 8.67	92.62 ± 11.15	− 0.75 ± 7.49	80.73 ± 13.71	88.16 ± 18.20	7.42 ± 14.06	0.368

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

Variable	RT-CGM (n = 9)			Blinded CGM (n = 6)			P value (ANCOVA)
	Baseline	12 weeks	Change	Baseline	12 weeks	Change	
CONGA-1 (mmol/L)	1.30 ± 0.36	1.03 ± 0.36	− 0.27 ± 0.36	1.24 ± 0.41	1.30 ± 0.48	0.06 ± 0.19	0.074
CONGA-2 (mmol/L)	1.72 ± 0.51	1.36 ± 0.55	− 0.36 ± 0.54	1.79 ± 0.633	1.84 ± 0.77	0.05 ± 2.88	0.110
CONGA-4 (mmol/L)	2.02 ± 0.68	1.58 ± 0.75	− 0.44 ± 0.67	2.18 ± 0.74	2.16 ± 0.93	− 0.02 ± 0.42	0.186
CONGA-8 (mmol/L)	2.09 ± 0.68	1.73 ± 0.83	− 0.36 ± 0.61	2.25 ± 0.73	2.22 ± 0.95	− 0.02 ± 0.52	0.298
MAGE (mmol/L)	3.69 ± 1.08	3.01 ± 1.44	− 0.69 ± 1.14	4.06 ± 1.23	4.05 ± 1.61	− 0.09 ± 0.80	0.250

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 glycaemic action of observations 1 h apart, *CONGA-2* continuous overall net glycaemic action of observations 2-h apart, *CONGA-4* continuous overall net glycaemic action of observations 4 h apart, *CONGA-8* continuous overall net glycaemic action of observations 8 h apart, *MAGE* mean amplitude of glycaemic 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.

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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.

REFERENCES

1. Maurizi AR, Pozzilli P. Do we need continuous glucose monitoring in type 2 diabetes? Diabetes Metab Res Rev. 2013. https://doi.org/10.1002/dmrr.2450.

2. American Diaebtes Associated (ADA): Standards of Medical Care in Diabetes—2017. Diab Care. 2017;40 (Suppl 1):S1–S5.

3. Dunkley AJ, Charles K, Gray LK, et al. Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment

comparison meta-analysis. Diabetes Obes Metab. 2012;14:616–25.

4. Terranova CO, Brakenridge CL, Lawler SP, et al. Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2015;17:371–8.

5. Franz MJ, Boucher JL, Rutten-Ramon S, et al. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet. 2015;115:1447–63.

6. Forouhi NG, Misra A, Mohan V, et al. Dietary and nutritional approaches for prevention and management of type 2 diabetes. BMJ. 2018;361:2234–43.

7. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102:780–90.

8. Tay J, Luscombe-Marsh ND, Thompson CH, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes Care. 2014;37:2909–18.

9. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J. 2015;39:273–82.

10. Cardoso CRL, Leite NC, Moram CBM, et al. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. Cardiovasc Diabetol. 2018;17–33.

11. Skrha J, Soupal J, Skrha JJR, et al. Glucose variability, HbA1c and microvascular complications. Rev Endocr Metab Disord. 2016;17:103–10.

12. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295:1681–7.

13. Gorst C, Kwok CS, Aslam S, et al. Long term GV and risk of adverse outcomes. Diabetes Care. 2015;38:2354–69. https://doi.org/10.2337/dc15-1188.

14. Hirsch IB. Glycemic variability and diabetes complications: does it matter? Of course it does! Diabetes Care. 2015;38:1610–4.

15. Wens J, Vermeire E, Royen PV, et al. GPs' perspectives of type 2 diabetes patients' adherence to treatment: a qualitative analysis of barriers and solutions. BMC Fam Pract. 2005;6:20–30.

16. Samdal GB, Eide GE, Barth T, et al. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. Int J Behav Nutr Phys Act. 2017;4:42–6.

17. Guerci B, Drouin P, Grange V, et al. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. Diab Metab. 2003;29:587–94.

18. Michie S, Abrahan C, Whittington C, et al. Effective techniques in healthy eating and physical activity interventions: a meta-regression. Health Psychol. 2009;28:690–701.

19. McAndrew L, Schneider SH, Burns E, et al. Does patient blood glucose monitoring improve diabetes control? A systematic review of the literature. Diabetes Educ. 2007;33:991–1011.

20. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract. 2008;82:73–9.

21. Bailey KJ, Little PJ, Jung ME. Self-monitoring using continuous glucose monitors with real-time feedback improves exercise adherence in individuals with impaired blood glucose: a pilot study. Diabetes Technol Ther. 2016;18:185–93.

22. Yoo HJ, Kim HS, Yang SJ, et al. Use of real time continuous glucose monitoring system as a motivational device for type 2 diabetes. Diabetes. 2008;57:55.

23. Ehrhardt NM, Chellappa M, Walker MS, et al. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol. 2011;5:668–75.

24. Vigersky RA, Fonda SJ, Chellappa M, et al. Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care. 2012;35:32–8.

25. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. Diabetol Metab Syndr. 2013;5:39–45.

26. Brinkworth GD, Taylor PJ. The CSIRO low carb diet. Sydney: Pan Macmillian; 2017.

27. Tay J, Thompson CH, Brinkworth GD. Glycemic variability: assessing glycemia differently and the

implications for dietary management of diabetes. Annu Rev Nutr. 2015;35:389–424.

28. Mayer SB, Jeffreys AS, Olsen MK, et al. Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. Diabetes Obes Metab. 2014;16:90–3.

29. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:93–203.

30. Taylor PJ, Lange K, Thompson CH, et al. Association of glycemic variability and the anti-glycemic medication effect score in adults with type 2 diabetes. Diabetes Management. 2018;8:117–27.

31. Chen Y, Zhang X, Pan B, et al. A modified formula for calculating low-density lipoprotein cholesterol values. Lipids Health Dis. 2010;9:52.

32. Bland MJ, Altman DG. Best (but oft forgotten) practices: testing for treatment effects in randomized trials by separate analyses of changes from baseline in each group is a misleading approach. Am J Clin Nutr. 2015;102:991–4.

33. Stratton IM, Neil Adler AA, Beil AW, et al. Association of glycaemia with macrovascular and microvasular complications of type 2 diabetes (UKPD 35): prospective observational study. BMJ. 2000;321:405–12.

34. Odgers-Jewell K, Ball LE, Kelly JT, et al. Effectiveness of group-based self-management education for individuals with type 2 diabetes: a systematic review with meta-analyses and meta-regression. Diabet Med. 2017;34:1027–39.

35. Gummesson A, Nyman E, Knutsson M, et al. Effect of weight reduction on glycated haemoglobin in weight loss trials in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19:1295–305.

36. Frontoni S, Di Bartolo P, Avogaro A, et al. Glucose variability: an emerging target for the treatment of diabetes mellitus. Diabetes Res Clin Pract. 2013;102:86–95.

37. Rodbard D. Glycemic variability: measurement and utility in clinical medicine and research—one viewpoint. Diabetes Technol Ther. 2011;11:1–4.

38. Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. Diabetes Obes Metab. 2013;15:3–8.

39. Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. Diabetes Technol Ther. 2017;19:S4–11.

40. Dandona P. Minimizing glycemic fluctuations in patients with type 2 diabetes: approaches and importance. Diabetes Technol Ther. 2017;19:498–506.

41. Lipska KJ, Krumholz HM. Is hemoglobin A1c the right outcome for studies of diabetes? JAMA. 2017;317:1017–8.

42. Ismail-Beigi F, Moghissi E, Kosiborod M, et al. Shifting paradigms in the medical management of type 2 diabetes: reflections on recent cardiovascular outcome trials. J Gen Intern Med. 2017;32:1044–51.

43. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycaemic control and rates of severe hypoglycemia 2006–2013. Diabetes Care. 2017;40(468–475):44.

44. Giorgino F, Bonadonna RC, Gentile S, et al. Treatment intensification in patients with inadequate glycemic control on basal insulin: rationale and clinical evidence for the use of short-acting and other glucagon-like peptide-1 receptor agonists. Diabetes Metab Res Rev. 2016;32:497–511.

45. Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: a systematic review of the effect on glycemic control. Patient Educ Couns. 2016;99:926–43.

46. Rodbard D. Continuous glucose monitoring: a review of recent studies demonstrating improved glycemic outcomes. Diabetes Technol Ther. 2017;19:25–37.

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

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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 adaptions, responsible for trial conduct, monitored adverse events of trail participants, managed data, analysed metabolic data, Co-designed behavioural questionnaire, prepared manuscript and corresponding author.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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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	Campbell Thompson		
Contribution to the Paper	Co-designed original trial protocol, contributed to ethics preparation, screened medical suitability of participant inclusion, monitored adverse events of trail participants, supervised and supported data analysis and interpretation, critically reviewed original and revised manuscript		
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Name of Co-Author	Natalie Luscombe-Marsh		
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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

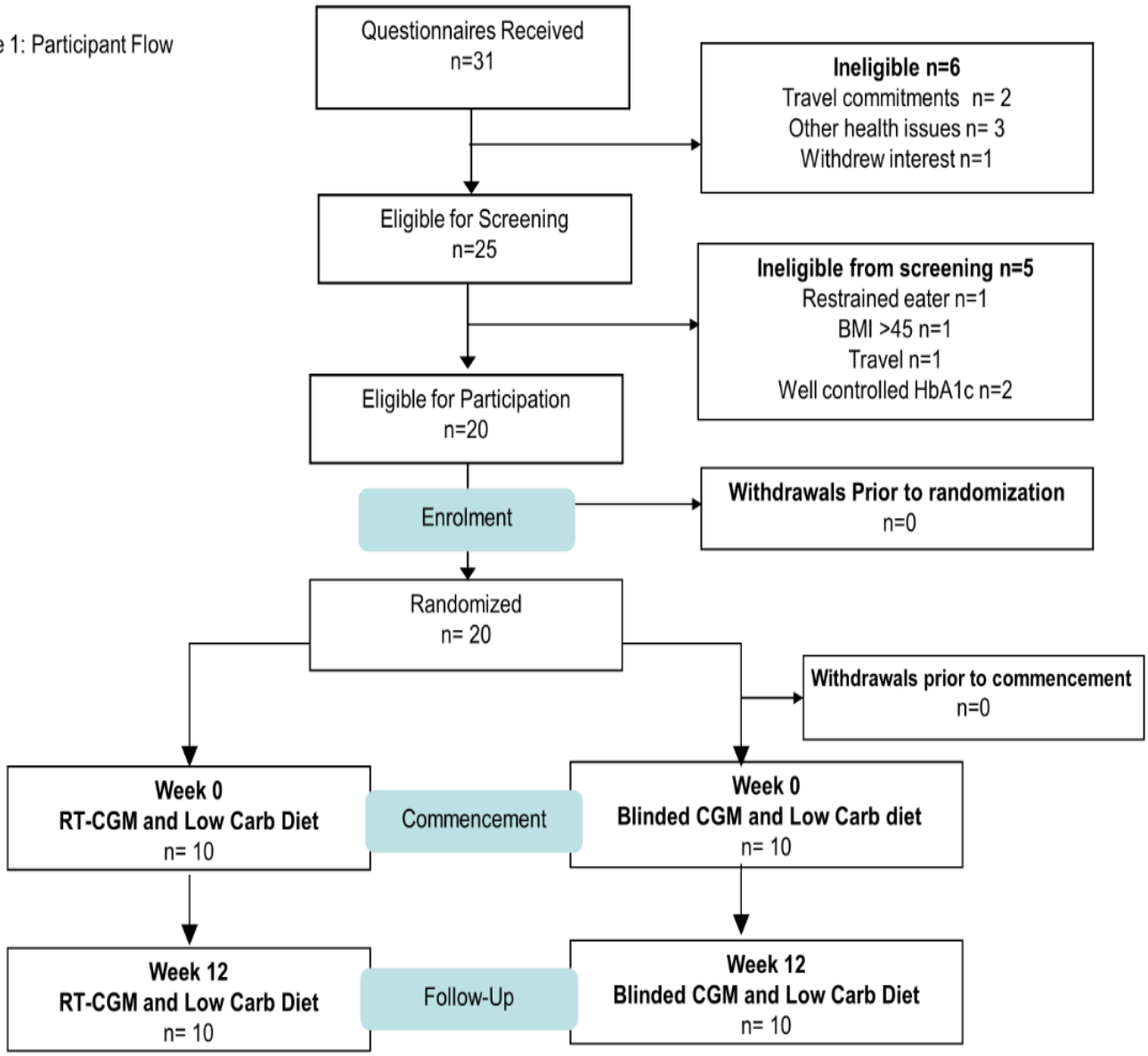
2.1 Study Participants

Recruitment criteria, study design and the primary study outcomes have been previously described [20]. In brief, 20 overweight/obese adults (BMI 26-45 kg/m^2, age range 20-75 yrs) with T2D (HbA1c: 5.9-6.9% [41.0 – 51.9 mmol/mol], Diabetes Duration mean 10.8 $\pm$ 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).

Figure 1: Participant Flow



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 α_r=0.96, acceptability α_r=0.85. Week 12: intolerance α_r=0.89, acceptability α_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 α_r=0.86, exercise α_r=0.84, blood glucose α_r=0.90, social α_r=0.82. Week 12: diet α_r=0.63, exercise α_r=0.83, blood glucose α_r=0.88, social α_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 α_r=.082, current α_r=0.85) and Week 12 (baseline α_r=0.71, current α_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

Measure	Condition	Baseline	6-weeks	12 weeks
Perceived Stress Survey¥	Blind CGM	35.5 ± 3.5	-	35.2 ± 2.53
	RT-CGM	33.2 ± 5.1	-	33.7 ± 4.67
Diabetes Management Behaviours	Blind CGM	53.3 ± 6.4	62.9 *[a] ± 8.87	58.9 ± 6.06
	RT-CGM	51.5 ± 8.90	67. 3 *[a] ± 9.86	66.3 *[a] ± 8.45
Acceptance of CGMS	Blind CGM	-	27.2 ± 5.31	27.5 ± 3.38
	RT-CGM	-	30.2 ± 3.79	31.2 *[b] ± 3.73
Intolerance of CGMS	Blind CGM	-	18.4 ± 11.55	16.3 ± 6.60
	RT-CGM	-	14.9 ± 4.51	13.4 ± 5.44
Social Behaviours	Blind CGM	-	9.8 ± 2.97	10.4 ± 1.58
	RT-CGM	-	10.0 ± 2.82	11.2 ± 2.49
Exercise Behaviour	Blind CGM	-	22.9 ± 4.09	21.4 ± 3.09
	RT-CGM	-	20.3 ± 5.48	23.0 ± 4.62
Diet Behaviour	Blind CGM	-	20.1 ± 4.12	19.7 ± 1.49
	RT-CGM	-	20.7 ± 2.98	21.5 ‡[b] ± 2.76
Blood Glucose Monitoring Behaviour	Blind CGM	-	21.8 ± 4.07	24.2 ± 2.57
	RT-CGM	-	26.4 **[b] ± 3.31	28.7 **[b] ± 1.70

Blind CGM, *n*=10; RT-CGM, *n*=10; RT-CGM = Real Time Continuous Glucose Monitoring; [a] Within group comparison to baseline; [b] 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.

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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. 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.

7. References

1. Baig MM, Gholam Hosseini H, Moqeem AA, et al. A Systematic Review of Wearable Patient Monitoring Systems - Current Challenges and Opportunities for Clinical Adoption. *J Med Syst,* 2017. 41(7): p. 115.
2. Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: A review of the technology and clinical use. *Diabetes Res Clin Pract*, 2017. 133: p. 178-192.
3. Tougas ME, Hayden JA, McGrath PJ, et al. A Systematic Review Exploring the Social Cognitive Theory of Self-Regulation as a Framework for Chronic Health Condition Interventions. *PLoS One*, 2015. 10(8): p. e0134977.
4. Czupryniak L, Barkai L, Bolgarska S, et al. Self-monitoring of blood glucose in diabetes: from evidence to clinical reality in Central and Eastern Europe--recommendations from the international Central-Eastern European expert group. *Diabetes Technol Ther*, 2014. 16(7): p. 460-75.
5. Bailey KJ, Little JP, Jung ME. Self-Monitoring Using Continuous Glucose Monitors with Real-Time Feedback Improves Exercise Adherence in Individuals with Impaired Blood Glucose: A Pilot Study. *Diabetes Technology Ther, 2016.* 18(3): p. 185-93.
6. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract*, 2008. 82(1): p. 73-9.
7. Kesavadev J, Vigersky R, Shin J, et al. Assessing the Therapeutic Utility of Professional Continuous Glucose Monitoring in Type 2 Diabetes Across Various Therapies: A Retrospective Evaluation. *Adv Ther,* 2017. 34(8): p. 1918-1927.
8. Meade LT. The use of continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Technol Ther*, 2012. 14(2): p. 190-5.

9. Farmer AJ, Perera R, Ward A, et al. Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose in people with non-insulin treated type 2 diabetes. *BMJ*, 2012. 344: p. e486.

10. Nam S, Chelsla C, Stotts NA, et al. Barriers to diabetes management: patient and provider factors. D*iabetes Res Clin Pract,* 2011. 93(1): p. 1-9.

11. Polonsky WH, Fisher L. When does personalized feedback make a difference? A narrative review of recent findings and their implications for promoting better diabetes self-care. *Curr Diab Rep,* 2015. 15(8): p. 50.

12. Polonsky WH, Fisher L, Hessler D, Edelman SV. What is so tough about self-monitoring of blood glucose? Perceived obstacles among patients with Type 2 diabetes. *Diabet Med*, 2014. 31(1): p. 40-6.

13. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetology & Metabolic Syndrome*, 2013. 5(39): p. 1-14.

14. Park C, Le QA. The Effectiveness of Continuous Glucose Monitoring in Patients with Type 2 Diabetes: A Systematic Review of Literature and Meta-analysis. *Diabetes Technol Ther,* 2018. 20(9): p. 613-621.

15. Taylor PJ, Thompson CH, Brinkworth GD. Effectiveness and acceptability of continuous glucose monitoring for type 2 diabetes management: A narrative review. *J Diabetes Investig*, 2018. 9(4): p. 713-725.

16. Turner J, Kelly B. Emotional dimensions of chronic disease. *West J Med, 2000.* 172(2): p. 124-8.

17. Fisher L, Gonzalez JS, Polonsky WH. *T*he confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision. *Diabet Med*, 2014. 31(7): p. 764-72.

18. Petrie JR, Peters AL, Bergenstal RW, et al. Improving the Clinical Value and Utility of CGM Systems: Issues and Recommendations: A Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetes Care,* 2017. 40(12): p. 1614-1621.

19. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. *J Diabetes Complications*, 2017. 31(1): p. 280-287.

20. Taylor PJ, Thompson CH, Luscombe-Marsh ND, et al. Efficacy of Real-Time Continuous Glucose Monitoring to Improve Effects of a Prescriptive Lifestyle Intervention in Type 2 Diabetes: A Pilot Study. *Diabetes Therapy*, 2019. pp1-14.

21. Brinkworth GD, Taylor PJ. *The CSIRO Low Carb Diet*, 1st ed. P. Macmillian. Sydney: Pan Macmillian. 2017,

22. Myette-Côté E, Durrer C. Neudorf H., et al., The effect of a short-term low-carbohydrate, high-fat diet with or without post meal walks on glycemic control and inflammation in type 2 diabetes: a randomized trial *America Journal of Physiology*. 315 (6).

23. Tay J, Luscombe-Marsh N, Thompson CH., et al., Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial*. Am J Clin Nutr*, 2015. 102(4): p. 780-90.

24. Sainsbury E, Kizirian NV, Partridge SR., et al., Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis. D*iabetes Res Clin Pract*, 2018. 139: p. 239-252.

25. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress *Journal of Health and Social Behav.*, 1983. 24(Dec.): p. 385-396.

26. Howard GS, Ralph KM, Gulanick NA, et al. Internal invalidity in pretest-posttest self-report evaluations and re-evaluation of retrospective pretest. A*pplied Psychological Measurement*, 1979. 3(1): p. 1-23.

27. Pratt CC, McGuigan WM, Katzev AR. Measuring program outcomes: using retrospective pretest methodology. *American Journal of Evaluation.* 21(3): p. 341-349.

28. Bland JM, Altman DJ. Best (but often forgotten) practices: testing for treatment effects in randomized trials by separate analyses of changes from baseline in each group is a misleading approach*. Am J Clin Nutr,* 2015. 102(5): p. 991-4.

29. Shlomowitz A, Feher MD. Anxiety associated with self monitoring of capillary blood glucose*. British Journal of Diabetes,* 2014. 14(2).

30. O'Kane MJ, Bunting B, Copeland M, et al. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial*. BMJ*, 2008. 336(7654): p. 1174-7.

31. Lin EHB, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence and preventative care*. Diabetes Care*, 2014. **27**: p. 2154-2160.

32. Tang TS, Digby EM, Wright AM, et al. Real-time continuous glucose monitoring versus internet-based blood glucose monitoring in adults with type 2 diabetes: a study of treatment satisfaction*. Diabetes Res Clin Pract,* 2014. 106(3): p. 481-6.

33. Ehrhardt EM, Challappa M, Walker S, et al. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus*. Journal of Diabetes Science and Technology,* 2011. 5(3): p. 668-675.

34. Vigersky RA, Fonda SJ, Chellappa M, et al. Short and long term effects of real-time continuous glucose monitoring in patients with type 2 diabetes*. Diabetes Care,* 2012. 35: p. 32-38.

35. Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized TrialContinuous Glucose Monitoring in Patients With Type 2 Diabetes*. Annals of Internal Medicine*, 2017. 167(6): p. 365-374.

36. Mohan V, Jain S, Kesavadev J, et al. Use of retrospective continuous glucose monitoring for optimizing management of ype 2 diabetes in India. J*ournal of the Association of Physicians of India*, 2016. 64: p. 16-21.

37. American Diabetes Association *(ADA):* Standards of Medical Care in Diabetes -2019*. Diabetes Care,* 2019. 41 Suppl 1: p. S1-187.

38. Bellou V, Belbasis L, Tzoulaki I., et al., Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. *PLoS On*e, 2018. 13(3): p. e0194127.

39. Schnell O, Alawi H, Battelinio T, et al. Self-Monitoring of Blood Glucose in Type 2 Diabetes: Recent Studies*. Journal of Diabetes Science and Technology*, 2013. **7**(2): p. 478-488.

40. Machry RV, Radps DV, Gregoria GR, Rodrigues TC. Self-monitoring blood glucose improves glycemic control in type 2 diabetes without intensive treatment: A systematic review and meta-analysis. *Diabetes Res Clin Pract*, 2018. 142: p. 173-187.

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:

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Installing the sensor was easy for me			X		

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

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

SECTION 2

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

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

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

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

Continued over page...

SECTION 4

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

Since starting this program I:	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
…set goals for managing my diabetes					
…take poor care of my diabetes					
…am effectively managing my diet					
…often make unhealthy dietary choices					
…set goals in regards to my body weight					
…understand how exercise affects my blood glucose levels					
…check my blood sugar levels regularly					
…feel in control of my diabetes					
…feel successful with regards to managing my diabetes					
…often skip exercising					
….I often feel my blood sugars were unacceptably high.					
…use physical activity to help manage my blood glucose levels					
…am satisfied with my exercise levels					
…actively choose foods that are good for my blood glucose levels					
…often eat foods rich in sugar and/or carbohydrates					
…often forgot to take my diabetes medication (insulin, tablets)					
…often binge on food					
….I often feel that my blood sugars were unacceptably low					

SECTION 5

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

Before starting this program I:	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
…often ate foods rich in sugar and/or carbohydrates					
…understood how exercise affected my blood glucose levels					
…took poor care of my diabetes					
…often binged on food					
…was effectively managing my diet					
…often skipped exercising					
…I often felt that my blood sugars were unacceptably high					
…often made unhealthy dietary choices					
…checked my blood sugar levels regularly					
…actively chose foods that were good for my blood glucose levels					
…felt successful with regards to managing my diabetes					
…set goals in regards to my body weight					
…was satisfied with my exercise levels					
…set goals for managing my diabetes					
…felt in control of my diabetes					
…often forgot to take my diabetes medication (insulin, tablets)					
…used physical activity to help manage my blood glucose levels					
… I often felt that my blood sugars were unacceptably low					

Appendix 2: List of peer-reviewed journal article publications, public reports (Outside Candidature), commercial publications and affiliations.

In Submission:

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1) Luscombe-Marsh ND, Wycherley T**, Taylor P**, Brinkworth G, Stonehouse W, Riley M. The role of dairy for the management of muscle mass and function in people aged 50+ years: A systematic review and meta-analysis. In preparation.

2) Jadczak AD, **Taylor P**, Barnard R, Makwana N, Visvanathan R, Luscombe-Marsh ND. The EXPRESS Study: EXercise and PRotein Effectiveness Supplementation Study Supporting Autonomy in Community Dwelling Frail Older People – Findings from a Feasibility Study. In prep for Age & Ageing.

Published

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3) Jadczak AD, Luscombe-Marsh ND, **Taylor P**, Barnard R, Makwana N, Visvanathan R. The EXPRESS Study: EXercise and PRotein Effectiveness Supplementation Study Supporting Autonomy in Community Dwelling Frail Older People - Study Protocol for A Randomized Controlled Pilot and Feasibility Study. Accepted 9th June 2017; Pilot and Feasibility Studies (PAFS-D-17-00011R3).

4) Welma Stonehouse[1,*], Thomas Wycherley[2], Natalie Luscombe-Marsh[1], **Pennie Taylor[1]**, Grant Brinkworth[1] and Malcolm Riley[1] 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, 20161;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

7) Camille E Short, Corneel Vandelanotte, Marcus W Dixon, Richard Rosenkranz, Cristina Caperchione, Cindy Hooker, Mohan Karunanithi, Gregory S Kolt, Anthony Maeder, Hang Ding, **Pennie Taylor,** Mitch J Duncan Examining participant engagement in an information technology-based physical activity and nutrition intervention for Men: the ManUp randomized trial; Journal of Medical Internet Research – Research Protocols January 2014 Vol [1]

8) Radhika V Seimon, **Pennie Taylor**, Tanya J Little, Manny Noakes, Scott Standfield, Peter M Clifton, Michael Horowitz, Christine Feinle-Bisset Effects of acute and longer-term dietary restriction on upper gut motility, hormone, appetite and energy intake responses to duodenal lipid in lean and obese men; Am J Clin Nutr. 2014 Jan;99(1):24-34. doi: 10.3945/ajcn.113.067090

9) Lutze J, **Taylor PJ,** Brinkworth G, Wyld B, Syrette, J and Noakes, MJ. Psychological well-being response to high protein and high carbohydrate weight loss diets in overweight and obese men: A randomized trial e-SPEN journal 01/2013; 8(6) e235-240

10) Nguyen, NQ, Game P, Bessel J, Debreceni TL, Neo M, Burgstad CM, **Taylor P,** Wittert GA. Outcomes of Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding, World Journal of Gastroenterology September 28th 2013.

11) **Taylor PJ,** Kolt, GS, Vandelanotte, C , Caperchione, C M, Mummery, WK; George, ES , Karunanithi, M. and Noakes MJ. A review of the nature and effectiveness of nutrition interventions in adult males – A guide for intervention strategies IJBNPA 2013, 10:13 (29th January 2013)

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.

13) Roupas, R., Keogh, J., Noakes, M., Margetts, C and **Taylor, P**. The role of edible mushrooms in health: Evaluation of the evidence. Journal of Functional Foods, Available online 26 May 2012

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

15) Roupas, R., Keogh, J., Noakes, M., Margetts, C and **Taylor, P.** Mushrooms and Agaritine – A mini-Review. Journal of Functional Foods, Volume 2, Issue 2, April 2010, Pages 91-98

INDUSTRY REPORTS

Taylor, PJ and Roupas, P. Mushrooms and Health Report prepared for: The Global Initiative on Mushrooms and Health June 2010 [online at: http://www.mushroomsandhealth.com/mushrooms-health-report-s101/]

Taylor, PJ., Chin, JH. and Noakes, MJ. Expert Consultants Literature Review for the Pregnancy Lifescripts Program: Nutrition and Physical activity Documents Prepared for the Australian General Practice Network, Lifescripts Initiative January 2011

Roupas, P., Noakes, N., Margetts, C., Keogh, J and **Taylor, P**. Mushrooms and Health Report prepared for: The Global Initiative on Mushrooms and Health June 2010 [online at: http://www.mushroomsandhealth.com/mushrooms-health-report-s101/]

Commercial Publications

2018 Co-Author: The CSIRO Healthy Gut Diet. Pan MacMillan Publishing 2018. Co Authored with Dr Michael Conlon, Dr Tony Bird. Launched Australia wide September 2018.

2018 Co-Author: The CSIRO Low-Carb Every Day diet plan. Pan MacMillan Publishing 2018. Co Author with Associate Professor Grant Brinkworth. Launched Australia wide March 2018.

2017 Co-Author- The CSIRO Low-Carb Diet. Pan MacMillan Publishing 2017. Co Author with Associate Professor Grant Brinkworth. Launched Australia wide March 2017.

2011 Contributor: Diabetes Diet and Lifestyle Plan. CSIRO and Baker IDI Penguin Publishing 2011

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

PROFESSIONAL MEMBERSHIPS AND AFFILIATIONS

Jan 2015 – Current	Member of the Dietitian Association Australia – Bariatric Surgery Short Course Working Group (Course development and implementation)
March 2014 – Current	Member for the Obesity Society (TOS) and American Society of Metabolic and Bariatric Surgery (ASMBS)
Feb 2010 –Current	University Nutrition and Dietetics Strategic Planning committee member, Flinders University Nutrition and Dietetics
Feb 2009- Current	Allied Health Member for Australia and New Zealand Metabolic and Obesity Surgery Society (ANZMOSS) Previously OSSANZ
Dec 2005 - Current	Accredited Practising Dietitian (APD) - Dietitians Association Australia (DAA)
Jan 2015 – 2017	Member of the Australia and New Zealand Metabolic and Obesity Surgery Society (ANZMOSS) Conference and workshop planning committee
Oct 2012 – Nov 2016	Committee Member (non-voting) for Obesity Surgery Society of Australia and New Zealand (Ossanz)
Jan 2010- 2016	DAA-SA Exec Committee Member, (2016) Vice -Chair and Chair