Thesis:

A retrospective analysis of diabetes management in people with type 1 diabetes switching from a CGM system without alerts to a system with alerts

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Statutory declaration

I declare on my honour that I have written the present work independently and without outside help, that I have not used sources other than those specified and that I have identified the passages, taken verbatim or in terms of content, as such.

Graz, 08.09.2022 Carlotta Elisabeth Mosch eh

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III. ABBREVIATIONS

ADA..... American Diabetes Association
ATTD..... advances technologies and treatments for diabetes
BMI..... body mass index
CGM..... continuous glucose monitoring
CSII..... continuous subcutaneous insulin infusion
CV..... coefficient of variations
DDP-4 ..... dipeptidyl peptidase-4
DKA..... diabetic ketoacidosis
DTSQ..... Diabetes Treatment Satisfaction Questionnaire
eA1c..... estimated HbA1c
eGFR ..... estimated glomerular filtration rate
FBR..... foreign body reaction
GAD65 ..... glutamate-decarboxylase 65
GDM..... gestational diabetes mellitus
GLP1..... glucagon-like peptide 1
GMI ..... glucose monitoring indicator
HBGI ..... high blood glucose index
HIV..... human immunodeficiency virus
HLA-DQ ..... human leukocyte antigen DQ isotype
HLA-DR..... human leukocyte antigen DR isotype
IAA..... insulin autoantibodies
IFIH1 ..... interferon induced with helicase C domain 1
INS..... insulin gene
isCGM..... intermittently scanned continuous glucose monitoring
ISO..... international organisation of standardisation
LADA..... late-onset autoimmune diabetes of adults
LBGI..... low blood glucose index
MARD ..... mean absolute relative difference
MDI ..... multiple daily injections
MODY ..... maturity-onset diabetes of the young
OGTT..... oral glucose tolerance test
PCOS..... polycystic ovary syndrome
PTPN22 ..... protein tyrosine phosphatase non-receptor type 22
rtCGM ..... real-stime continuous glucose monitoring
SD..... standard deviation
SGLT2..... sodium-glucose cotransporters-2

SLE ..... systemic lupus erythematosus
SMBG ..... self-monitoring of blood glucose
T1DM ..... type 1 diabetes mellitus
T2DM ..... type 2 diabetes mellitus
TAR..... time above range
TBR..... time below range
TIR ..... time in range
TYK2 ..... tyrosine kinase 2
WHO ..... World Health Organisation
ZnT8A ..... zinc transporter 8 antibody

IV. ABSTRACT

Introduction

Continuous glucose monitoring (CGM) has become an important part of diabetes therapy over the last years and its benefits for people with diabetes have been proven on a large scale. Over the years, alarms for hypo- and hyperglycaemic events have been integrated into many CGM systems. This study was carried out to see if users of an intermittently-scanned CGM (isCGM) system without alerts would benefit from switching to an isCGM system with alerts.

Materials and Methods

This retrospective, single-centre study included 18 users (72% male, 28% female, mean age 38.8 years, mean HbA1c 58.39 mmol/mol, mean duration of diabetes 18.5 years) of an isCGM without alerts (Abbott Libre 1, Abbott Diabetes Care), who were switched during routine care to an isCGM with alerts (Abbott Libre 2, Abbott Diabetes Care). The data 90 days prior to the switch and 90 days after the switch was analysed and included CGM metrics as time in range (TIR), average glucose levels, HbA1c, glucose monitoring indicator (GMI) etc.

Results

TIR was 56.6% (46.85%-73.53%) for isCGM without alerts and 58.7% (47.14%-72.44%) for isCGM with alerts. TBR <70 mg/dl was 4.76% (1.93%-6.17%) without alerts vs. 3.63% (2.09%-7.21%) with alerts. For the CGM system without alerts time above range (TAR) >180 mg/dl was 39.2% (21.86%-50.91%) and for TAR >250 mg/dl 11.11% (3.49%-19.08%), respectively. With the CGM system with alerts, the TAR >180 mg/dl was 35.65% (22.41%-42.23%) and for TAR >250 mg/dl 9.15% (3.68%-17.83%). Average glucose levels were 167.49 mg/dl (140.28 mg/dl-186.96 mg/dl) without alerts and 161.44 mg/dl (141.02 mg/dl – 186.97 mg/dl) with alerts. The GMI was 56.45 mmol/mol (41.93 mmol/mol – 61.3 mmol/mol) for CGM systems without alarms and 54.87 mmol/mol (43.72 mmol/mol – 61.54 mmol/mol) with alarms.

Basal insulin doses could be obtained for all 18 people with diabetes before the switch and for 8 people with diabetes after the switch. Mean total daily insulin dose was 25.0 IU daily (20.0 IU – 30.0 IU) while using the isCGM without alerts and 24.0 IU (19.0 IU – 30.3 IU) while using the isCGM system with alerts.

Conclusion

Switching to an isCGM with alerts resulted in a slight improvement in TIR, TBR and TAR, but overall, the change in GMI was not significant. Like other CGM trials, glycaemic targets were not achieved for the majority of the users. Further studies and research are needed to enable further improvement in blood glucose control for people with diabetes.

V. ZUSAMMENFASSUNG

Einleitung

Die kontinuierliche Glukoseüberwachung (CGM) ist in den letzten Jahren zu einem wichtigen Bestandteil der Diabetestherapie geworden und ihre Vorteile für Personen mit Diabetes sind in großem Umfang nachgewiesen worden. Im Laufe der Jahre wurden Alarme für hypo- und hyperglykämische Ereignisse in viele CGM-Systeme integriert. Diese Studie wurde durchgeführt, um herauszufinden, ob Nutzer/-innen eines isCGM-Systems ohne Alarme von einem Wechsel zu einem isCGM-System mit Alarmen profitieren würden.

Materialien und Methoden

Diese retrospektive, single-center Studie umfasste 18 Nutzer*innen (72% männlich, 28% weiblich, Durchschnittalter 38,8 Jahre, durchschnittlicher HbA1c 58,39 mmol/mol, durchschnittliche Diabetesdauer 18,5 Jahre) eines isCGM ohne Alarme (Abbott Libre 1, Abbott Diabetes Care), die auf ein isCGM mit Alarmen (Abbott Libre 2, Abbott Diabetes Care) umgestellt wurden. Die Daten wurden von 90 Tage vor dem Wechsel bis 90 Tage nach dem Wechsel analysiert und umfassten CGM-Kennzahlen wie time in range (TIR), durchschnittliche Glukosewerte, HbA1c, Glucose management indicator (GMI) usw.

Ergebnisse

Die TIR betrug 56,6 % (46,85 %-73,53 %) für isCGM ohne Alarme und 58,7 % (47,14 %-72,44 %) für isCGM mit Alarmen. Die TBR <70 mg/dl lag bei 4,76% (1,93%-6,17%) ohne Alarme gegenüber 3,63% (2,09%-7,21%) mit Alarmen. Beim CGM-System ohne Alarme lag die Zeit über dem Messbereich (TAR) >180 mg/dl bei 39,2 % (21,86 %-50,91 %) und für TAR >250 mg/dl bei 11,11 % (3,49 %-19,08 %). Mit dem CGM-System mit Alarmen lag die TAR >180 mg/dl bei 35,65 % (22,41 %-42,23 %) und für TAR >250 mg/dl bei 9,15 % (3,68 %-17,83 %). Die durchschnittlichen Glukosewerte betrugen 167,49 mg/dl (140,28 mg/dl-186,96 mg/dl) ohne und 161,44 mg/dl (141,02 mg/dl - 186,97 mg/dl) mit Alarmen.

Der GMI betrug 56,45 mmol/mol (41,93 mmol/mol - 61,3 mmol/mol) für CGM-Systeme ohne Alarme und 54,87 mmol/mol (43,72 mmol/mol - 61,54 mmol/mol) mit Alarmen.

Die Basalinsulindosen konnten bei allen 18 Personen mit Diabetes vor der Umstellung und bei 8 Personen mit Diabetes nach der Umstellung ermittelt werden. Die durchschnittliche tägliche Gesamtinsulindosis betrug 25,0 IE täglich (20,0 IE - 30,0 IE) bei der Verwendung des isCGM ohne Alarme und 24,0 IE (19,0 IE - 30,3 IE) bei der Verwendung des isCGM-Systems mit Alarmen.

Fazit

Die Umstellung auf ein isCGM mit Alarmen führte zu einer leichten Verbesserung von TIR, TBR und TAR, aber insgesamt war die Veränderung des GMI nicht signifikant. Wie bei anderen CGM-Studien wurden die glykämischen Zielewerte bei der Mehrheit der Teilnehmer*innen

nicht erreicht. Es sind weitere Studien und Untersuchungen erforderlich, um eine weitere Verbesserung der Diabeteseinstellung für Personen mit Diabetes mellitus zu ermöglichen.

VI. INTRODUCTION

1. DIABETES MELLITUS

Diabetes mellitus is a chronic disease, that is characterised as a dysfunction of the glucose metabolism due to insufficient insulin secretion or insufficient insulin action, resulting in hyperglycaemia.(1,2) This condition is by no means a rare one. According to the World Health Organisation (WHO) in 2014 422 million adults (over 18 years old) were living with diabetes mellitus.(3) Estimates suggested a prevalence of global diabetes in 2019 of 463 million people (adults aged 20-79), rising to 578 million adults in 2030 and continuing to rise to 700 million adults by 2045, accounting for approximately 10% of the world population.(4) The Global Burden of Disease study of 2017 stated that 475 million people were living with diabetes at that time.(4) Additionally around 1.2 million children (below the age of 19) currently are diagnosed with type 1 diabetes mellitus.(5) As of 2019, diabetes – as a result of its related comorbidities and complications - ranks as the 9th most common cause of death worldwide.(6)

Diabetes mellitus is a highly heterogenic disease.(1) Depending on the pathogenesis, one can differentiate between type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes and other forms of diabetes mellitus.(7)

1.1. Type 1 diabetes mellitus

T1DM is an autoimmune disease characterised by the destruction of the beta cells in the pancreas due to autoantibodies.(8) About 5–10% of all people living with diabetes mellitus fall into this category.(2)

Nowadays there are 5 different autoantibodies identified(8):

- Islet autoantibodies
- Insulin autoantibodies (IAA)
- Autoantibodies against GAD (GAD65)
- Autoantibodies to the tyrosine phosphates
- Autoantibodies to the zinc transporter (ZnT8A)

In 80% of all people living with T1DM, one or more of these autoantibodies can be found. GAD antibodies are typically found in adults, whereas IAA are commonly present in children.(8) As the disease progresses the number of autoantibodies decreased, as more of the beta cell mass is destroyed and less tissue exists, effectively removing the target tissue of the autoantibodies.(8) The pancreas can compensate the loss of beta cell mass for a reasonably long period of time, so that hyperglycaemia and the corresponding symptoms occur after a loss of over 80% of all beta cells.(1)

Even though the exact pathophysiological process of why autoantibodies are produced is still unknown, T1DM is linked to both genetic and environmental factors.(9)
When referring to genetic factors, T1DM is strongly associated with variants in the HLA-regions, specifically the HLA-DR and HLA-DQ.(9) Additionally, about 50 other gene loci to increase the risk for T1DM have been identified, most prominently the INS and PTPN22, which lead to polymorphism in insulin, and IFIH1 and TYK2, which induce interferon production. The reduced function of either gene seemingly has a protective quality against T1DM.(9) The presence of certain genetic mutations make these people with diabetes also more susceptible to other autoimmune diseases like Hashimoto thyroiditis, celiac disease, autoimmune hepatitis and others.(7) In total, about 80% of T1DM can be explained through genetic variations.(10)
Environmental factors for the development of T1DM include enterovirus infection, rubella or mumps infections, an altered microbiome, high/early intake of gluten, a diet rich in saturated fats as well as low levels of vitamin D. Even though all these factors are not the trigger for the autoimmune response in the first place, they can play a significant role in accelerating the process.(9)

A rare form of T1DM is idiopathic diabetes, meaning that the affected individuals lack immunological evidence for T1DM. Their requirement for insulin replacement therapy varies and is rarely predictable, making them prone to ketoacidosis.(2) This form is mostly hereditary, though not HLA-associated, and often found in people of African or Asian descent. (2,7,8)
Another variant, or more precisely hybrid-form, is the late-onset autoimmune diabetes in adults, also called LADA. With this type of diabetes individuals show attributes of T1DM and T2DM. On one hand, people with LADA produce autoantibodies, often GAD antibodies, but their progression to an absolute insulin deficiency is slower than in common T1DM. They usually do not require insulin in the first 6 months after diagnosis.(11) On the other hand, most people with LADA share similar risk and environmental factors with people with T2DM, leading to reduced insulin sensitivity.(11)

The diagnosis of T1DM consists of a thorough medical history, clinical presentation, lab results and certain diagnostic criteria.(12)
Symptoms of hyperglycaemia are amongst others polyuria, polydipsia, night sweats, vision blurring and weight loss. Clinically, patients with an initial manifestation of T1DM are young (<35 years) and present with an extreme metabolic imbalance. Many patients present with ketoacidosis and usually blood glucose is over 360 mg/dl at the time of clinical presentation.(12)

The diagnostic criteria according to the American Association of Diabetes are the following(7):

Fasting plasma glucose ≥ 126 mg/dl

or

2-h plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT)

or

HbA1c ≥ 6.5 % (or 48 mmol/mol)

or

Symptoms of hyperglycaemia + random plasma glucose ≥ 200 mg/dl

Regarding the HbA1c it is important to use a standardised method to receive accurate results. If the individual suffers from sickle cell disease or glucose-6-phosphate dehydrogenase deficiency, the HbA1c is not reliable and one depends on fasting glucose and 2-h glucose for the diagnosis. Additionally, if the individual is undergoing haemodialysis, received blood transfusion or erythropoietin therapy, one should also not rely on the HbA1c.(7)
The differentiation between T1DM and T2DM is usually established through the presence of autoantibodies and the C-peptide value, as a marker for intrinsic insulin production.(12) Depending on age of onset, duration of disease, extraordinary symptoms, presentation etc., the differences between the different diabetes forms are not often that clear, and misdiagnosis can occur.(12)

The therapy for T1DM is a multimodal one and consists of glucose monitoring, insulin supplementation, healthy eating habits, physical activity and healthy psychological coping mechanisms.(12)
As for glucose monitoring, a well-known method is the SMBG (self-monitoring of blood glucose), also called finger-pricking. Nowadays most people living with T1DM use a continuous glucose monitoring (CGM) device. Those are usually tools, that are inserted in the subcutaneous adipose tissue and remain in the tissue for up to 14 days, allowing for a continuous measuring of the interstitial glucose concentration.(12)
As T1DM is caused by an absolute insulin deficiency, the primary aspect of the therapy is insulin supplementation. This replacement therapy can be achieved through different regimens. The most used form is the MDI – multiple daily injections – method. Here, the insulin is administered through subcutaneous injections by the patient. Rapid or ultra-rapid acting insulin are used to cover carbohydrate intake during meals and long-acting basal insulin to supplement basal insulin requirements that are present also during fasting conditions.(12)
Alternatively, insulin can be administered through an insulin pump, the so-called CSII-system (continuous subcutaneous insulin infusion). These systems dispense a basal insulin rate and offer the administration of correction boluses to cover meals or hyperglycaemia. If an insulin pump is combined with a CGM device and a control algorithm, it is called a hybrid closed-loop

system. This would be the most efficient way to treat T1DM, but also the most cost-intensive.(12)
Additional therapeutic measures are nutrition adjustments, regular physical activity, especially endurance training, and the development of healthy coping mechanisms to deal with the psychological strain the diagnosis brings with it.(12)
The overall goal for T1DM therapy is to maintain a physiological, normal glucose pattern as best as possible, in order to avoid long-term complications.(12)

1.2. Type 2 diabetes mellitus

The majority, around 90%, of all people with diabetes are diagnosed with diabetes mellitus type 2 (T2DM). This form of diabetes is characterized by normal to elevated insulin secretion, but reduced insulin sensitivity of the peripheral tissues, leading to relative insulin deficiency.(8) In contrast to T1DM, these individuals do not produce autoantibodies.(2)
Even though genetic and environmental factors have been found to be associated with the development of T2DM, genetic variations have proven minimal compared to the environmental risk factors.(10) The most common influences being age, obesity, energy-dense (Western) diet, low socioeconomic status, previous gestational diabetes, high blood pressure, dyslipidaemia, little physical activity, respectively high sedentary time, certain infections, chronic stress, depression and smoking.(13,14)
When it comes to obesity, it does not only depend on the body mass index (BMI), but also on the area of the fat deposits and the muscle mass. Higher risk of developing T2DM is associated with high amount of visceral fat and liver fat. If individuals display such fat deposits, but combined with low muscle mass, putting them in a normal BMI range, they still have an increased risk of T2DM. This is often the case in people of Asian descent, which has subsequently resulted in the recommendation that the BMI cut-off for these people actually should be at 23 kg/m^2. (7,13)
When referring to a high-density diet, the most impactful foods overall are refined grains, sweetened drinks, saturated fats and a high meat consumption.(13)
With sedentary time as well as with depression the interaction seems to be bidirectional. Meaning, that high sedentary time/depression increases the risk for T2DM, and a pre-existing T2DM increased the risk for depression or a lot of time spent inactive.(13)
As for infections, related to the development of T2DM are hepatitis C infection, Chlamydia pneumonia infections and human immunodeficiency virus (HIV). With HIV it is important to mention that the antiviral therapy itself results in a higher risk for T2DM.(13) Other medication promoting T2DM are certain diuretics, statins and beta-blockers.(14)

When speaking about diagnostic criteria, the same apply for T2DM as for T1DM. As mentioned above, making the differentiation between T1DM and T2DM is not always clear. Higher age

(>35 years), higher BMI, the absence of autoantibodies and normal to elevated C-peptide can be guiding parameters towards a T2DM diagnosis.(15)

The baseline of T2DM therapy are lifestyle changes. Such lifestyle changes include weight loss, adapting healthy eating patterns, regular physical activity, averting from smoking etc.
If glycaemic control is not reached through these actions, pharmaceutical intervention and measurement of blood glucose to reduce glycaemia should be introduced. The first line medication is metformin, which is a biguanide that lowers hepatic glucose production and interferes with the glucose metabolism also through non-insulin routes. If the glycaemic target is still not achieved and certain risk factors are present, dual therapy is the next step. Depending on the risk factors, it is recommended to add either SGTL2-inhibitors (sodium glucose cotransporter 2) or GLP-1 receptor agonists (glucagon-like peptide 1) to the therapy plan. SGLT2-inhibitors have proven to be beneficial when heart failure or chronic kidney disease are comorbidities. But it has to be mentioned, that SGLT2-inhibitor function greatly depends on the estimated glomerular filtration rate (eGFR), making it therapeutically non-valid in case of critically reduced kidney function. If atherosclerotic cardiovascular factors play a role, the use of GLP-1 receptor agonists should be added, as they show an improvement in the patient's cardiovascular outcome.(15)
Other possible oral medications are dipeptidyl peptidase 4 (DDP-4) inhibitors (increase insulin and lower glucagon secretion), thiazolidinediones (increase insulin sensitivity) and sulfonylureas (increase insulin secretion). If normoglycaemia cannot be reached with oral medication, patients are advised to switch to insulin injections. The initial therapy is the use of intermediate or long-term basal insulins. Rapid or ultra-rapid insulin should only be introduced if needed.(15)
Patients with immense overweight and high BMI (≥40 kg/m²) might profit from bariatric surgery, however, the surgical risks must be kept in mind here.(15)
The primary goal of T2DM therapy is to delay long-term complications and preserve the patient's quality of life.(15)

1.3. Gestational diabetes mellitus

Originally, gestational diabetes was defined as diabetes occurring in pregnancy. Nowadays, it is important to differentiate between gestational diabetes, meaning diabetic metabolism being present only during pregnancy, and presence of T1DM or T2DM in pregnancy.(16)
Throughout pregnancy the insulin secretion and resistance vary, due to physical and metabolic changes. In early pregnancy the insulin sensitivity and secretion are heightened, then decline and switch into an insulin resistance, as the pregnancy progresses. Gestational diabetes mellitus (GDM) usually develops around the same time this metabolic change occurs, which is approximately halfway through the pregnancy.(16)

Factors like obesity, polycystic ovary syndrome (PCOS), higher maternal age, positive family history for T2DM, previous GDM, recurring abortions or stillbirths, history of hypertension and ethnicity contribute to a high chance of developing GDM.(16) Untreated or unsuccessfully treated GDM can lead to preeclampsia, eclampsia, polyhydramnios, preterm labour and birth weight over 4.000 grams, which leads to risk of shoulder dystocia, birth trauma and higher morbidity when delivering via C-sections for the mother and higher risk for neonatal hypoglycaemia, hyperbilirubinemia, hypocalcemia, polycythemia and respiratory stress for the child.(16,17)

In order to prevent labour complications for mother and child, the OGTT (oral glucose tolerance test) is carried out at 24-28 weeks of pregnancy. In 2010, the criteria for diagnosing GDM were altered from needing two out-of-range values to only needing one, which almost doubled the diagnoses of gestational diabetes. The pregnant woman is given a 75 g glucose solution to drink and the blood glucose is measured before the intake, 1 and 2 hours after intake. The measured values must not exceed certain thresholds:

Fasting plasma glucose ..... 92 mg/dl
1h-plasma glucose ..... 180 mg/dl
2h-plasma glucose ..... 153 mg/dl

Only one elevated value suffices to diagnose GDM and start treatment.(17)

The first line of treatment consists of lifestyle alterations, including daily physical activity and nutrition counselling. In case this therapy is insufficient, the next step is initiating insulin therapy. Depending on the blood glucose dynamics, either basal or bolus or basal-bolus-therapy should be started. Certain oral antihyperglycaemic medication is available, but one has to be cautious of congenital abnormalities and teratogenicity. Glyburide and metformin are both category B drugs, meaning that is no evidence suggesting animal or fetal toxicity or teratogenicity. In clinical practice, neither of these drugs have been causing long-term negative effects on the unborn child when used during pregnancy. For both medications the failure rate lies between 20-46%, which has to be taken into consideration when choosing a therapy option.(17)

GDM usually resolves as soon as the placenta is delivered. Postpartum glucose should still be observed for 24 to 72 hours to ensure a return to normal glucose dynamics. As GDM bears the risk of developing T2DM in the following years, it is recommended that these women are screened for diabetes annually for the subsequent three years.(17)

1.4. Other types of diabetes

1.4.1. Genetic defects of the beta-cells

This form of diabetes is also referred to as the maturity-onset diabetes of the young (MODY) and is associated with a malfunction in insulin secretion, but normal insulin action. The causes

are monogenetic. So far, six different genetic mutations have been found, most often they affect hepatocyte nuclear factor 1 alpha on chromosome 12q (MODY 3), the glucokinase on chromosome 7p (MODY 2), hepatocyte nuclear factor 4 alpha on chromosome 20q (MODY 1) or hepatocyte nuclear factor 1 beta on chromosome 17q (MODY5). All forms are strongly autosomal-dominantly inherited.(1,2)

Additionally, under this category fall genetic mutations that prohibit proinsulin to be transformed into insulin. This form of diabetes displays a strong autosomal-dominant inheritance pattern as well.(2)

1.4.2. Genetic defects in insulin action

Principally, this diabetes type is mostly due to defects of the insulin receptors. Those can occur as part of certain congenital syndromes like Leprechaunism and Rabson-Mendenhall syndrome.(2) With these patients, hyperglycaemia can vary from one end of the spectrum to the other and is rarely predictable.(2)

Genetic defects can also occur in the postreceptor signal transduction pathways, as it is the case with lipoatrophic diabetes.(2)

1.4.3. Endocrinopathies

Hyperglycaemia can be a symptom of certain endocrinopathies, primarily regarding excess release of hormones that lower insulin action, such as cortisol, growth hormone, glucagon, epinephrine etc. Thus, diseases like Mb. Cushing, acromegaly, pheochromocytoma, glucagonoma, hyperthyroidism etc. can cause diabetes. It mostly affects individuals who have pre-existing, unnoticed insulins deficiencies.(2)

As soon as hormone levels return to normal, so does the metabolic status.(2)

1.4.4. Drug- or chemical-induced diabetes

Many drugs are known to have diabetogenic side effects. As with endocrinopathies, this usually effects individuals with pre-existing insulin resistance. Medications like thyroid hormone, nicotinic acid, glucocorticoids, thiazides, gamma-Interferon etc. are all linked to interfering with the glucose metabolism.(2)

1.4.5. Diseases of the exocrine pancreas

Extensive injuries to the pancreas can also lead to diabetes. As a rule, this involves pancreatitis incl. alcohol-induced pancreatitis, pancreatic cancer, trauma, pancreatectomy, neoplasia, cystic fibrosis, severe forms of hemochromatosis etc.(2)

1.4.6. Others

Some infections, predominantly congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus and mumps have been associated with the development of diabetes.(2)

Additionally, diabetes can be part of other autoimmune diseases. A lot of patients with stiff-man syndrome develop GAD autoantibodies, which leads to 1/3 of the patients becoming diabetic.(2)

Sporadically in patients with systemic lupus erythematosus (SLE) anti-insulin receptor antibodies can be found, which block the insulin from binding to its receptor on the target tissue, thus leading to hyperglycaemia.(2)

There are also some genetic syndromes associated with a higher risk of developing diabetes, a few of them being: Down syndrome, Klinefelter syndrome, Turner syndrome, Huntington chorea, myotonic dystrophy, porphyria and Prader-Willi syndrome.(2)

Many patients, who received transplants, primarily kidneys, show signs of hyperglycaemia after the first weeks. This usually resolves and they return to a normoglycaemic metabolism over time. (7)

1.5. Long-term complications

Even though the pathogenesis differs greatly for every type of diabetes, they are all affected by the same long-term complications, as the common problem is prolonged hyperglycaemia.(10) Generally, there can be made a division into microvascular and macrovascular complications.(18)

Microvascular complications include diabetic nephropathy, retinopathy and neuropathy.

As for retinopathy, it can be said that it is the worldwide primary cause of blindness in adults.(18) At first, micro lesions at the background of the eye occur, not impacting the patient's vision. As the disease progresses it can come to haemorrhages, retinal detachment and macular oedema, causing vision loss, if not properly treated.(18)

As for diabetic neuropathy, it can be divided into peripheral and autonomic neuropathy. The peripheral version usually affects the feet, but can also be found in any other body part and is accompanied by numbness, altered reflexes, impaired vibratory awareness, burning pain and tingling sensations in the affected area. Autonomic neuropathy affects – as the name suggests – the autonomic nervous system, leading to symptoms like bowel and bladder dysfunction, resting tachycardia, gastroparesis, erectile dysfunction and orthostatic hypotension.(18)

Peripheral neuropathy combined with reduced peripheral circulation often leads to poor wound healing, making diabetic individuals prone to ulcers.(18,19)

It also should be mentioned, that people with diabetes have an impaired immune system. This can make it easy for various pathogens to cause infections. Often seen are periodontal infections or infections of the feet. This, combined with the tendency to develop ulcers, can lead to the diabetic foot syndrome, which in severe case can make amputation necessary.(19,20)

Another microvascular complication is diabetic nephropathy. First signs are hyperfiltration and heightened renal plasma flow, leading to microalbuminuria, which progresses to

macroalbuminuria to end-stage-kidney failure. Many patients then require regular dialysis or kidney transplantation.(18)

Concerning the macrovascular complications, they consist of an elevated risk for atherosclerosis, cardiovascular comorbidities and cerebrovascular diseases.(20)

Furthermore there is evidence suggesting that diabetes from a young age leads to mild cognitive impairments and differences in brain structure, usually affecting memory and learning.(18)

2. CONTINUOUS GLUCOSE MONITORING

Continuous glucose monitoring (CGM) systems are nowadays small sensors that are inserted into the subcutaneous adipose tissue to measure interstitial glucose. This allows people with diabetes to track their glucose levels without finger pricking, whenever and wherever they want.(21)

2.1. Historical development

Monitoring of blood glucose has always been a crucial part of diabetes management.(22) Until the 1950ies this was accomplished through measuring urinary glucose.(23) In the late 1950ies the enzyme glucose oxidase was discovered, which allowed for plasma glucose to be measured.(23) At first this method was only available in laboratories, but in the early 1980ies the development of test strips was advanced enough to make self-monitoring of blood glucose (SMBG) commonly available for people with diabetes.(23) CGM systems were initially developed in the late 1990ies, with the first one being commercially sold in 1999 by Minimed/Medtronic.(24–26) It could be worn for a maximum of three days and provided only retrospective data, meaning that people with diabetes themselves could not see their glucose levels in real-time.(25) Rather, this type of system was used in a clinical setting and allowed health-care professionals to retrospectively analyse glucose patterns. Medtronic followed with a CGM system for personal use, including a wireless transmission of the data and glucose alerts in 2004.(24,25) Two years later, Dexcom launched their first CGM system as well.(25) These early systems had a few shortcomings. The sensor data was often inaccurate, sensors had a short lifespan and needed frequent calibrations.(24,27)

In 2007, Dexcom then managed to extend the wear of their CGM system to seven days.(24,25) Around the same time Abbott Diabetes Care developed and launch their first FreeStyle Navigator.(25) Both Dexcom and Medtronic continued to improve their established systems and develop new systems over the decades, improving handling, sensor lifetime, calibrations and accuracy.(25,27) In 2016, Eversense developed a fully implantable sensor with a lifespan of 90 days, following with an extension to 180 days the subsequent year.(25) A year later, Abbott Diabetes Care released a new type of sensor using flash glucose monitoring.(25) With this sensor the company was able to extend the wear period to 14 days and cut out the repeating calibration processes by the user.(25)

Over the years the development of CGM sensors has shown a massive improvement.(24,25) Nowadays most systems are able or almost able to match the accuracy of SMBG and thus, allowing people with diabetes to make treatment adjustments based on CGM data.(24)

2.2. Different types of CGM

Differences can be found inter alia in features, sensor lifetime, usage, calibration frequency, accuracy and compatibility with other systems.(27)

2.2.1. Function

The majority of approved and commercially sold CGM sensors share one common factor, namely the use of the enzyme glucose oxidase to measure interstitial glucose levels.(28) Glucose oxidase is a fungal enzyme that oxidates ß-D-Glucose to gluconic acid under the production of hydrogen peroxide.(29) To achieve this, the enzyme uses oxygen as an electron acceptor. It can be used for glucose removal or glucose detection and is highly specific for ß-D-Glucose. As for CGM, the biosensor measures the electric charge of the electrons passing through the enzyme during the catalysis, allowing an inference to the interstitial glucose levels.(29)

However, one commercially available sensor uses a different system.(28) It is based on a fluorescent diboronic acid hydrogel. To measure the interstitial glucose, it uses an optical detection system, rather than measuring electric charge.(28)

2.2.2. Personal or professional usage

Professional CGM systems are, in comparison to personal ones, designed to be applied in a clinical setting and evaluated by properly trained staff. They provide only episodic, retrospective data. Often those systems are utilized to check on the person's glycaemic control and glycaemic variability patterns. They can be of either real-time or masked set up. Currently available are the Dexcom G6 Pro, the Medtronic iPro2 Professional and Abbott's FreeStyle Libre Pro for that use.(23)

CGM systems for personal use on the other hand are primarily applied to make instant treatment decisions. This can concern the dose of insulin, diet, physical activity etc. With these systems it is important that the person with diabetes is properly educated on how to use, read and make decision based on the CGM data. There are two different operation modes for personal use CGM: either real-time (rtCGM) or intermittently scanned (isCGM).(23)

2.2.3. Real-time CGM or intermittently scanned CGM

The salient difference between both modes is the transmission to the receiver. With rtCGM the data is automatically transferred to the reader, whereas with isCGM the user has to swipe over the sensor to attain the data on the receiver. Depending on the sensor, smartphone apps or a separate reading device can serve as receivers.(23)

Currently available models for rtCGM are the Dexcom G6, the Medtronic Guardian Sensor 3 and 4, and Senseonics Eversense, as well as the Medtrum TouchCare and Menarini's Glucomen Day.(23,30,31) As of this moment the only available isCGM system is Abbott's FreeStyle Libre and, newly developed, FreeStyle Libre 2.(32,33)

2.2.4. Lifespan and calibration

The average sensor lifespan lies between 5 and 14 days.(27,34) The only exception is the Senseonic sensor, which remains functional up to 180 days after implantation.(23)

Until recent, rtCGM systems required calibration at least twice a day.(27) Abbott was able to eliminate the calibration process by making their isCGM sensors factory calibrated.(28) Dexcom's and Medtronic's newest launches, the Dexcom G6 and the Medtronic Guardian 4, are factory-calibrated as well and do not need calibration during their 10-day lifespan.(27,34) Medtronic's predecessor, the Guardian 3, as well as Eversense by Senseonics, still require regular calibration.(28)

In order to match the best fitting sensor to the person with diabetes, the individual's needs and requirements have to be assessed.(22)

2.3. Sensor accuracy

Accuracy is a crucial measurement in order to make therapy decisions based on CGM readings.(22) To this day there is no standardised method to calculate the performance of CGM systems, like there is for SMBG.(35)

2.3.1. MARD

The most used metric to describe accuracy in CGM systems is the so-called MARD (mean absolute relative difference).(22) It is defined as the "average of absolute values of relative differences between CGM measurement results and the corresponding comparison method result".(36) MARD is frequently used because it is simple to calculate and represents the data in a single value.(37,38) Thus it is easy to compare and interpret.(38) A closer proximity between the CGM reading and the comparison value accounts for a lower MARD.(38)

On the downside MARD can be influenced by a variety of external factors like study design, insertion site, rate of change in glycaemia, algorithms used etc., which can lead to inconsistency of MARD values for one and the same device.(35,38) Additionally, the MARD does not differentiate between precision and bias or between systematic and random errors.(38) This can make it difficult to single out the reason for some sensors lack of accuracy.(38) Furthermore, the MARD can fluctuate depending on the glycaemic status and the rate of glucose change of the patient. Many CGM systems show a higher MARD in hypoglycaemia than in euglycaemia, raising the question of an introduction of a stratified MARD.(22,38)

Overall, the MARD is a metric that enables CGM systems to be compared to one another in an simple and widely applicable manner, as well as allow patients to make therapy decision based on CGM readings, but does not come without limitations.(38)

MARD for the stand-alone sensors currently on the market:(24,28,39)

Medtronic Guardian 3.....8.7%-10.5%, depending on placement
Dexcom G6.....9.9%
Senseonics Eversense.....8.8%
FreeStyle Libre.....11.4%
FreeStyle Libre 2.....9.2%

2.3.2. Comparison to SMBG accuracy

For SMBG systems, there does exist a standard to assess performance, the ISO 15197.(36) It states, that at least 95% of all BGM values must fall within ± 15 mg/dl of the comparison methods when glucose is <100 mg/dl and ± 15% when glucose is ≥100 mg/dl.(36) Every SMBG released on the market must adhere to those standards.(35)

Unfortunately MARD is not directly comparable, respectively translatable, to ISO.(35) A 10% MARD would translate to an approximately 25% ISO.(35) When reversed, to achieve a 10% ISO, the CGM system would have to attain a 4% MARD, which no currently available CGM system is able to achieve.(35,36) This shows, that MARD/CGM and ISO/SMBG are not easily convertible into each other, making it difficult to directly compare CGM and SMBG.(35) Additionally, MARD alone is insufficient to satisfy ISO criteria.(35) It needs extra, preferably standardised parameters, to fully assess CGM performance in a comparable way.(35) Furthermore, it has to be mentioned that CGM systems, that require calibration, rely on the accuracy of SMBG as they set the base line for the CGM accuracy.(35)

But even though CGM systems do not yet reach the accuracy of SMBG, they can compensate this through providing a glucose dynamic rather than a high accuracy single measurement.(38)

2.3.3. Systemic measurement difference

It is also possible to calculate accuracy through the systemic measurement difference, also called bias. This value represents the systematic difference between the measurement results and the comparison method.(36) In comparison to the MARD, the bias differentiates between positive and negative values, whereas the MARD sees every deviation as an absolute value without direction.(36)

In conclusion, measurement of accuracy for CGM systems still have room for improvement in order to provide a holistic picture of CGM performance.(36,38)

2.4. Benefits of CGM

CGM has been proven to be beneficial in many ways.(24)

2.4.1. Features

Nowadays, almost all CGM systems provide alarms and alerts for low or high glucose values, and, sometimes also impending low or high glucose values.(22) The only CGM on the market currently not having this feature is the FreeStyle Libre.(22) With the development of the FreeStyle Libre 2, this feature was added.(40)

All current CGM systems feature trend arrows.(23) They visualize the impending changes in glucose levels and allow the patient to make decision in order to prevent hypo- or hyperglycaemia.(23)

Another feature of most CGM systems is remote monitoring, which can be especially beneficial for paediatric or elderly persons with diabetes.(22) It enables caregivers, parents or clinicians to remotely access the data from the sensor and supervise the glycaemic status of the individual.(22) The Dexcom G6, the Eversense sensor and the Guardian 4 (only available in combination with the Minimed 780G insulin pump) allow real-time monitoring. FreeStyle Libre and the Guardian 3 only offer to share retrospective data.(22,41)

2.4.2. HbA1c

When looking at HbA1c, several studies have shown that consistent CGM use lowers the overall HbA1c.(42) A reduction of 0.3% of HbA1c is generally observed to provide a beneficial outcome concerning long-term complications.(43)

Regarding HbA1c, the DIAMOND Trial showed a mean reduction in HbA1c of 1.0% after 24 weeks, which accounts for a -0.6% change in comparison to the control group, that performed SMBG.(44) Similar results were observed in the GOLD Trial.(43) Here, the mean difference between the CGM group and the control group lay with -0.43%, favouring the CGM group.(43) Both studies mentioned above used rtCGM systems. In comparison, the IMPACT study used isCGM sensors, namely the FreeStyle Libre, for their trial. Regarding HbA1c, this trial showed no difference between the intervention group and the control group.(45) One has to keep in mind that the IMPACT trial only included people with diabetes who already achieved their glycaemic targets (<7.5% HbA1c), whereas the GOLD Trial and the DIAMOND Trial included with people with diabetes with glycaemic control above target (>7.5% HbA1c).(43–45)

Additionally, a meta-analysis comparing 22 studies on how CGM benefits people with T1DM over SMBG, has found that all show an improvement in HbA1c, especially those whose HbA1c was over 8.0%.(42)

2.4.3. Hypoglycaemia and Hyperglycaemia

Overall, all studies demonstrated a reduced time spent in hypoglycaemia. In the DIAMOND Trial the intervention group spent less time in hypoglycaemia during the day and the night.(44)

The GOLD Trial showed similar effects.(43) With the IMPACT study, hypoglycaemia was the primary outcome. It demonstrated a reduction from 3:38 h/day to 2:03 h/day spent below <70 mg/dl. In comparison to the control group this results in a 38% difference, favouring CGM.(45) Neither the GOLD Trial nor the IMPACT Trial differentiated between daytime and nighttime hypoglycaemic events. But, in both trials it was reported, that participants using CGM stated reduced fear of hypoglycaemic events.

In a follow-up trial, the GOLD-3 trial, individuals using CGM spent less time hypoglycaemia during the day and night and also reported higher confidence concerning hypoglycaemic events.(46)

The DIAMOND Trial was the only study that looked at time spent in hyperglycaemia as well and reported an improvement, meaning less minutes per day over >180 mg/dl in the CGM group.(44)

2.4.4. Glycaemic variability and time in range

Time in range (TIR) is usually defined as the time spent between 70 mg/dl and 180 mg/dl.(47) Depending on the individual, the TIR can be tightened to 70 mg/dl to 140 mg/dl (so-called time in tight range).(47) The TIR itself, as well as the time spent over and under the defined target values, can provide relevant information about an individual's glycaemic control.(47)

Glycaemic variability is a value not measured, but calculated by the coefficient of variation (CV), the standard deviation (SD) or the mean amplitude of glycaemic excursions.(47) It has been defined that glucose levels with a CV below 36% are stable.(47)

When looking at time in range the CGM group showed improvement as wells as stabilized glucose variability using rtCGM or isCGM.(44,45) The IMPACT Trial reported better glycaemic variability by 4.4% in the intervention group.(45) The DIAMOND Trial has found similar results. Here, the CGM group showed lower glycaemic variability by 4.0% in comparison to the control group.(44)

In conclusion, it can be said that both TIR and GV are important CGM metrics when looking at glycaemic control. TIR has already been successfully linked to diabetes complications and HbA1c.(48) With GV on the other hand the correlation to diabetes complications and outcome has yet to be determined.(24,49)

2.4.5. Quality of Life

Additionally, all three studies reported high satisfaction with the treatment within the CGM group.(43–45) The GOLD Trial used the WHO-5 questionnaire to assess participants' quality of life and found an improvement in comparison to the control group.(26,44) Treatment satisfaction was measured with the Diabetes Treatment Satisfaction Questionnaire (DTSQ). It also favoured CGM use.(26,43,45)

Throughout the Trials the participants using CGM showed improved quality of life, higher well-being and increased treatment satisfaction.(26,46)

2.5. Barriers of CGM

Although CGM systems offer various benefits and advantages, there are still barriers and shortcoming to this type of glucose monitoring.(27)

2.5.1. Clinical reluctance and CGM metrics

There still is inertia related to the implementation of CGM in clinical use.(27,32)
Reason for this may be the lack of standardised metrics for CGM evaluation, which makes it hard to interpret the data properly.(47,48) With CGM, a greater variety of data is accessible to analyse, which calls for a standard in assessing and evaluating this glycaemic information.(48)
Battelino et al recommended 10 metrics from the International Consensus, that should be used to interpret CGM data.(48)
Those are:

1. Number of days CGM worn	6. Time >250 mg/dl (13.9 mmol/l)
2. Percentage of time CGM is active	7. Time >180 mg/dl (10.0 mmol/l)
3. Mean glucose	8. Time 70–180 mg/dl (3.9–10.0 mmol/l)
4. Glucose management indicator (GMI)	9. Time <70 mg/dl (3.9 mmol/l)
5. Glycaemic variability (%CV or SD)	10. Time <54 mg/dl (3.0 mmol/l)

Table 1 - recommended metrics for CGM data interpretation

The important thing about the metrics chosen is their relationship to clinical outcome.(48) Time in range has shown significant correlation to diabetes complications and HbA1c.(48)
Using standardised metrics to analyse glycaemic control should help clinicians to interpret data more easily, allowing them to set more personalized goals with their patients to achieve better glycaemic control.(48)

2.5.2. User education

CGM users must be properly educated on how to insert and use their sensor as well as how to interpret the data in order to make therapy decisions based on its data.(23,27,47) Such education requires time, that can often be lacking in a clinical setting.(27,47)

2.5.3. Payment

To this day, CGM is not available to many people with diabetes in large parts of the world, because neither insurance nor the government cover the cost.(27) The financial situation of patients therefore often limits their treatment possibilities.(27)

2.5.4. Therapy adherence

Over half of CGM users do not use their systems >70% of the time.(32) This “usage goal” is recommended in order to gain enough sensor data to successfully depict the patient’s glucose

dynamics and calculate an estimated HbA1c.(48) 41% stop using CGM systems at all.(32) Reason for this can be high cost, if not covered by insurance, alarm fatigue, perceived inaccuracy of the sensor, etc.(24)

2.5.5. Interference with chemical substances

Glucose oxidase based sensors experience interactions with certain substances as acetaminophen and ascorbate, which influences sensor function.(24) Other substances that inhibit glucose oxidase are p-chloromecuribenzoate, silver, quicksilver, copper, hydroxylamine, hydrazine, phenylhydrazine, dimedone and sodium bisulphate(29)

2.5.6. Tissue reactions

As a biosensor is a foreign body inserted into human tissue, it can cause reactions.(25) Such reaction can interfere with the sensor performance and sensitivity.(25) The foreign body reaction (FBR) is an inflammatory response, which leads to an accumulation of immune cells in the interstitial space, especially macrophages. Additionally, it leads to the recruitment of fibroblast and hence the production of fibrous tissue around the sensor insertion site. In consequence, this can negatively affect sensor accuracy, leading to unreliable readings.(25)
Furthermore, the sensor insertion site is at risk for bacterial infection and biofilm formation. In case of inadequate adhesion to the skin, the sensor would not be properly fixated and cause mechanical tissue destruction through micro-movements.(25) Moreover, this would again set inflammatory reactions in action.(25)
On the other hand, the CGM skin adhesive can contain sensitizing ingredients, which can lead to allergic reactions and skin irritation, mainly due to substance isobornyl acrylate.(21,50)

2.5.7. Rapid obsolescence

CGM technology is developed and evolved quickly. This accounts for making systems and their reviews rapidly obsolete as new and improved technology is released frequently.(27)

2.6. Integration of CGM into other systems and future outlook

CGM sensors can be used as a stand-alone product or in combination with other diabetes technology.(32) Often, they are combined with a CSII system, for either manual insulin disposal or automated, making it a hybrid closed-loop system.(32) Those systems consistently suspend a basal rate of insulin with additional manual meal-time boluses.(32) Currently commercially available hybrid closed-loop systems (or nowadays also known as automated insulin delivery systems – AID systems) are the Medtronic 670G/770G/780G /Guardian 3, the Tandem t:slimX2/Dexcom G6 or the CamAPs FX DanaRS/Dexcom G6 combination.(34) A further advance from a hybrid closed-loop system is a fully automated closed loop, which would also account for automatic mealtime boluses. The next step of development following the fully automated closed loop would be a fully automated multi-hormone closed-loop. Such a system would be able to dispense insulin and glucagon, making it an artificial pancreas.(28,32)

VII. MATERIAL AND METHODS

This single-site, retrospective study was carried out to analyse the benefit of switching from an isCGM system without alerts to an isCGM system with alerts.

1. STUDY DESIGN

This study included 18 people with T1DM that switched from the FreeStyle Libre to the FreeStyle Libre 2 system in routine care. The main difference between the two CGM systems is the availability of alerts. Six months of data were analysed: three months prior to the switch and three months after the switch. Clinical data was derived from the electronic patient documentation (MEDOCS), laboratory data and patient letters. Participants were recruited from sensor prescription data documented in MEDOCS during the planned time period.
There was no patient contact during the study. No informed consent was needed as it was a retrospective data analysis.

1.1. Inclusion criteria

- type 1 diabetes mellitus
- adult population: male or female > 18 years
- routine use of commercially available CGM and who were switched within routine care from a CGM systems without alerts to a CGM systems with alerts with data available within the electronic patient record

1.2. Exclusion criteria

- Diabetes mellitus other than T1DM

2. OBJECTIVES

The primary objective was to assess the TIR (70 mg/dl – 180 mg/dl) in people with T1DM using an isCGM systems with alerts, compared to an isCGM systems without alerts.
The secondary objectives were the investigations whether the use of an isCGM system with alerts results in a

- reduction of time in hypoglycaemia
- reduction of time in hyperglycaemia
- improvement of glycaemic control as measured via Hba1 and glucose monitoring indication (GMI)
- change in insulin dose

- change in level 3 hypoglycaemia requiring third party help, the frequency of diabetic ketoacidosis and hospitalisations/emergency room presentations due to acute diabetes-related complications

compared to an isCGM without alerts.

3. ENDPOINTS

The primary endpoint was the time spent with sensor glucose levels between 70 and 180 mg/dl between the 3-months analysis periods.

Secondary endpoints included:

- Time spent above target glucose (>180 mg/dl)
- Time spent above target glucose (>250 mg/dl)
- HbA1c (mmol/mol)
- GMI (glucose monitoring indicator; mmol/mol)
- Time spent below glucose target (<70mg/dl)
- Time spent below glucose target (<54mg/dl)
- Average glucose levels (mg/dl)
- Insulin doses (basal, bolus, total)
- Level 3 hypoglycaemia requiring third-party help
- Frequency of diabetic ketoacidosis (DKA)
- Hospitalizations due to acute diabetes-related complications

4. HYPOTHESIS

The purpose of the study was to find out whether the switch from an isCGM system without alerts to an isCGM system with alerts improved the glycaemic control of people living with T1DM.

Null hypothesis: Time in target range (70-180 mg/dl) is not improved when using a CGM system with alerts compared to the use of a CGM without alerts.

Alternative hypothesis: Time in target range (70-180 mg/dl) is improved when using a CGM system with alerts compared to the use of a CGM without alerts.

5. STATISTICAL ANALYSIS

Sample size was expected to be 50 people with T1DM who use a CGM system to manage their diabetes and switched from a CGM system without alerts to a CGM system with alerts. All eligible patients seen during the observational period (Jan 2020 to Dec 2021) are included in the analysis.

All data is displayed in median, Q1-Q3.

VIII. RESULTS

In total, 18 patients were available for analysis. Two of the patients had to be excluded prior to analysis. One subject because of a different type of diabetes, the other subject because of pregnancy.

1. PRIMARY ENDPOINT

TIR was categorized as a glucose level between 70 mg/dl and 180 mg/dl. TIR was 56.6% (46.85%-73.53%) for isCGM without alerts. For isCGM with alerts the median was 58.7% (47.14%-72.44%).

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
TIR 70-180 mg/dl	without alert	18	17.21	46.85	56.60	57.08	18.11	4.27	50.06	64.10	73.53	92.11	0
TIR 70-180 mg/dl	with alert	18	37.65	47.14	58.70	59.72	15.71	3.70	53.63	65.81	72.44	90.17	0

Table 2 - percentage of values in target range (70 mg/dl - 180 mg/dl)

2. SECONDARY ENDPOINTS

2.1. Time spent below glucose target

As seen in table 2 and 3 the time below range (TBR) <54 mg/dl was 0.43% (0.21%-0.83%) for the CGM systems without alerts and 0.39% (0.18%-0.82%) for the system with alerts.
As for TBR <70 mg/dl, it was 4.76% (1.93%-6.17%) without alerts vs. 3.63% (2.09%-7.21%) with alerts.

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
TBR <54mg/dl	without alert	18	0.00	0.21	0.43	1.22	1.89	0.44	0.49	1.95	0.83	7.27	0
TBR <54mg/dl	with alert	18	0.00	0.18	0.39	0.84	1.08	0.25	0.42	1.26	0.82	3.81	0

Table 3 - percentage of values below target (<54 mg/dl)

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
TBR <70mg/dl	without alert	18	0.33	1.93	4.76	4.97	4.08	0.96	3.39	6.56	6.17	14.96	0
TBR <70mg/dl	with alert	18	0.02	2.09	3.63	4.50	3.35	0.79	3.20	5.80	7.21	11.03	0

Table 4 - percentage of values below target (<70 mg/dl)

2.2. Time spent above target glucose

For the CGM system without alerts time above range (TAR) >180 mg/dl was 39.2% (21.86%-50.91%) and for TAR >250 mg/dl 11.11% (3.49%-19.08%), respectively. With the CGM system with alerts the TAR >180 mg/dl was 35.65% (22.41%-42.23%) and for TAR >250 mg/dl 9.15% (3.68%-17.83%).

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
TBR >180mg/dl	without alert	18	3.55	21.86	39.20	37.95	19.13	4.51	30.53	45.37	50.91	80.28	0
TBR >180mg/dl	with alert	18	6.04	22.41	35.65	35.77	16.66	3.93	29.31	42.23	51.74	55.95	0

Table 5 - percentage of values above target (>180 mg/dl)

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
TBR >250mg/dl	without alert	18	0.11	3.49	11.11	14.76	14.95	3.52	8.96	20.56	19.08	58.98	0
TBR >250mg/dl	with alert	18	0.23	3.68	9.15	12.08	10.25	2.42	8.10	16.06	17.83	34.38	0

Table 6 - percentage of values above target (>250 mg/dl)

2.3. Average glucose levels

Average glucose levels were 167.49 mg/dl (140.28 mg/dl-186.96 mg/dl) without alerts and 161.44 mg/dl (141.02 mg/dl – 186.97 mg/dl) with alerts.

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
Avg.gluc.[mg/dl]	without alert	18	111.86	140.28	167.49	170.68	39.41	9.29	155.40	185.96	186.06	280.09	0
Avg.gluc.[mg/dl]	with alert	18	118.74	141.02	161.44	165.68	29.13	6.87	154.38	176.97	186.97	215.81	0

Table 7 - average glucose (mg/dl)

2.4. Glucose management indicator

Many CGM systems have the ability to calculate the user's estimated HbA1c value (eA1c) after gaining an appropriate amount of data.(51) This metric is a useful tool in diabetes management, but there can be discrepancies between the eA1c and the actual HbA1c, leading to confusion amongst patients and clinicians.(51) In order to avoid such confusion, a new term was introduced, the glucose management indicator (GMI).(51) It is calculated through a standardised formula. In this study, this formula:

GMI (mmol/mol) = 12.71 + 4.70587 OE [mean glucose in mmol/L] of Bergenstal et al was used.(51)

A 25 mg/dl increase of mean glucose would account for a 0.6% increase in GMI.(51)

In this analysis GMI was 56.5 mmol/mol (41.9 mmol/mol – 61.3 mmol/mol) for CGM systems without alerts and 54.9 mmol/mol (43.7 mmol/mol – 61.5 mmol/mol) with alerts.

Parameter	Libre Type	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
GMI[mmol/mol]	without alert	18	41.93	49.35	56.45	57.29	10.29	2.43	53.30	61.28	61.30	85.86	0
GMI[mmol/mol]	with alert	18	43.72	49.54	54.87	55.98	7.61	1.79	53.03	58.93	61.54	69.08	0

Table 8 - GMI (mmol/mol)

2.5. HbA1c (mmol/mol)

HbA1c for the CGM system without alerts was 58.0 mmol/mol (49.25 mmol/mol – 68.25 mmol/mol).

At the switch HbA1c was 60.0 mmol/mol (51.5 mmol/mol – 68.0 mmol/mol) and afterwards with the CGM system with alerts 65.6 mmol/mol (55.75 mmol/mol – 71.5 mmol/mol). HbA1c data was available for 7 out of 18 people with diabetes at the point of the isCGM switch and for 10 out of 18 people with diabetes after using the CGM system with alerts for three months.

Parameter	Time	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
HbA1c	Libre 1	18	40.00	49.25	58.00	59.39	12.06	2.84	54.71	64.07	68.25	84.00	0
HbA1c	Switch	7	37.00	51.50	60.00	58.29	12.62	2.97	53.39	63.18	68.00	72.00	11
HbA1c	Libre 2	10	38.00	55.75	65.50	62.10	13.52	3.19	56.86	67.34	71.50	81.00	8

Table 9 - HbA1c (mmol/mol)

2.6. Insulin doses

Basal insulin doses could be obtained for all 18 people with diabetes before the switch and for 8 people with diabetes after the switch. Mean total daily insulin dose was 25.0 IU daily (20.0 IU – 30.0 IU) while using the isCGM without alerts and 24.0 IU (19.0 IU – 30.3 IU) while using the isCGM system with alerts.

Parameter	Time	N Subj.	Min	Q1	Median	Mean	SD	SE	CI.lower	CI.upper	Q3	Max	NA
Basal TDD	Libre 1	18	11.00	20.00	25.00	25.53	10.60	2.50	21.42	29.64	30.00	54.00	0
Basal TDD	Libre 2	8	12.00	19.00	24.00	24.55	8.94	2.11	21.08	28.02	30.30	38.00	10

Table 10 - basal insulin, daily dose (IU)

As insulin doses (basal, bolus and total) were obtained from routine care, they were not documented thoroughly and completely. Thus, bolus and total insulin doses could not be analysed.

The same goes for the secondary endpoints level 3 hypoglycaemia requiring third-party help, frequency of diabetic ketoacidosis and hospitalisations due to acute diabetes-related complications.

IX. DISCUSSION

As mentioned in the introduction, there are undeniable benefits of using CGM systems for people with diabetes. The main improvement in the development of the FreeStyle Libre 2 in comparison to the FreeStyle Libre 1 is the addition of alarms. Those alarms can either be activated or deactivated. If activated, they inform the user when their blood sugar is below a certain value or too high for their set target value, as well as when the connection between the senor and the reading device is lost. After the users are notified, they have to swipe their reading device over the sensor in order to receive the actual glucose value. The FreeStyle Libre 2 is not able to set off alarms for impending low glucose, as some rtCGM systems can. But, with the FreeStyle Libre 2, the user also can turn off the alarms at any given point, and can use the isCGM system without them. Additionally, the MARD was improved from 11.2% with the FreeStyle Libre 1 to 9.2% with the FreeStyle Libre 2.(39,52)

The main findings from this study show that switching from an isCGM without alerts to an isCGM with alerts leads to a slight improvement in TIR and a decrease in TBR and TAR. Furthermore, a decrease in the average glucose was shown, but overall, the GMI reduction of 1.58 mmol/mol was not significant.
A similar study by Boscari et al from early 2022 also investigated such a switch.(53) The primary endpoint was, as well, the TIR. Additionally, they looked at TBR, TAR, mean glucose, coefficient of variation, GMI, sensor scans, treatment satisfaction and hypoglycaemia fear. While our study investigated the data over a time span of 3 months, Boscari et al evaluated data over 12 weeks total (4 weeks before the switch and 8 weeks after the switch).(53)
Similar to our findings, they discovered an improvement in TIR, as well as a reduction in TBR. Concordant with our study, Boscari et al also did not observe a significant change in GMI. But interestingly, they reported a significant improvement in the CV from 39.6% to 36.1%.(53)
In Boscari et al a reduction in fear of hypoglycaemia and higher treatment satisfaction was reported, both of which were not investigated in this study.(53)

This study has several limitations that have to be taken into account. First and foremost, the number of participants was small and the majority of the participants did not achieve the clinically recommended glycaemic targets. Furthermore, this was a single-centre study, that was performed in a diabetes-experienced centre. This data does not allow drawing conclusion to other healthcare centres nationally or internationally.
Additionally, this study was carried out in retrospect and the analysed data was of a short period of time. In order to evaluate the long-term effects in depth, a long-term study would be necessary.

There are two other studies from Styles et al and Wilmot et al, which evaluate the use of the FreeStyle Libre 2 in comparison to SMBG in paediatric and adult patients, but neither have published results at this point.(54,55)

X. CONCLUSION

In conclusion, this study was carried out to investigate whether users of isCGM without alerts profit from switching to an isCGM with alerts and if that helps achieve their treatment goals.
According to our study this switch resulted in an improved TIR, TBR and TAR, but the change in GMI was not clinically significant. A comparable study from Boscari et al has found similar results. All in all, it can be said, that alerts alone do not significantly improve glycaemic control in people with diabetes. In order to achieve more physiological blood sugar levels, a combination of CGM systems with decision support algorithms and continuous insulin dispense systems might be necessary.
But it has to be mentioned, that the FreeStyle Libre 2 might be a good stepping stone for people with diabetes who are unsure or insecure about the use of blood sugar alerts. The option to turn them off can allow flexibility in different life situations, making this CGM system a viable therapy option, depending on the patient's individual wants and needs.

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