Diploma Thesis

Feasibility to Use a Continuous Glucose Monitoring System to Manage Diabetes During Hospitalisation

submitted by

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Statutory declaration

I hereby declare that I have written this diploma thesis fully on my own, that I have not used any other than the declared sources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, 11.11.2021 *Kujtim Bytyqi eh.*

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“I suppose it’s not so bad that an old friend is the same as ever.”
Katsura Kotaro

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Glossary and Abbreviations

%	percent
®	Registered trademark
A priori	Latin: from the earlier
ADA	American Diabetes Association
AGE	Advanced glycation end-products
AR	Aldose reductase
ATPase	Adenosinetriphosphatase
BG	Blood glucose
BMI	Body mass index
CA	California
cDSS	Clinical decision support system
CGM	Continuous glucose monitoring
CII	continuous insulin infusion
COVID-19	Coronavirus disease 2019
CSII	Continuous subcutaneous insulin infusion
CSV	Comma-separated values
CT	Computed tomography scan
DKA	Diabetic ketoacidosis
dl	decilitre
DPP-4	Dipeptidyl peptidase-4
e.g.	Latin: Exempli gratia - for example
et al.	Latin: et alii - and others
etc.	Latin: Et cetera – and so on/and more
FGM	Flash Glucose Monitoring
FPG	Fasting plasma glucose
g	gram
GAD	Glutamic acid decarboxylase autoantibodies
GLP-1	Glucagon-like peptide-1
h	hours
H0	Null hypothesis
H1	Alternative hypothesis
HbA1c	Glycated hemoglobin

HDL	High density lipoprotein
HHS	Hyperosmolar hyperglycaemic state
IA-2	Tyrosine phosphatase-related islet antigen 2 autoantibodies
IAA	Insulin autoantibodies
ICA	Islet cell autoantibodies
ICU	Intensive care unit
IE	Internationale Einheiten
IN	Indiana
IQR	Interquartile range
isCGM	Intermittently scanned CGM
IU	International Units
K^+	Potassium ion
kg	kilogram
L	litre
LADA	Latent autoimmune diabetes in adults
m^2	square metres
MARD	Mean absolute relative difference
MDI	Multiple daily injections
mg	milligrams
min	Minutes
mmHg	millimetre of mercury
mmol	millimole
MODY	Mature onset diabetes of the young
mol	mole
MRI	Magnetic resonance imaging
n	sample size
Na^+	Sodium ion
NEFA	Non-esterified fatty acids
NPH insulin	Neutral Protamine Hagedorn insulin
ÖDG	Austrian Diabetes Association
OGTT	Oral glucose tolerance test
OHA	Oral antihyperglycaemic agents
PCOS	Polycystic ovary syndrome
POCT	Point-of-care testing
PPE	Personal protective equipment

Pros and cons	Latin: Pro – for, contra - against
rtCGM	real-time CGM
SAPs	Sensor-augmented insulin pumps
SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2
SD	Standard deviation
SGLT-2	sodium-glucose linked transporter 2
U	Units
USA	United States of America
vs.	Latin: versus - against
x	times
ZnT8	Zinc transporter-8 autoantibodies
β	Greek: beta

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Zusammenfassung

Einleitung

“Continuous glucose monitoring” (CGM) und “clinical decision support systems” (cDSS) werden heutzutage immer häufiger im klinischen Alltag verwendet. Da CGM detaillierte Informationen zur Glukosekontrolle liefert, könnte dies eine wichtige Alternative zur klassischen kapillären Blutzuckermessung mittels point-of-care-testing (POCT) sein, welche weiterhin als Standard für Diabetesmanagement im Krankenhaus gilt. Das Ziel unserer Studie war es, die Umsetzbarkeit eines mittels CGM gesteuerten cDSS zum Management von stationären Patient*innen mit Diabetes mellitus Typ 2 zu simulieren und analysieren.

Material und Methoden

Eine retrospektive Analyse stationärer Patient*innen, welche unter Nutzung eines cDSS (GlucoTab®) behandelt wurden, wurde durchgeführt. GlucoTab® wurde während der Behandlung mittels viermal täglich (vor Mahlzeiten und vor dem Schlafen) gemessener kapillärer Blutzuckerwerte gesteuert. CGM wurde währenddessen im “blinded mode” verwendet. Die kapillären Blutzuckerwerte wurden mit den CGM-Werten gepaart, die bis zu 15 min vor oder nach der kapillären Messung gemessen wurden. In der Analyse wurden die Insulindosisvorschläge von GlucoTab®, welche auf den kapillären Blutzuckerwerten basierten, mit simulierten Insulindosisvorschlägen, welche auf den gepaarten CGM-Werten sowie allen zusätzlich detektierten hypoglykämischen Events basierten, verglichen.

Ergebnisse

Daten von 30 Patient*innen (Alter 74,1±10,9 Jahre, 60% weiblich, BMI 28,6±5,6 kg/m², Diabetesdauer 13,2±11,6 Jahre, HbA_{1c} 72±22 mmol/mol, Kreatinin 1,5±1,2 mg/dl) wurden verwendet. Der Median (Q1; Q3) der mittels POCT gemessenen Glukosewerte war 135 (106; 181) mg/dl (n=885), der Median der mit CGM gemessenen Glukosewerte lag bei 110 (69; 160) mg/dl (n=1075).
Die Daten der Insulindosisvorschläge basierend auf CGM- und POCT-Werten finden sich in Tabelle 1.

Conclusio:

CGM mit einem cDSS zu kombinieren führte in einer Simulation zu ähnlichen Insulindosisvorschlägen wie die Kombination von kapillären Blutzuckermessungen mittels POCT-Geräten mit cDSS. Da CGM mehr hypoglykämische Events detektierte, sind die Insulindosisvorschläge von GlucoTab® basierend auf den CGM-Werten tendentiell niedriger, wodurch insgesamt weniger Hypoglykämie zu erwarten wäre. Die Verwendung von CGM-Werten um ein cDSS zu steuern wird in einer klinischen Studie analysiert werden.

Table 1. 1

Insulindosisvorschläge von 2 Systemen (n = Anzahl berechneter Vorschläge für den jeweiligen Insulintyp)

	POCT		**CGM**	
	Median (Q1; Q3)	**n**	**Median (Q1, Q3)**	**n**
Bolusinsulindosisvorschläge (nur Korrekturinsulin nachts)	3 (2; 3) IE	73	2 (1; 3) IE	73
Bolusinsulindosisvorschläge (morgens – abends)	6 (3; 10) IE	643	6 (2; 10) IE	643
Basalinsulindosisvorschläge	14 (10; 20) IE	215	13 (10; 19) IE	215
Tagesdosisvorschläge	28 (20; 42) IE	213	25 (19; 39) IE	207

Abstract

Introduction

Continuous glucose monitoring (CGM) systems and clinical decision support systems (cDSS) are frequently used in diabetes management nowadays. As CGM offers detailed information on glycaemic control, it can be an important alternative to capillary glucose measurements taken with point-of-care (POCT) devices, which are current best practice in inpatient care. The aim of our study was to assess the feasibility of using a cDSS steered with CGM vs. POCT glucose values.

Methods:

A retrospective analysis of inpatients with type 2 diabetes treated using a cDSS was performed. The cDSS was fed with POCT glucose values measured four times per day (pre-meal, bedtime). CGM was used in blinded mode. POCT measurements were matched to corresponding CGM values within 15min of each other. Conventional insulin dosing suggestions using POCT data were compared to simulated insulin dose calculations based on paired CGM data plus any CGM-based hypoglycaemic event.

Results:

Data from 30 patients (age 74.1±10.9 years, 60% female, BMI 28.6±5.6 kg/m², diabetes duration 13.2±11.6 years, HbA_{1c} 72±22 mmol/mol, creatinine 1.5±1.2 mg/dl) were used. Median (Q1; Q3) POCT glucose was 135 (106; 181) mg/dl (n=885), median CGM glucose was 110 (69; 160) mg/dl (n=1075). Insulin data are indicated in table 1.

Conclusion:

Combining CGM with cDSS provides similar insulin dose suggestions compared to POCT measurements in a simulation study. As CGM detects more hypoglycaemic events, the insulin dose suggestions by cDSS are slightly lower, thus less hypoglycaemia can be expected. Using CGM data to steer a cDSS will be evaluated within a clinical study.

Table 1. 2

Insulin dose suggestion over two systems (with n being the number of calculated insulin dose suggestions per insulin type)

	POCT		**CGM**	
	Median (Q1; Q3)	**n**	**Median (Q1, Q3)**	**n**
Bolus insulin dose suggestion (only correction doses at night)	3 (2; 3) IU	73	2 (1; 3) IU	73
Bolus insulin dose suggestion (morning – evening)	6 (3; 10) IU	643	6 (2; 10) IU	643
Basal insulin dose suggestion	14 (10; 20) IU	215	13 (10; 19) IU	215
Daily insulin dose suggestion	28 (20; 42) IU	213	25 (19; 39) IU	207

Data are median plus IQR.

1 Introduction

Despite the advent of modern medicine and the eradication of various diseases over the course of the last century, diabetes mellitus has prevailed as both a disease of affluence (type 2 diabetes) and as a hereditary disease (type 1 and type 2 diabetes). Not only has it succeeded in affecting many people around the world, but it has also become more and more prevalent over time, a phenomenon that is likely to proceed. (1)

Because of the high prevalence of diabetes mellitus, there is a lot of research going on in this field. This has led to new methods of therapy during the last few decades, such as multiple daily injections (MDI) of insulin, continuous subcutaneous insulin infusion (CSII), and “closed-loop” systems, mimicking the function of the pancreas. (2–4)

A very important part of diabetes therapy consists of the monitoring of glucose levels. During the last decade, new devices have been invented to perform “continuous glucose monitoring” (CGM); depending on the device, this technique allows clinicians to analyse glucose levels measured in real-time and use information on glucose levels gathered by the CGM device over a few weeks prior in order to get a better understanding of the efficacy of the patient’s diabetes therapy. (5)

While CGM devices have been mostly used in outpatient settings in the past, and data on the use of CGM in a hospital setting were scarce, this changed rapidly during the coronavirus 19 (COVID-19) pandemic. Due to the pandemic, the safety of healthcare professionals is more than ever linked to reduced exposure to potentially infectious patients, and the need for personal protective equipment (PPE) when dealing with COVID-19 patients is skyrocketing.

Therefore, it became necessary to try to reduce exposure and decrease the use of PPE. In the case of hospitalized patients with diabetes mellitus, this could be achieved by implementing CGM devices to monitor glucose levels remotely. (6,7)

By making use of the newest technological advancements, accurate monitorization of hospitalized patients glucose levels could be achieved without the need for calibration, regular fingersticks or exposure to patients caring infectious diseases, such as COVID-19.

Another important component of the treatment of insulin-treated diabetes mellitus is the accurate calculation of the required insulin dose for any given glucose level. As already mentioned above, modern technology comes into play: by using a “decision support system”, such as GlucoTab®, clinicians can use the systems’ suggestions to assess the required insulin dose. Studies have proven these systems to be accurate and safe and to even improve glucose levels, time in range and hypoglycaemia rates in hospitalized patients. (8–10)
By combining both the decision support system and the CGM technology, treatment for hospitalized patients could become easier for both staff and patients by not requiring painful fingersticks to monitor glucose levels, recognizing heretofore undetectable hypoglycaemic events (for example during the night), and having a reliable decision support system to manage diabetes therapy.
The simulation conducted for this diploma thesis aims to evaluate the feasibility of combining these technologies.

1.1 Diabetes mellitus

Diabetes mellitus is an ancient, very well-known disease, characterized first and foremost by hyperglycaemia, be it due to a lack of insulin production (e.g. type 1 diabetes) or due to a heightened insulin resistance in fat and muscle cells (type 2 diabetes).

There are also other types of diabetes, which shall only briefly be named here, such as LADA (latent autoimmune diabetes in adults), MODY (mature onset diabetes of the young) or gestational diabetes. The latter is rather common and serves as a risk factor for various complications during pregnancy and childbirth. The risk of developing type 2 diabetes mellitus later in life is also heightened in individuals with gestational diabetes. (11)

Furthermore, any damage to the pancreas may cause diabetes mellitus, such as partial or complete pancreatectomy resulting in loss of endogenous insulin secretion and thus requiring insulin substitution.

The most frequent type of diabetes nowadays is type 2 diabetes, encompassing over 90% of all cases of diabetes mellitus (12,13).

Even though type 2 diabetes is commonly viewed as the more “self-induced” type of diabetes, meaning that with a proper, healthy lifestyle, one could minimize the risk of getting type 2 diabetes, it is actually also the type which shows a higher familial incidence (12).

1.1.1 Diagnostics

Since hyperglycaemia develops slowly and continuously, it is sometimes difficult to differentiate between patients with diabetes mellitus and patients that do not (yet) have diabetes mellitus, if only clinical manifestation and symptoms are considered. Fortunately, there are certain standards and diagnostic tests that define diabetes mellitus and prediabetes. Prediabetes will be further explained in paragraph 1.1.3.1.

There are four separate criteria for the diagnosis of diabetes mellitus described by the American Diabetes Association (ADA), which are based on fasting plasma glucose levels (FPG), random plasma glucose levels or plasma glucose levels

during the oral glucose tolerance test (OGTT), as well as HbA_{1c} levels, and can be seen in the following table. (14)

Table 2: Criteria for the diagnosis of diabetes mellitus (14)

Fasting plasma glucose ≥ 126mg/dl *or* 2-h plasma glucose ≥ 200mg/dl during OGTT *or* In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200mg/dl *or* HbA1c ≥ 6.5%

The American Diabetes Association defines fasting in this context as no caloric intake for at least 8h. (14)

1.1.1.1 Oral glucose tolerance test (OGTT)

The oral glucose tolerance test is used to diagnose diabetes mellitus and impaired glucose tolerance, which is one of the signs of prediabetes. (13)
The test is performed the following way:

- A diet rich with carbohydrates (more than 150 grams per day) should be maintained for at least 3 days prior to testing
- The OGTT starts in the morning after fasting for approximately 10-16 hours (no caloric intake) and should be performed while sitting or lying down, with little to no physical activity during the test
- A fasting blood glucose sample is taken, and 75g of glucose (1.75g/kg for children, up to 75g in total) is dissolved in water and given to the patient orally
- Another blood sample is taken after 2 hours
- If gestational diabetes is suspected, one blood sample is taken after one hour, and another after 2 hours

If the 2-h plasma glucose value is higher than or equal to 200mg/dl, the diagnosis of diabetes mellitus is confirmed. (13,15)
If, however, the value is lower than 200mg/dl, but higher than or equal to 140mg/dl, the diagnosis of impaired glucose tolerance (and thereby prediabetes) is confirmed. (12,14)
This test and the criteria described in Table 1 can only be used to diagnose diabetes mellitus in general, without distinguishing which type is prevalent.

1.1.2 Type 1 diabetes mellitus

Type 1 diabetes is caused by a destruction of the pancreatic β-cells of the islets of Langerhans, which are responsible for insulin production. This could be caused by an autoimmune reaction in which T cells, macrophages and autoantibodies attack the β-cells and thereby destroy them, causing an absolute insulin deficiency, but many other possibilities for the destruction of the β-cells are discussed. (13) The precise cause of this process is not yet fully understood. However, there are a couple of risk factors for the development of type 1 diabetes.

1.1.2.1 Aetiology and risk factors

There is evidence that autoimmune processes are involved in the pathogenesis of type 1 diabetes mellitus. In pancreatic biopsies of patients with a recent diagnosis of type 1 diabetes mellitus, chronic inflammatory infiltrates can be found in the islets of Langerhans, pertaining to the leftover β-cells. As the disease goes on, and while the other islet cell types survive, the β-cells are destroyed. (13)
Autoantibodies play a decisive role in this process and present an important marker for this type of inflammation of the β-cells.

The antibodies relevant for this process are:

- Islet cell autoantibodies (ICA)
- Insulin autoantibodies (IAA)
- Glutamic acid decarboxylase autoantibodies (GAD)
- Tyrosine phosphatase-related islet antigen 2 autoantibodies (IA-2)
- Zinc transporter-8 autoantibodies (ZnT8)

These antibodies can be used to predict the development of type 1 diabetes and diagnose latent autoimmune diabetes in adults (LADA). (13,16)
The correlation of type 1 diabetes mellitus with other autoimmune diseases, such as Graves' disease, Addison's disease, coeliac disease, etc. further suggests autoimmunity as a base for the pathogenesis of type 1 diabetes mellitus. (17)
Furthermore, there are implications that infections with viruses, especially enteroviruses, serve as a trigger to the aforementioned autoimmune processes causing the destruction of β-cells. (13,18,19)
Other potential factors relevant for the development of type 1 diabetes mellitus consist of, but are not limited to, the human microbiome, chemical substances, toxins, and dietary factors. (19)

1.1.2.2 Clinical manifestation

Typical signs and symptoms in patients who suffer from type 1 diabetes mellitus include:

- Polydipsia
- Polyuria
- Exsiccosis
- Fatigue and weakness
- Hyperventilation
- Vomiting and nausea

These and other symptoms can appear rapidly and are mainly caused by hyperglycaemia resulting from uncontrolled diabetes, usually at the initial manifestation of type 1 diabetes mellitus. (13,20)
If type 1 diabetes mellitus remains uncontrolled or insufficiently treated, dangerous complications can arise.

1.1.2.3 Acute complications

The most important acute complication in patients with type 1 diabetes mellitus is “diabetic ketoacidosis” (DKA). It is defined by (12,13):

- hyperglycaemia (typically above 250mg/dl)
- hyperketonaemia (above 3 mmol/l)
- metabolic acidosis (with arterial pH < 7.3)

Polyuria and polydipsia are also symptoms of DKA, leading to exsiccosis and (pseudo-)hypernatraemia and fatigue, while hyperventilation (“Kussmaul” breathing) and vomiting can also occur.
DKA often occurs as the initial manifestation of type 1 diabetes, since the previously unknown absolute insulin deficiency leads to hyperglycaemia and hyperketonaemia. Other causes for this metabolic derailment, such as acute infections, need to be investigated. Since DKA can lead to unconsciousness or even coma, and can be potentially lethal, treatment should be started immediately. (12,13)

The most important parts of DKA treatment include:

- rehydration
- administration of insulin intravenously
- replacement of potassium (cellular uptake increased by insulin and correction of acidosis, leading to hypokalaemia)
- administration of glucose intravenously if blood glucose < 200mg/dl to prevent hypoglycaemia with further insulin administration

Serum electrolytes, blood glucose values and pH should be monitored regularly. When the acidosis has been corrected and blood glucose is stable, subcutaneous insulin treatment can commence. (12,13)

1.1.2.4 Therapy of type 1 diabetes mellitus

Since the main problem for patients with type 1 diabetes mellitus is the absolute insulin deficiency, a substitution of insulin is immediately required. Insulin can be administered by injection, for example as a basal-bolus-insulin regimen, or via an insulin pump. The different types of insulin are listed below. Anti-hyperglycaemic drugs such as metformin, commonly used in patients with type 2 diabetes mellitus, are usually not part of type 1 diabetes therapy. (21) Life-style management, sufficient glucose control (e.g., through regular training and medical checks) and preventive measures regarding late diabetic complications must be set.

In general, for patients with type 1 diabetes mellitus, the following blood glucose target ranges apply:
Fasting blood glucose: 80 – 110mg/dl
Before meals and at bedtime: 110 – 130mg/dl
Postprandial blood glucose: <180mg/dl

Table 1: Types of insulin (22)

Insulin	Onset (minutes)	Peak time (hours)	Duration (hours)
Regular insulin	30	1,5-3,5	7 - 8
Rapid-acting	5 - 15	1 - 3	3 - 5
NPH insulin	30-60	4 - 6	8 - 14
Long-acting	30-60	Flat dose-response curve	Up to 24
Ultra-long-acting	30-60	Flat dose-response curve	30 - 42

1.1.3 Type 2 diabetes mellitus

Type 2 diabetes mellitus is the most common type of diabetes mellitus. It is primarily defined by an insulin resistance in muscle, fat, and liver cells, combined with a secretory dysfunction of the pancreatic β-cells, which is another major pathophysiological factor in type 2 diabetes mellitus. (13,23)

1.1.3.1 Aetiology and risk factors

The development of type 2 diabetes is associated with a multitude of different risk factors. The most important risk factors are the following:

- Abdominal obesity and metabolic syndrome (“diabesity”)
- Genetics
- Prediabetes

Other factors that could play a role are hormones and cytokines correlated with adipose tissue, such as leptin and adiponectin, as well as other substances like NEFA (non-esterified fatty acids). (13,24)

Prediabetes is very important risk factor in the development of diabetes. It is defined as the patient showing at least one of the following:

- Impaired glucose tolerance
- Impaired fasting glucose
- heightened HbA_{1c} levels that do not meet the criteria for diabetes ($HbA_{1c} \geq 5.7$ % (39 mmol/mol), but ≤ 6.4 % (46 mmol/mol)). (12,14)

Impaired fasting glucose is defined by fasting plasma glucose levels between 100 and 125mg/dl, whereas impaired glucose tolerance is defined as 2 hour plasma glucose levels during 75-g OGTT (oral glucose tolerance test) between 140 and 199mg/dl. (12,14)
All these risk factors make the development of type 2 diabetes more likely.
When insulin resistance and β-cell dysfunction reach a certain threshold, prediabetes turns into type 2 diabetes.

1.1.3.2 Screening

The Austrian Diabetes Association (ÖDG) recommends the following screening schedule for asymptomatic adults (12):

1) Screening for hyperglycaemia if the following risk factors are present:
    - BMI ≥ 25 kg/m² (for Asian ethnicities ≥23 kg/m²)
    - Positive family history in first-degree relatives
    - Ethnicity with a higher risk of diabetes
    - Vascular diseases
    - Hypertension (≥ 140/90 mmHg or antihypertensive therapy needed)
    - HDL-cholesterol for males < 35mg/dl and or triglycerides > 250mg/dl
    - Polycystic ovary syndrome (PCOS)
    - Hypogonadism
    - Physical inactivity
    - Acanthosis nigricans
    - Non-alcoholic fatty liver disease
    - Chronic tobacco use
2) If prediabetes is diagnosed: annual screening
3) If a history of gestational diabetes is known: screening every 3 years
4) For any other patients: screening after the age of 45
5) If screening results are unremarkable: further screenings every 3 years with continuous monitoring of risk factors and screening results

Screening for type 1 diabetes is only recommended for patients with first-degree relatives who suffer from type 1 diabetes. In that case, autoantibodies associated with type 1 diabetes are used for the screening. (12)

1.1.3.3 Prevention

The development of type 2 diabetes from prediabetes or any composition of multiple risk factors can possibly be prevented by certain means and methods. In the case of prediabetes, all modifiable risk factors should be controlled regularly. (12)

As far as pharmacological prevention methods go, metformin has been successfully used in the prevention of type 2 diabetes and has received a Grade A recommendation from the ADA for preventing diabetes.(25)

However, the most important factor in diabetes prevention is lifestyle change: People that suffer from obesity should strive to normalize their body weight and improve physical activity. An important part in this endeavour is a proper diet. One typical diet generally considered healthy is the Mediterranean diet.

It is characterized by a high intake of fruits, nuts, vegetables, legumes, unprocessed cereals, fish, and olive oil, while maintaining a low consumption of meat and dairy products. (26,27)

Research has shown that abiding by a Mediterranean diet can reduce the incidence of diabetes in high-risk patients. This is achieved by the Mediterranean diet having a beneficial impact on cardiometabolic disease risk factors and all components of metabolic syndrome. (26,28)

During the European Prospective Investigation into Cancer (EPIC)-InterAct Study, it was found that replacing red and processed meats with other protein sources such as cheese, yogurt, nuts, or cereals was associated with a lower rate of type 2 diabetes. However, replacement of red and processed meats with poultry, fish, eggs, legumes, or milk was not associated with a lower hazard for type 2 diabetes. (29)

Smoking is also considered to be an important risk factor for the development of diabetes mellitus. Therefore, patients should be informed of this and asked to reduce or tobacco use or to quit smoking entirely. (12)

1.1.3.4 Clinical manifestation

Type 2 diabetes mellitus is often associated with obesity, metabolic syndrome and other risk factors mentioned previously.
Therefore, patients who develop type 2 diabetes are typically above the age of 40 and overweight. Recently however, more and more younger patients have been diagnosed with type 2 diabetes. Even adolescents and children can develop non-type 1 diabetes mellitus, known as MODY (maturity onset diabetes of the young). (12,14,30,31)
Patients who suffer from type 2 diabetes mellitus usually present with non-specific symptoms such as:

- Polydipsia
- Polyuria and exsiccosis
- Fatigue
- Pruritus and other dermatological manifestations (e.g., necrobiosis lipoidica)

In general, it can be said that type 2 diabetes manifests more slowly than type 1 diabetes. Therefore, symptoms may be absent for a long time after the onset of type 2 diabetes and patients may be diagnosed with it while still being asymptomatic. The symptoms mentioned above (and generally speaking, non-specific symptoms of any type of diabetes mellitus) usually originate from hyperglycaemia. (31)
Untreated diabetes can lead to acute complications and long-term effects, which will be explained in more detail in the following chapters.

1.1.3.5 Acute complications

Untreated diabetes mellitus can lead to serious, sometimes lethal, acute complications and can have many long-term effects. As previously explained, in patients with type 1 diabetes, diabetic ketoacidosis is the most important and dangerous acute complication. This, however, is very rare in patients with type 2 diabetes. Instead, type 2 diabetes can typically lead to a complication known as hyperosmolar hyperglycaemic state (HHS). HHS has a gradual onset and typically occurs when blood glucose levels rise above 600mg/dl. In comparison to DKA, HHS usually does not lead to ketosis and the blood pH stays above 7.30. Patients typically present with an altered level of consciousness, ranging from stuporous to comatose, with a mortality of 5-20%. Thromboembolic events can also arise due to the hyperosmolality. (12,13)

In general, treatment is similar to DKA. In both cases, rehydration is the most important part of therapy to combat the severe exsiccosis.
Furthermore, the substitution of potassium is clinically indicated, since osmotic diuresis and polyuria causes hypokalaemia, which is often masked by reduced activity of, among other mechanisms, Na^+/K^+-ATPase, leading to potassium flowing out of cells and into extracellular space. The administration of insulin, which could lead to severe hypokalaemia if potassium is not substituted properly, is also part of the treatment to lower blood glucose levels. Insulin is given according to blood glucose values, and, somewhat counterintuitively, a 5%-glucose solution is given when blood glucose levels fall below 250mg/dl in order to prevent hypoglycaemia with further insulin administration. (12,13,30)

1.1.3.6 Long-term effects

Unlike the complications mentioned above, long-term effects appear after years of suffering from poorly controlled diabetes.
These long-term effects include, among others:

- peripheral neuropathy (such as polyneuropathy) and/or autonomic neuropathy
- macro- and microangiopathy (such as arteriosclerosis, retinopathy, and nephropathy)
- chronic kidney disease
- diabetic foot syndrome
- arterial hypertension
- heightened susceptibility to infectious diseases and thrombotic events
- impaired vision, blindness

The main factor for the development of all these long-term effects is near-constant hyperglycaemia. (30,31)
For example, neuropathy and impaired vision can be explained by the following concept:
In cells that possess the enzyme “aldose reductase” (AR), a small part of the glucose inside them will be reduced to sorbitol, which is the start of the polyol pathway. In patients with diabetes however, much more glucose is present, and therefore a much bigger part of that is reduced to sorbitol, which cannot leave through the cell membrane. Through osmosis, the cell will then swell up, which can lead to severe cell damage and impairs the cell function. (30)
Because aldose reductase is present in many different tissues, including the lens and in the Schwann cells that create the myelin sheaths of peripheral nerves, this process can lead to the aforementioned effects.
On the contrary, cells that do not have a large glucose intake will shrink due to hyperosmolarity in the extracellular space. Such is the case with lymphocytes, where shrinking leads to impaired function, making patients suffering from diabetes more susceptible to infections. Furuncles and pyelonephritis are two common infections seen in these patients.

Infections are especially problematic for patients with diabetes, since battling an infection leads to heightened insulin demand due to the release of insulin-antagonistic hormones (such as glucagon, adrenalin, and glucocorticoids), which in turn can lead to higher blood glucose levels. (30)

Hyperglycaemia also increases the production of certain glucose-containing plasma proteins such as fibrinogen or coagulation factors V and VIII, leading to a higher blood viscosity and coagulability, which increase the risk for thrombotic events. (30)
Elevated blood glucose can also lead to an increased production of advanced glycation end-products (AGE), which can, among other things, cause oxidative stress and increase the deposition of collagen in the basal lamina of blood vessels. This can lead to glomerulosclerosis, which, in combination with microangiopathy (also caused by hyperglycaemia), causes diabetic nephropathy and can turn into chronic kidney disease. (30,32)

Due to these and many other possible long-term effects of diabetes mellitus and specifically poorly controlled hyperglycaemia, it is advisable to start adequate therapy as soon as possible and try to achieve the best possible glycaemic control.

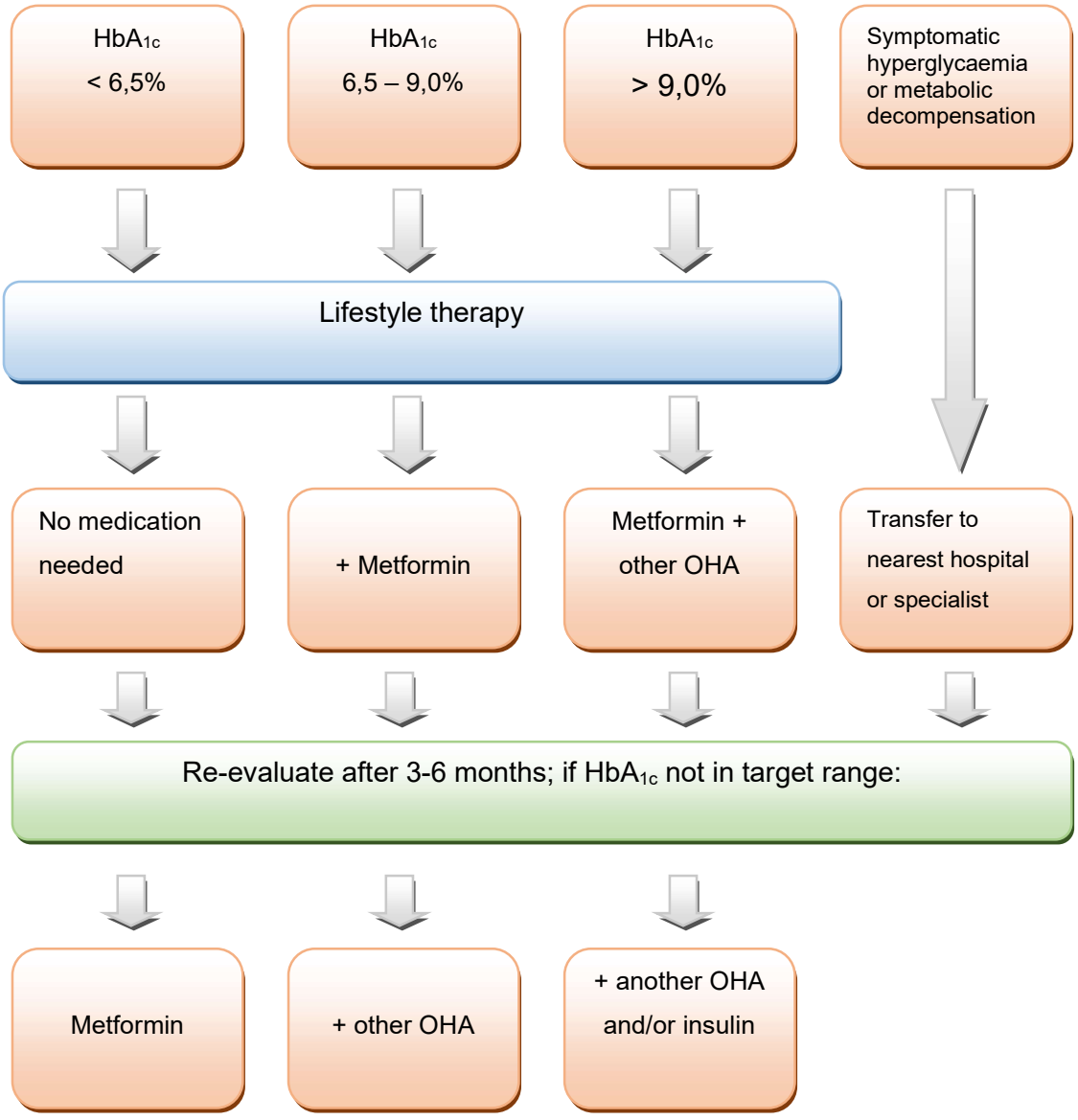
1.1.3.7 Therapy

In general, the therapeutic goals for type 2 diabetes are:

- Avoiding acute complications (such as hyperosmolar hyperglycaemic state)
- Avoiding long-term complications
- Achieving freedom of symptoms and maintaining/restoring quality of life

After the diagnosis of type 2 diabetes in an individual, the therapy schedule depends on a few different factors such as symptoms and HbA_{1c}. (33)
The following diagram shows the different paths that initial therapy can take:

Figure 1: Therapy pathways for patients with recently diagnosed type 2 diabetes (33)



As mentioned above in chapter 1.1.3.3, lifestyle modification plays a big part in the prevention of type 2 diabetes mellitus, as well as for disease management. Lifestyle modification specifically refers to weight loss in obese patients, improving one's physical condition through exercise and maintaining a "healthy" diet. Additionally, there are several different types of drugs used for the therapy of diabetes mellitus called oral anti-hyperglycaemic agents (OHA). According to Figure 1, a relatively low HbA_{1c} value of below 6.5% percent, which represents the target range for HbA_{1c} values for patients who were recently diagnosed with type 2 diabetes and have a normal life expectancy, does not warrant the use of OHAs. If OHAs are needed, for example if the HbA_{1c} value is higher, metformin is the first drug of choice.

If contraindications against OHAs are an issue or if the therapeutic goals cannot be achieved by lifestyle change and therapy with OHAs, insulin therapy is indicated. The algorithm for insulin therapy in patients with type 2 diabetes mellitus can be found in Figure 2. A temporary switch to insulin therapy may also be indicated in cases of acute illness or perioperatively.

In general, insulin therapy reduces blood glucose values and HbA_{1c} and can improve glycaemic control. The main adverse effects to be expected when initiating insulin therapy are a heightened risk of hypoglycaemic events and weight gain. Furthermore, the patient needs to be educated in proper insulin therapy and administration in order to learn the right use of the necessary equipment and the risks of misuse.

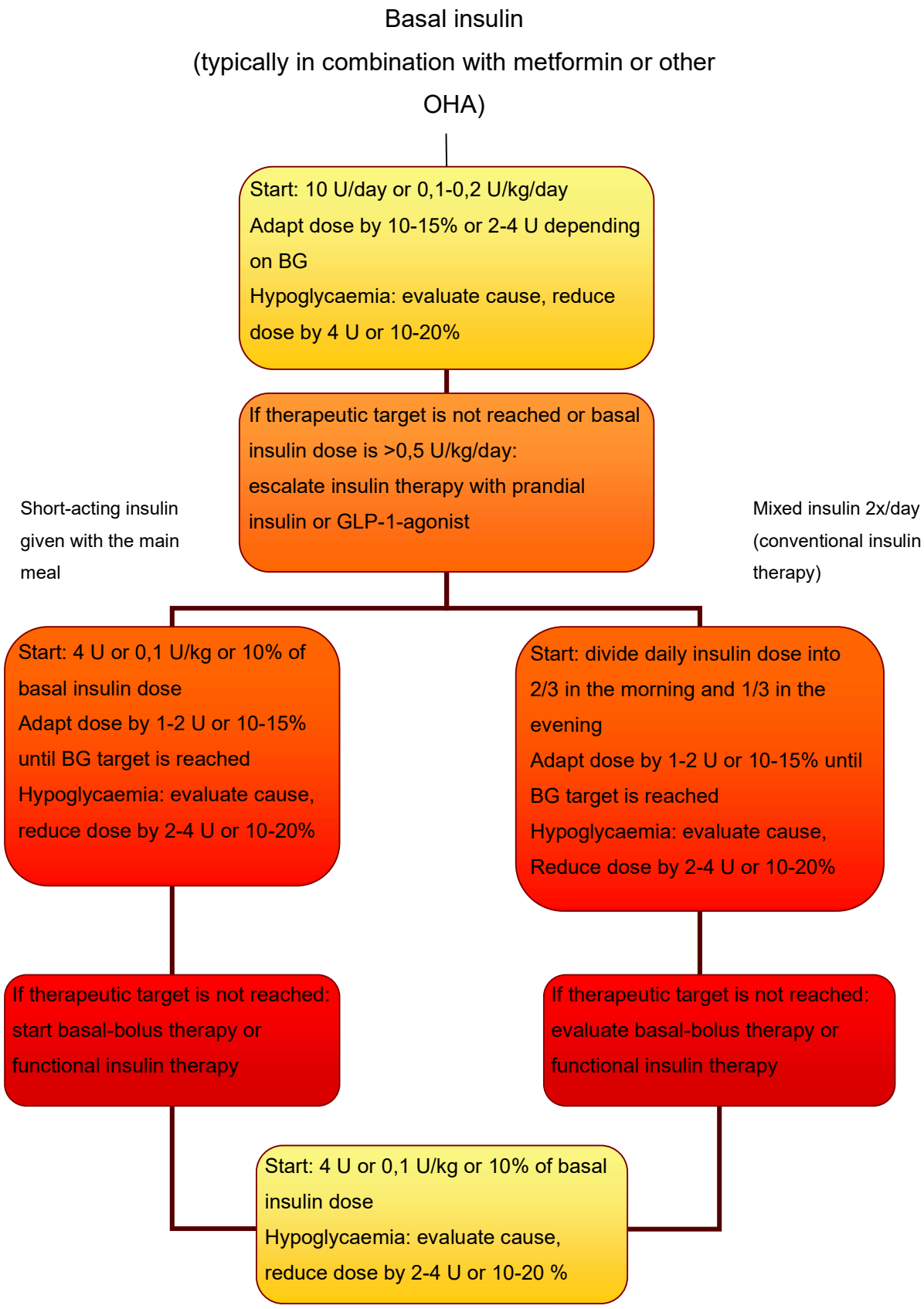
The most common types of drugs used as OHAs as well as their pros and cons are:

Table 2: Comparison of OHAs (33)

OHA class	**HbA1c reduction (in %)**	**Hypoglycaemia**	**Pros**	**Cons**
Metformin	1-2	No	Does not cause weight gain, Reduces macrovascular events	Gastrointestinal adverse effects, contraindications
SGLT-2-Inhibitors	0.5-1	No	Can reduce weight and cardiovascular events	Urogenital infections, normoglycaemic ketoacidosis possible
GLP-1-Agonists	1-2	No	Can reduce weight and cardiovascular events	Nausea, subcutaneous injection necessary
Pioglitazone	1-2	No	Reduces cardiovascular events	Weight gain, peripheral oedema, risk of heart failure
DPP-4-Inhibitors	0.5-1	No	Does not cause weight gain	Risk of heart failure
Sulfonylureas	1-2	Yes	Reduces blood glucose quickly	Possible weight gain and hypoglycaemia
Glinides	1-2	Yes	Improved postprandial glycaemic control	Administered 3 times a day, possible weight gain
Alpha-glucosidase inhibitors	0.5-1	No	Does not cause weight gain, improves postprandial glycaemic control	Gastrointestinal adverse effects, mediocre effectiveness

The algorithm for the initiation of insulin therapy in patients with type 2 diabetes mellitus recommended by the Austrian Diabetes Association is as follows:

Figure 2: Insulin algorithm for type 2 diabetes (34)



Typically, when OHAs are already in use, insulin therapy is initiated while continuing OHA therapy. In most cases, the OHA used is metformin, but any other OHA may be used instead. Metformin should be kept in use with every type of insulin therapy unless there are any contraindications present.
The combination of insulin with SGLT-2-Inhibitors showed promising results regarding glycaemic control and weight loss. Some SGLT-2-Inhibitors, like Empagliflozin, were shown to have cardiovascular benefits. However, when using SGLT-2-Inhibitors, normoglycaemic ketoacidosis can occur, especially during acute infections.
When combining insulin and sulfonylureas, a higher risk of hypoglycaemia and, possibly associated with that, a higher cardiovascular risk must be considered.
An alternative option would be the combination of basal insulin with GLP-1-agonists.
This combination was shown to achieve weight reduction and lower risk of hypoglycaemia when compared to prandial insulin administration. Liraglutid, a GLP-1-agonist, also showed positive cardiovascular effects. (34)

1.2 Continuous glucose monitoring

Continuous glucose monitoring (CGM) is a relatively new way of measuring glucose levels painlessly and efficiently.
CGM devices work by implanting a glucose sensor into the subcutaneous tissue (usually on the back of the upper arm), where it can continuously measure the glucose levels in the tissue. (35,36)
The only problem, however, is that because the sensor lies in the subcutaneous tissue, there is quite a bit of delay regarding the changes of blood glucose levels. When the blood glucose increases or decreases, glucose levels in the subcutaneous tissue do not follow that change immediately. The interstitial fluid, which relays the change of the blood glucose levels to the CGM sensor, is basically filtered blood plasma. This means that in order to be able to measure the glucose levels in the interstitial fluid, it first needs to be filtered from the plasma in the surrounding blood vessels. Because this takes a bit of time, during which the concentration of glucose in the interstitial fluid changes according to the actual blood glucose concentration, the sensor measurement shows the glucose levels not at the exact point of measurement, but at the point at which they were 5-20 minutes ago. (12)
The CGM sensor, depending on the type of the device, can be linked to either a designated reader, a smartphone, or both, where the user then can read and interpret the blood glucose levels as the sensor measures them in real time. Some devices are only connected to a reader for retrospective analysis that clinicians can use to analyse therapy efficacy, time in range and other important parameters. These devices cannot be used by the patients to track their glucose levels in real time. (22)

By using the different kinds of CGM devices, it can be possible for the user to avoid invasive glucose level measurement in order to administer the correct amount of insulin needed. Some types of CGM even have built-in alarms, which alert the user to hypo- and hyperglycaemia. This way, the user can quickly and safely counteract the abnormal increase or decrease in glucose levels before the appearance of possibly dangerous events. (22)

1.2.1 CGM sorted by type of analysis

Retrospective analysis:

These devices use blinded, continuous interstitial glucose monitoring, which can only be analysed retrospectively.

Intermittently scanned CGM (isCGM) or Flash Glucose Monitoring (FGM):

With these devices, continuous interstitial glucose monitoring is used, with the user receiving the latest glucose measurement and trend only when the device is scanned. Retrospective analysis of previous glucose measurements is possible as well. These systems do not have a built-in alarm.

Real-time monitoring:

As with the previous two devices, continuous interstitial glucose monitoring is used. However, these devices show the measured glucose values on their display in real time. Trends are presented as well, showing whether interstitial glucose values are currently rising or falling. Built-in alarms warn the patients of hyper- or hypoglycaemia. If sensor-augmented insulin pumps (SAPs) are used in conjunction with this kind of CGM device, insulin administration can be suspended temporarily if interstitial blood glucose values fall below certain thresholds.

Diagnostic use of CGM:

These systems are sometimes used to identify specific glucose excursions. With the knowledge gained from using the CGM device, therapy can be optimized without using a CGM device permanently. (22)

1.2.2 CGM sorted by duration of use

Intermittent use of CGM:

CGM can be used in blinded mode or in real time for a predefined timeframe (for example 1-2 weeks) for diagnostic and/or therapeutic purposes.

Therapeutic use of CGM:

Permanent use of continuous interstitial glucose monitoring allows the user to put in place therapy adjustments based on trends and glucose values. (22)

1.3 Decision support systems

A decision support system is a system that helps clinicians with diabetes treatment by suggesting an insulin dose according to a predefined algorithm. This way, administering the proper dose of insulin when managing many patients at once becomes much easier.
The decision support system that was used in our study is GlucoTab® (decide Clinical Software GmbH, Austria). Therefore, continuing from here, in all instances in which a “decision support system” is mentioned, it is referring to GlucoTab®, if not explicitly stated otherwise.

The algorithm used by GlucoTab® also asks the user to perform the necessary tasks such as measuring glucose levels, calculating the amount of insulin needed every day, and administering the proper insulin dose for every meal. It works by splitting every day into four parts (“time of day”): morning, noon, evening, and night.
Every time of day, with the exception of “night”, the patient is supposed to have a meal, which then means that insulin must be administered. Whether or not the patient actually ate something, the level of their blood glucose and the a priori set daily insulin dose as well as possible “insulin on board” (insulin that is still active from the last injection) all affect the insulin doses calculated for every time of day. When the blood glucose levels are too high, correction insulin may be given, which the decision support system also calculates. However, when the blood glucose levels fall too much, the system shows a warning for hypoglycaemia and usually recommends not giving any insulin. (8)

Neubauer et al. showed that, by using GlucoTab® for glycaemic management of patients with type 2 diabetes in an inpatient setting, the mean percentage of blood glucose measurements in the target range of 70-140mg/dl was 50.2 – 22.2%, which is significantly higher than the value reported in a then recent best-practice study by Umpierrez et al.
The overall mean blood glucose value was 154 ± 35 mg/dL. (8,37)

Aberer et al. further demonstrated that using GlucoTab® with insulin glargine U300 enables glycaemic control with low risk of hypoglycaemia in hospitalised patients with type 2 diabetes. They achieved a mean percentage of blood glucose values in target range of 56.1% ± 23.5%. Regarding insulin doses, mean total daily insulin dose was 63.8 ± 39.8 IU, with a mean bolus insulin dose of 34.9 ± 19.9 IU and a mean basal insulin dose of 29.0 ± 21.0 IU.
During the study, only 0.9% of a total of 894 blood glucose measurements were in the hypoglycaemic range (below 70mg/dl). (38)

Both of these studies, as well as another study by Lichtenegger et al. published recently, show that using GlucoTab® allows for a safe, efficacious, and user-accepted way of implementing standardized glycaemic management in an inpatient setting. (10)

1.4 Impact of the COVID-19 pandemic on diabetes technology and patients suffering from diabetes mellitus

By the time this paragraph was written, the 26th of July 2021, close to 200 million people across the globe have been infected with SARS-CoV-2 and more than 4 million people have died following an infection. (39)
For patients who suffer from chronic diseases such as diabetes mellitus, the COVID-19 pandemic is especially concerning.
A meta-analysis by Kumar et al. 2020 showed that patients who suffer from diabetes mellitus have an approximately 2-fold increase in severity and mortality when they contract COVID-19. (40)
One of the reasons for the poor prognosis of COVID-19 patients with diabetes mellitus could be a vicious cycle that is set up by the interaction of COVID-19 and diabetes mellitus. Stress hyperglycaemia, treatment with corticosteroids and possibly even β-cell dysfunction and insulin resistance exacerbated by the infection with SARS-CoV-2 can lead to a deterioration in glycaemic control. Their immune system, being somewhat compromised in patients with diabetes mellitus, together with diabetes itself resulting in a pro-inflammatory state, could cause these patients to be more prone to developing a cytokine storm, which is a very severe complication in patients with COVID-19. (41)
Because of the many ways of interaction between these two diseases, patients with diabetes mellitus should be especially careful regarding the prevention of infectious disease, especially during a pandemic. At a time like this, diabetes management in a hospital setting can be rather difficult for healthcare professionals. Repeated exposure to potentially infectious patients and the consumption of personal protective equipment (PPE) should be minimized as much as possible. This is true not just on the general ward, but also when dealing specifically with critically ill patients who are stationed in the intensive care unit (ICU).
To further the advance of diabetes technology and minimize exposure, CGM has been used in multiple studies to manage hospitalized patients with diabetes mellitus during the COVID-19 pandemic.

Nair et al. presented a postoperative mean absolute relative difference (MARD) of 9.4% when comparing the Dexcom G6 CGM Device (Dexcom, San Diego, CA) with the POCT device Accu-Chek Inform II (Roche Diagnostics, Indianapolis, IN) in hospitalized patients who were scheduled for general surgery. (42)
In a similar vein, Reutrakul et al. showed a MARD of 9.77% when comparing the same CGM and POCT devices in non-critically ill patients with COVID-19. PPE use was likely reduced, although no official count was performed. (43)
In both of these studies however, accuracy in hypoglycaemia, which is a known weakness in CGM devices, was not assessed. (7)
Haberl et al. presented the MARD when using a CGM (Abbott FreeStyle Libre Pro, Abbott Diabetes Care, Alameda, USA) and POCT device (Accu-Chek Inform II), in hospitalized patients, sorted by glycaemic ranges: for hypoglycaemia, euglycaemia and hyperglycaemia, MARDs of 11.7%, 8.9% and 7.06%, respectively, were reported. (44)

Regarding the use of CGM to manage diabetes in hospitalized, critically ill patients at the ICU, a study by Agarwal et al. performed during the COVID-19 pandemic in New York City showed that the use of real-time CGM (rtCGM) in combination with POCT seems to be feasible and reliable, resulting in a reduction of needed POCT of approximately 60% for patients requiring continuous insulin infusion (CII). An important factor for this study is the fact that it included critically ill patients, while one of its shortcomings was a low sample size of n = 11. (45)

2 Clinical Study

2.1 Overview

An analysis was performed on a data set obtained in a clinical study involving hospitalized patients with type 2 diabetes.
Within this study, the patients were treated with basal-bolus insulin therapy using a decision support system (GlucoTab®), capillary blood glucose values were measured at least four times per day using a point of care device (Accu-Check Inform II, Roche Diabetes Care) and glucose was monitored additionally using a blinded CGM system (Abbott FreeStyle Libre Pro, Abbott Diabetes Care) during hospitalisation at the general ward of the Division of Endocrinology and Diabetology at the Medical University of Graz.

The aim of this analysis was to evaluate the feasibility of titrating insulin during hospitalisation of patients with type 2 diabetes at the general ward using data from continuous glucose monitoring by using a modelling approach.
CGM is currently commonly used for diabetes management in outpatient settings, and with the COVID-19 pandemic, new data regarding the accuracy of CGM devices used during hospitalization at the general ward has surfaced. However, steering a clinical decision support system using CGM data has not been widely tested yet.

Within the present study, data were modelled by using a demo-version of GlucoTab® that would calculate an insulin dose according to blood glucose levels by using the same algorithm that was used in the previous clinical study.
Firstly, capillary blood glucose values were matched to the corresponding CGM measurements taken at approximately the same time. Additionally, any hypoglycaemic glucose values that the CGM device measured in periods between capillary measurements, which were therefore missed by capillary glucose measurements, as they are only performed at discrete intervals, were added as well. In a second step, the CGM-based glucose values were used for insulin dose calculations instead of the capillary blood glucose values.

Results of the insulin doses suggested by using the POCT values vs. the CGM-based values were compared. This modelling approach aimed to assess the feasibility of using CGM-based values for insulin dose calculation and to see if there are any relevant differences in the suggested insulin doses.

Because this analysis was performed on a data set gathered in both adult male and female patients with type 2 diabetes, the study results, when translated into routine care, will be relevant for both male and female patients.

2.2 Material

2.2.1 GlucoTab® System

GlucoTab® is a clinical decision support system developed and marketed by decide Clinical Software GmbH, Graz, Austria. GlucoTab® covers various types of therapy forms for diabetes, including insulin therapy for the general ward. The system incorporates a decision support component featuring a basal-bolus algorithm for patients with type 2 diabetes.
GlucoTab® supports medical professionals in diabetes management of inpatients with diabetes mellitus by offering a computerized workflow that shows any open tasks and presents past blood glucose values, administered insulin doses and any meal intake of the respective patient. In case that the built-in algorithm for basal-bolus therapy is used, the algorithm gives a suggestion for total daily insulin dose, bolus insulin dose suggestions based on blood glucose values 4 times a day – once for every scheduled meal and once at bedtime to correct high blood glucose values - and basal insulin suggestions once a day. (8,46)
The target range for the GlucoTab® algorithm is defined as a blood glucose between 100mg/dl and 140mg/dl.

2.2.2 Abbott FreeStyle Libre Pro Flash Glucose Monitoring System

The FreeStyle Libre Pro (Abbott Diabetes Care, Alameda, USA) was used for continuous glucose monitoring (CGM). The FreeStyle Libre Pro CGM is a professional CGM system intended to be applied by healthcare professionals only. The system can only be used in blinded mode and is intended to measure and document glucose values over the wear period and thus provide insight into daily patterns of glycaemia. (35,36)

The FreeStyle Libre Pro can be used for up to 14 days, during which it analyses glucose values at 15-minute intervals. The system does not require fingerstick calibration. (36,47)

It was inserted at the beginning of the study period and removed at the end of the treatment period or after 14 days. Sensors that were removed early by accident or due to interventions such as CTs or MRIs were replaced. Data were downloaded as CSV files and synchronized to the data of the hospital information system.

2.2.3 Accu-Chek® Inform II by Roche Diabetes Care

The Accu-Chek Inform II (Roche Diabetes Care, Germany) is a point of care (POCT) device linked to the hospital information system. The POCT device is routinely used within the Department of Internal Medicine at the Medical University of Graz. It was used for capillary blood glucose measurements during the aforementioned clinical study. Capillary blood glucose values obtained by using the Accu-Chek Inform II were used to steer the clinical decision support system during the clinical study. (48)

2.3 Methods

2.3.1 Study design

The clinical study, upon which this analysis is based, was an open, single-centre, non-controlled, single-arm prospective pilot study with a sample size of 30 patients.

2.3.1.1 Hypotheses

In the analysis, the following hypotheses were made:

Null Hypothesis (H0): CGM values cannot be used to steer insulin therapy in the hospital setting.
Alternative Hypothesis (H1): CGM values can be used to steer insulin therapy in the hospital setting.

2.3.2 Study duration

The study duration per patient was defined as the length of the hospital stay or a maximum of 21 days after admission. To get evaluable data, the lowest possible duration of the hospital stay for a patient to be included in the clinical study was at least 48 hours after therapy initiation with the study insulin.

2.3.3 Primary objective

The primary objective was to investigate the feasibility of using a continuous glucose monitoring system to manage diabetes through a clinical decision support system during hospitalisation.

2.3.4 Secondary objectives

- Comparison of capillary blood glucose values measured with POCT vs. CGM
- Differences in insulin dose suggestions made by GlucoTab® when using POCT measurements vs. CGM values
- Hypoglycaemic events detected with POCT vs. CGM
- To investigate potentially avoidable hypoglycaemic events when adhering to insulin dose suggestions based on POCT measurements vs. CGM values

2.3.5 Primary endpoints

The primary endpoint of this study was to calculate the median insulin dose suggestions made by GlucoTab® when using POCT vs. CGM blood glucose values, sorted by insulin type (basal, bolus, total daily insulin dose).

2.3.6 Secondary endpoints

The secondary endpoint was to test the safety, usability, and efficacy of GlucoTab®.

2.3.7 Study population

The study included 30 patients with type 2 diabetes or newly diagnosed hyperglycaemia requiring subcutaneous insulin therapy irrespective of the admission diagnosis. Data from all patients that were included in the clinical study who were treated by using the decision support system with insulins aspart and degludec and for whom both CGM and capillary glucose data were available were included in the analysis. Baseline characteristics can be found below in Table 2.

2.3.7.1 Main inclusion criteria

- Informed consent obtained after being advised of the nature of the study
- Male or female aged ≥18 years

- Type 2 diabetes (treated with diet, oral agents, non-insulin injected anti-diabetic medicine, insulin therapy or any combination of the four) or newly diagnosed hyperglycaemia which requires subcutaneous insulin therapy

2.3.8 Main exclusion criteria

- Type 1 diabetes, gestational diabetes
- Any disease or condition which the investigator or treating physician feels would interfere with the trial or the safety of the patient
- Continuous subcutaneous insulin infusion (CSII)
- Hyperglycaemic episodes (ketoacidosis, hyperosmolar state) if they require intravenous insulin therapy
- Pregnancy
- Any mental condition rendering the patient incapable of giving his consent
- Known or suspected allergy to insulin degludec or insulin aspart
- Continuous parenteral nutrition
- Participation in another trial which can influence outcome of the trial

2.3.9 Demographics and baseline characteristics

Table 3: Baseline characteristics

Variable	**Mean + SD**
Age	74.1 ± 10.9 years
BMI	28.6 ± 5.6 kg/m²
Diabetes duration	13.2 ± 11.6 years
HbA1c	72 ± 22 mmol/mol
Creatinine	1.5 ± 1.2 mg/dl
Sex	60% female, 40% male

3 Results

3.1 Comparison of glucose values between CGM and POCT measurements

The following table shows a comparison of the blood glucose values measured with CGM devices and with POCT devices. For the simulation, capillary blood glucose measurements taken with the POCT devices were matched to the corresponding CGM values measured at approximately the same time (± 15 minutes). However, any additional hypoglycaemic events detected by the CGM device were added as well, explaining the discrepancy between the number of hypoglycaemic glucose values seen in the table below.

Table 4: Comparison of median glucose values between CGM and POCT measurements

	CGM		**POCT**	
	Median (Q1; Q3)	**n**	**Median (Q1, Q3)**	**n**
Glucose measurements overall	110 (69; 160) mg/dl	1075	135 (106; 181) mg/dl	885
Only BG < 70mg/dl	67 (63; 68) mg/dl	270	60 (54; 66) mg/dl	8

Data are median plus IQR.

Due to there being many more hypoglycaemic glucose values measured by the CGM devices, the median glucose level is much lower when looking at the CGM measurements compared to the POCT measurements.
The histograms below show the distribution of blood glucose values measured by the CGM devices. The spike around 60-70mg/dl in the CGM histogram shows the many additional hypoglycaemic measurements.

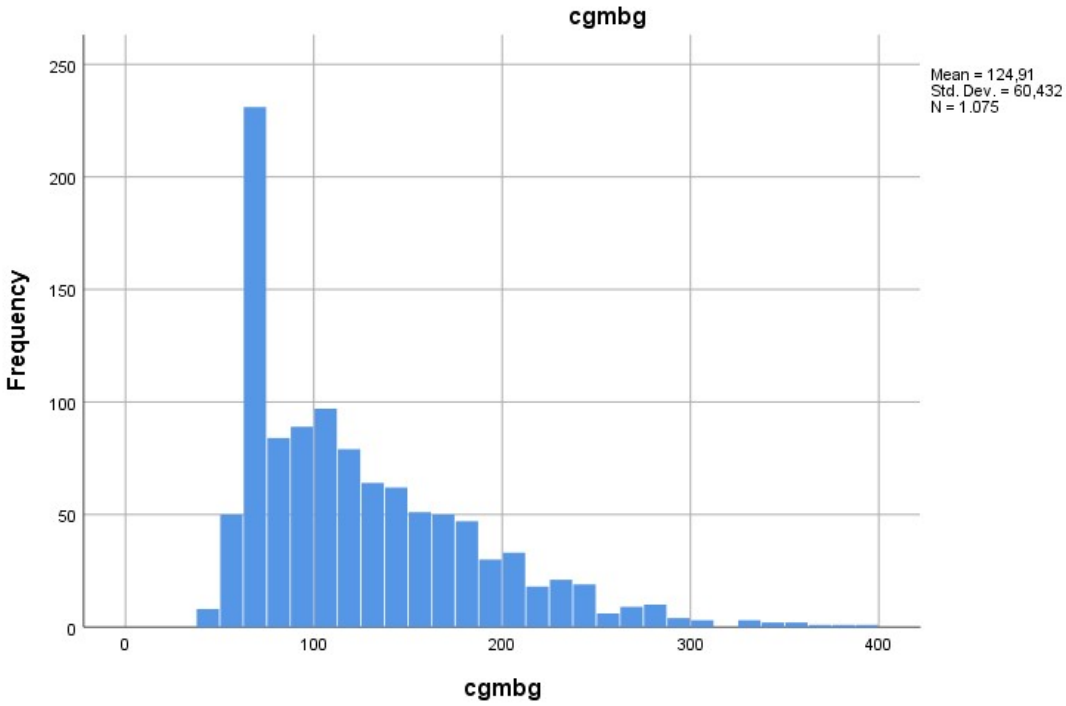


Figure 3: Glucose values (CGM)

The next histogram shows the distribution of capillary blood glucose values measured with POCT devices. Except for the difference at the 60-70mg/dl mark, the histograms have quite similar curves, as can be expected.

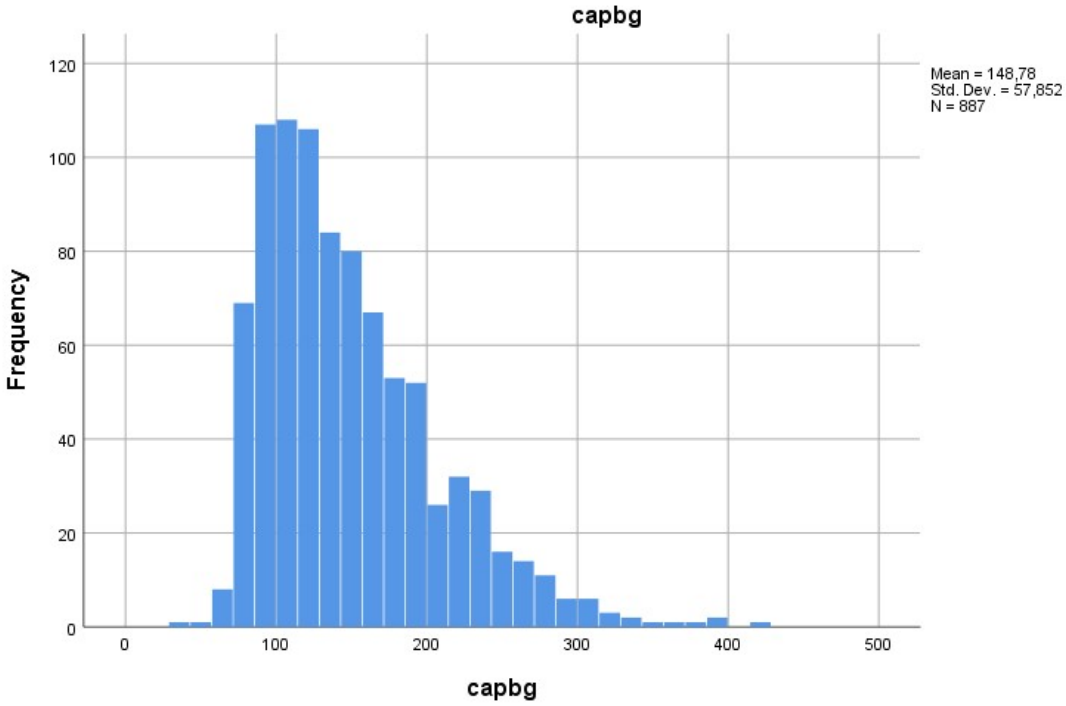


Figure 4: Blood glucose values (POCT)

3.1.1 Comparison of insulin dose suggestions based on CGM vs POCT

The following table shows the comparison of insulin doses suggested by GlucoTab® when using CGM measurements vs. using POCT measurements. In general, the insulin doses suggested by GlucoTab® when using CGM measurements were lower compared to the suggestions made when using POCT measurements. This can be attributed to a few factors, the most important being the additional hypoglycaemic measurements made by the CGM devices, thereby lowering the insulin dose suggestion made by the algorithm. Another factor is that CGM devices generally tend to show lower glucose values compared to POCT devices.
In the table, bolus insulin dose suggestions were split up into suggestions made for an unscheduled, correctional administration of insulin for hyperglycaemia at bedtime (without having a meal) and general bolus insulin dose suggestions during the day, since the small correctional doses given at bedtime would skew the values of “actual” bolus insulin dose suggestions.

Table 5: Insulin dose suggestion over two systems (with n being the number of calculated insulin dose suggestions per insulin type)

	CGM		**POCT**	
	Median (Q1, Q3)	**n**	**Median (Q1; Q3)**	**n**
Bolus insulin dose suggestion (only correction doses at night)	2 (1; 3) IU	73	3 (2; 3) IU	73
Bolus insulin dose suggestion (morning – evening)	6 (2; 10) IU	643	6 (3; 10) IU	643
Basal insulin dose suggestion	13 (10; 19) IU	215	14 (10; 20) IU	215
Daily insulin dose suggestion	25 (19; 39) IU	207	28 (20; 42) IU	213

Data are median plus IQR.

As can be seen in Table 6, the biggest difference is in the suggestion for the daily insulin dose when comparing calculations based on CGM and POCT measurements. This can be explained by the fact that GlucoTab® lowers the daily insulin dose suggestion by 20% whenever a hypoglycaemic event is registered in the timeframe since the last daily insulin dose adjustment, which is usually every 24 hours. Since many more hypoglycaemic values were added to the algorithm by using CGM measurements, the daily insulin dose suggestion was often lower compared to the suggestions based on capillary blood glucose measurements taken with POCT devices.

The histograms below show the distribution of the suggestions made by GlucoTab® for the daily insulin doses. The histogram for the suggestions based on CGM measurements show a slight general shift towards lower doses when compared to the histogram showing the daily insulin dose suggestions based on POCT measurements.

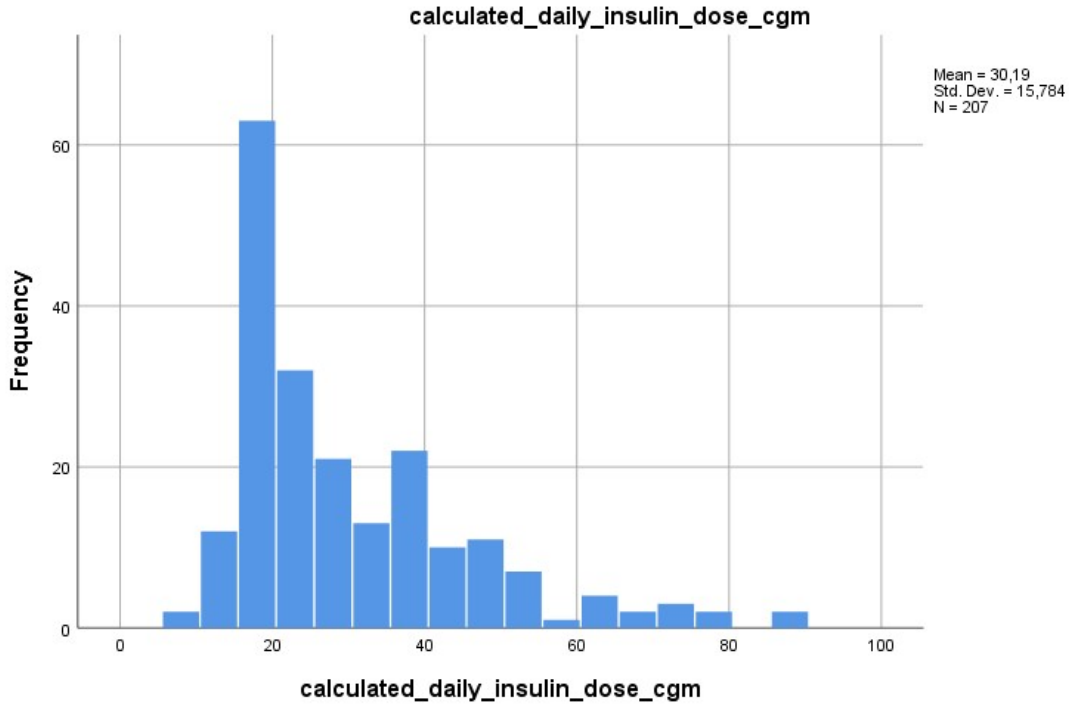


Figure 5: Daily insulin dose suggestions (CGM)

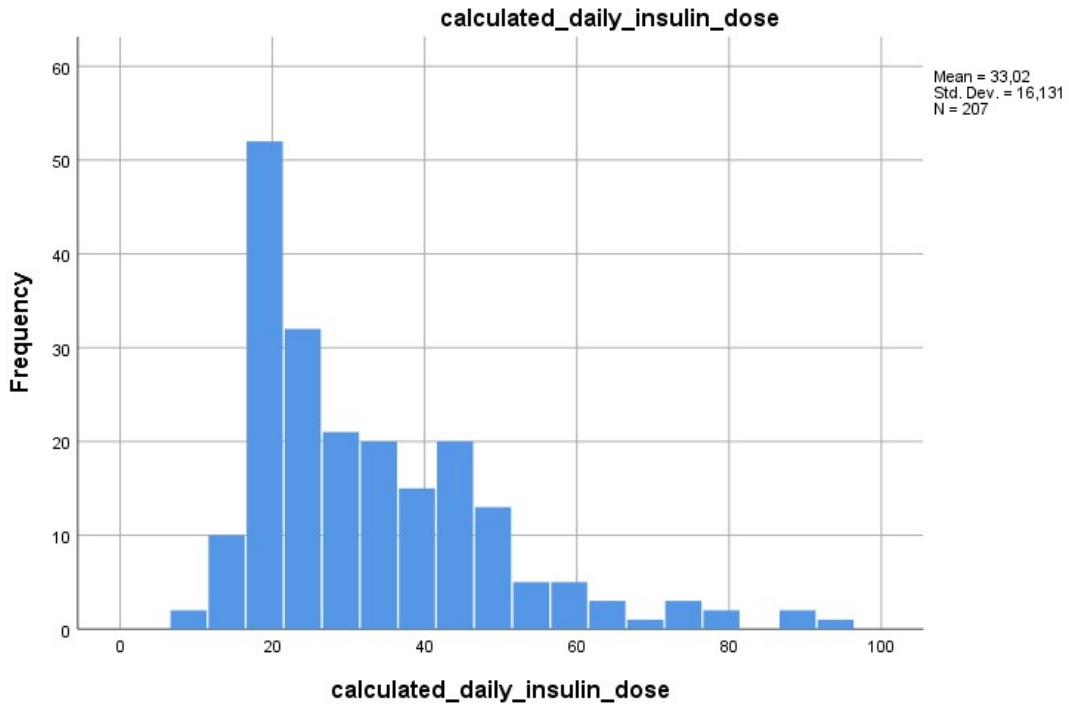


Figure 6: Daily insulin dose suggestions (POCT)

3.2 Analysis of potentially avoidable hypoglycaemic events

An analysis of potentially avoidable hypoglycaemic events when using CGM instead of POCT measurements to steer GlucoTab® was performed as well. This was done by looking at all hypoglycaemic blood glucose measurements taken by the CGM device and analysing in how many cases an insulin dose was suggested based on the POCT measurements that would have been lower when using the CGM device with GlucoTab®.

The result was that in 72 cases, a hypoglycaemic event occurred right after a dose of insulin was given based on the POCT measurement, which would have been lower when calculated with the corresponding CGM value, meaning a hypoglycaemic event could have possibly been avoided that way.

The opposite was also analysed: how many hypoglycaemic events occurred after an insulin dose was given that would have been even higher when based on the CGM measurement?

There were 14 cases in which a hypoglycaemic event occurred and GlucoTab®, using CGM values, suggested a higher insulin dose than was given in the study.

4 Discussion

4.1 Feasibility of using CGM with cDSS

The primary objective of this analysis was to investigate the feasibility of using a continuous glucose monitoring system to manage diabetes through a clinical decision support system during hospitalisation.
To this end, the cDSS GlucoTab® was used to compare insulin dose suggestions when inputting capillary blood glucose values vs. when inputting CGM glucose values.
Looking at the results, which show only a small difference between insulin dose suggestions based on CGM-derived glucose measurements and suggestions based on POCT blood glucose measurements when using the clinical decision support system GlucoTab®, it can be said that it is feasible to use CGM devices when managing patients with type 2 diabetes in a hospital setting. The safety and efficacy of CGM devices has already been investigated in clinical studies, showing that using a CGM can improve time in range and reduce time in hyperglycaemia. (49–51)
This is true for GlucoTab® as well, with recent studies by Aberer et al. and Lichtenegger et al. showing that using GlucoTab® in a clinical setting is safe, efficacious and user-accepted, with its insulin dose suggestions being accepted by clinicians in well over 90% of cases across multiple studies. (8,10,38)
Combining these two technologies could possibly further improve time in range, reduce hypoglycaemic events and make glycaemic management easier for clinical staff, especially during a pandemic, where utmost priority lies in reducing exposure to patients carrying infectious diseases such as COVID-19.
Using CGM data to steer a cDSS will therefore be evaluated within a clinical study.

4.2 Possible positive effects of using CGM with cDSS

Due to CGM devices being able to detect more hypoglycaemic events than would be detected by point of care testing, the insulin dose suggestions by GlucoTab® are slightly lower when based on the CGM measurements, which would generally result in lower rates of hypoglycaemia. This ability to detect hypoglycaemic events even outside of the normal blood glucose measurement times, for example at night, and even when the patient does not show any symptoms of hypoglycaemia, could be very useful in a clinical setting. (50)
This could prevent the onset of symptoms when the patient is drifting into hypoglycaemia, and it would allow clinical staff to decrease insulin doses when hypoglycaemic events are detected, especially when combined with a cDSS.
In general, CGM devices also tended to show slightly lower blood glucose values in our study when compared to capillary blood glucose measurements, which in turn could reduce the rate of insulin overdosing.

Another positive effect would be that fingersticks would become mostly unnecessary, which would make diabetes management painless for patients and easier for clinical staff.
Furthermore, with the COVID-19 pandemic still ongoing, CGM devices can make it much easier and safer for health care professionals to manage patients suffering from diabetes mellitus. They can remotely, safely, and accurately measure blood glucose values and even detect hypoglycaemic events without the need to expose themselves to potentially dangerous infectious diseases and use up important and scarce personal protective equipment, especially during a pandemic.

4.3 Possible negative effects of using CGM with cDSS

Although CGM has in general proven to be safe in diabetes management, its measurements can be slightly inaccurate compared to capillary blood glucose measurements. Usually, they have a tendency of showing lower values compared to capillary blood glucose levels. This inaccuracy is further exacerbated in the hypoglycaemic range, where CGM devices can be notoriously inaccurate compared to the euglycaemic and hyperglycaemic ranges.(52)
Furthermore, CGM shows a “delay” compared to capillary blood glucose values, since it measures the glucose in the interstitial fluid instead of the blood itself. This means that CGM devices tend to present an image of how high the blood glucose was a few minutes ago, instead of how high it is at the time of testing. Exactly how long this “delay” is, differs from patient to patient and cannot be generalized. This could possibly present a problem, since an insulin dose based on CGM measurements showing the glucose levels 15-20 minutes ago could be different than it would be if it were based on the capillary blood glucose levels at the time the measurement was taken.
An example could be an insulin dose suggested for a CGM measurement at the border between euglycaemia and hyperglycaemia. If, for example, the CGM device showed 142mg/dl and the patient had regular insulin resistance for a patient with type 2 diabetes, GlucoTab® would suggest 5 units of bolus insulin. However, if in this example the “actual” blood glucose level at the time of measurement were lower, for example 137mg/dl, GlucoTab® would only suggest 1 unit of bolus insulin for this blood glucose value, since it corrects hyperglycaemia between 140 and 180mg/dl by adding 4 units of insulin for a patient with regular insulin resistance. This would mean a higher chance of administering too much insulin and causing hypoglycaemia in the process. However, there are trend markers built into some CGM devices in order to show whether the glucose levels are rising or falling, making a correction to the suggested insulin dose easier to implement.

4.4 Limitations

As with most studies, there were a few limitations that have to be considered when discussing this study, its results, and the conclusions gained from it.
The first limitation would be that the study had a rather small sample size of n = 30 patients.
Another one could be that by using a simulation to compare insulin dose suggestions, it was not possible to notice any differences in glycaemic control or hypoglycaemic events as it would be during a clinical trial of a cDSS steered with CGM data.
Furthermore, CGM data was not always continually available for every patient, meaning that in a few cases, it was not possible to compare insulin dose suggestions based on the two different systems, since there were no CGM data for that time period.
Finally, there are many different CGM systems in use, of which only one system was used for this analysis. It is entirely possible that using a different CGM system gives very different results.

5 Conclusion

Using a cDSS with CGM data results in similar insulin dose suggestions in a simulation study and offers a new, easier, safer, and potentially better way of steering insulin therapy when compared to using POCT data.
Moreover, with CGM being able to detect many more hypoglycaemic events than point-of-care testing, an argument can be made that using CGM would result in better detection and prevention of hypoglycaemia, since physicians could take quick action against imminent hypoglycaemia, and cDSS would suggest lower insulin doses when faced with hypoglycaemic blood glucose values, making further hypoglycaemia less probable.
The feasibility of using CGM to steer a cDSS in a hospital setting will have to be evaluated further in a clinical trial.

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