THE UNIVERSITY OF HULL

Interventions to improve the quality of life in patients living with endocrine conditions

A Thesis submitted for the degree of Doctor of Medicine

University of Hull and University of York

By

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Dedication

This thesis is dedicated to the people living with type 1 diabetes, type 2 diabetes and adrenal insufficiency who participated in the studies included in this thesis.

Table of Contents

List of Tables

List of figures

List of abbreviations

ABCD-Association of British Clinical Diabetologists

ACTH-Adrenocorticotropic hormone

AI-Adrenal insufficiency

BMI-Body mass index

CAH-Congenital adrenal hyperplasia

CGM-Continuous Glucose Monitoring

CI-Confidence interval

CKD-Chronic Kidney Disease

COPD-Chronic obstructive pulmonary disease

CRP-C-reactive protein

CS-Cognitive skills

DCTW-Diabetes care technology waste

DDS-Diabetes Distress Scale

DHEA-Dehydroepiandrosterone

DKA-Diabetic Ketoacidosis

DRD-Diabetes related distress

DR-HC-Dual-release hydrocortisone

ER-Emotional regulation

FSL-FreeStyle Libre

GLP-Glucagon-like peptide

GMI-Glucose management indicator

GP-General practitioner

GRT-Glucocorticoid replacement therapy

HCL-Hybrid closed loop

HDL-High density lipoprotein

HPA-Hypothalamic-pituitary-adrenal axis

HR-Hazard ratio

HUTH-Hull University Teaching Hospitals

IGF-1-Insulin-like Growth factor

IQR-Interquartile range

MD-Doctor of Medicine

MDT-Multi-disciplinary team

NHSE-National Health Service England

NHS-National Health Service

NICE-National Institute for Health and Care Excellence

PAID-Problem Areas in Diabetes

PAI-Primary adrenal insufficiency

PIS-Participant Information sheet

QOL-Quality of life

RBC- Red blood cell

SAI-Secondary adrenal insufficiency

SD-Standard deviation

SF-36-Thirty-six item short form Health survey

SHS-Subjective health status

SMBG-Self monitoring of blood glucose

SRAT-Self reported adherence to treatment

T1DM-Type 1 diabetes

T2DM-Type 2 diabetes

TAI-Tertiary adrenal insufficiency

TIR-Time in Range

UK-United Kingdom

WHO-World Health Organisation

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Publications

Two of the studies presented in this thesis has been published in peer-reviewed journals and are cited below.

Ssemmondo E, Deshmukh H, Wilmot EG, Adeleke KA, Shah N, Walton C, Barnes D, Ryder REJ, Sathyapalan T. Effect of intermittently scanned continuous glucose monitoring in people with diabetes with a psychosocial indication for initiation. Diabetes Obes Metab. 2024 Apr;26(4):1340-1345. doi: 10.1111/dom.15435. Epub 2024 Jan 16. PMID: 38228571.

Ssemmondo E, Shah N, Newham M, Rigby A, Buckland R, Deshmukh H, Sathyapalan T. Effect of introduction of intermittently scanned continuous glucose monitoring on glycaemic control in individuals living with type 2 diabetes mellitus treated with non-insulin therapies-A randomised controlled trial. Diabetes Obes Metab. 2024 Dec 11. doi: 10.1111/dom.16116. Epub ahead of print. PMID: 39663609.

Abstract

Introduction

Patients living with chronic endocrine conditions experience a burden of disease which affects their quality of life compared to healthy controls. In people living with type 1 and type 2 diabetes, this may be due to micro or macrovascular complications, as well as the negative emotions associated with living with diabetes. In individuals with adrenal insufficiency, the reduced quality of life may be due to failure to mimic the circadian rhythm during glucocorticoid replacement. Interventions to improve the management of these endocrine conditions can have an impact on the specific disease related distress. This would in turn affect the quality of life in these individuals. The first study assessed the impact of intermittently scanned continuous glucose monitoring (isCGM) on glycaemic control and diabetes distress in a predominantly type 1 diabetes population with psychosocial issues. The effect of this technology on diabetes distress in people living with type 2 diabetes but not yet on insulin has been evaluated in the second study. In the final study, we compared the effect of prednisolone to hydrocortisone on the quality of life in patients with adrenal insufficiency.

Methods:

The first study was a retrospective analysis of baseline and follow-up data from the Association of British Clinical Diabetologists (ABCD) nationwide audit of people with diabetes who initiated the isCGM for psychosocial reasons in the United Kingdom. In the second study, a randomized

controlled trial, the effect of use of Free Style Libre 2 over 12 weeks on glycaemic control and diabetes distress in patients with type 2 diabetes was assessed. The final study was an observational study that compared the cardiovascular risk and quality of life of patients with adrenal insufficiency, at the start and 4 months after switching from hydrocortisone to prednisolone.

Results

In the first study, with the initiation of isCGM, after a mean follow-up period of 6.9 months, there was a significant reduction in Diabetes Distress Scale score; 4 at baseline vs. 2.5 at follow up (P<0.001). The prevalence of high Diabetes Related Distress (DRD) reduced from 76% to 38% at follow-up (50% reduction in DRD, P<0.001). There was also a significant reduction in HbA1c (HbA1c 78.5 mmol/mol (9.3%) at baseline vs 66.5 mmol/mol (8.2%) at follow-up (P<0.001).

In the second study, the use of Libre 2, a form of isCGM, increased the mean time in range at 12 weeks by 18% (CI 2-35, p=0.028). Participants in the Libre 2 arm exhibited a non-significant reduction in HbA1c levels of 8 mmol/mol compared to the control arm. However, no significant differences were observed in other isCGM metrics or diabetes distress between the study arms.

In the final study, the use of prednisolone was associated with an average reduction in weight of 1.2kg (p=0.007) and relatedly, a reduction in body mass index (BMI) of 0.4kg/m^2. The systolic blood pressure reduced by an average of 6mmHg (p=0.027). The total cholesterol, non-HDL cholesterol, triglycerides levels were lower at follow up compared to baseline levels. These changes were however not statistically significant (p>0.05). Data from the modified SF-36 quality of life questionnaire showed significant increase in the energy scores and scores relating to the

participants' general health (p=0.003 and p=0.019 respectively), indicating an improvement in the quality of life.

Conclusion:

Analysis of real-world data of people with T1DM using isCGM initiated for psychosocial reasons shows a significant improvement in diabetes related distress, glycaemic control and hospital admissions due to hyperglycaemia/diabetic ketoacidosis. The use of isCGM in T2DM patients on non-insulin therapy showed promise in improving glycaemic control, as evidenced by increased time in range. There was, however, no significant reduction in HbA1c or impact on diabetes distress. The use of prednisolone was associated with a significant reduction in systolic blood pressure, weight and BMI. Prednisolone did not affect the lipid profile, signifying no increase in cardiovascular risk. Patients felt more energetic and had higher general health scores. These findings suggest that low dose prednisolone may be a better glucocorticoid option than hydrocortisone. In this thesis, we have shown that the disease specific interventions had an overall positive impact on the management of individuals living with diabetes and adrenal insufficiency. This generally resulted in improvement in the quality of life as evidenced by the disease related distress. Interventions also had an impact on the individuals' biochemical health as shown by various outcome measures.

Format of the thesis

The first chapter is a literature review which introduces the background to the studies undertaken in this thesis. Chapters 2-5 describe the three studies that form this thesis. The final chapter summarises my findings and conclusions.

Aims of the work

1. To understand the effect of intermittently scanned continuous glucose monitoring (isCGM) on glycaemic control and diabetes distress in people with diabetes with a 'psychosocial' indication for access.
2. To assess the effect of Free Style Libre 2 monitoring on glycaemic control and quality of life in people with T2DM on one or more non-insulin glucose-lowering agents over a period of 12 weeks.
3. To compare the effect of low dose prednisolone to hydrocortisone on the markers of cardiovascular risk and quality of life in patients with adrenal insufficiency.

Chapter 1: Introduction

1.1 Wellbeing in chronic endocrine conditions

Patients living with chronic endocrine conditions experience a burden of disease that arises not only from the aetiology of the particular condition, but also from the systemic manifestations of either the deficiencies or hormonal excess(1). These factors along with the interventions involved in diagnosis or treatment of the condition can contribute to the psychosocial issues associated with chronic endocrine conditions. Age and comorbidities are examples of important factors that contribute to the quality of life of individuals living with endocrine conditions. Older patients may have reduced physiological reserve(2), cognitive decline or lack a social support system all of which may have an impact on their mental health and quality of life. In addition, individuals with multiple comorbidities experience increased symptom burden, polypharmacy and significant mental health strain which affects their quality of life(3).

Type 1 diabetes (T1DM) is a chronic metabolic disorder which generates several negative consequences that affect health related quality of life(4, 5). Before the introduction of continuous glucose monitoring, but also for individuals who cannot access this technology, there is need for frequent self-monitoring of blood glucose and individuals worry about hypoglycaemia. With the aim of avoiding complications, T1DM requires extensive self-management, and this negatively affects the life of individuals living with this condition(6). People living with T1DM have increased fear, depression and anxiety(4, 6, 7). In addition, people living with T1DM must make lifestyle changes and more time is needed to plan for everyday activities like exercise, going out for a meal or going on a holiday, among others. In fact, compared to the general population, people living

with T1DM experience lower health related quality of life, poor sleep and are likely to be unemployed(6, 8). Interventions to improve the quality of life in this cohort are therefore important.

Type 2 diabetes (T2DM), just like T1DM can cause both short term and long-term complications if not adequately managed(9). The quality of life of people living with T2DM is also lower compared to healthy controls(10, 11). In one systematic review and meta-analysis, the presence of complications, longer duration of diabetes and depression negatively affected the quality of life in T2DM(12). In addition, individuals using insulin to manage their diabetes have a lower quality of life compared to those on oral medication(13). There is therefore a need to assess interventions that improve the glycaemic control which may delay the introduction of insulin, and thereby improve the quality of life in this population.

In patients with adrenal insufficiency, there is impaired subjective health status and quality of life(14). In fact, irrespective of the type of adrenal insufficiency, there is increased mortality reported amongst patients with this condition(15). Reduced quality of life is also seen in patients with other chronic endocrine conditions. Even after biochemical cure, patients with pituitary tumours, for example, can still have an impaired quality of life(16, 17). One study found that patients who were treated for a pituitary tumour and had increased disease burden were more often not having paid employment(18). Further to that, evidence from another study has shown reduced quality of life in patients with pituitary adenoma which in a significant proportion is due to reduced sleep and depression(19). In acromegaly, there are changes in bone and cartilage due to excess growth hormone and insulin like growth factor-1 (IGF-1). These changes play an important role in the health-related quality of life in patients with acromegaly(20).

Treatment choice as well as duration of treatment of endocrine conditions may significantly impact the quality-of-life following treatment. A cross-sectional study in patients with acromegaly who underwent surgery (transsphenoidal or transcranial) compared the quality of life between the group that received radiotherapy post-surgery due to recurrent disease, to the group that were treated with long-acting somatostatin analogues. The results showed that the need for long term postoperative treatment with somatostatin analogues is associated with impairment of quality of life in this group of patients(21).

In this thesis, we examine the quality of life in patients living with type 1 diabetes, type 2 diabetes and adrenal insufficiency. Although the aetiologies and treatment approaches are different, these three chronic endocrine conditions can be associated with reductions in the quality of life of individuals. We examine each condition in turn and describe the findings of an intervention to improve the quality of life for individuals living with these conditions.

1.2 Type 1 diabetes (T1DM)

1.2.1 Pathophysiology and prevalence of T1DM

T1DM is a chronic, immune-mediated disorder of glucose regulation arising from failure of the beta cells of the pancreas to produce enough insulin due to destruction (22). This immune-mediated destruction commonly occurs in childhood or adolescence and environmental alongside epigenetic factors are thought to play a part. CD8+ cells are known to play a part in the auto-destruction of the beta cells(22). Of the 4.3 million people with diabetes living in the UK, 8% have T1DM(23).

1.2.2 Management of T1DM

National Institute for Health and Care Excellence (NICE) guideline (NG17) recommends measurement of HbA1C every 3 to 6 months in people with T1DM. In addition, it recommends offering people with T1DM an option of either real time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM)(24). For individuals not using CGM, self-monitoring of blood glucose is recommended at least 4 times a day including one before bed. In regards to insulin, the recommendation is for multiple daily injections of insulin in basal-bolus regimens(24).

1.2.3 Psychosocial issues in T1DM

Management of T1DM requires the use of insulin delivered using the appropriate technology/device that is acceptable to the individual. This may be via multiple daily insulin injections, insulin pump therapy or hybrid closed loop systems (HCL). In addition, addressing psychosocial issues also helps to optimize outcomes in addition to education and support(25). Psychosocial issues in diabetes encompass the psychological and social factors that affect the well-being, self-care behaviours, and overall management of the condition. They include the broader emotional, behavioural and societal challenges faced by individuals living with diabetes. Patient centred care is essential to promote psychological wellbeing and optimal clinical

outcomes(26). Figure 1.1 below demonstrates the overlap between Diabetes related distress and psychosocial issues in people living with diabetes.

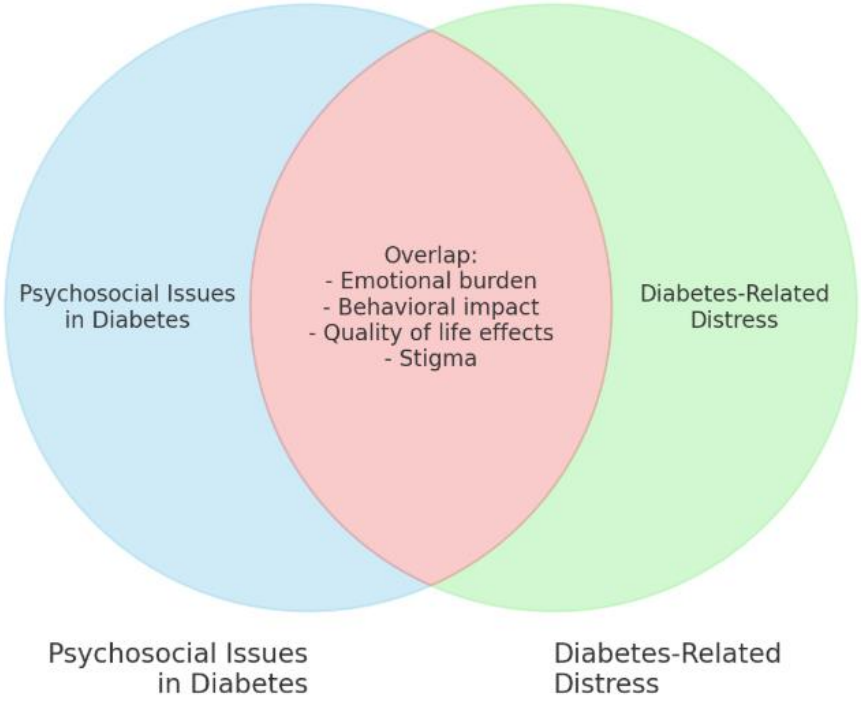


Figure 1.1: Overlap between psychosocial issues in diabetes and diabetes related distress

A review undertaken during the COVID-19 pandemic showed that patients with T1DM experienced a wide range of psychological burdens. This included stress, worry, burn out, social factors, anxiety and reduction in the quality of life(27). A survey amongst mainly T1DM participants to better understand the prevalence of self-reported psychosocial burdens showed that majority of participants had experienced self-reported anxiety and depression(28). In addition, 68% of the respondents experienced negative effects to their self-esteem due to diabetes, while 62% felt lonely. The authors concluded that to improve outcomes of people living

with diabetes, healthcare professionals ought to integrate psychosocial discussions when seeing people with diabetes during routine clinic visits(28). The psychosocial factors coupled with the demands of self-management for patients with T1DM affects adherence to prescribed medication regimes(29). This may result in suboptimal diabetes control. In adolescents with T1DM for example, one study found that the quality of life was affected by diabetes-specific anxiety and called for targeted interventions to improve the quality of life in this group of patients(30).

There is an association between anxiety symptoms and less frequent blood glucose monitoring amongst adolescents with T1DM(31). Self-monitoring of blood glucose (SMBG) has been characterised as invasive and this has been found to be one of the reasons why patients skip testing and do not adhere to the recommended frequency of testing(32). Even in individuals without blood or injection phobia, invasiveness has been associated with SMBG anxiety. Moreover, in individuals with pre-existing anxiety, the invasiveness worsens SMBG anxiety(32). The authors of this study concluded that the QOL of people with diabetes would improve if SMBG was non-invasive(32). Despite the benefits of SMBG, one review highlighted theoretical disadvantages which may be associated with blood glucose monitoring. Firstly, there is a possibility that patients performing SMBG may find it as a constant reminder of their condition. Secondly, high blood glucose readings may cause anxiety which may affect the patients' experience with diabetes management. Lastly, finger pricking is painful, and some patients may find having to perform it daily as uncomfortable(33).

Interventions to improve quality of life in individuals living with T1DM

Interventions towards psychosocial issues in diabetes have been studied amongst people with T1DM and T2DM. One study looking at psychological interventions to improve self-management concluded that for self-management to be successful, patients not only need to be confident in their abilities but also should be able to observe changes in the specific outcomes(29). Amongst the youth transitioning to adulthood, one study noted a decline in glycaemic control as youth with T1DM assume more responsibilities in diabetes-related tasks. They recommended interventions to enhance impulse control skills to improve outcomes in this group of patients(34). Other interventions that have been studied were related to diabetes distress. In one study, improvements in emotional regulation (ER) and cognitive skills (CS) were associated with a reduction diabetes distress and the authors suggested that interventions to reduce diabetes distress ought to focus on ER and CS(35).

The increased use of continuous glucose monitoring (CGM) in T1DM poses the question of whether this technology can be used as an intervention in the management of people living with T1DM with psychosocial issues. It is important to note that there is a noticeable absence of population-based studies focused on the use of CGM in this specific subpopulation. Concerns have been raised regarding the potential reluctance of individuals with T1DM and psychosocial disorders to engage with technological solutions, which could limit the utility of CGM in this group. If this technology could be found useful in this group of patients, then it could underscore the importance of promoting the adoption and confidence in its use amongst this subpopulation.

1.3 Continuous glucose monitoring (CGM)

1.3.1 Overview and mechanism of action

Continuous glucose monitoring (CGM) is a mechanism of glucose sensing that uses the glucose oxidation reaction. This technology uses a needle which is a platinum electrode, coated with glucose oxidase(36). Once inserted in the subcutaneous tissue, glucose oxidation is ignited and catalysed which leads to production of an electrical current as well as gluconolactone and hydrogen peroxide(36). The electrical current is converted into a glucose concentration. The earlier CGM devices required a few SMBG blood samples to help calibrate the devices. In 2016 however, Abbott commercialized the FreeStyle Libre (FSL) CGM system that did not require a finger prick for calibration(36). The FreeStyle Libre 2 system received the CE mark in 2018 with upgrades that included smart alarms(36). The FSL has a wear time of up to 14 days. There are currently 2 types of personal CGM technologies; intermittently scanned continuous glucose monitoring (isCGM) also known as flash glucose monitoring, and real time continuous glucose monitoring (rtCGM)(37).The isCGM devices require the user to pass the receiver (reader) over the transmitter (sensor) in order for blood glucose readings to be acquired. This process is known as scanning or swiping. An FSL user is required to scan at least once every eight hours in order not to lose glucose data(36). On the other hand, however, 'real time' continuous glucose monitoring (rtCGM) devices transmit glucose data automatically to the receiver or user's smart phone without the need for scanning(37). In addition, rtCGM also gives the user the direction and rate at which the glucose readings are changing. There are also alarms for either impending or actual hypoglycaemia or hyperglycaemia(38). The user can opt out of the low or high readings alarms. The glucose levels for high and low alarms can be set based on the individuals' situation. CGM

devices measure the glucose in the interstitial fluid. There is a time lag of between 5 and 10 minutes between blood glucose and interstitial glucose readings, which has been identified as a potential limitation to CGM(36). The time lag has been observed mainly when the blood glucose is rapidly changing. This can be during or after meals, but can also occur around exercise(39).

CGM can also be used in a blinded form where the person wearing the sensor does not see the glucose readings in real time. The data can then be reviewed retrospectively by the health care professional following the period of monitoring. This allows the health care professional to get the true picture of the person's glucose profile without affecting their behaviour. One example of a blinded CGM is the Freestyle Libre Pro iQ system from Abbott. Others include Medronic iPro2 system(36). When used in real time, the rtCGM user can see current glucose readings as well as the trend on their smart phones or a portable receiver, also known as a reader. Blinded CGMs are used more commonly for research purposes(38).

1.3.2 The use of Continuous Glucose Monitoring (CGM) in T1DM

NICE recommends that all adults with T1DM are offered a choice of real-time (rt-CGM) or intermittently scanned continuous glucose monitoring (is-CGM). This would enable the patients to respond to glucose changes throughout the day(24). The choice between the two technologies is based on the patient's needs, characteristics, individual choice and the functionality of the available device(24).

The use of intermittent scanning continuous glucose monitoring (isCGM) in T1DM in adults has been shown to improve hypoglycaemia awareness, improve glycaemic control, reduce diabetes related distress and acute events including hospital admissions(40-46). In patients with T1DM on

either a continuous subcutaneous insulin infusion (insulin pump) or multiple daily injections, the use of CGM has been shown to improve HbA1c(47).

In addition, the improvement in glycaemic control has also been observed amongst adolescents and young adults with T1DM using CGM over 26 weeks(48). Among adults aged 60 years or older, CGM reduced the time patients spent in hypoglycaemic range compared to self-monitoring of blood glucose (SMBG) by 27 minutes per day(49). Further to that, the use of CGM in elderly patients with well controlled diabetes on multiple daily insulin injections showed high satisfaction with CGM. In fact, there was no additional diabetes distress imposed by CGM(50). A study looking at the effect of isCGM in the older adults showed significant improvements in HbA1c, diabetes-related distress, hypoglycaemia unawareness, and resource utilization in the group of individuals with T1DM (51). In patients living with T1DM and chronic kidney disease, CGM is useful in providing precise estimation of mean glucose as well as glucose variability and other CGM derived indicators. Although it is still unknown whether CGM can improve overall glucose control in patients with CKD and also on dialysis, it none the less provides an alternative and more reliable way of estimating glucose control without using HbA1c which has known pitfalls in CKD and dialysis patients(52).

1.3.3 Comparing real time CGM (rtCGM) to intermittently scanned CGM (isCGM)

Few studies have compared rtCGM to isCGM in T1DM. A study conducted in Belgium compared switching from isCGM to rtCGM in 254 patients with T1DM. The results after 6 months showed that the rtCGM group had significant improvement in time in range and lower HbA1c compared to the isCGM group. There were also fewer cases of severe hypoglycaemia in the rtCGM group(53). After 24 months, switching from isCGM (without alerts) to rtCGM (with alerts) still

showed improved glycaemic control and hypoglycaemia worry(54). This may make the case for use of rtCGM compared to isCGM in countries where this is affordable. The current isCGM (Libre 2) has alarms that users can set for low and high readings.

1.4 Type 2 diabetes (T2DM)

1.4.1 Prevalence of T2DM

Unlike T1DM, T2DM is a chronic metabolic condition characterised by insulin resistance and impaired insulin secretion which leads to high blood sugars(55). The prevalence of T2DM in the UK, just like other Western countries, has been increasing in recent years, largely due to sedentary lifestyles, unhealthy dietary habits, an aging population and obesity(56). In the UK, 4.3 million people live with diabetes. Of these, 90% have T2DM (23). It is estimated that an additional 850,000 people could be living with diabetes but are yet to be diagnosed(23). Although anyone can develop T2DM,it is more common in persons over the age of 25 who have a family history of T2DM(23). Genetic predisposition plays an important role in T2DM risk, but if the modifiable risk factors of diet, exercise and obesity are addressed, many cases of T2DM can be avoided(57).

1.4.2 Pathophysiology and treatment of T2DM

The core pathophysiology of T2DM is due to deficiency of insulin secretion by the islet beta cells of the pancreas, as well as increased insulin resistance in the muscles and the liver(57, 58). As the disease progresses, the production of insulin is unable to maintain glucose homeostasis, which leads to elevated blood glucose(57). Other mechanisms in the pathophysiology of T2DM include accelerated lipolysis, incretin deficiency or resistance, hyperglucagonaemia, increased glucose absorption in the kidneys and insulin resistance in the brain(58, 59). These 8 mechanisms lead to

T2DM and have therefore been targets for the different diabetes medications. National Institute for Health and Care Excellence (NICE) recommends individualising care when managing individuals with T2DM(60). Following a diagnosis of T2DM, individuals should be offered structured diabetes education which includes dietary advice(60). Metformin is offered as the first line medication for patients with T2DM. Other medications can be added and the choice will depend on the glycaemic control of the individual as well as other factors including; comorbidities, individual preferences, tolerability and monitoring requirements(60). During any phase of T2DM treatment, a sulfonylurea or insulin can be introduced if patients develop symptomatic hyperglycaemia(60). Other factors may also influence progression to the use of insulin. One study identified that sitagliptin users were less likely to be initiated on insulin over 6 years when compared to patients on a sulfonylurea ($p=0.003$)(61). In addition, patients with T2DM who show evidence of catabolic state, for example weight loss or ketosis, should be initiated on insulin(62). The introduction of insulin, however, has challenges and may not be the preferred choice for some patients despite not meeting their glycaemic targets. Maximisation of treatment using non-insulin diabetic medications therefore becomes a priority in such groups of patients and delays in intensification of treatment have been reported(63).

1.4.3 Self-Monitoring of Blood Glucose (SMBG) in T2DM

The National Institute for Health and Care Excellence (NICE) does not recommend routine monitoring of blood glucose in adults with type 2 diabetes except in certain situations. These include people living with T2DM on insulin, oral medications that cause hypoglycaemia or a previous history of hypoglycaemia episodes(60). Frequent monitoring of blood glucose in patients with T2DM, on insulin is likely to have added benefits like those seen in patients with T1DM(64).

Self-monitoring of blood glucose (SMBG) in patients with T2DM who are not on insulin remains a subject of debate. One study looking at the impact of self-monitored blood glucose in patients with T2DM on one or more glucose lowering medications including insulin, showed a reduction in glycated haemoglobin (HbA1c) after 16 weeks of 0.82% (65). A cross-sectional observational study however showed no difference in HbA1c among 6495 type 2 diabetes patients who used SMBG and those who did not. This was true for patients treated with either insulin and or oral hypoglycaemic agents(66) A meta-analysis of 12 randomized controlled trials investigating the effects of SMBG on HbA1c levels showed mixed results based on the follow-up period(67). SMBG induced a statistically significant decrease in HbA1c of -0.3 (95% confidence interval -0.4 to -0.1) in nine trials with a follow up period of up to 6 months(67). In the same meta-analysis however, two trials with a follow up period of up to 12 months showed no overall statistically significant decrease in HbA1c induced by SMBG (-0.1 95% CI -0.3 to 0.04). Another study looking at poorly controlled patients with T2DM who were insulin-naive found that structured SMBG led to physicians implementing treatment modification recommendations which were timely, frequent and effective(68). This led to improvements in HbA1c when compared to the active control group(68). A systematic review examined 30 studies involving patients with T2DM doing self-testing of blood glucose(69). This showed that patients and health care professionals often failed to act on the results from the SMBG. It concluded that appropriate education of both patients and health care professionals was required for SMBG to improve the overall glycaemic control. This review also questioned the cost-effectiveness of SMBG(69).

In addition to mixed results regarding reduction of HbA1c, SMBG has been associated with several challenges. One qualitative study among 40 patients with T2DM not on insulin showed that SMBG

could result in anxiety and self-blame if the blood glucose readings remained high during monitoring(70). Another 4-year longitudinal qualitative study explored the perspectives of patients with T2DM about SMBG. The findings showed that some patients saw glucose readings as a proxy to good and bad behaviour(71). This may potentially affect the frequency and consistency of testing. This study also saw no evidence that SMBG could be used to cause or maintain behavioural change(71). For SMBG to be effective, patients must be in position to self-adjust their drug treatment. Further research is needed to explore the circumstances under which SMBG causes anxiety and or depression(69). In newly diagnosed patients with T2DM, SMBG has been found to have no effect on glycaemic control but is associated with higher depression scores(72). Given the inconsistent evidence of the benefits of SMBG on glycaemic control in T2DM patients not on insulin, the probable psychosocial issues associated with using SMBG as well as the cost(73), there is need to explore the role of newer technologies of blood glucose monitoring in patients living with T2DM.

1.4.4 Psychosocial issues in T2DM

Depression and anxiety amongst people living with T2DM has been associated with poor medical outcomes and less than expected engagement in selfcare(74). A study carried out in the United States of America amongst adolescents showed that those with T2DM had more depression and a poorer quality of life when compared to T2DM(75). The authors concluded that the psychosocial burden had an impact on the glycaemic control, with poor quality of life contributing to suboptimal glycaemic control(75).

1.5 Diabetes distress

1.5.1 Definition and prevalence of diabetes distress

Living with diabetes can be a psychological burden. Diabetes distress (or diabetes related distress-DRD) is defined as the negative emotional impact of living with diabetes (76). Depending on the tool used to assess it, diabetes distress is experienced in relation to treatment regimens, current diabetes related complications as well as the fear of future complications and distress related to food, hypoglycaemia, and to health care worker interactions(76). Diabetes distress is common in both T1DM and T2DM across people of all age groups and has been shown to be present in all countries where it has been studied(77). Although there exists a correlation between diabetes distress and depression, the two are distinct from each other. The prevalence of diabetes distress in T2DM was estimated in a meta-analysis to be 36% in 2017(76). The estimates in T1DM put the prevalence of diabetes distress at 20 to 40%(77). According to Diabetes UK, evidence from 50 studies has shown that one in four people living with T1DM and one in five people with T2DM have high levels of diabetes distress(78).

1.5.2 Measurement of diabetes distress

Several tools have been developed and validated to measure diabetes distress. The most commonly used tools are; Problem Areas In Diabetes (PAID) and the Diabetes Distress Scale (DDS)(76).PAID was developed in the 1990s as a measure of psychosocial adjustment specific to diabetes(79). In its current form, the questionnaire is made up of twenty questions. Each question has 5 possible answers with values between 0 and 4. Participants are asked to choose the number that gives the best response. The responses are on a scale with “0” representing no problem and

"4" representing a very serious problem(78). The scores for each item are summed and then multiplied by 1.25 to generate a total score, which is out of 100. Individuals with total score of 40 have severe diabetes distress(80). DDS was developed in 2005 to measure psychosocial distress in diabetes(81). The questionnaire is made up of 17 questions (DDS17). Each question has up to 6 possible responses (1 to 6). Participants are asked to choose the number that best represents how they feel regarding each question. Response "1" represents "not a problem" while "6" represents a "very serious problem"(82).The DDS17 produces a total distress score and four sub scale scores. The subscales correspond to different kinds of distress including emotional burden, regimen-related distress, physician related distress and interpersonal distress. Mean scores are calculated by adding up the responses to the appropriate items and then dividing by the number of items in each scale/subscale. Individuals are grouped as having high diabetes distress if their mean item score is 3 or higher(82).

1.6 Continuous glucose monitoring in T2DM

1.6.1 The use of CGM in patients with T2DM on insulin

In T2DM, there is progression to relative insulin deficiency over time, which eventually necessitates the use of insulin(64). The current National Institute for Health and Care Excellence (NICE) guidelines on the use of isCGM outline the criteria that people living with T2DM on multiple daily insulin injections must fulfil if they are to be offered the technology(60). Among the indications include; severe or recurrent hypoglycaemia, impaired hypoglycaemia awareness or if they are unable to do SMBG due to a medical condition or disability(60). Real-world data from the Swedish National diabetes register showed that the use of FreeStyle Libre (FSL) for 6 and 12 months amongst patients with T2DM who were previously naïve to CGM significantly reduced

their HbA1c(83). In this study, 79% of the patients were treated with insulin. Further to this, a meta-analysis of 75 real world observational studies, 13 of which involved the use of FSL in T2DM showed a reduction in Hba1c of -0.59% (-6.5mmol/mol) which continued through 4.5 to 7.5 months(84). The reductions are sustained for 12 months in people with T2DM. In another study, retrospective analysis of real world data involving FSL in patients with T2DM on rapid acting insulin, the use of isCGM caused a 61% reduction in acute diabetes-related events and a 32% reduction in all-cause inpatient hospitalisations(85). These reductions were independent of gender or age.

In clinical trials, the use of CGM in patients with T2DM on multiple daily insulin injections has also shown significant improvements in HbA1c. A meta-analysis of 7 randomized controlled trials (RCTs) comparing CGM to SMBG showed that HbA1c and time spent in hypoglycaemia were lower in the CGM group compared to SMBG(86). CGM however did not have an effect on blood pressure and body weight. In another prospective study examining the use of FSL in T2DM, after 12 weeks, it showed a reduction in HbA1c and hypoglycaemia episodes. In addition, this study also demonstrated an improvement in diabetes self-management(87). Improvement in patient reported satisfaction has also been documented in prospective observational study following use of isCGM(88).

1.6.2 The use of CGM in people living with T2DM not on insulin

Patients with type 2 diabetes not on insulin are not included in the NICE guideline as a group to be considered for isCGM. A randomised controlled trial amongst T2DM patients not on insulin examined the effect of intermittent short-term use of rtCGM on the HbA1c at six months. The findings showed a reduction in HbA1c at three months amongst the groups that received at least

one session (1 week) of rtCGM. At six months however only the group that received two sessions of rtCGM (1 week per session, 3 months apart) achieved a significant HbA1c reduction(89). Evidence from another study in T2DM patients suggests an improvement in HbA1c (1.01% or 10.12mmol/mol decrease in HbA1C) using retrospective continuous glucose monitoring. This improvement was independent of patients being on insulin or not(90). Further to this, a retrospective observational study involving 728 T2DMs patients on non-insulin treatments showed a significant reduction in HbA1c of -1.6% ($p<0.001$)(91). An expert opinion on the use of isCGM in T2DM patients, not on insulin, stated that the use of isCGM improves HbA1c and time in range(92). It further lists added benefits of isCGM in this cohort which included among others; improvement in diabetes distress and behaviour modification(92). More studies are however needed to further assess the effect on diabetes distress and the cost effectiveness of CGM when used in patients not yet on insulin.

1.7 Challenges of using CGM

Continuous glucose monitoring has been reported to have challenges associated with it. These may occur when used as part of sensor augmented insulin pumps or when used in isolation in patients with T1DM or T2DM. Among adolescents and children using CGM as part of sensor augmentation, one study highlighted alarm fatigue as one of the challenges. In addition, problems related to sensor application including reaction to adhesive, pain on sensor insertion, sensors falling off accidentally as well as bruising/local bleeding at the site of the sensor were reported(93). In a study amongst patients using insulin pumps or CGM or both, more than half reported skin problems, with itching being the commonest complaint. This study also identified an association between skin problems and increased diabetes related distress(94). Another

limitation of CGM is its lower accuracy when used during exercise. This may be because of the lag time between blood glucose and interstitial fluid glucose which is thought to increase to up to 15 minutes during exercise. This may lead to over or underestimation of blood glucose(95). During the earlier days of introduction of CGM amongst middle aged and older people living with T2DM in Taiwan, some participants in a qualitative study found CGM somewhat inconvenient and perceived introduction of CGM as a mark of disease progression. The same study however still found CGM to be helpful in diet and behaviour modification(96). Lastly, as more and more patients increase the use of CGM and other diabetes related technologies including insulin pumps for example, there is an increase in the amount of diabetes care technology waste (DCTW)(97). Questions are raised to the manufacturers of these technologies regarding reduction of waste and increasing the number of components in these products that can be recycled to minimize the carbon footprint. It is likely that as this technology becomes more readily available throughout the world, manufacturing companies will have to create new solutions to the ever-increasing amount of waste generated through their use.

In the next section, we describe a background to adrenal insufficiency, another chronic endocrine condition.

1.8 Adrenal insufficiency: causes and diagnosis

Adrenal insufficiency is characterized by a relative or absolute lack of cortisol production from the adrenal glands. Secondary adrenal insufficiency (SAI) is more common than primary adrenal insufficiency (PAI) and is a result of conditions affecting the pituitary gland(98, 99). These conditions lead to destruction of the pituitary gland, resulting in reduced adrenocorticotropic

hormone (ACTH) production. Examples include pituitary tumours, inflammation or infiltration(99). Among pituitary tumours, adenomas are the commonest causes of SAI. Other hypothalamic-pituitary tumours include craniopharyngiomas and meningiomas(100). Tertiary adrenal insufficiency (TAI) refers to decreased stimulation of the pituitary gland by the hypothalamus to secrete ACTH. It is the most common form of adrenal insufficiency and is due to exogenous use of glucocorticoids(98). Glucocorticoid doses equivalent to more than 5mg of prednisolone, taken over 4 weeks irrespective of the route (parenteral, oral, topical, or inhaled) can suppress the hypothalamic-pituitary-axis, leading to adrenal insufficiency(100). PAI is rare. In adolescents and adults, it is caused by autoimmune adrenal destruction whereas congenital adrenal hyperplasia (CAH) is the commonest cause in childhood(101).

The diagnosis of adrenal insufficiency is based on measurement of cortisol alongside the stimulatory hormone (ACTH) and may involve stimulation tests(98). A cortisol level below 100nmol/L with a raised ACTH is sufficient to diagnose primary adrenal insufficiency(102). Cosyntropin (Synacthen) stimulation can be used to confirm adrenal insufficiency. Cortisol is checked at baseline, and then at 60 minutes after administration of 250microgram of Synacthen(102). Baseline ACTH helps to differentiate between primary and secondary adrenal insufficiency. The gold standard for identifying adrenal insufficiency is the insulin stress test also known as the insulin tolerance test. It involves measurement of cortisol levels during insulin induced hypoglycaemia. This test is however contraindicated in patients with epilepsy, ischemic heart disease or severe hypothyroidism(102). In such cases, the glucagon stimulation test can be used as an alternative. Irrespective of the cause, treatment involves replacement of cortisol. The overall goal is to try and establish a cortisol replacement regimen that mimics the physiological

diurnal variation in the production of cortisol(98). This varies from individual to individual based on their needs.

1.8.1 Quality of life in adrenal insufficiency

Despite development of steroid replacement therapies, people with adrenal insufficiency have been shown to have reduced QOL as well as increased morbidity and mortality(15, 100, 103). A systematic review on the QOL in patients with adrenal insufficiency found that these patients had reduced quality of life irrespective of adrenal hyperfunction or hypofunction. It also concluded that despite biochemical remission following treatment, quality of life was not completely reversed to the pre-morbid state in these individuals(104). In fact, patients with isolated adrenal insufficiency with no comorbidities still have impaired quality of life compared to controls(100). Despite these findings, there is evidence to suggest that quality of life may be related to under or over replacement in patients with established glucocorticoid regimes. The available hydrocortisone preparations may not mimic the physiological circadian cortisol production, and this may in turn affect QOL.

On the other hand, however, people with adrenal insufficiency may have comorbidities. In addition to trying to closely match cortisol rhythmicity during steroid replacement, the treatment of associated comorbidities can improve outcomes in adrenal insufficiency. Comorbidities in patients with adrenal insufficiency may include panhypopituitarism, poor quality sleep, infertility, deranged metabolic profile and sexual dysfunction(105). One study showed improvement in well-being and sexuality in women with adrenal insufficiency following dehydroepiandrosterone (DHEA) replacement(106). Similarly, administration of 25mg of daily DHEA to adolescent girls with

secondary adrenal insufficiency caused a significant improvement in their psychological well-being(107).

1.8.2 Measurement of quality of life (QOL) in adrenal insufficiency

The World Health organization (WHO) defines quality of life as "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"(108). The QOL can be assessed using qualitative methods including structured interviews. Although such qualitative means can collect data which quantitative methods would not be able to collect, they require a skilled interviewer, are time consuming and only a small number of respondents can be included in the interview. Validated questionnaires have been used as quantitative methods to assess QOL in patients with adrenal insufficiency. One systematic review reported a total of 92 tools that had been used in different studies to assess aspects of QOL(104). The SF-36 is the most widely used questionnaire. It is made up of 36 questions spread across 8 scales. The eight scales measured include physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotion and mental health(109, 110).

1.8.3 Treatment of adrenal insufficiency

Treatment of adrenal insufficiency is by oral glucocorticoids. The endocrine society recommends use of hydrocortisone (15-25mg) or cortisone acetate (20-35mg) per day in two or three divided doses(111). The same society guideline also recommends Prednisolone (3-5mg) daily as an alternative to hydrocortisone. Monitoring is by clinical response including assessment of signs of steroid excess, energy levels, weight and postural hypotension(111). In addition to steroid replacement, patients must be educated and this empowers them to better manage their

condition(102). Patients taking hydrocortisone three times a day are advised not to take the last dose of hydrocortisone too late as it may cause insomnia(102). A study undertaken amongst patients with adrenal insufficiency showed significant heterogeneity in the type of steroid taken as well as doses, frequency and timing of the medication. It showed most patients were taking hydrocortisone (87.4%) but up to 25 different regimens were being used to administer 20mg of hydrocortisone a day(112). Although the different combinations may reflect clinicians' efforts to individualize patients' requirements based on lifestyle and quality of life, these multiple combinations further highlight the lack of data to support an optimal regime that clinicians and patients could rely on. One study looked at the effect of dual-release hydrocortisone (DR-HC) in patients with secondary adrenal insufficiency. The results showed significant reduction in waist circumference and body mass index. However, high-density lipoprotein (HDL) reduced following use of DR-HC(113)

1.8.4: Hydrocortisone

Hydrocortisone immediate release tablets remain the cornerstone of cortisol replacement in patients with adrenal insufficiency with the majority receiving hydrocortisone compared to other glucocorticoids. Results from a randomised controlled trial on different doses of hydrocortisone concluded that the pharmacokinetics of hydrocortisone can differ up to 10-fold between individuals(114). Factors such as the rate of absorption and the half-life of cortisol in circulation play a role in determining the overall exposure to glucocorticoids in an individual(115). This would in turn affect the dosing schedule that would be ideal for those individuals. In a pharmacokinetic study of cortisol involving patients with adrenal insufficiency, the authors identified that a treatment regime of 10+5+5mg at 0730 hours, 1200 hours and 1630 hours gave the highest

proportion of simulated patients within the physiological targets. Despite this however, up to 54% of patients would remain under or over treated at 0800 hours which further highlights the importance of individual dosing(116). Rectal administration of 100mg of hydrocortisone results in absorption of only a small proportion with a mean absolute bioavailability of only 4.5% in patients(117).

1.8.5 Prednisolone

Up to 20-26% of patients with adrenal insufficiency are treated with prednisolone(118, 119). Real world data from the UK has identified no significant difference in resource utilisation between patients treated with immediate release hydrocortisone compared to prednisolone(119). A study carried out to optimise prednisolone dosing in patients with adrenal insufficiency concluded that once daily prednisolone doses of 2-4mg were both safe and effective in patients with adrenal insufficiency(120). Titrations of prednisolone doses could be achieved by using a single 4 hour, 6 hour or 8 hour single time point drug level(120). Other studies have also argued that prednisolone replacement mimics the circadian rhythm more closely than other glucocorticoids and have provided further evidence to support once daily dosing of prednisolone(121, 122). There is still a lack of studies comparing low dose prednisolone (2-4mg) to current multiple regimens of immediate release hydrocortisone.

Chapter 2: Effect of intermittently scanned continuous glucose monitoring (isCGM) in people with diabetes with a psychosocial indication for initiation

2.1 Introduction

The nationwide audit for FreeStyle Libre (FSL), a form of intermittently scanned continuous glucose monitoring (isCGM), conducted by the Association of British Clinical Diabetologists (ABCD) in the United Kingdom has provided real-world insights into the use of isCGM and its effect on several key aspects of diabetes care(41-43). The use of isCGM has been shown to significantly improve glycaemic control, hypoglycaemia awareness and to reduce diabetes related distress(40-46, 123, 124)

Type 1 diabetes (T1DM) is a chronic condition that requires continuous management to achieve glycaemic control and prevent long-term complications. Managing T1DM can be challenging, and individuals with T1DM often face a significant burden of disease management(125). This can include monitoring blood glucose levels, administering insulin, managing diet and exercise, and dealing with potential complications. Despite the best efforts of individuals with T1DM to manage their condition, it can be difficult to achieve glycaemic targets, which can lead to long-term complications such as retinopathy, neuropathy, and nephropathy(126). According to the International Diabetes Federation, the global prevalence of T1DM is estimated to be around 1 in 300 people, with an estimated 1.1 million children and adolescents living with T1DM worldwide(127). In addition to the physical challenges of managing T1DM, individuals with the condition may also experience diabetes-related distress, which can have a significant impact on

their quality of life(128, 129). Diabetes-related distress can be caused by factors such as the constant need for self-management, fear of hypoglycaemia, and anxiety about long-term complications(129). The prevalence of diabetes-related distress among adults with T1DM ranges from 10% to 45%, depending on the measurement tool used(43, 130). Recognising the significant psychological burden that people with T1DM face, the National Health Service England (NHSE) in 2019 published national guidance to support glucose monitoring in this population. The guidance recommends using continuous glucose monitoring (CGM) systems, which can provide individuals with glucose data and help them to make informed decisions about their diabetes management(131). The guidance also recommends that healthcare professionals provide education and support to help individuals with T1DM manage their condition more effectively and reduce the burden of disease management(131-133). One of the criteria set out in this guidance for initiation of isCGM in T1DM at that time, was for psychosocial reasons(131). In clinical practice, the decision to initiate isCGM for psychosocial reasons was determined by the Diabetes multi-disciplinary team (MDT). Examples of diagnoses in this category include (but are not limited to), depression, anxiety, sleep disorders and risk of suicide. Other indications for initiation of isCGM were also outlined in this guideline(131).

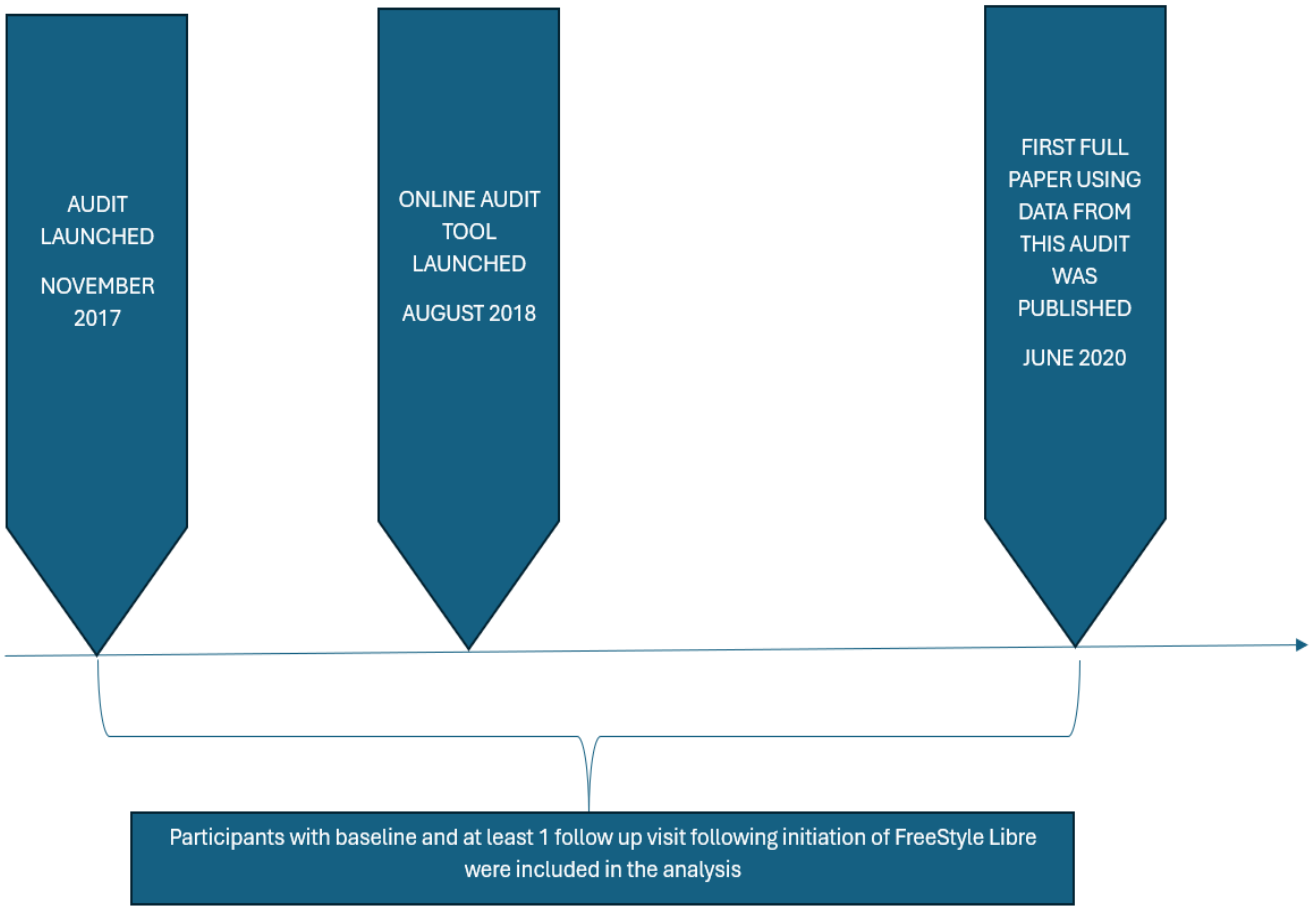
There are no data looking at the effect of isCGM on glycaemic control, diabetes-related distress and resource consumption in people living with diabetes who were started on isCGM for "psychosocial" reasons. It is unclear to what extent the benefits of isCGM identified from previous studies would be seen in this cohort of patients. The objective of this study therefore was to use data from the ABCD FSL national audit to understand the effect of intermittently scanned

continuous glucose monitoring in people living with diabetes with a psychosocial indication for access to isCGM.

2.2 Materials and methods

The study was performed using baseline and follow-up data from the Association of British Clinical Diabetologists (ABCD) nationwide audit of people with diabetes who initiated the isCGM (FreeStyle Libre 1) in the United Kingdom. Clinicians from 102 NHS hospitals across the whole of the UK submitted FSL user data(43). This nationwide audit was launched in November 2017 with an online tool launched in August 2018. The baseline and follow-up data were collected as part of routine clinical care (see figure 2.1). Baseline data, reason for initiation of isCGM, previous diabetes structured education, hypoglycaemia awareness using the GOLD score(134), diabetes-related distress (DRD) and demographics were collected. DRD was assessed using the two-item diabetes-related distress scale (DDS)(135) defined as the average of the two-item score of greater or equal to three (≥3). The DDS asks respondents to indicate the degree to which each item may be bothering them in their life. If the item is not a bother or a problem for them, they indicate "1" and they would indicate "6" if the item is very bothersome. The two items are 1) Feeling overwhelmed by the demands of living with diabetes, 2) Feeling that I am often failing with my diabetes routine. People living with diabetes were categorized into two groups: those with high DRD, defined as an average DDS score of ≥3 and those with low DRD, expressed as a DDS score of < 3. Baseline and follow up data were also collected on hypoglycaemia, severe hypoglycaemia, admission with hyperglycaemia/Diabetic ketoacidosis (DKA) and Haemoglobin A1c (HbA1c).

Figure 2.1: Timeline of the ongoing ABCD FreeStyle Libre Audit



2.2.1 Ethical approval

The ABCD nationwide audit program has Caldicott Guardian approval. The program is an audit, not research. The NHS encourages audit of clinical practice. There are guidelines, which were followed, that contributing centres only collect data from routine clinical practice, and all data collected were anonymized at the point of submission to the central secure online database.

2.2.2 Research Methods

The study was conducted using the national ABCD-FSL audit data. The audit consisted of baseline and follow-up forms, where clinicians were able to input the demographics, clinical characteristics and the indications for starting isCGM. Data was also collected at baseline and follow-up for resource utilisation, such as paramedic callouts, hospital admissions for hyper and hypoglycaemia and DKA, one year prior to starting isCGM and during the follow-up period after starting isCGM.

2.2.3 Statistical methods

We compared the baseline characteristics of participants by indication of isCGM initiation. We then restricted the analysis to participants initiated on isCGM for psychosocial reasons who had at least one follow-up visit following the initiation of isCGM. We used the Chi-square test to assess the difference between categorical variables, while the t test assessed the difference in pre and post isCGM continuous variables.

To identify factors associated with a reduction in DDS, the change in diabetes distress following use of isCGM was modelled as a dependent variable in a linear logistic regression model with age, gender, baseline body mass index (BMI), duration of diabetes, time in range (TIR), baseline DRD and number of scans per day as independent predictors. All statistical analyses were performed using R statistical software (v4.1.2; R Core Team 2021).

2.3 Results

The study consisted of 17,036 people with diabetes, of which 1314 (7%) were initiated on isCGM because of a ‘psychosocial’ indication. Table 2.1 compares the demographic characteristics of two

groups: those using isCGM for psychosocial indication (n=1314) and those using isCGM for other indications (n=15722).

There was no significant difference in the number of females between the two groups (47% vs 50%, P=0.28). The mean duration of diabetes was significantly shorter in the isCGM for psychosocial indication group (15.7 ± 13) years compared to the isCGM for other indication group (20.8 ± 4.9) years (P<0.001). Participants with isCGM for psychosocial indication had a higher mean baseline HbA1c (80.4±18.6 mmol/mol) compared to the other group (70.2±18.6 mmol/mol) (9.5% Vs 8.6%) (P<0.001). The mean baseline DDS score was higher in the psychosocial indication group (3.5±1.5) compared to the other indications (2.8±1.3) (P<0.001). The isCGM for psychosocial indication group had a lower mean baseline Gold score (2.1±2.8) compared to the isCGM for other indication group (2.35±1.3) (p=0.002). The percentage of individuals using insulin pump therapy was significantly lower in psychosocial indication group (9%) compared to the other indication group (19%) (P<0.001). The median number of times the psychosocial indication group tested blood glucose levels (SMBG) was 4.5 (IQR 4-6) per day. This was lower than the group initiated on isCGM for other indications (Median is 7 (IQR- 4-8).

Table 2.1: Demographic characteristics of the study population

	isCGM for psychosocial indication (n=1314)	isCGM for other indication (n=15722)	P-value
Age (years)	38.9 (±17.7)	40.7 (±18.5)	**<0.001**
Type 1 diabetes n (%)	1275(97%)	15140(96%)	0.17
Number (%)Female	618 (47%)	7861 (50%)	0.28
BMI (kg/m^2)	25.7 (±7)	26(±23.8)	0.3
Duration of diabetes (years)	15.7(±13)	20.8(±4.9)	**<0.001**
Baseline HbA1c	80.4(±18.6) (9.5%)	70.2(±18.6) (8.6%)	**<0.001**
Baseline DDS score	3.5(±1.5)	2.8(±1.3)	**<0.001**
Baseline Gold score	2.1 (±2.8)	2.35(±1.3)	**0.002**
% on Insulin Pump	9%	19%	**<0.001**

DDS=Diabetes Distress screening score, BMI=Body mass index

Unfortunately, this variable (SMBG) was missing in more than 50% of the sub-population initiated on isCGM for psychosocial indication.

Of the 1314 participants initiated on isCGM for psychosocial reasons, follow up data was available for 327 participants. The prevalence of DRD was high in this study population. 76% had high DRD.

With the initiation of isCGM, after a mean follow-up period of 6.9 months, there was a significant reduction in DRD. The median DRD score fell from 4 (IQR=2.8-5) at baseline to 2.5 (1.5-3.0) at follow-up (P<0.001) as shown in figure 2.1. In addition, the prevalence of high DRD reduced from 76% at baseline to 38% at follow up. This represents a 50% reduction in DRD (P<0.001).

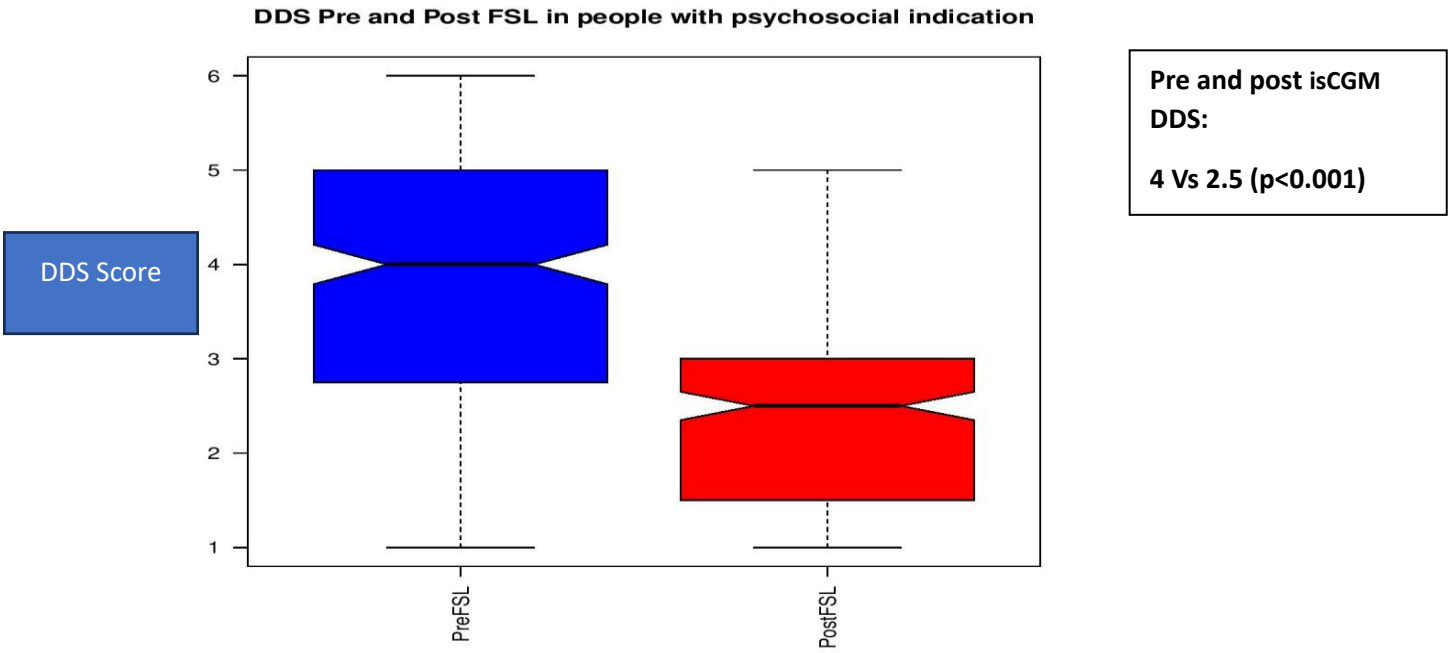


Figure 2.2: Distribution of Diabetes Distress scores change pre- and post-isCGM use in the ABCD nationwide audit of isCGM for participants initiated on isCGM for psychosocial reasons: FSL=Free Style Libre, DDS=Diabetes distress screening , isCGM=Intermittently scanned continuous glucose monitoring.

There was also a significant reduction in the HbA1c with the use of isCGM (figure 2.3). The mean HbA1c decreased from 78.5 mmol/mol (equivalent to 9.3%) at baseline to 66.5 mmol/mol (equivalent to 8.2%) at follow up (P<0.001).

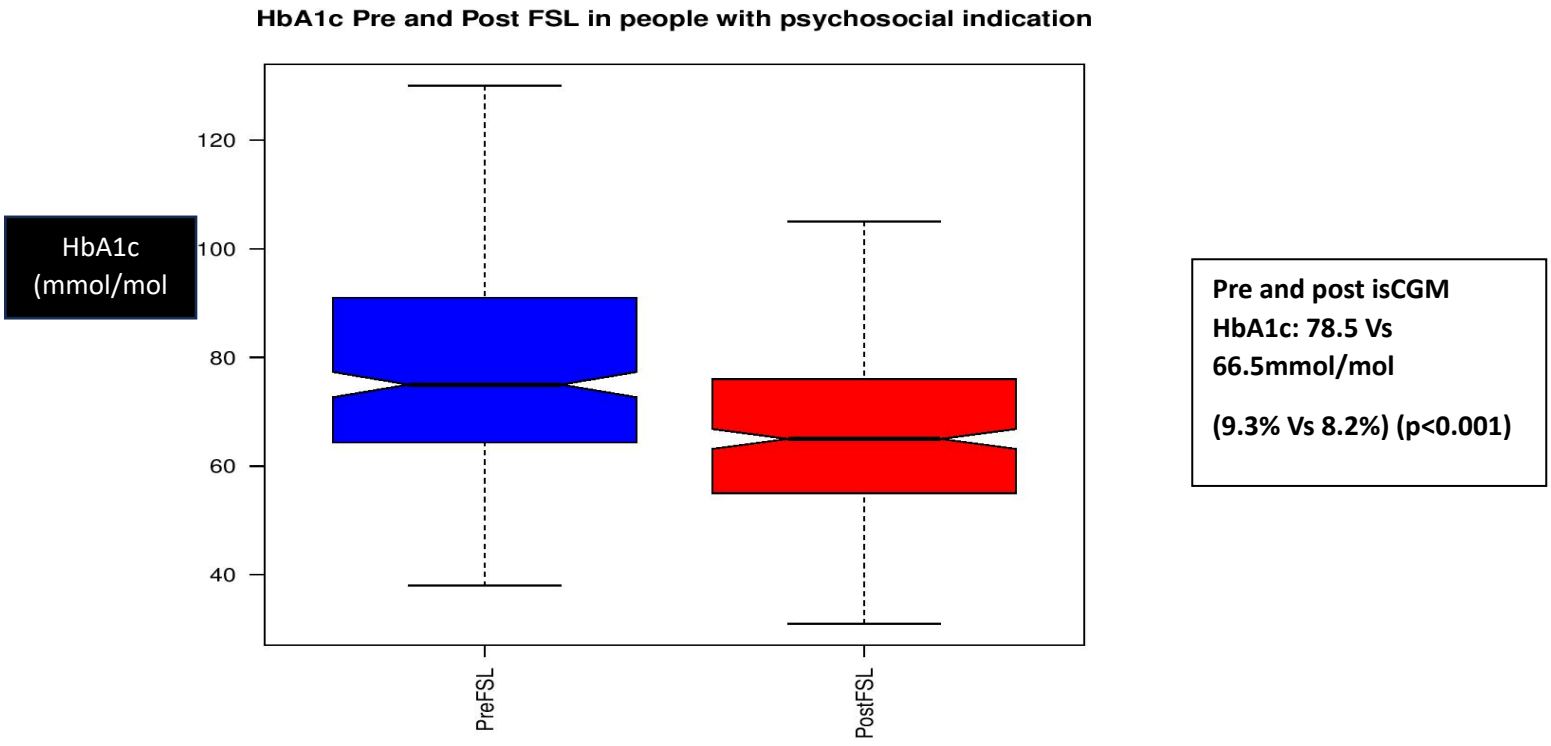


Figure 2.3: Distribution of HbA1c change pre- and post-isCGM use in the ABCD nationwide audit of isCGM for participants initiated on isCGM for psychosocial reasons:

FSL=Free Style Libre, isCGM=Intermittently scanned continuous glucose monitoring.

The use of isCGM was not associated with a change in Gold score; median (IQR) Gold scores pre and post isCGM were similar, 2 (1-3) (P=0.44). This group experienced a reduction in some diabetes-related acute events but not others. The number of hospital admissions due to hyperglycaemia/DKA reduced from 40 in 12 months at baseline, to 3 in 7 months at follow up, representing an 87% reduction (P<0.0001). Hypoglycaemia-related admissions reduced from 7 admissions in 12 months at baseline to 1 admission in 7 months, although this reduction was not statistically significant (P=0.154). Similarly, paramedic call outs for hypoglycaemia reduced by 74%

(from 13 call outs in 12 months at baseline to 2 call outs in 7 months at follow up), but this was not statistically significant(P=0.059).

The factors associated with a reduction in DRD at follow-up (Table 2.2) were time in range (β = 0.015 [±0.004]) (*P*<0.001), baseline DDS score (β = 0.611 [±0.056]) (*P* <0.001) and number of isCGM scans per day (β =0.023 [±0.010]) (*P* =0.02). BMI, age, duration of diabetes and gender were not associated with reduction in DRD following use of isCGM. The model however only explained 47.8% of the variation in DRD following isCGM use (adjusted R^2 = 0.478).

Table 2.2: Linear regression model showing factors associated with reduction in Diabetes-related distress following use of isCGM

Characteristic	**Beta (β)**	**Standard error**	**P value**
Age	0.010	0.006	0.066
Gender (female)	-0.019	0.161	0.907
BMI	0.002	0.014	0.889
Duration of diabetes	0.001	0.006	0.915
Time in range	0.015	0.004	**<0.001**
Number of scans per day	0.023	0.010	**0.02**
Baseline DDS score	0.611	0.056	**<0.001**

2.4 Discussion

In this nationwide study, we show that the prevalence of diabetes-related distress (DRD) is remarkably high in those with psychosocial indication for use of isCGM. Three in every four participants had high DRD. Our study shows that the use of isCGM in individuals initiated for psychosocial reasons improved glycaemic control, as well has having reduced DRD and resource utilisation.

In the national audit data, we have previously shown a reduction in HbA1c of 5.5 mmol/mol with the use of isCGM in the people living with diabetes. A similar reduction in HbA1c was seen in the Flash UK randomized control trial (136). However, in this subgroup of people living with diabetes with a psychosocial indication for isCGM initiation, we show a larger improvement in the mean HbA1c of 12mmol/mol. This is possibly because these participants had a higher baseline HbA1c. Furthermore, those with a psychosocial indication for isCGM had high DRD which is known to negatively impact glycaemic control.

Our study showed a significant reduction in DRD, with a nearly 50% reduction in the overall DDS. The use of isCGM has previously been associated with a reduction in diabetes related distress in the larger national UK audit(43). Another observational study reported a reduction in DRD following the use of isCGM. The same study however noted unexplained likelihood of increase in anxiety and depression scores with use of isCGM(137). Our study has also shown that the number of scans performed by an individual per day and time in range were associated with a reduction in diabetes-related distress. These data demonstrate an association rather than causation and further work to explore the relationship between DRD and the interaction and subsequent benefit from diabetes technology is much needed. Although our study showed a significant reduction in

DDS in this subgroup of population it remains to be seen if there is a return to baseline levels of DDS or a worsening of DDS with long-term use of isCGM. Population based studies with large follow-up time will be needed to answer this question.

Regarding hospital admissions, the findings of our study agree with two observational studies(137, 138) of T1DM patients using isCGM that showed fewer admissions with DKA. One of these studies(137), like our findings, reported no changes in the GOLD scores. In our study, the use of isCGM did not reduce hypoglycaemia related admissions or paramedic call outs due to hypoglycaemia. The use of isCGM did not affect hypoglycaemia awareness in this group of participants, in contrast with the wider ABCD audit results, which showed significant improvement in hypoglycaemia awareness following use of isCGM. This likely reflects the fact that impaired awareness of hypoglycaemia was also an indication for isCGM funding, and this group were the most likely to demonstrate benefit in terms of Gold score. This is further supported by the fact that the cohort with a psychosocial indication had good hypoglycaemia awareness at baseline (median GOLD score of 2), indicating normal hypoglycaemia awareness.

Our study has several limitations. This is an observational study with no comparator arm, and hence a randomized controlled trial will be needed to confirm these findings. In addition, although the prevalence of psychosocial issues in this population may be comparable to the general T1DM population, follow-up data was available for only 25% of them. This may not be representative of the whole population. Furthermore, the high DRD in this population are likely related to patient selection with the 'psychosocial indication' criteria; it is possible that the high DRD itself contributed to the initiation of people on isCGM. Nonetheless, we show a significant

reduction in DDS and improvement in glycaemic control and resource utilization in this subgroup of people with diabetes.

The NICE UK guidelines released in March 2022(139) now recommend isCGM or real time Continuous Glucose Monitoring (rtCGM) to all adults living with T1DM. These recommendations will widen access and ensure more equitable access to this technology, which has been shown in multiple studies to improve a range of clinical and psychological outcomes. Further work is now required to explore the wider impact of isCGM on psychological outcomes in those living with T2DM and rarer forms of diabetes.

2.4.1 Conclusion

This analysis of real-world data of people with T1DM using isCGM initiated for psychosocial reasons shows a significant improvement in DRD, glycaemic control and hospital admissions due to hyperglycaemia/DKA.

Chapter 3: Effect of introduction of FreeStyle Libre monitoring on glycaemic control in people with type 2 diabetes mellitus (T2DM)

3.1 Introduction

The prevalence of type 2 diabetes (T2DM) in the UK, just like other Western countries, has been increasing in recent years, largely due to sedentary lifestyles, unhealthy dietary habits, an aging population and obesity(56). In the UK, 4.3 million people live with diabetes, of which 90% have T2DM(23). The National Institute for Health and Care Excellence (NICE) recommends individualising care when managing individuals with T2DM(60). Although several new classes of pharmacological agents have been developed, a significant number of people living with T2DM remain with suboptimal glycaemic control(140). There is a need to optimize treatment of individuals with T2DM before the introduction of Insulin.

For adults living with T2DM who are not on insulin, NICE does not recommend routine monitoring of blood glucose unless they are on medications that cause hypoglycaemia or have a previous history of hypoglycaemia episodes(60). However, with the advent of Continuous Glucose Monitoring (CGM), many people with T2DM have started monitoring their blood glucose levels using these devices. One such device, the FreeStyle Libre system, is a form of intermittent scanning Continuous Glucose Monitoring (isCGM) that measures interstitial fluid glucose. The system is composed of a single use sensor, placed on the back of the upper arm which lasts 14 days. The individual scans the sensor using a compatible smartphone, or a separate portable reader and 'real-time' glucose levels can be obtained every 15 minutes(141-143).

The use of isCGM in people with T2DM has been widely studied in people on basal insulin, bolus insulin or basal-bolus insulin regimes(144-146). Real world evidence in T1DM shows that the use of isCGM is associated with significantly improved glycaemic control(43). However, evidence for the effect of isCGM on glycaemic control has been limited in populations living with T2DM, but not yet on insulin(89-91).

There is some evidence to suggest that the use of CGM can be used as a teaching tool to help individuals with T2DM with lifestyle modifications and behavioural change (147, 148). The changes to the blood glucose seen on the isCGM can influence the patient's choice of food and the level of physical activity(148). It is possible that through these mechanisms, isCGM can positively impact the overall glycaemic control. This study therefore sought to assess the effect of introduction of isCGM on glycaemic control and diabetes distress in people living with T2DM on non-insulin medications. This study is presented in two parts. The impact of isCGM on glycaemic control is presented in chapter 3 while chapter 4 of this thesis will present the impact on diabetes distress.

3.2 Materials and methods

3.2.1 Study site

The study was carried out at the Allam Diabetes Centre, Hull University Teaching Hospitals NHS Trust (HUTH), in Hull. The protocol and informed consent forms were approved by West Midlands - The Black Country Research Ethics (No. 22/WM/0152). The trial was registered at ClinicalTrials.gov (NCT05597293) and conducted in accordance with the Declaration of Helsinki.

3.2.2 Study design

This was a prospective, randomised, open-labelled, pilot study. Participants meeting the inclusion criteria and who consented to participate in the study were randomised on a 1:1 ratio to receive either FreeStyle Libre 2 (Libre 2) or FreeStyle Libre pro iQ (Libre Pro). Randomisation was carried out using an online randomisation tool to allocate a participant to a treatment group (https://www.sealedenvelope.com/simple-randomiser/v1/trials/fsl-in-t2dm).

3.2.3 Study population

The study was conducted amongst adults with T2DM, aged ≥ 18 and ≤ 75 years old who met the inclusion criteria.

3.2.4 Sample size

This was a pilot, proof of concept study, as there was little evidence, or experience, to guide expectations and determine an appropriate target difference for two arms in the study (Libre 2 vs Libre pro iQ in deteriorating T2DM). Forty participants who met the inclusion criteria for the study were recruited. Each study arm (Libre 2 Vs Libre Pro) therefore had 20 patients (1:1 ratio).

3.2.5 Primary and secondary outcomes

Primary outcome

a) Fall in HbA1c of 5.5 mmol/mol at 12 weeks

Secondary outcomes

a) Time in range at 12 weeks compared between the FreeStyle Libre 2 arm and Libre Pro arm.

b) A change in weight at 12 weeks.

c) A change in hip and waist circumference.

d) A change in quality of life measured using the diabetes distress screening questionnaire (DDS-17). This outcome is evaluated in detail in chapter 4 of the thesis.

3.2.6 Conduct of the study: Approaching potential participants

All Consultant Diabetologists, diabetes specialist nurses and Specialty Registrars in HUTH were informed about the study, and recruitment flyers were put up in the clinic rooms. All willing and eligible participants were referred to the study coordinator or study physician for screening which was performed against the participant's past medical history and point of care HbA1c (done during their routine clinical care). The clinical research team provided a full verbal explanation of the study and a Participant Information Sheet (PIS). Participants were given time to read over the PIS at home and discuss it with friends, family, and their GP if they wished before a baseline visit was booked.

3.2.6 Informed consent

Participants gave their written informed consent prior to participation in any study procedures. The investigator discussed the study with the participant, talking through the participant information sheet and explaining the nature and scope of the study, potential risks and benefits of participation and answered any questions the participants had. Potential participants were given ample time to consider their participation and to ask questions. For some that desired, they took a copy of the participant information sheet and a sample of the informed consent document home to review with friends and family members prior to deciding whether to participate. If the participant was willing to participate, they signed and dated the informed consent form, which

was also countersigned by the investigator. One copy of the informed consent was given to the participant while another was retained within the participant's notes and the original in the site study file. After providing informed consent each participant was assigned a unique participant identification number. The participant ID number was documented on the screening/enrolment log with the participant's date of enrolment. The screening/enrolment log was retained only at the study site. All participants enrolled in the study had a letter sent to their GP informing them of enrolment in the study and providing a brief study overview.

3.2.7 Eligibility criteria

After obtaining informed consent, participants were screened for eligibility. Participants were enrolled if they met all the inclusion criteria and none of the exclusion criteria as described below.

Inclusion criteria

- Males and females living with type 2 diabetes mellitus (T2DM) who are aged ≥ 18 years and ≤ 75 years.
- On one or more non-insulin glucose-lowering agents.
- HbA1c ≥ 69 mmol/mol. This cut off was chosen because previous studies had shown a bigger reduction in HbA1c in participants whose baseline HbA1c is higher(43)
- Able to provide written consent.

Exclusion criteria

- Participants with a life expectancy of less than 1 year.
- Participants with cognitive dysfunction or neurological disorder, which would interfere with regular flash glucose monitoring.

- Participants with chronic kidney disease (CKD) with eGFR < 45ml/min/1.73m^2 .
- Participants with decompensated liver disease.
- Participants with decompensated congestive cardiac failure.
- Myocardial infarction in the preceding 3 months or if percutaneous coronary intervention is planned in the next 6 months.
- Participants on supra-physiological doses of steroids, for example, Prednisolone for the treatment of Rheumatoid arthritis.
- Participants on active dialysis or planned for dialysis treatment during the study.
- Individuals who were participating in another device or drug study that could affect glucose measurements or management.
- Women who were pregnant, breastfeeding or planning to become pregnant. Women of childbearing age were to use a reliable form of contraception throughout the study.
- Participants who were already using continuous glucose monitoring (CGM).
- Participants who had pacemakers, implanted cardioverter defibrillator devices or neurostimulators.
- Participants with an allergy to medical grade adhesives.
- Participants who received a blood transfusion in the preceding 3 months or if a blood transfusion is planned during the study.
- Participants who had a medical intervention which could alter the red blood cell (RBC) life span e.g. Chemotherapy/Major surgery (blood loss) in the preceding 3 months or if planned during the study.

- In the investigators' opinion if the participant was unsuitable to participate in the study for any other reason.

3.2.8 Study procedures

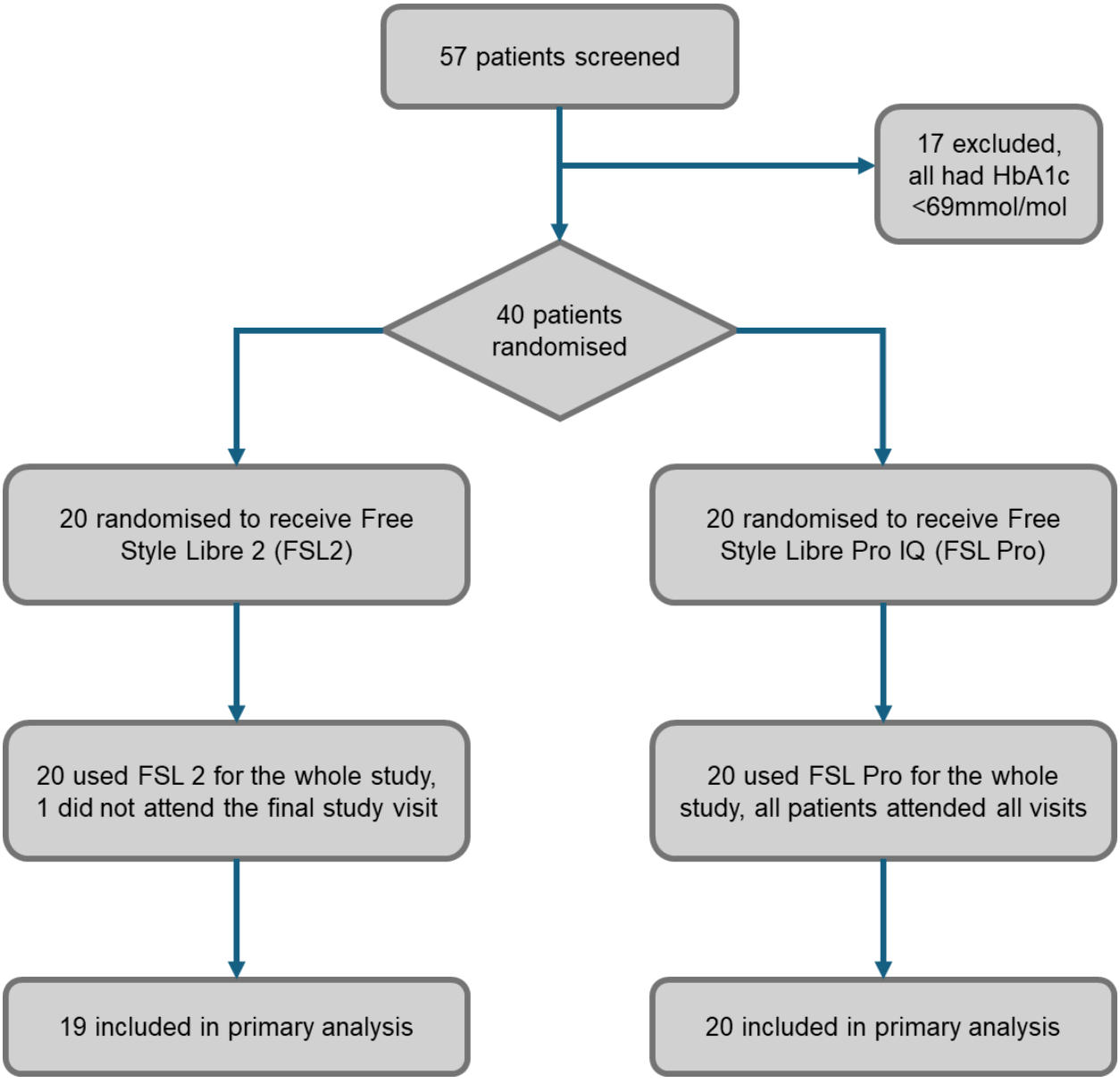


Figure 3.1: Flow chart showing participant screening, enrolment, randomisation, and study completion following the 12 weeks in the FSL study: FSL=Free Style Libre

3.2.8.0 Randomisation

Randomisation of eligible participants was performed using online randomisation software (Sealed envelope). Participants were assigned in a 1:1 ratio to either FreeStyle Libre 2 (intervention arm) or FreeStyle Libre Pro (control).

3.2.8.1 Study intervention

Free Style Libre 2

The FreeStyle Libre 2 (Libre 2) sensor system was the intervention used in those randomized to this study arm. The FSL monitoring System uses a subcutaneously implanted electrochemical sensor, which incorporates wired enzyme glucose sensing technology to monitor glucose levels in interstitial fluid. The system consists of three primary components:

a) A disposable on-body assembly (Sensor) that incorporates a subcutaneously implanted electrochemical glucose sensor and associated electronics.
b) A disposable sensor insertion device (Sensor Kit), consisting of two secondary components (Sensor Applicator and Sensor Pack), which is used to insert the sensor tail about 5.5 millimetres (mm) below the surface of the skin and to adhere the sensor to the skin of the participant.
c) A handheld device (Reader) which collects and displays glucose readings obtained from the sensor during a scan; the reader has a user interface, which includes event-logging features.

The System allows the user to query glucose data from the sensor by bringing a handheld reader close to the sensor. The act of scanning a sensor provides the user with real-time glucose measurements (glucose values) accompanied by trend information (glucose arrows) that are presented on the reader display. The reader, based upon glucose sampling performed by the sensor, calculates the real-time glucose measurements and glucose arrows. The sensor automatically stores glucose data every 15 minutes. During a scan, which takes less than a second, the preceding 8 hours of glucose data are transferred to the Reader, where that data is logged and may be viewed by the user. The sensor has an 8-hour memory capacity and must be scanned at least every 8 hours to ensure complete data capture by the Reader. The System is intended for single participant use. The Reader can only pair to one Sensor at a time; if the Reader activates a sensor, it cannot activate a second one without discontinuing its interaction with the first. The Sensor is disposable and may be worn for up to 14 days before it must be replaced.

Participants in this study arm who had compatible mobile phone devices were allowed to use their phones to scan instead of readers. The Libreview app was downloaded by the participant onto their smart phone. A Libreview account was then created by the study team and patients logged onto their phones using the account created by the study. Data would then be shared with the study team as the participants used their mobile phones to scan the sensors.

FreeStyle Libre Pro iQ

The Libre pro iQ monitoring system was used for participants randomized to this study arm. It is a continuous ambulatory glucose monitoring device using a similar principle to the Libre 2

monitoring system with a crucial difference, where the participants using the Libre pro iQ device are blinded from the real-time glucose information. As we hypothesised that FSL monitoring may cause behavioural change in participants, resulting in more engagement in self-management of their condition, the Libre pro iQ device acted as the control group as participants were unaware of their blood glucose readings in real time. On the other hand, participants using the Libre 2 monitoring system were actively aware of their glucose readings and were able to make decisions to address them in real time. Participants randomised to the Libre pro iQ device continued self-blood glucose monitoring as per their routine. There was no requirement for self-monitoring of blood glucose in those who were not testing prior to the study.

Using self-adhesive pads, a sensor measuring 5mm × 0.4mm was applied to the back of the upper arm by the investigator. No participant interaction was required. Once applied and activated, the Libre Pro sensor measured and stored glucose readings every 15 minutes for 14 days. The sensor would be removed after 14 days and brought to the next study appointment. The investigator used the Libre pro iQ reader to scan the sensor and download the glucose results. This information provides a snapshot view of a participants' glycaemic control facilitating effective treatment decisions from the treating clinician(149).

3.2.8.2 Study visits: Libre 2 arm

Participants randomized to this study arm had 3 study visits in total; screening visit (visit 1), visit 2 and the final visit, visit 3. Below is an outline of the study activities for each visit.

Visit 1 – Week 1 (day 0)

1. Informed consent.

2. Medical history and physical examination.
3. Anthropometric measurements (height, weight, hip, waist circumference and body mass index).
4. Blood pressure and pulse after the participant was seated for 5 minutes.
5. Point of care HbA1c (Siemens DCA Vantage® Analyzer).
6. A urine pregnancy test was performed to exclude pregnancy in women of childbearing age. Participants of childbearing age were requested to use a barrier method for contraception for the duration of the study. Three pregnancy testing kits were provided, so a test could be done by the participant every month till the end of the study.
7. Sealed Envelope online randomisation system was used to randomize the participant
8. Participants randomised to Libre 2 received face to face education on the application and routine use of the Libre 2 sensor. Participants that had compatible mobile phones downloaded the Libreview app onto their smart phones. The study team created an account, and this allowed the patient to use their phones to scan. Data was shared from the patient's account to the study's Libreview account.

9. Blood sampling for Full blood count, Iron profile, CRP, Liver function, Renal function, Bone profile, Coagulation profile and Lipid profile.
10. A Diabetes Distress Screening (DDS) tool was completed. A paper copy was used.
11. One Libre 2 sensor was applied, and the participant received a further 3 sensors. Each of the sensors was to be applied on day 14 and 28 by the participant. One spare sensor was provided at this visit for use, in case of a faulty sensor or if it needed to be changed prematurely, for example during medical imaging.

Visit 2 – Week 6 (day 42)

1. Participants were assessed for eligibility and safety to continue the study.
2. Screened for any adverse effects, changes to medication or compliance issues regarding wearing the device.
3. Point of care HbA1c (Siemens DCA Vantage® Analyzer).
4. Data from the Libre 2 sensors were downloaded for participants who used a reader for scanning. Participants who used their phones had data automatically uploaded as they scanned with their phones.
5. Libre 2 sensor was applied at this visit (day 42) and activated. Participants received a further 2 sensors to be applied at day 56 and 70 by the participant. All previous sensors were returned to the research team.
6. Educational elements for use of Libre 2 sensor system were reinforced.

Visit 3 – Week 12 (day 84)

1. Blood samples were collected for Full blood count, Iron profile, CRP, liver function, renal function, bone profile, coagulation profile and lipid profile.
2. Point of care HbA1c (Siemens DCA Vantage® Analyzer).
3. Anthropometric measurements (weight, hip, waist circumference and body mass index).
4. Blood pressure and pulse after the participant was seated for 5 minutes.
5. Completed the paper copy of the DDS questionnaire

6. Data from the Libre 2 sensors were downloaded for participants who used the reader for scanning.

7. All sensors were removed and returned to the research team.

3.2.8.3 Study visits: Libre Pro iQ arm

Visit 1 – Week 1 (day 0)

1. Informed consent.
2. Medical history and physical examination.
3. Anthropometric measurements (height, weight, hip, waist circumference and body mass index).
4. Blood pressure and pulse after seated for 5 minutes.
5. Point of care HbA1c (Siemens DCA Vantage® Analyzer).
6. A urine pregnancy test was performed to exclude pregnancy in women of childbearing age. Participants of childbearing age were requested to use a barrier method for contraception for the duration of the study. Three pregnancy testing kits were provided, so a test could be done by the participant every month till the end of the study.
7. Randomised to the Libre 2 monitoring system or the Libre pro iQ system using Sealed Envelope online randomisation system.
8. Blood sampling for Full blood count, Iron profile, CRP, Liver function, Renal function, Bone profile, Coagulation profile and Lipid profile.
9. A Diabetes Distress Screening (DDS) tool was completed (paper version).

10. Participants received face to face education on the application and use of the Libre pro iQ system. No participant had to apply the Libre Pro sensor
11. Libre pro iQ sensor applied
12. Instructed to remove the sensor after 2 weeks and bring it at the next visit

Visit 2 – Week 6 (day 42)

1. Participants were assessed for eligibility and safety to continue the study.
2. Screened for any adverse effects, changes to medication or device incidents regarding wearing the device.
3. Point of care HbA1c (Siemens DCA Vantage® Analyzer).
4. Data from the Libre pro iQ sensors were downloaded.
5. Libre pro iQ sensor applied. All previous sensors were returned to the research team.
6. Instructed to remove the sensor after 2 weeks and bring it at the next visit

Visit 3 – Week 10 (day 70)

1. Participants attended the research centre and had a Libre Pro sensor applied and activated on day 70.
2. Data from the Libre pro iQ sensors were downloaded.
3. Adverse events and changes to medication discussed and documented
4. Instructed to remove the sensor after 2 weeks and bring it at the next visit

Visit 4 – Week 12 (day 84)

1. Blood samples were collected for Full blood count, Iron profile, CRP, Liver function, Renal function, Bone profile, Coagulation profile and Lipid profile.

2. Point of care HbA1c (Siemens DCA Vantage® Analyzer).
3. Anthropometric measurements (weight, hip, waist circumference and body mass index).
4. Blood pressure and pulse after seated for 5 minutes.
5. Completed the DDS tool.
6. Data from the Libre pro iQ sensors were downloaded.
7. Libre pro iQ sensor removed and all sensors returned to the research team

3.2.9 Data Management

Source data

Demographics, physical examination, vital signs, body weight, height, BMI, dates of visits and assessments were recorded on the case report forms (CRFs). The CRFs were completed at the time of the participant's visit, and they therefore reflected the latest observations about the participant. Different CRFs collected data at different visits, and these reflected the study arm of the participant. The CRFs also captured data on the sensors applied and those given to the patient to insert when appropriate. Other information collected included comorbidities and concomitant medication. Pathology results were available on the hospital's electronic records system. Pathology reports were printed, reviewed and signed before being inserted into participants' medical records.

Sensor data

Libre 2 and Libre pro data was downloaded onto the Libre view website. The study created a professional account on Libre View which only study staff had access to. Patients were given login details that were unique using their study numbers. Data collected by the patients using their

phones for scanning was shared with the study team and downloaded onto the study's Libre View account. Data from the Libre View account was printed per participant and stored in the study folders.

Database and data entry

The data from the source documents was entered into the study database created in Microsoft Excel. All the data entered was anonymized by only the participant's study number. Participant pathology results were transcribed from the Trust's electronic patient record system onto the database. The database is kept on NHS computers on the Trust's secure networks that are password protected. HUTH IT Services Department had a backup procedure approved by auditors for disaster recovery of files held on the Y drive servers. Servers were backed up to disk media each night. The final dataset was sent to the sponsor prior to the statistical analysis.

3.2.10 Data analysis plan

This was a pilot, proof of concept study, as there was little evidence, or experience, to guide expectations and determine an appropriate target difference for two arms in the study (Libre 2 vs Libre pro iQ) in deteriorating T2DM. Forty participants, who met the inclusion criteria for the study, were recruited. Each study arm (Libre 2 Vs Libre Pro) therefore had 20 patients (1:1 ratio).

Analysis was performed following the intention to treat principle. Baseline characteristics were described per study arm. For continuous variables, median values (25^{th} and 75^{th} percentiles) were presented unless otherwise stated. The primary analysis was a comparison between control and intervention groups of the change in HbA1c level from baseline to 12 weeks. We also compared, between the groups, the proportions of participants who achieved the primary outcome and

those that needed pharmacological optimisation due to clinical deterioration in HbA1c, using the Chi-square test. For sensor data, we compared the change in the following items from 2 weeks to 12weeks between the 2 study groups: time in range, glucose variability, glucose management indicator, average glucose, high glucose (10-13.9mmol/L) and very high glucose (>13.9mmol/L) using the T-test. Anonymized data were analysed using R statistical package (R Foundation for Statistical Computing Platform; version 3.5.6).

3.3 Results

A total of 57 potential participants were screened. Out of these, we enrolled 40 participants, with 20 individuals randomised to each study arm, namely the FreeStyle Libre 2 (Libre 2) arm and the FreeStyle Libre Pro IQ (Libre Pro) arm (Figure 3). All participants in the Libre Pro arm completed the 4 visits within the 12 weeks of the study. In the Libre 2 arm, nineteen participants (95%) completed the study. One participant did not attend the final visit but continued to use the Libre 2 sensors and sensor data were therefore available (Figure 3.1).

Overall, the median age at screening was 59.5 (IQR:54.75 to 64.25) years. Gender distribution revealed that 57.5% were male. The median diabetes duration was 8.5 (IQR: 6-14) years and the median HbA1c was 78.5 (IQR: 74.8-86) mmol/mol. At baseline, 5 participants (12.5%) were using a Glucagon like peptide-1 Receptor Agonist (GLP-1RA). On average, participants were using 2.25 (SD:0.84) non-insulin antidiabetic medications. Table 3.1 shows participant characteristics according to the randomized group.

Table 3.1: Baseline characteristics of participants randomised to either Libre 2 or Libre Pro glucose monitors.

Variable	Libre 2 arm n=20	Libre Pro IQ arm n=20
Age at screening (years)	59.5 (54-62)	60.5 (55.5-65.8)
Females, n (%)	9 (45%)	8 (40%)
BMI (kg/m^2)	33.6 (29.0-36.9)	31.2 (28.8-33.7)
Duration of diabetes (years)	8 (5-14)	10 (6-13)
HbA1c (mmol/mol)	79 (75-86)	78 (75-84)
Total cholesterol (mmol/L)	4.5 (4-5)	4.0 (4-5)
Systolic blood pressure (mmHg)	131 (123-139)	134 (115-141)
Diastolic blood pressure (mmHg)	82 (77-87)	82 (76-86)
Hip Circumference (cm)	110 (104-119)	109 (99-118)
Waist circumference(cm)	112 (103-123)	109 (100-115)
Number of oral antidiabetic medication, mean (SD)	2.35(0.93)	2.15(0.75)

Primary outcome

Overall, 53% (10/19) of participants in the intervention arm achieved a reduction in HbA1c of 5.5mmol/mol or more compared to 35% (7/20) in the Libre pro arm (p=0.34). Eight participants in the Libre 2 arm (42%) achieved an HbA1c reduction of 5.5mmol/mol or more without rescue

medication. The corresponding proportion in the Libre Pro IQ arm was 25%. These 2 proportions were not statistically different when compared (p=0.32). A total of eleven participants received non-insulin oral 'rescue' medication due to deterioration in their HbA1c during the study. Of these, five participants (45%) were in the intervention group while 6 were in the control group. The 2 proportions of participants who received rescue medication were comparable (p=1).

Glycaemic control

After 12 weeks of follow up, the mean HbA1c reduced from 82mmol/mol, to 74mmol/mol in the Libre 2 arm, representing a 9.8% reduction in HbA1c. There was no reduction in the mean HbA1c in the Libre pro IQ arm (81mmol/mol at baseline and follow-up). When compared to Libre Pro, the use of Libre 2 led to a reduction in mean HbA1c of 8mmol/mol. This reduction was, however, not statistically significant (p=0.136).

In the intervention group, the use of Libre 2 resulted in a reduction of mean Glucose Management Indicator (GMI) from 70mmol/mol at baseline to 64mmol/mol after 12 weeks. There was no change in the mean GMI in the Libre pro arm (69mmol/mol at baseline and follow up). The use of Libre 2 therefore resulted in an average reduction in GMI of 5mmol/mol when compared to the control group. This difference was, however, not statistically significant (p=0.30) (Table 3.2).

Secondary outcomes

CGM data

Data from CGM metrics for hypoglycaemia, hyperglycaemia and glucose variability were comparable between study groups except for the Time in Range (TIR). In the Libre 2 arm, the average TIR was 30% at baseline, increasing to 50% at follow up. In the Libre Pro arm, TIR was 37% and 39% at baseline and follow up, respectively. The use of FreeStyle Libre 2, therefore, increased the mean time in range at 12 weeks by 18 percentage points (CI 2-35, p=0.028) as shown in figure 3.2. There was no difference between groups in the changes observed in high glucose readings (Time >10mmol/L but <13.9mmol/L). In the Libre 2 arm, the average time that participants spent in high readings was 42% at 2 weeks, reducing to 33% at 12 weeks. The corresponding time for the Libre Pro arm was 39% at 2 weeks, reducing to 35% at 12 weeks. The mean difference between the 2 arms was -5% (p=0.382). The use of FreeStyle Libre 2 did not significantly impact time spent in very high glucose readings (Time above 13.9mmol/L) or average glucose (p=0.21 and 0.11 respectively) (see Table 4). No participants experienced an episode of hypoglycaemia. The time spent below 3.9mmol/L was zero for all participants including those participants who were taking a sulfonylurea.

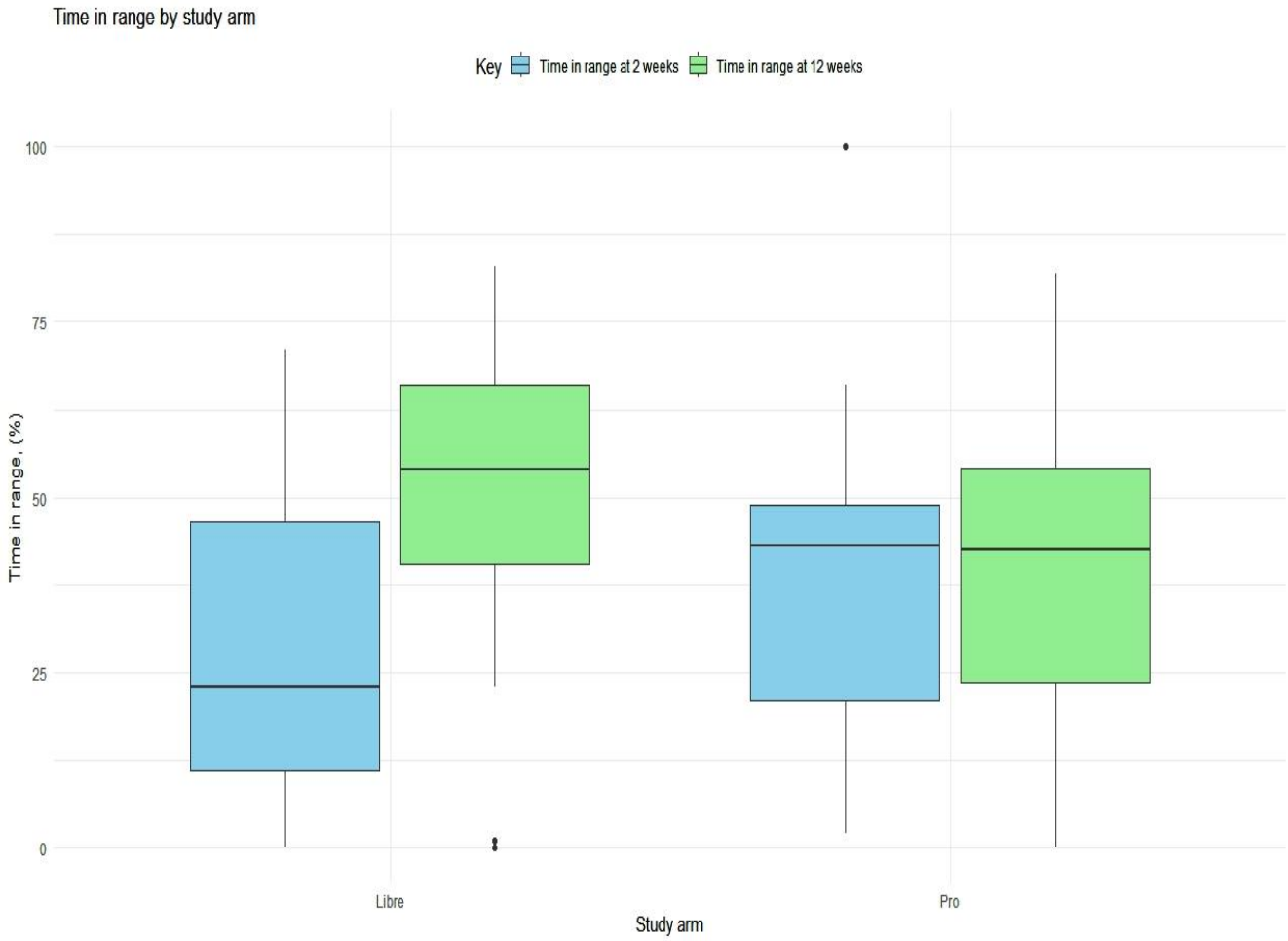


Figure 3.2: Box plot showing the percentage of time that participants spent in the desired glucose range (3.9-10mmol/L) at 2 weeks and 12 weeks between the Libre 2 arm (Libre) and the Libre Pro arm (Pro)

Exploratory outcomes

As shown in table 3.2, the use of FreeStyle libre 2 had no effect on body mass index (BMI) and related waist or hip circumference. The mean systolic blood pressure was 130mmHg in the Libre 2 arm, reducing to 127mmHg in 12 weeks. The corresponding change in the Pro arm was from 130mmHg at baseline to 127mmHg at follow up. These changes were not statistically significant when compared between groups (P=0.89).

Table 3.2: Baseline and week 12 outcome measures for the Libre 2 and Libre Pro arms

Outcome measure	Libre 2 arm		Libre Pro arm		Difference of the difference		
	Baseline Mean (SE)	Week12 Mean (SE)	Baseline Mean (SE)	Week 12 Mean (SE)	Mean Difference	CI	P value
HbA1c (mmol/mol)	82(2)	74(3)	81(2)	81(4)	-8	-19 – 3	0.136
BMI (kg/m^2)	33.2(1.2)	33.2(1.3)	32.1(1.2)	31.9(1.2)	-0.1	-0.5– 0.3	0.697
Time in Range (%)	30(5)	50(6)	37(6)	39(5)	18	2– 35	**0.028**
Time above 10 but<13.9mmol/l (%)	42(3)	33(3)	39(3)	35(4)	-5	-17 – 7	0.382
Time above 13.9mmol/L (%)	27(5)	17(6)	25(5)	26(6)	-12	-32 – 7	0.212
Glucose variability (%)	24.6(1.2)	24.4(1.1)	23.6(1.8)	24.3(1.8)	-0.2	-3.9 – 3.5	0.917
Average Glucose (mmol/L)	12.2(0.5)	10.9(0.7)	11.6(0.5)	12(0.7)	-1.6	-3.6 – 0.4	0.109
Glucose management Indicator(mmol/mol)	70 (3)	64(3)	69(2)	69(3)	-5	-16 – 5	0.30

Total cholesterol (mmol/L)	4.6(0.2)	4.3(0.2)	4.5(0.3)	4.4(0.2)	-0.2	-0.8 – 0.5	0.606
Triglycerides	2.8(0.5)	2.6(0.6)	2.4(0.2)	2.7(0.5)	-0.6	-1.5 – 0.3	0.15
Haemoglobin (g/L)	145(3)	143(3)	144(3)	143(3)	0.3	-4.2 – 4.8	0.889
Hip circumference (cm)	112(3)	114(3)	109(3)	109(3)	1.6	-2.5 – 5.7	0.431
Waist circumference (cm)	112(3)	114(3)	110(3)	110(3)	0.5	-1.9 – 2.8	0.692
Systolic blood pressure (mmHg)	130(3)	127(2)	130(3)	127(4)	0.6	-9 – 10	0.893
Diastolic blood pressure (mmHg)	82(2)	77(2)	82(2)	81(2)	-2	-9 – 5	0.543

CI= confidence interval, SE=standard error, HbA1c-Glycated haemoglobin, BMI=body mass index

3.4 Discussion

In this pilot study, we observed an 8mmol/mol reduction in HbA1c following the use of isCGM among adults with T2DM on non-insulin treatment, however this was not statistically significant. We also show that the use of isCGM was associated with a significant improvement in TIR of 18 percentage points in people with T2DM.

The non-significant reduction in HbA1c in this study is similar to findings from a randomised controlled trial that compared the use of isCGM to self-monitoring of blood glucose (SMBG) in people with T2DM not on insulin(150). In this study, like ours, both SMBG and isCGM reduced HbA1c at 12 weeks compared to their respective baseline. There was however no significant between group difference at 12 weeks(150). Significant between group reductions in HbA1c were however reported at 24 weeks(150). Similarly, another randomised controlled trial comparing intermittent rtCGM to SMBG found no between group difference in HbA1c at 12 weeks(151). In the IMMEDIATE trial however, different to our findings, the use of isCGM led to a smaller but significant reduction in HbA1c of 3mmol/mol compared to control(152). This study however used a bigger sample size of 116 participants and a longer follow up period of 16 weeks and included a component of diabetes self-management education, which may have impacted the results(152). It is therefore possible that significant changes to HbA1c following isCGM use in people living with T2DM require more than 12 weeks to be observed.

We show in our study that the use of isCGM increased the time that participants remained within the target glucose range (3.9-10mmol/L). Our results agree with another study that showed that the use of isCGM increased the time patients remained in target within a 24-hour period(150).

Similarly, another trial using intermittent rtCGM reported a clinically meaningful, more than 5% increase in TIR after 8 weeks, despite a modest, non-significant reduction in HbA1c(151). The current study has however shown no significant reduction in the average glucose levels following isCGM use despite the increase in TIR.

There are some limitations to our study. Although this was a pilot study, with no means of calculating the sample size, a comparable study(152) which was published during the course of our study shows that our sample size was small. In that study, for an absolute difference of 8% in the primary outcome, for 80% power, 50 participants were required in each arm. Using results from our study however, 53% of participants in the Libre 2 arm achieved a reduction in HbA1c of 5.5mmol/mol or more (primary outcome) compared to 35% in the control arm. To have an 80% chance of detecting as significant, at 5% level, 116 participants would be required in each arm, bringing the total number of participants to 232.

There were no serious adverse events throughout the study. No hypoglycaemia events occurred in either study arms. One case of skin rash occurred to one participant in the Libre pro arm which was mild. No adverse events were related to using the study isCGM devices.

3.4.1 Conclusion

The use of isCGM in T2DM patients on non-insulin therapy showed promise in improving glycaemic control, as evidenced by increased TIR. There was however no significant reduction in HbA1c. Improvement in TIR suggests isCGM could potentially have long-term benefits in this population including delaying insulin initiation.

Chapter 4: The Effect of FreeStyle Libre monitoring on Diabetes Distress in people with T2DM not on insulin

4.1 Introduction

Studies in people living with T2DM have identified varying levels of DRD across the different countries. The differences in the prevalence of DRD reported by different studies could be due to the composition of the participants, the tool used to measure DRD but could also be related to ethnicity (153).For example, the prevalence of DRD was 63.7% in Iran(154), 49.2% in Malaysia(155) and 37.6% in Ethiopia(156). A cross-sectional study undertaken in Thailand amongst T2DM patients in primary care showed a prevalence of DRD of 8.9%(157). In the same study, high HbA1c was positively associated with high levels of DRD. There is therefore a link between DRD and poor glycaemic control(158). A study in China identified age, smoking and diabetes complications as factors associated with DRD in a multiple regression analysis(159). There is also evidence suggesting that duration of diabetes and glycaemic control are associated with high levels of DRD(160). Using the Diabetes Distress Scale-17 items (DDS17), diabetes distress can further be subdivided into the components contributing to the most distress. These are emotional burden, physician related distress, regimen related distress and interpersonal distress(79). In a cross-sectional study in Saudi Arabia amongst patients with T2DM, 25% of patients had moderate to severe DRD of which emotional distress was the most prevalent, followed by physician-related distress(161). Other studies have indeed highlighted emotional distress as the most prevalent form of diabetes related distress(162-164). In young adults with

youth onset T2DM, one study reported that 40% of the participants had high regimen-related distress. It further reported that treatment with insulin was associated with a high emotional burden(165). There is an indirect correlation between DRD and self-reported adherence to treatment (SRAT). Low SRAT and high levels of DRD lead to overall poor glycaemic control(166).

The use of intermittently scanned continuous glucose monitoring (isCGM) in people living with T1DM with psychosocial issues has been shown to reduce levels of DRD(167). In patients living with T2DM, one study showed preliminary evidence that real time continuous glucose monitoring (rtCGM) did not increase diabetes distress(168). Furthermore, the use of continuous glucose monitoring (CGM) amongst a small proportion of T2DM patients in a cross-sectional study was associated with a reduction in disease burden(169). Data on the effect of isCGM on diabetes distress in patients with T2DM not on insulin are scarce. We hypothesize that cohorts of people living with T2DM with poor glycaemic control will have high levels of diabetes distress. The use of isCGM would delay the introduction of insulin which would reduce emotional distress. It is also hypothesized that isCGM would improve the overall glycaemic control which in turn is likely to reduce DRD and improve the quality of life in this cohort.

4.2 Materials and methods

4.2.1 Design

This study involved participants who were enrolled in the FreeStyle Libre (FSL) randomized controlled trial. Twenty participants were randomized to the intervention arm (FreeStyle Libre 2) while 20 participants were randomized to the control arm (FreeStyle Libre Pro IQ). All participants were required to complete 2 Diabetes Distress Scale (DDS) 17 questionnaires; one at enrolment

(day 0), and the second at the end of the study (after week 12). The questionnaires were self-administered and were completed in the clinic room during the visits in a paper form.

4.2.2 Measures

The DDS questionnaire is made up of 17 items. It assesses the negative emotions and stressors associated with living with T2DM. Participants were required to rate how much each of the items listed was a problem over the past month. The responses are on a scale from 1 to 6 (1=not a problem, 6=very significant problem). The different components of DRD (emotional burden, physician related distress, regimen related distress and interpersonal distress(79)) are calculated using the 4 subscales from the DDS questionnaire(165). The emotional burden subscale (feeling overwhelmed, fearful) was calculated from items 1, 3, 8, 11 and 14 of the questionnaires. Regimen-related distress (feeling badly about not managing diabetes well was calculated from items 5, 6, 10, 12 and 16 of the questionnaires. Interpersonal distress (receiving insufficient support from family/friends) is calculated from items 7, 13 and17 whereas physician related distress (worries about health care provider expertise and support was calculated from items 2, 4, 9 and 15(165). Mean item scores were calculated to produce the overall DDS score as well as subscale mean scores. In this study, a score ≥3 was considered high DRD.

4.2.3 Statistical analysis

Descriptive statistics were used to describe the participants' characteristics by the intervention arm. The overall and subscale average scores were calculated. Proportions of participants with overall and subscale average DDS scores of ≥3 were calculated. We compared proportions of participants with high DRD (overall and in the subscales) by intervention arm using the Chi-square test. $P<0.05$ was statistically significant.

Multivariate logistic regression model was used to identify the factors associated with having high DRD. Similar multivariate logistic regression models were created for the individual components (forms) of DRD.

4.3 Results

Forty participants were enrolled in the study. Details of the baseline characteristics are described in chapter 3 of this thesis. The median age was 59.5 (IQR: 54.75 to 64.25) years. Overall, 42.5% of the participants had diabetes for more than 10 years. 18 (45%) participants had a baseline HbA1c of greater than 80mmol/mol. Regarding medication, fourteen participants were on 3 or more medications while 20% were on gliclazide, a sulfonylurea. Twenty-seven (67.5%) of the participants were obese. The distribution of the additional baseline characteristics by intervention group are shown in table 4.1.

Table 4.1: Baseline characteristics of participants

Variable	Libre 2 (N=20)	Libre Pro IQ (N=20)
Age (years)	59.5	60.5
Diabetes for >10 years n (%)	8(40%)	9(45%)
HbA1c>80mmol/mol n (%)	9(45%)	9(45%)
On gliclazide n (%)	4(20%)	4(20%)
On total ≥3 oral antidiabetic medication n (%)	9(45%)	5(25%)
BMI <30 Kg/m^2 n (%)	7(35%)	6(30%)

Using the 2-item diabetes distress screening questions (DDS2), 20 (50%) participants had high diabetes distress at baseline. At the start of the study, the overall mean (SD) DDS2 score was 2.7(±1.3). The mean DDS score was 2.6 at baseline in the Libre 2 arm, reducing to 2.4 at follow up. The corresponding score in the Libre Pro arm was 2.8 and 2.7 at baseline and follow up, respectively. The mean reduction in DDS2 score was 0.3 following the use of Libre 2, although this was not statistically significant (p=0.47).

Using the total DDS-17 score, 11 (27.5%) participants had high diabetes distress at baseline. The mean total DDS-17 score was 2.4(±1.1) at the start of the study. The mean DDS score was 2.3 at

baseline in the Libre 2 arm, reducing to 1.8 at follow up. The corresponding score in the Libre Pro arm was 2.5 and 2.3 at baseline and follow up, respectively. The mean reduction in DDS-17 score was 0.2 following the use of Libre 2, although this was not statistically significant (p=0.42).

Overall, emotional burden, physician related distress, regimen related distress and interpersonal distress scores were lower at follow-up when compared to baseline across both intervention and control groups. When compared between groups, none of the reductions in the diabetes distress scores were statistically significant (p>0.05) (see table 4.2).

Table 4.2: Changes in Diabetes Distress Screening Scores: Baseline Vs 12 weeks following use of Free style Libre 2.

Variable Mean (SD)	Libre 2		Libre Pro IQ		Difference of the difference		
	Baseline Mean (SE)	Follow up Mean (SE)	Baseline Mean (SE)	Follow up Mean (SE)	Mean difference	CI	P value
DDS2	2.6 (0.3)	2.4 (0.2)	2.8 (0.3)	2.7 (0.3)	-0.3	-1.1- 0.5	0.47
Total DDS Score (DDS17)	2.3(0.2)	1.8 (0.2)	2.5 (0.2)	2.3 (0.2)	-0.2	-0.8 – 0.4	0.42
Emotional burden	2.3(0.3)	2.0 (0.3)	2.4 (0.3)	2.2 (0.3)	-0.2	-1 – 0.6	0.59
Physician-related distress	2.3 (0.4)	1.9 (0.3)	2.4 (0.3)	2.4 (0.3)	-0.3	-1 – 0.3	0.31
Regimen-related distress	2.6 (0.3)	2.0 (0.2)	2.9 (0.3)	2.6 (0.2)	-0.3	-1.1 – 0.4	0.38
Interpersonal distress	1.6 (0.2)	1.5 (0.2)	2.3 (0.3)	2.0 (0.2)	0.1	-0.6 – 0.9	0.77

DDS2-Diabetes distress 2 screening questions

We looked at proportions of participants with high diabetes distress based on DDS2 score, total DDS-17 score as well as subscales of the DDS-17 questionnaire. Overall, at baseline, 42.5% of the participants had high regimen-related distress. This was followed by physician related distress at 35%. The proportion of participants with high emotional burden was 30%. The most prevalent forms of high diabetes distress at baseline in the Libre 2 arm were emotional burden and regimen related distress at 35% each. In the control arm, Regimen related distress was the most prevalent with 50% of the participants reporting high levels. The use of FreeStyle libre 2 in this study reduced the proportions of participants with high levels of emotional, physician-related and regimen related distress. This reduction however was not statistically significant when compared to the changes observed in the control arm ($p>0.05$) as shown in Table 4.3. The use of Libre 2 did not influence participants with high interpersonal distress.

Table 4.3: Proportions of participants with high Diabetes related distress by intervention arm

Variable	Libre 2		Libre Pro IQ		P value*
	Baseline	Follow up	Baseline	Follow up	
DDS2≥3 (%)	50	25	50	55	0.26
Total DDS Score ≥3 (%)	15	10	40	25	0.16
Emotional burden score ≥3(%)	35	20	25	35	0.73
Physician-related distress score ≥3(%)	30	10	40	35	0.74
Regimen-related distress score ≥3(%)	35	10	50	35	0.52
Interpersonal distress score ≥3(%)	10	10	25	30	0.41

*Compares the change in proportions (from baseline to follow up) between Libre and Pro arms

In a linear regression model, with the change in the total DDS score as the dependent variable, and gender, use of Libre 2, baseline BMI, duration of diabetes, age and baseline HbA1c as exploratory variables, no factors were identified to predict reduction in overall DRD ($p>0.05$) as shown in table 4.4.

Table 4.4: Linear regression model showing factors associated with a reduction in Total diabetes distress score

Characteristic	**Beta (β)**	**Standard error**	**P value**
Libre 2	0.29	0.32	0.38
Gender (Male)	0.25	0.32	0.44
BMI at baseline	-0.002	0.03	0.94
Duration of diabetes	-0.012	0.03	0.7
Age	0.014	0.03	0.56
Baseline HbA1c	0.009	0.02	0.61

We produced 4 other linear regression models using the change in emotional distress, physician related distress, regimen-related distress and interpersonal distress in turn as dependent variables and the same independent variables used in the model above. We have shown the results for the physician related distress model in table 4.5. In this model, baseline HbA1c was shown to predict a reduction in physician related distress. Participants with higher baseline HbA1c were more likely to have a reduction in physician related distress. For every 1mmol/mol increase

in baseline HbA1c, physician related distress reduced by 4% (p=0.02) in this group of participants. The use of FreeStyle Libre 2 did not have an impact on physician related distress or any other type of distress. Other models did not identify any factors that could predict changes in regimen related, emotional or interpersonal distress.

Table 4.5: Linear regression model showing factors associated with reduction in Physician related distress

Characteristic	**Beta (β)**	**Standard error**	**P value**
Intervention: Libre 2	0.36	0.32	0.26
Gender (Male)	0.19	0.32	0.56
BMI at baseline	-0.01	0.03	0.63
Duration of diabetes	0.01	0.03	0.65
Age	0.02	0.02	0.50
Baseline HbA1c	0.04	0.02	0.02

4.4 Discussion

In this study of patients with T2DM, not on insulin, using the DDS-17 questionnaire, one in four patients had high diabetes distress. When the two-item diabetes-related distress screening questionnaire (DDS-2) was used, 1 in 2 participants had high diabetes related distress. The prevalence of high diabetes distress in type 2 diabetes is comparable to a previous study that reported a prevalence of 22.4%(170) using the DDS-17. This study also reported similar mean total DDS(170). The variation in the prevalence of high DRD based on the tool used to measure DRD has been previously described. A cross-sectional study examining three diabetes distress instruments (DDS-2, DDS-17 and PAID-5) in patients with T2DM concluded that the association between aspects of diabetes care and diabetes distress depend on the way diabetes distress is measured as well as a number of confounders(171). A meta-analysis of studies on DRD amongst individuals with T2DM reported an overall DRD prevalence of 36%(172). It has been previously shown that high DRD is associated with the use of insulin(173). It is interesting to note the high prevalence of distress observed in our study amongst patients on non-insulin treatment. It is however worth noting that there is a corelative relationship between severe DRD and HbA1c(174). This may partly explain the high prevalence of DRD noted in our sample of participants with a high baseline HbA1c.

We have shown that at baseline, the most common form of high DRD was regimen related, followed by physician related distress. Like our study, a previous cross-sectional survey using the DDS-17 questionnaire identified that regimen related distress was higher in T2DM compared to T1DM(175). The authors concluded that efforts needed to be made to reduce regimen related distress and emotional burden. In addition, other studies have also reported higher mean scores

for emotional burden and regimen related distress compared to other forms of distress (176, 177).

The use of FreeStyle libre 2 did not impact DRD in this group of patients. The lack of impact was observed in both the total DDS and in each of the 4 forms of distress. A recent service evaluation showed a reduction in diabetes distress following the use of isCGM among patients with T2DM on premixed insulin(178). This study, however, had only 10 participants and lacked the power for statistical analysis. Like our study, results from a randomised controlled trial in patients with T2DM on intensive insulin therapy showed no improvement in diabetes distress following the use of isCGM(179). Similarly, another randomized controlled trial of T2DM patients treated with diet and exercise alone or other glucose lowering therapies other than prandial insulin showed no impact of rt-CGM on diabetes related distress(140). Although the use of CGM has been reported to improve treatment satisfaction among participants with T2DM(180), our study shows that this does not translate into less diabetes related distress, including regimen related distress.

It is worth noting that although the use of Libre 2 in this study improved the time in range, it did not significantly improve the point of care HbA1c. Evidence from real life studies in T1DM showed a reduction in HbA1c and diabetes distress following the use of isCGM(167). In our study, it was hypothesized that when participants see their blood sugars in real time, their behaviour would change, and this would improve their glycaemic control and in turn relieve diabetes distress. The lack of significant improvement in blood glucose may therefore have affected the impact of Libre 2 on DRD in this cohort. However, it is important to note that there are limited studies examining diabetes distress in people with T2DM not on insulin, and therefore the mechanisms through which isCGM affects DRD are still not clear. We have however shown in this study that isCGM

does not increase DRD in this group of patients. This technology can therefore be adopted in individuals with T2DM not on insulin.

Chapter 5: Effect of Hydrocortisone versus Prednisolone on quality of life of patients with adrenal insufficiency disease

5.1 Introduction

Adrenal insufficiency (AI) is a life-threatening condition if left untreated. It is caused by primary adrenal disease but could also be secondary to disorders of the pituitary or the hypothalamus(181). Patients with adrenal insufficiency are managed through lifelong glucocorticoid replacement therapy (GRT)(182, 183). Irrespective of the medication used, glucocorticoid replacement in patients with AI should ideally mimic the physiological diurnal pattern of cortisol production in healthy individuals. This means an early morning peak of cortisol and a trough level at midnight(184). When compared to the general population, patients with AI have poor health outcomes. These include increased morbidity and mortality, cardiovascular disease, osteoporosis, and osteopenia(185, 186). In addition, individuals with adrenal insufficiency have reduced quality of life including reduced general health perception and fatigue(187). Although the mechanisms responsible for increased morbidity and mortality in patients with AI remain poorly understood, some argue that this could partly be due to chronic exposure to high doses of glucocorticoids(188). Another reason that has been put forward is the mismatch between the daily hydrocortisone profile in patients taking multiple doses of hydrocortisone for adrenal insufficiency and the normal circadian rhythm of cortisol production in patients with a normal hypothalamic-pituitary-adrenal (HPA) axis(183).

In the UK, patients with adrenal insufficiency can be given either hydrocortisone or prednisolone as standard care. There are no studies showing any difference between these two glucocorticoids. The glucocorticoid that patients get depends on the individual clinician's choice. Studies conducted comparing immediate release hydrocortisone to modified release hydrocortisone have shown early metabolic benefits including reduced fat mass and increased sleeping metabolic

rate(183, 188). A systematic review of studies comparing standard hydrocortisone to modified release hydrocortisone showed a significant improvement in weight and HbA1c(188). In this review however, they noted a reduction in HDL (high density lipoprotein) and an increase in Triglycerides. This has raised questions about the possible increase in cardiometabolic risk associated with the use of modified release tablets.

Data comparing prednisolone at the currently prescribed doses of less than 5mg to hydrocortisone are scarce. Prednisolone has a longer duration of action and smoother pharmacokinetic profile compared to standard hydrocortisone. It is therefore administered once a day which in theory is more convenient to patients who may sometimes struggle with the timing of the third dose of hydrocortisone later in the day. Historically, 5mg of prednisolone was assumed to be equivalent to 20mg of hydrocortisone (ratio 1:4). One study has however shown that this ratio could well be nearer to 1:6-8, meaning that a lower dose of prednisolone could be sufficient(189). Further to that, it is cheaper to use prednisolone compared to standard hydrocortisone. A 30 days' supply of hydrocortisone 20mg costs 157 GBP compared to 28 days' supply of prednisolone which costs 1.24 GBP.

We therefore sought to compare standard regimen of hydrocortisone to prednisolone in the treatment of patients with AI. The focus was on the well-being of patients with AI, assessed using the subjective modified SF-36 questionnaires. We also examined the effect of once daily prednisolone on glycaemic control, lipid metabolism and markers of cardiovascular risk.

5.2 Materials and methods

5.2.1 Study site

The study was conducted at Hull University Teaching Hospitals NHS Foundation Trust, a UK tertiary hospital.

5.2.2 Study design

This was a prospective observational study of patients who switched from hydrocortisone to prednisolone as part of their routine care of adrenal insufficiency.

5.2.3 Study population

The study was conducted amongst patients with adrenal insufficiency irrespective of the cause.

5.2.4 Sample size and sample size calculation

The sample size was based on achieving a mean difference in weight of 2kg. Using a significance level of 0.05 and power of 80% with a standard deviation of 4.9, the required group size was 50. We assumed a non-completion rate of 20%, therefore the sample size for this study was 62 accounting for the participants who would fail to complete both visits.

5.2.5 Primary and secondary outcomes

Primary end point: Efficacy of replacement and wellbeing as assessed using a previously customized subjective questionnaire.

Secondary end points:

1. Cardiovascular risk: We used blood pressure, waist-hip circumference ratios. Blood tests including lipid profiles and high-sensitivity C reactive protein (CRP).

2. Glycaemia: as assessed by glycated Haemoglobin (HbA1c).
3. Safety: This was through a review of safety bloods including full blood count, renal function and liver function.

5.2.6 Conduct of the study: Approaching potential participants

Patients were identified from endocrinology clinics by members of the clinical care team. Patients with AI on any dose of hydrocortisone were invited to participate in the study. Prospective participants were sent patient information leaflets at least 24 hours prior to their appointments. Participant information sheets were used to provide information about the study. When it was not possible to send patient information leaflets prior to the clinic visit, participants were consented on the same day in clinic, given that they felt they had sufficient time to adequately review the patient information leaflet. Patients who agreed to switch to prednisolone as part of the study then signed a consent form. Data at baseline prior to switching to prednisolone and then at least 4 months after switching from hydrocortisone to prednisolone were collected. These included biological, biochemical, and subjective data using questionnaires.

5.2.7 Informed consent

Participants gave their written informed consent prior to participation in any study procedures. The investigator discussed the study with the participant, talking through the participant information sheet and explaining the nature and scope of the study, potential risks and benefits of participation and answered any questions the participants had. Potential participants were given ample time to consider their participation and to ask questions. For some that desired, they took a copy of the participant information sheet and a sample of the informed consent document home to review with friends and family members prior to deciding whether to participate. If the

participant was willing to participate, they signed and dated the informed consent form, which was also countersigned by the investigator. One copy of the informed consent was given to the participant while another was retained within the participant's notes and the original in the site study file. After providing informed consent each participant was assigned a unique participant identification number. All participants enrolled in the study had a letter sent to their GP informing them of enrolment in the study and providing a brief study overview. The GP was also asked to update the participant's repeat medication by removing hydrocortisone and replacing it with an agreed dose of prednisolone. This would ensure that the patient received a supply of prednisolone moving forward.

5.2.8 Eligibility criteria

Inclusion criteria

- Aged 18-85 years.
- Male or female
- Diagnosed with adrenal insufficiency (AI) for over 6 months according to standard diagnostic criteria
- Established on a stable dose of hydrocortisone replacement, dose not altered for at least 4 months
- Individuals taking other hormone replacements were included providing that their replacement doses were not altered for at least 3 months.
- Individuals who were able and willing to give written informed consent

Exclusion

- Individuals who were unable to give informed consent.
- Patients who were pregnant
- Patients who were using a combined oral contraceptive pill
- Recent (within 3 months) changes to other replacement hormones

5.2.9 Study procedures

Clinic visit 1:

This visit occurred immediately after being consented. Participants had their details checked to ensure that they met all the inclusion criteria and none of the exclusion criteria. Baseline measurements were then done including blood pressure, pulse, hip circumference, waist circumference, height, and weight. Baseline blood samples were taken including Full blood count (FBC), Lipid profile, renal profile, bone profile, liver function tests (LFTs), HbA1c and CRP were ordered as part of routine patient care. Participants also completed a modified SF-36 subjective questionnaire. Participants who were unable to complete the questionnaire on site were sent a link with the questionnaire to complete at their earliest opportunity.

Participants were then given a prescription to collect the appropriate dose of prednisolone which was to be started the next day. Participants were given the contact details of the research unit to update the research team regarding any concerns. The dose of prednisolone was modified as necessary based on clinical picture. No blood tests or drug profiles were performed to titrate the dose of prednisolone.

Clinic visit 2

This visit took place after the participant had been on a steady dose of prednisolone for a minimum of 4 months. Measurements and observations as per the baseline visits were carried out. Blood samples were taken for tests as per the baseline investigations. Participants then completed the modified SF-36 questionnaire.

The participants were subsequently followed up as usual in endocrine clinic. Data from their clinic visit and subsequent investigations were collected after each visit and entered in the study database.

5.2.10 The modified SF-36 Questionnaire

The SF-36 Questionnaire is made up of 8 health scales with a total of 36 items. The physical functioning scale has ten items, role-limitations due to physical health has 4 items, bodily pain has 2 items, general health has 5 items, vitality has 4 items, social functioning has 2 items, role-limitations due to emotional problems has 3 items and mental health has 5 items. 1 item is used to assess the change in health over 1 year(110, 190, 191).

In this study, the modified SF-36 questionnaire was used. 1 item was taken from the general health perceptions domain. This corresponds to question 1 of the SF-36. Nine items were made up of the 4 questions on vitality (questions 23, 27, 29 and 31 of the SF-36) and 5 questions on mental health (24, 25, 26, 28, and 30 of the SF-36). 1 item on nausea was included. This made a total of 11 items making up the modified version of the SF-36 used in this study (see copy in appendix).

Scoring of the modified version of the SF-36 questionnaire

Scores for each of the 11 items in the modified SF-36 questionnaire range from 0 to 100 with higher scores indicating a better health state. The maximum total score for an extremely healthy, happy person was 1100 while the total minimum score for the least healthy unhappy person was 0. Methods for calculating the scores are set out in detail by Ware et al(192). In our study, we grouped scores from the 11 items into 4. One was the score for general health, the second was a score corresponding to questions about energy, third was a score about wellbeing and final group was a score for nausea. Further analysis of the scores is presented under the 4 groups.

5.2.11 Data management

Source data

Demographics, body weight, height, BMI, hip circumference, waist circumference, blood pressure, pulse were recorded on the case report forms (CRPFs). The CRFs completed were similar for both visit 1 and visit 2. The CRFs were completed at the time of the participant's visit. Other information collected included comorbidities, concomitant medication, and the duration the participant has been on glucocorticoids. We also recorded the dose of hydrocortisone the patient was taking and the corresponding prednisolone dose to which they were switched. Pathology results were available on the hospital's electronic records system (Lorenzo).

Data from the modified SF-36 questionnaire

This modified SF-36 questionnaire was developed using Survey Monkey(193). Participants completed this questionnaire online either using their devices at home or in clinic. A few participants who had no access to internet completed a paper copy of the questionnaire which

was then used to complete the online version. These data were compiled by the software and presented in Microsoft Excel. Participants were identified by the study number.

Database and data entry

The data from the source documents were entered into the study database created in Microsoft Excel. All the data entered were anonymized by only the participant's study number. Participant pathology results were transcribed from the Trust's electronic patient record system onto the database. The database was kept on NHS computers on the Trust's secure networks that are password protected. Servers were backed up to disk media each night.

5.2.12 Data analysis plan

Anonymized data were analysed using statistical package R 3.5.6. Baseline characteristics were described per type of AI (primary versus secondary AI). For continuous variables, mean (standard deviation) were presented unless otherwise stated. Baseline and follow up mean outcome measures were compared using a paired T-test.

Baseline and follow up mean modified SF-36 questionnaire scores were compared using the T-test. We used linear regression to establish the factors associated with a change in SF-36 scores. The change in SF-36 scores was modelled as a dependent variable with sex, age, type of AI, duration on glucocorticoids, concomitant hormonal replacements, and comorbidities as independent variables. A P value of <0.05 was considered statistically significant.

5.2.13 Ethical considerations

This study was part of the bigger HYPER-AID study (ClinicalTrials.gov ID NCT03608943). Ethical approval was obtained from the Yorkshire and the Humber - Bradford Leeds Research Ethics

Committee and the HRA. The study was conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions.

5.3 Results

Baseline characteristics

Sixty-two participants were enrolled in the study. Forty-eight participants completed the study. Of the 14 participants who did not complete the study, thirteen switched back to hydrocortisone before the second study visit. One patient died during the study. The participant's death was not related to prednisolone. This means the completion rate was 77.4%(48/62). Out of the 48 participants who completed the trial, the mean (SD) age at enrolment was 54.5±13 years. Twenty-seven (56.3%) were female while 8 (16.8%) had PAI. The mean duration that participants had been on glucocorticoids was 11.4±8.6 years. The mean baseline weight was 90.6 kilograms with a mean systolic blood pressure of 132±20mmHg. Most participants (62.5%) were on levothyroxine replacement. The baseline characteristics by type of AI are shown in Table 5.1. At enrolment, the mean (SD) hydrocortisone dose was 20±4.5mg while at the end of the study, the mean prednisolone dose was 3.88±0.53mg. There were 10 participants with diabetes representing 20.8%. Three participants had asthma, five had chronic obstructive pulmonary disease (COPD) whereas 4 (8.3%) had a history of ischaemic heart disease.

Table 5.1: Baseline characteristics of study participants

Variable	Primary AI N=8	Secondary AI N=40	P Value
Age, years	51±4.8	55±14.4	0.12
Duration on Glucocorticoids, years	9.1±6	11.9±9	0.29
Gender-male, n (%)	2 (25)	19(47.5)	0.43
Weight, Kg	87.5±20.3	91.2±19.5	0.65
BMI, Kg/M^2	29.9±6.9	31.9±6.6	0.46
Daily Hydrocortisone dose, mg	21.3±4.4	19.8±4.5	0.40
On Levothyroxine n (%)	3(37.5)	27(67.5)	0.23
Living with Diabetes, n (%)	0(0)	10(25)	0.27
Ischaemic heart disease, n (%)	0(0)	4(10)	0.82
On 3 or more hormone replacements, n (%)	0(0)	11(27.5)	0.22

AI=Adrenal Insufficiency

Anthropometric measurements

After 4 months of follow up on prednisolone, the mean weight decreased significantly from 90.6kg to 89.6kg. The use of prednisolone therefore was associated with an average reduction in weight of 1.2Kg (p=0.007). This represents a 1.3% reduction in weight. Relatedly, there was a mean reduction in BMI of 0.4Kg/m^2 (p=0.006) (figure 5.1). We observed an average reduction in hip circumference of 3cm (p=0.006). The waist circumference reduced from 102.6cm at baseline to 101.1cm at follow, although this was not statistically significant (p>0.05).

Blood pressure

The use of prednisolone was associated with a reduction in systolic blood pressure but not diastolic blood pressure (see table 5.2). Following 4 months of prednisolone, the systolic blood pressure reduced by an average of 6mmHg (p=0.027).

Glycaemic control

The overall HbA1c was 44mmol/mol at baseline, increasing to 45mmol/mol at follow up. This difference was however not statistically significant. We further sub-divided participants into those with pre-existing diabetes and those who were non-diabetic. In the pre-existing group, the use of prednisolone did not impact HbA1c. In the non-diabetic group, however, the HbA1c increased by an average of 1mmol/mol following the switch to prednisolone for 4 months. This increase was statistically significant (p=0.014).

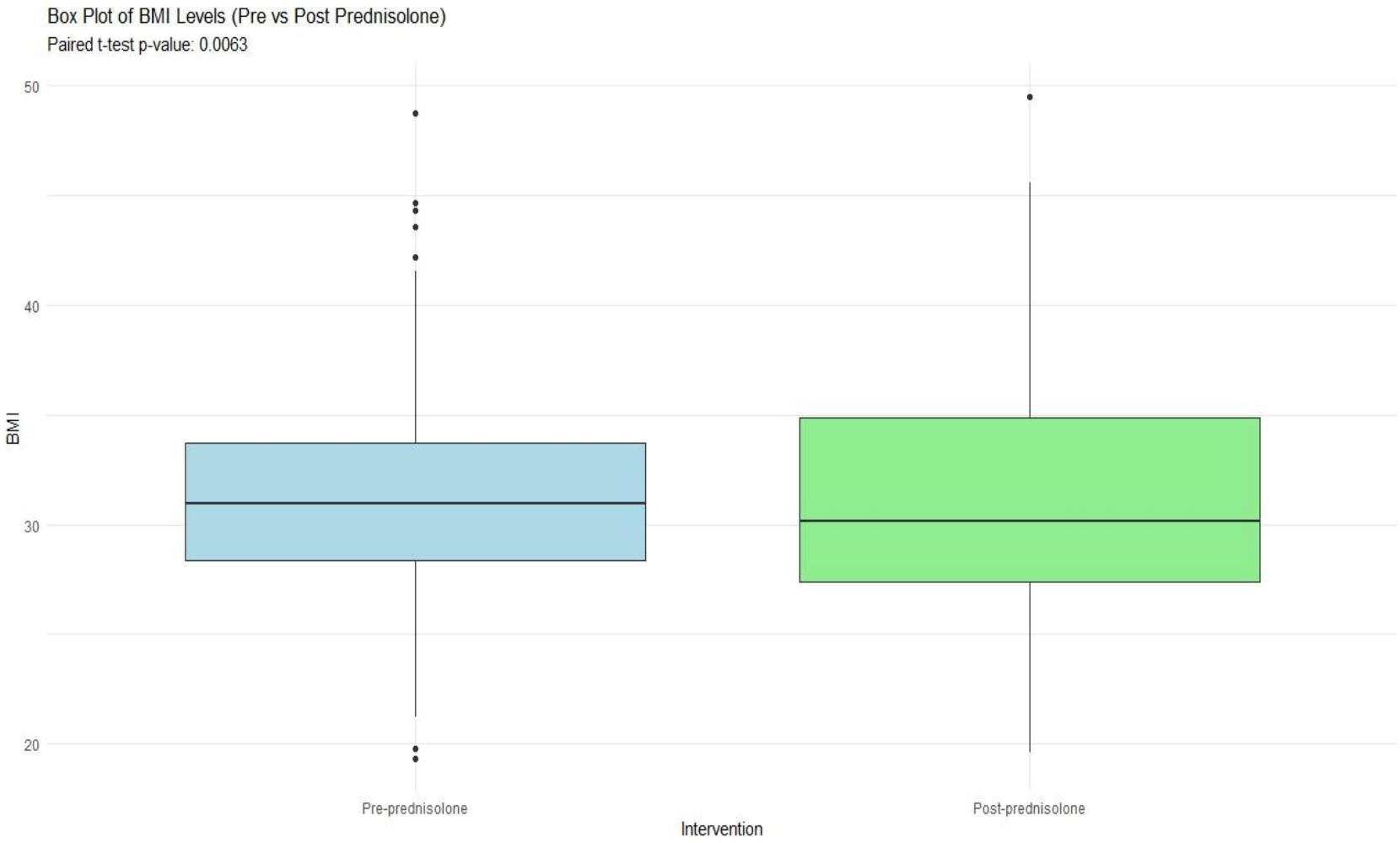


Figure 5.1: Box plot showing the change in BMI from baseline to 4 months of follow up following initiation of prednisolone

Bone profile

The baseline adjusted calcium level was 2.43mmol/L, reducing to 2.40mmol/L at the end of the 4 months follow up period. This represents a small but statistically significant reduction in calcium level of 0.04mmol/L (p=0.017). In addition, there was a small but significant reduction in the serum phosphate level at the end of the follow up period. Phosphate levels reduced from 1.08mmol/L at enrolment to 1.04 mmol/L at follow up (p=0.037). There were changes in alkaline phosphatase observed.

Kidney function

The use of prednisolone had no impact on renal function. Baseline and follow up values for urea, creatinine, sodium and potassium were not significantly affected.

Lipid profile

The total cholesterol, non-HDL cholesterol, triglycerides levels were lower at follow up compared to baseline levels. These changes were however not statistically significant (p>0.05). There was however a non-statistically significant increase in LDL cholesterol and HDL cholesterol at follow up compared to baseline (p>0.05), as shown in Table 5.2.

C-reactive protein (CRP)

The use of prednisolone did not have an impact on CRP during this study. The baseline and follow up mean CRPs were similar (5mg/L).

Haematology

We observed an increase in total white cell count and neutrophils. On average, at follow up, the total white cell count increased by 0.7X10^9 cells per litre(p=0.003). Relatedly, the neutrophils increased from 4.8 X10^9 to 5.9 X10^9cells per litre, representing an average increase of 1 X10^9 cells per litre(p<0.001). There was no change in haemoglobin observed in this study (see table 5.2).

Table 5.2: Comparison between baseline and 4 month follow up of outcomes

Outcome measure	**Baseline**	**Follow-up**	**Mean difference**	**P value**
Weight (Kg)	90.6±19.4	89.6±20	-1.2	**0.007**
BMI (Kg/m^2)	31.6±6.6	31.1±6.8	-0.4	**0.006**
Waist circumference (cm)	102.6±15.3	101.1±17	-1.4	0.159
Hip Circumference (cm)	110±13.4	106.9±14	-3.0	**0.006**
Systolic Blood pressure (mmHg)	132±20	126±21	-6	**0.027**
Diastolic Blood pressure (mmHg)	79±13	79±9	-0.5	0.806
Total cholesterol (mmol/L)	5.0±1.3	4.9±1	-0.02	0.860
Non-HDL cholesterol (mmol/L)	3.4±1.2	3.3±0.9	-0.04	0.725
Triglycerides (mmol/L)	2.0±1.2	1.8±1.4	-0.1	0.543
HDL cholesterol (mmol/L)	1.6±0.6	1.6±0.4	0.01	0.918
LDL Cholesterol (mmol/L)	2.5±1.01	2.5±0.9	0.04	0.683
Adjusted calcium (mmol/L)	2.43±0.08	2.40±0.07	-0.04	**0.017**
Phosphate (mmol/L)	1.08±0.25	1.04±0.20	-0.06	**0.037**

Alkaline phosphatase (IU/L)	77.4±21	77±21	0.08	0.965
HbA1c (overall), mmol/mol	44±13	45±13	0.8	0.324
HbA1c (Diabetic participants) mmol/mol	62±18	63±16	-0.9	0.789
HbA1c (non-diabetic participants) mmol/mol	39±4	40±4	1.3	**0.014**
Sodium(mmol/L)	140±3	139±2	-0.3	0.311
Potassium (mmol/L)	4.3±0.33	4.3±0.3	-0.01	0.911
White cells count $x10^9$/L	7.4±1.9	8.1±2.3	0.7	**0.003**
Haemoglobin (g/L)	140±16	139±17	-0.5	0.647
Neutrophils $x10^9$/L	4.8±1.5	5.9±2.1	1	<0.001

Quality of life measures

Baseline and follow-up modified SF-36 questionnaire data were available for 40 out of the 48 participants who completed the trial. The mean scores are presented in Table 5.3. The scores are presented under subcategories of general health, energy, wellbeing, nausea and total quality of life scores. The baseline mean energy score was 134, increasing to 170 at follow up. This means that the use of prednisolone increased the subjective energy scores of participants by 36.5 points. This increase in energy was statistically significant (p=0.003) (figure 5.2).

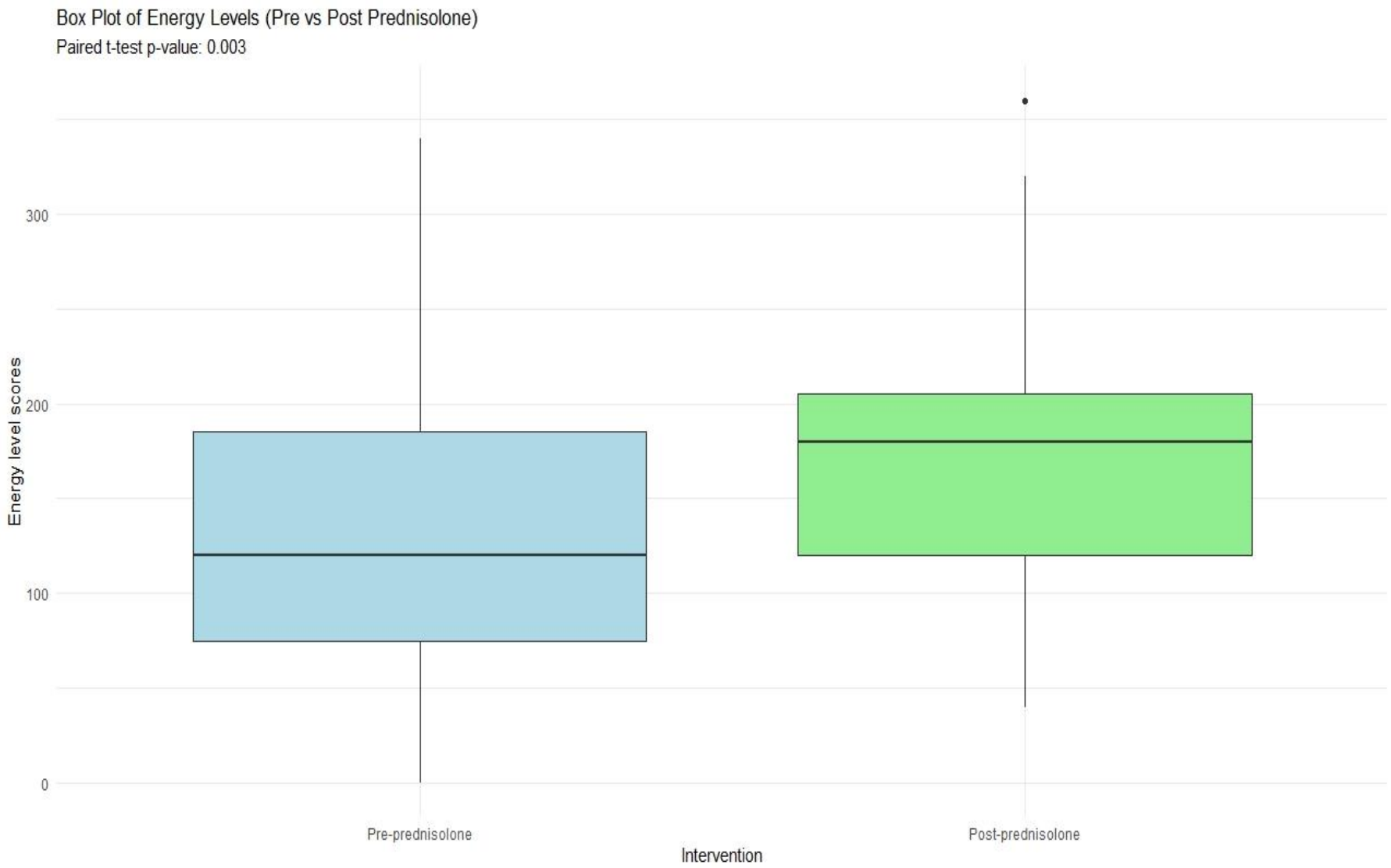


Figure 5.2: Box plot showing the change in energy levels from baseline to 4 months of follow up following initiation of prednisolone

In addition, the total QOL scores at follow-up were significantly higher when compared to baseline (648 at follow up versus 593 at baseline) (p=0.019). There were however no changes in the general health, wellbeing and nausea scores following the 4 months on prednisolone (Table 5.3).

Table 5.3: Baseline and follow up scores from the modified SF-36 questionnaire

Item	**Baseline score Mean (SD)**	**Follow-up score Mean (SD)**	**Mean difference**	**P value**
General health	39(22)	44(21)	5	0.118
Energy	134(87)	170(73)	36.5	**0.003**
Well-being	332(88)	341(84)	10	0.420
Nausea	89(21)	93(13)	4	0.263
Total scores	593(167)	648(146)	55.5	**0.019**

In the linear regression model using the change in energy scores as the dependent variable, no factors were shown to predict an increase in energy levels in this study. A similar model using the change in total quality of life scores as the dependent variable and independent variables as shown in Table 5.4, no factors were identified as predictors of improvement in the quality of life. There was therefore no correlation between baseline characteristics and improvement in the quality of life in this group of participants.

Table 5.4: Linear regression model showing factors associated with improvement in total quality of life scores following 4 months on prednisolone

Characteristic	**Beta (β)**	**Standard error**	**P value**
Age	-1.7	2.3	0.474
Gender-male	-48.7	72.3	0.506
Secondary AI	-93.5	81.5	0.261
Duration on steroids	0.16	3.1	0.958
Hydrocortisone dose	-10.7	7.1	0.140
On testosterone	69.8	86.9	0.429
On thyroxine	-48.2	70.7	0.502
On Growth hormone	-28.8	76.3	0.709
Diabetic	17.5	83.3	0.835
COPD	30.3	126.3	0.812
Asthma	-28.4	134.7	0.834
Weight difference	12.3	12.9	0.35

Results comparing the convenience of the different glucocorticoids regimes are shown in Table 5.5. The proportion of participants who said hydrocortisone was very convenient was 25%. Following 4 months of prednisolone, 60% of participants found prednisolone to be very convenient. These 2 proportions of participants were statistically significant when compared (p=0.002).

Table 5.5: Convenience of prednisolone compared to hydrocortisone

	Hydrocortisone N=40 (Baseline)	Prednisolone N=40 (Follow up)
Very convenient n (%)	10 (25)	24 (60)
Convenient n (%)	12 (30)	9 (22.5)
Okay n (%)	17(42.5)	7 (17.5)
Not convenient n (%)	1 (2.5)	0 (0)

5.4 Discussion

In this observational study of patients with AI, switching patients from multiple times a day hydrocortisone to low dose prednisolone led to a significant reduction in weight of 1.2kg over 4 months. There are limited studies comparing prednisolone once a day administration to multiple doses of immediate release hydrocortisone in patients with AI. In a re-audit of a cohort of patients with AI, one study reported that patients who switched from hydrocortisone to prednisolone had significantly lower body weight and BMI(194). This study observed a mean reduction in weight of 5.4kg over a period of 4 years(194). Another study examined the effect of once daily modified release hydrocortisone compared to hydrocortisone in patients with AI(195). In this single blind randomised trial, like our study, modified release hydrocortisone was associated with significant weight reduction of 4kg over 24 weeks, when compared to standard glucocorticoid replacement(195). Previous data from six day-curves have shown that the prednisolone profile is similar to the modified release hydrocortisone profile(122). It is not clear whether the reduction in weight observed in patients on prednisolone is due to the different exposure pattern of prednisolone or it is due to the reduced bioavailability of prednisolone compared to the multiple doses of hydrocortisone, like what is observed with modified release hydrocortisone(196). The reduction in weight could also be related to levels of activity. It is plausible that with improved energy levels following use of prednisolone, participants were more active and this increased levels of activity could contribute to the reduction in weight observed. We did not measure activity levels in this observational study and therefore this would require further assessment with another study.

We have shown that the use of prednisolone was associated with a significant reduction in systolic blood pressure of up to 6mmHg on average. A previous retrospective observational study compared 64 patients on prednisolone to 82 patients on hydrocortisone. In this study different to ours, there was no difference in the systolic blood pressure between the 2 groups(197). In addition, another observational study involving AI patients in a 1:3 matched ratio (prednisolone: hydrocortisone) showed no significant difference in the systolic blood pressure(198). Excess hydrocortisone can lead to salt and water retention which can lead to weight gain and hypertension(196). The reduction in the blood pressure observed in this study, together with associated weight reduction may therefore be related to more physiological doses of prednisolone being used in this study compared to the multiple hydrocortisone doses.

In our study, there was no difference observed in the markers of cardiovascular risk measured. A retrospective observational study compared patients on prednisolone to those on hydrocortisone. Importantly, this study used lower doses of prednisolone 2-4mg comparable to our study(197). They reported, like in our study no significant difference in Low Density Lipoprotein (LDL), total cholesterol (TC) or high density lipoprotein(HDL) (197). The authors concluded that neither prednisolone nor hydrocortisone possesses a higher cardiovascular risk than the other. One study, however, has previously reported a higher TC and LDL in patients taking prednisolone compared to the hydrocortisone group(198). Although participants in the 2 groups were matched for gender, age, type of AI and duration of disease, most participants were taking 5 to <6mg of prednisolone. Although the evidence is still limited, the default 5mg dose of prednisolone is above the 2-4mg which is deemed adequate replacement(122). The rise in TC and LDL observed in that study could therefore, we argue, reflect changes in lipid profile related to

over replacement. Cardiovascular disease is associated with increased mortality in patients with secondary adrenal insufficiency(199). Although our findings have not shown increased markers of cardiovascular risk following the switch to prednisolone, in one retrospective cohort study, mortality was higher in patients with primary AI who took prednisolone than those who took hydrocortisone when compared to healthy controls (HR 2.92 Vs 1.9, p=0.002). There was no increased risk of mortality observed in patients with SAI(200). This study, however, used secondary data, and the prednisolone doses used were ≥ to 5mg but less than 7.5mg which may still constitute over replacement.

We observed a small (1.3mmol/mol) but significant increase in HbA1c in patients who were not diabetic. The effect of prednisolone in AI on glycaemic control has shown mixed results. In a study involving 2-4mg of prednisolone in patients with adrenal insufficiency, there was no difference in the HbA1c between participants on hydrocortisone compared to those on prednisolone(197). In this study, however, although the proportion of participants with pre-existing diabetes was like our study's, the authors did not examine the changes in HbA1c in participants without diabetes which may have impacted the findings. Similarly, there was no difference in HbA1c noted between participants on prednisolone compared to hydrocortisone in a matched multi-centre study (198). Although the matching reduced the confounding in most characteristics, failure to examine the HbA1c of participants without diabetes separately from those with preexisting diabetes, like we did, may have affected the results. A re-audit of a cohort of patients with AI examined the changes in HbA1c among patients on different glucocorticoid preparations. They reported that patients who remained on hydrocortisone over a period of 4 years had significantly higher HbA1c compared to those who remained on prednisolone(194). It was not clear from this audit the

proportions of participants who had preexisting diabetes and whether this could have played a role in the findings. None the less, we report that the rise in HbA1c is small and unlikely to be clinically significant in patients with no pre-existing diabetes.

Regarding white cell count, we report a small but significant increase in the total white cell count which is due to an increase in the neutrophil count. These results are not surprising because earlier publications have documented granulocytosis associated with prednisolone(201, 202). The authors concluded that even small doses of prednisolone administered over a period may result in persistent leucocytosis. Glucocorticoids, like prednisolone, regulate the proliferation, differentiation and apoptosis of white cell counts(203). Most of the work of glucocorticoids is via glucocorticoid receptors and the mechanisms are both genomic and non-genomic(203). Although the rise in white cell count observed in our study was small, this change in neutrophils could result in diagnostic challenges in patients who are immunocompromised and being investigated for a potential infection. Clinicians would have to rely on other parameters like the shift to the left in the peripheral white blood cells as well as presence of toxic granules to diagnose infection induced neutrophilia(202).

Our study showed an increase in calcium and phosphate levels. The reasons for this increase remain unclear. A previous study that looked at hydrocortisone and prednisolone in AI patients reported no changes in calcium or phosphate levels over a follow up period of 5 years(204). Despite worse bone mineral density in patients on prednisolone reported in that study, alkaline phosphatase, calcium and phosphate levels remained comparable across the immediate hydrocortisone, modified release hydrocortisone and prednisolone groups. It is however worth reporting that the doses of prednisolone used in his study were higher, giving an equivalent dose

of 32mg of hydrocortisone(204). There are no studies that have reported an increase in calcium or phosphate associated with low dose prednisolone and our results could possibly represent a type 1 error (false positive). A randomized controlled trial examining different outcomes together with calcium and phosphate levels in patients on prednisolone could provide more evidence on the effect of prednisone on calcium and phosphate.

We report a significant increase in energy levels and how well patients feel whilst taking prednisolone compared to hydrocortisone. In addition, patients find the once daily prednisolone dose to be very convenient. There has been uncertainty from a previous study regarding the reasons behind the significantly higher satisfaction scores seen in patients on prednisolone compared to the hydrocortisone group(197). Although the higher satisfaction score could be due to the convenience in taking prednisolone as reported in the current study, our findings further show that patients on prednisolone feel subjectively more energetic and better compared to how they felt whilst taking hydrocortisone. A cross-sectional study on subjective health status (SHS) in patients with AI found, different to our findings, no relevant differences in the SHS of patients taking different glucocorticoid preparations(205). There were no specific characteristics in our study that could predict which patients would feel better and more energetic whilst taking prednisolone.

This study has several limitations. This was a prospective observational study and data on several confounders were not collected. For example, we did not capture information about participants who may have gone onto a weight loss program, on had hospital admissions or procedures performed which could impact on weight and quality of life. Blood pressure readings were single point measurements in clinic and may not represent the true picture of a person's blood pressure

variation that is captured by 24-hour ambulatory blood pressure monitoring. In this analysis, we did not adjust for participants who were taking lipid lowering medication during the study. The selection of participants who were willing to switch from hydrocortisone to prednisolone may have an inherent bias as this would represent a cohort of individuals who were not happy with hydrocortisone. In this situation any alternative to hydrocortisone may therefore lead to improved energy and satisfaction as observed in our study which may not necessarily be the case. A randomized controlled trial would minimize this selection bias. Nonetheless, we have shown that switching to prednisolone improved energy levels and how well participants felt about their health.

5.4.1 Conclusion

When compared to daily multiple hydrocortisone doses, participants who switched to once daily prednisolone (2-4mg) found it to be very convenient. There was a significant reduction in systolic blood pressure, weight and BMI. Prednisolone did not affect the lipid profile, signifying no increase in cardiovascular risk. Patients felt more energetic and had higher general health scores. This study adds to the evidence that low dose prednisolone may be a better option than hydrocortisone in patients with AI based on convenience and improvement in QOL measures.

Chapter 6: Summary discussion

Patients with chronic endocrine conditions experience reduced QOL compared to healthy controls. In T1DM and T2DM, the micro and macrovascular complications can have an impact on the health-related QOL(206, 207). In AI, self-perceived health status and QOL is impaired, and this is well documented(186, 205, 208, 209). This thesis examines three questions regarding the quality of life of patients living with chronic endocrine conditions. Firstly, what is the effect of intermittently scanned continuous glucose monitoring (isCGM) in people with diabetes with a psychosocial indication for initiation? Secondly, in people with T2DM but not yet on insulin, what is the effect of isCGM on glycaemic control and quality of life? Third, does prednisolone improve the quality of life of patients living with AI when compared to hydrocortisone?

In patients with T1DM, intensified insulin treatment is the standard of care. This has been shown to improve glycaemic control and reduce diabetes related complications(210). There are, however, problems associated with the process of achieving decent glycaemic control. These include the risk of hypoglycaemia and weight gain(210). People living with T1DM worry about their day-to-day life. They have to work out how much insulin to administer, estimate the carbohydrates in their diet, adjust their doses based on physical activity(211) as well as planning their journeys that may require back up insulin. These demands coupled with the fear of hypoglycaemia create negative emotions associated with living with diabetes, a phenomenon called diabetes distress(76). In the first study, we examined the impact of diabetes technology in the form of CGM on glycaemic control and DRD in a population of predominantly T1DM patients. There was already existing evidence showing that the use of isCGM improves glycaemic control, hypoglycaemia awareness and reduces DRD (41, 43-46, 123). However, questions remained whether individuals with psychosocial issues would engage with the technology and what impact continuous glucose readings would have on their wellbeing. In

our first study, we have shown that relative to other individuals living with T1DM, people with diabetes and psychosocial issues (anxiety, depression, sleep disorders and risk of suicide) experience high levels of DRD. In addition, this group also has high levels of HbA1c, indicating sub-optimal control. The use of isCGM improved diabetes related distress, glycaemic control and reduced hospital admissions due to hyperglycaemia or DKA. Although these results came at a time when the indications for starting CGM in people with T1DM had been updated to provide access to all people with T1DM(24), they nonetheless add to the evidence that this technology improves glucose control and distress levels in this group of patients.

Building on from the first study, there was a need for further work to explore the wider impact of isCGM on psychological outcomes in those living with T2DM and rarer forms of diabetes. In the second study, we introduced isCGM in people living with T2DM but not on insulin. We hypothesized that when individuals can see their blood glucose readings on a continuous basis, there would be a behavioural change to prevent high glucose readings thereby improving glycaemic control and delaying insulin introduction. There was however uncertainty regarding the impact of isCGM on diabetes distress and well-being. Evidence from self-monitoring of blood glucose (SMBG) studies showed that SMBG would result to anxiety and self-blame (70)which would have an impact on diabetes distress. In the second study, we have shown that the use of isCGM in people with T2DM increases the time in range by an average of 18%. This is also associated with a non-significant reduction in HbA1c of 8mmol/mol. The lack of significant reduction in HbA1C observed despite an increase in time in range could be due to 2 reasons. Firstly, it could be because the sample size used in our pilot study was small. A previous comparable study had reported a significant improvement in time in range and a small but significant reduction in HbA1c of 3mmol/mol(152). This study used a bigger sample size compared to our study. It is therefore likely that our second study was not powered enough to detect changes in the HbA1c at the small sample size we used despite an increase in time in range. The second reason could be due to the correlation between time in range and HbA1c. A study examining the relationship between CGM parameters

and glycated albumin, glycated haemoglobin and fructosamine for 24 weeks concluded that glycated albumin is the most accurate predictor of TIR over 8 weeks compared to other glycaemic indices(212). In fact, at week 4 and 8, glycated albumin correlations with time in range were higher than HbA1c correlations in one of the study groups(212). This could potentially have an impact on the results we observed in our study. None the less, the improvement in time in range over 12 weeks following the use of isCGM suggests that this technology could be potentially beneficial in people living with T2DM.

In the second study, we also examined the impact of isCGM on diabetes distress using the DDS-17 questionnaire. The results showed that 1 in 4 T2DM participants had severe DRD. The use of isCGM did not affect the overall diabetes distress nor the different forms of diabetes distress including emotional distress, physician related distress, regimen related distress or interpersonal distress. These negative findings on one hand add to the growing evidence that continuous glucose monitoring can be used in T2DM patients not on insulin, without the worry of worsening diabetes distress of any form but expecting an increase in time in range as demonstrated in our study. On the other hand, however, the negative findings call for more studies to explore strategies to reduce diabetes distress among people living with T2DM. With the growing use of technology in diabetes care, strategies that combine diabetes technology with other interventions to reduce diabetes distress would be welcome if proved successful.

Unlike the first and second studies in this thesis that involved the use of technology as interventions, the third study compared prednisolone to hydrocortisone in patients with AI. Up until now, there were limited studies comparing the effect of hydrocortisone to prednisolone on the quality of life of patients living with AI. Previous studies explored if prednisolone increased the cardiovascular risk in these patients compared to hydrocortisone. The results were mixed with one study showing increased markers of cardiovascular risk(198) while another reported no difference in the cardiovascular risk profile when compared to hydrocortisone(197). It is worth noting that the study that showed increased cardiovascular risk with prednisolone used slightly

higher doses compared to what we used in our study. The findings from the third study show no changes to the lipid profile related to prednisolone. We have also shown a reduction in systolic blood pressure, body weight and BMI following a switch from hydrocortisone to prednisolone. In addition, the use of prednisolone increased the energy levels of individuals with AI as well as generally how well participants felt their health was. The mechanisms by which prednisolone improves energy levels compared to hydrocortisone are not clearly understood. It is possible that this improvement in perceived QOL is because prednisolone is better than hydrocortisone in mimicking the circadian rhythm. One limitation to these findings is the selection bias. Participants who agreed to switch from hydrocortisone to prednisolone were more likely to be unhappy with how they felt whilst on hydrocortisone. Although the improvement in the quality of life could be attributed to prednisolone, there is a chance that the selected sample could have contributed. To minimize this bias and further provide evidence of improved QOL attributed to prednisolone a randomized controlled trial would be required. Participants would have to be assigned to a treatment group (prednisolone or hydrocortisone) at the time of diagnosis or soon after.

In this thesis, the use of isCGM improved glycaemic control and reduced diabetes distress in people living with T1DM with psychosocial issues. isCGM increased the time in range in people with T2DM, not on insulin but had no effect on diabetes distress. Prednisolone has the same cardiovascular risk as hydrocortisone in patients with AI and is associated with increased energy levels. Future work would examine the long-term impact of this technology and whether the benefits observed would persist after a number of years. The impact of isCGM in people living with diabetes from an ethnic minority background is another area that future studies would focus on. These groups have challenges in accessing this technology and exploring this and how it impacts their quality of life would add to the existing knowledge. In this thesis, the impact of low dose prednisolone on bone markers and bone health has not been assessed. Further work on this area as well as mechanisms through which prednisolone is associated with improved energy levels would be important to undertake.

Appendix

The Diabetes Distress Screening Scale

THE DIABETES DISTRESS SCREENING SCALE

DIRECTIONS: Living with diabetes can sometimes be tough. There may be many problems and hassles concerning diabetes and they can vary greatly in severity. Problems may range from minor hassles to major life difficulties. Listed below are 2 potential problem areas that people with diabetes may experience. Consider the degree to which each of the 2 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

Please note that we are asking you to indicate the degree to which each item may be bothering you in your life, NOT whether the item is merely true for you. If you feel that a particular item is not a bother or a problem for you, you would circle "1". If it is very bothersome to you, you might circle "6".

	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
1. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
2. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6

DDS

DIRECTIONS: Living with diabetes can sometimes be tough. There may be many problems and hassles concerning diabetes and they can vary greatly in severity. Problems may range from minor hassles to major life difficulties. Listed below are 17 potential problem areas that people with diabetes may experience. Consider the degree to which each of the 17 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

Please note that we are asking you to indicate the degree to which each item may be bothering you in your life, NOT whether the item is merely true for you. If you feel that a particular item is not a bother or a problem for you, you would circle "I 11. If it is very bothersome to you, you might circle 11611.

	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
1. Feeling that diabetes is taking up too much of my mental and physical energy every day.	1	2	3	4	5	6
2. Feeling that my doctor doesn't know enough about diabetes and diabetes care.	1	2	3	4	5	6
3. Feeling angry, scared, and/or depressed when I think about living with diabetes.	1	2	3	4	5	6
4. Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	1	2	3	4	5	6
5. Feeling that I am not testing my blood sugars frequently enough.	1	2	3	4	5	6
6. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6
7. Feeling that friends or family are not supportive enough of self-care efforts (e.g. planning activities that conflict with my schedule, encouraging me to eat the "wrong" foods).	1	2	3	4	5	6
8. Feeling that diabetes controls my life.	1	2	3	4	5	6

	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
9. Feeling that my doctor doesn't take my concerns seriously enough.	1	2	3	4	5	6
10. Not feeling confident in my day-to-day ability to manage diabetes.	1	2	3	4	5	6
11. Feeling that I will end up with serious long-term complications, no matter what I do.	1	2	3	4	5	6
12. Feeling that I am not sticking closely enough to a good meal plan.	1	2	3	4	5	6
13. Feeling that friends or family don't appreciate how difficult living with diabetes can be.	1	2	3	4	5	6
14. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
15. Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	I	2	3	4	5	6
16. Not feeling motivated to keep up my diabetes self management.	1	2	3	4	5	' 6
17. Feeling that friends or family don't give me the emotional support that I would like.	1	2	3	4	5	6

DDS17 SCORING SHEET

INSTRUCTIONS FOR SCORING:

The DDS17 yields a total diabetes distress scale score plus 4 sub scale scores, each addressing a different kind of distress. To score, simply sum the patient's responses to the appropriate items and divide by the number of items in that scale. The letter in the far-right margin corresponds to that item's subscale as listed below.

We consider a mean item score of 3 or higher (moderate distress) as a level of distress worthy of clinical attention. Place a check on the line to the far right if the mean item score is 3 to highlight an above-range value.

We also suggest reviewing the patient's responses across all items, regardless of mean item scores. It may be helpful to inquire further or to begin a conversation about any single item scored 3 or higher.

Total DDS Score:

a. Sum of 17 item scores. _____
b. Divide by: 17
c. Mean item score: _____

A. Emotional Burden:

a. Sum of 5 items (1, 3, 8, 11, 14) _____
b. Divide by: 5
c. Mean item score: _____

B. Physician-related Distress:

a. Sum of 4 items (2, 4, 9, 15) _____
b. Divide by: 4
c. Mean item score: _____

C. Regimen-related Distress:

a. Sum of 5 items (5, 6, 10, 12, 16) _____

b. Divide by: ___5____

c. Mean item score:

D. Interpersonal Distress:

a. Sum of 3 items (7, 13, 17)
b. Divide by 3

c. Mean item score:

Modified SF-36 Questionnaire

Wellbeing study on Hormone replacement (Modified SF-36 Questionnaire)

1. In general, would you say your health is

1. Excellent

2. Very good

3. Good

4. Fair

5. Poor

2. These questions are about how you feel and how things have been with you during the past 7 days. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 7 days . . .

	1. All of the Time	2. Most of the Time	3. A Good Bit of the Time	4. Some of the Time	5. A Little of the Time	6. None of the Time
Did you feel full of pep?	Did you feel full of pep? 1. All of the Time	Did you feel full of pep? 2. Most of the Time	Did you feel full of pep? 3. A Good Bit of the Time	Did you feel full of pep? 4. Some of the Time	Did you feel full of pep? 5. A Little of the Time	Did you feel full of pep? 6. None of the Time
Have you been a very nervous person?	Have you been a very nervous person? 1. All of the Time	Have you been a very nervous person? 2. Most of the Time	Have you been a very nervous person? 3. A Good Bit of the Time	Have you been a very nervous person? 4. Some of the Time	Have you been a very nervous person? 5. A Little of the Time	Have you been a very nervous person? 6. None of the Time
Have you felt so down in the dumps that nothing could cheer you up?	Have you felt so down in the dumps that nothing could cheer you up? 1. All of the Time	Have you felt so down in the dumps that nothing could cheer you up? 2. Most of the Time	Have you felt so down in the dumps that nothing could cheer you up? 3. A Good Bit of the Time	Have you felt so down in the dumps that nothing could cheer you up? 4. Some of the Time	Have you felt so down in the dumps that nothing could cheer you up? 5. A Little of the Time	Have you felt so down in the dumps that nothing could cheer you up? 6. None of the Time

	1. All of the Time	2. Most of the Time	3. A Good Bit of the Time	4. Some of the Time	5. A Little of the Time	6. None of the Time
Have you felt calm and peaceful?	Have you felt calm and peaceful? 1. All of the Time	Have you felt calm and peaceful? 2. Most of the Time	Have you felt calm and peaceful? 3. A Good Bit of the Time	Have you felt calm and peaceful? 4. Some of the Time	Have you felt calm and peaceful? 5. A Little of the Time	Have you felt calm and peaceful? 6. None of the Time
Did you have a lot of energy?	Did you have a lot of energy? 1. All of the Time	Did you have a lot of energy? 2. Most of the Time	Did you have a lot of energy? 3. A Good Bit of the Time	Did you have a lot of energy? 4. Some of the Time	Did you have a lot of energy? 5. A Little of the Time	Did you have a lot of energy? 6. None of the Time
Have you felt downhearted and blue?	Have you felt downhearted and blue? 1. All of the Time	Have you felt downhearted and blue? 2. Most of the Time	Have you felt downhearted and blue? 3. A Good Bit of the Time	Have you felt downhearted and blue? 4. Some of the Time	Have you felt downhearted and blue? 5. A Little of the Time	Have you felt downhearted and blue? 6. None of the Time
Did you feel worn out?	Did you feel worn out? 1. All of the Time	Did you feel worn out? 2. Most of the Time	Did you feel worn out? 3. A Good Bit of the Time	Did you feel worn out? 4. Some of the Time	Did you feel worn out? 5. A Little of the Time	Did you feel worn out? 6. None of the Time
Have you been a happy person?	Have you been a happy person? 1. All of the Time	Have you been a happy person? 2. Most of the Time	Have you been a happy person? 3. A Good Bit of the Time	Have you been a happy person? 4. Some of the Time	Have you been a happy person? 5. A Little of the Time	Have you been a happy person? 6. None of the Time

	1. All of the Time	2. Most of the Time	3. A Good Bit of the Time	4. Some of the Time	5. A Little of the Time	6. None of the Time
Did you feel tired?	**Did you feel tired? 1. All of the Time**	**Did you feel tired? 2. Most of the Time**	**Did you feel tired? 3. A Good Bit of the Time**	**Did you feel tired? 4. Some of the Time**	**Did you feel tired? 5. A Little of the Time**	**Did you feel tired? 6. None of the Time**
Did you feel nauseous?	**Did you feel nauseous? 1. All of the Time**	**Did you feel nauseous? 2. Most of the Time**	**Did you feel nauseous? 3. A Good Bit of the Time**	**Did you feel nauseous? 4. Some of the Time**	**Did you feel nauseous? 5. A Little of the Time**	**Did you feel nauseous? 6. None of the Time**

3. How convenient is your hydrocortisone or prednisolone replacement therapy?

1. Very convenient

2. Convenient

3. OK

4. Inconvenient

5. Very inconvenient

4. I am currently on

1. Hydrocortisone

2. Prednisolone

5. What dose are you taking in total each day (in mg) of hydrocortisone or prednisolone?

6. I take my prednisolone or hydrocortisone

1. Once daily

2. Twice daily

3. Three times daily

4. Four times daily

I split my dose as follows (eg 10mg in the morning, 5 at lunchtime and 5 at 4pm)

7. When do you take your FIRST dose in the morning

Immediately on waking before doing anything else

At least 30 minutes after waking

I make sure I have something to eat before taking my first dose

8. Finally, please fill in the following details

Study ID/ (Name)

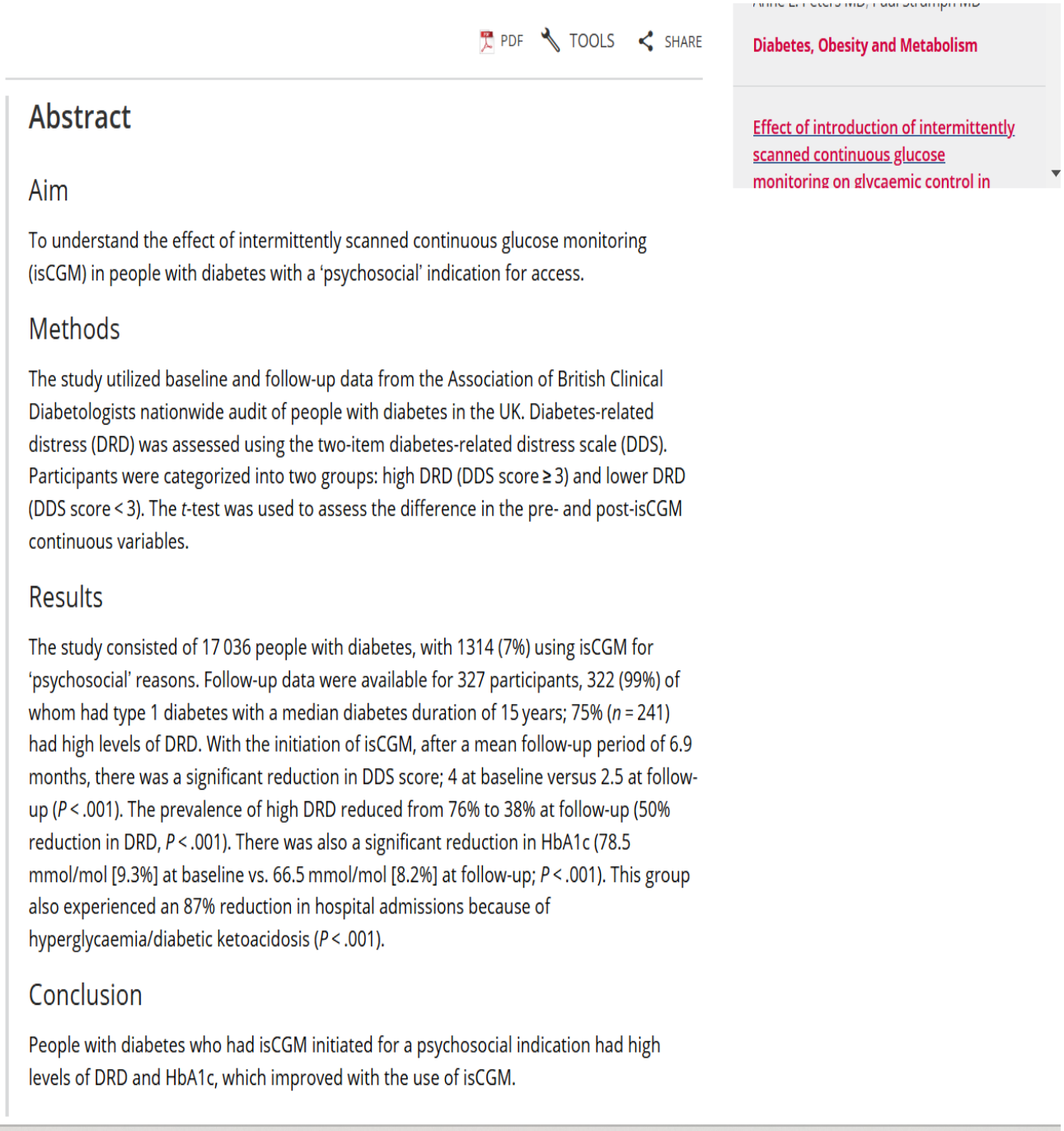
e-mail (optional)

date

Any other comments

Abstracts from published papers from the thesis

Effect of intermittently scanned continuous glucose monitoring in people with diabetes with a psychosocial indication for initiation



PDF TOOLS SHARE

Diabetes, Obesity and Metabolism

Effect of introduction of intermittently scanned continuous glucose monitoring on glycaemic control in

Abstract

Aim

To understand the effect of intermittently scanned continuous glucose monitoring (isCGM) in people with diabetes with a 'psychosocial' indication for access.

Methods

The study utilized baseline and follow-up data from the Association of British Clinical Diabetologists nationwide audit of people with diabetes in the UK. Diabetes-related distress (DRD) was assessed using the two-item diabetes-related distress scale (DDS). Participants were categorized into two groups: high DRD (DDS score ≥ 3) and lower DRD (DDS score < 3). The *t*-test was used to assess the difference in the pre- and post-isCGM continuous variables.

Results

The study consisted of 17 036 people with diabetes, with 1314 (7%) using isCGM for 'psychosocial' reasons. Follow-up data were available for 327 participants, 322 (99%) of whom had type 1 diabetes with a median diabetes duration of 15 years; 75% ($n = 241$) had high levels of DRD. With the initiation of isCGM, after a mean follow-up period of 6.9 months, there was a significant reduction in DDS score; 4 at baseline versus 2.5 at follow-up ($P < .001$). The prevalence of high DRD reduced from 76% to 38% at follow-up (50% reduction in DRD, $P < .001$). There was also a significant reduction in HbA1c (78.5 mmol/mol [9.3%] at baseline vs. 66.5 mmol/mol [8.2%] at follow-up; $P < .001$). This group also experienced an 87% reduction in hospital admissions because of hyperglycaemia/diabetic ketoacidosis ($P < .001$).

Conclusion

People with diabetes who had isCGM initiated for a psychosocial indication had high levels of DRD and HbA1c, which improved with the use of isCGM.

Effect of introduction of intermittently scanned continuous glucose monitoring on glycaemic control in individuals living with type 2 diabetes mellitus treated with non-insulin therapies—A randomised controlled trial

Abstract

Aims

This pilot randomised controlled trial aimed to evaluate the effect of introducing isCGM on glycaemic control and diabetes distress in individuals with T2DM receiving non-insulin therapies.

Materials and Methods

Forty adults with T2DM were randomised to either receive FreeStyle Libre 2 (Libre 2), an isCGM system, or FreeStyle Libre Pro iQ (Libre Pro) also known as 'blinded' CGM. Participants were followed for 12 weeks. The primary outcome was a fall in haemoglobin A1c (HbA1c) of ≥5.5 mmol/mol. Diabetes distress was assessed using the two-item diabetes distress scale (DDS2).

Results

The median age was 59.5 years; 57.5% were male. Of the Libre 2 users, 53% achieved a ≥5.5 mmol/mol reduction in HbA1c compared to 35% in the Libre pro group ($p = 0.34$). Compared to Libre Pro, the use of Libre 2 was associated with an improved time in range at 12 weeks of 18 percentage points (confidence interval 2–35, $p = 0.028$). Participants in the Libre 2 group exhibited a non-significant reduction in HbA1c levels of 8 mmol/mol compared to the Libre Pro group after 12 weeks. However, no significant differences were observed in other CGM metrics or diabetes distress between the study groups.

Conclusions

The use of isCGM in individuals living with T2DM on non-insulin therapy showed promise in improving glycaemic control, as evidenced by increased TIR, albeit without a significant reduction in HbA1c or impact on diabetes distress, suggesting this could be potentially beneficial in individuals with T2DM.

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