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THE TECHNICAL SOLUTIONS AND CHALLENGES OF REMOTE MONITORING AND SELF-CARE IN TREATMENT OF DIABETES

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ABSTRACT

Kerttu Ojala: The technical solutions and challenges of remote monitoring and self-care in treatment of diabetes
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Diabetes is a group of chronic diseases affecting millions of people worldwide. The costs of diabetes for the public economy are vast, and the life quality of diabetics could often bear improving, so new therapies are needed. In this literature review, telehealth solutions for the treatment of diabetes are researched. The goal of this work is to summarise the current state of telehealth diabetes treatment, research rising trends and to figure out the greatest challenges to be solved in the future.

First, the current treatment of diabetes and currently available telehealth solutions are presented. It was found out that despite the advances in the field made in recent years, a large part of the treatment of diabetes still relies on old-fashioned methods. Instead of insulin pumps and continuous glucose measurement devices, finger-prick tests for blood glucose monitoring and manual insulin injections are often still in use. The data transfer from self-care measurements to healthcare providers is often still dependent on manually transferring the data from a measurement device to computer where it can be then sent to a healthcare provider. The second part of the work focuses on the future of telehealth. There the greatest new developments are focused on better artificial pancreases and interoperable devices.

This review shows that there is a vast need for better telehealth solutions in the treatment of diabetes. Considering that the costs of just diabetic foot ulcers can be as high as 250 million euros per year in Finland alone, any savings in the field are bound to be significant to the public economy. The most important trend in telehealth currently is the increasing interoperability. As of now there is much to improve there, as strict regulation keeps companies from developing interoperable devices.

Keywords: diabetes, telehealth, remote monitoring, artificial pancreas, continuous glucose monitoring

TIIVISTELMÄ

Kerttu Ojala: Tekniset sovellukset ja haasteet diabeteksen omahoidossa ja etäseurannassa
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Diabetes on joukko kroonisia sairauksia, jotka vaikuttavat maailmanlaajuisesti miljoonien ihmisten elämään. Diabeteksen hinta julkiselle taloudelle on huomattava, ja diabeetikkojen elämänlaatua olisi usein mahdollista parantaa. Tässä kirjallisuuskatsauksessa tutkitaan diabeteksen hoitoon soveltuvia telelääketieteen ratkaisuja. Työn tavoite on tutkia telelääketieteellisen diabeteksen hoidon nykytilaa, esitellä nousevia trendejä ja selvittää alan tulevaisuuden suurimpia haasteita.

Ensiksi esitellään tämänhetkinen diabeteksen hoito ja tällä hetkellä saatavilla olevia telelääketieteellisiä ratkaisuja. Selvisi, että alan viime vuosina tapahtuneesta kehityksestä huolimatta, huomattava osa diabeteksen hoidosta nojaa edelleen vanhanaikaisiin toimintatapoihin. Insuliinipumppujen ja jatkuva-aikaisen glukoosinseurannan sijaan usein käytössä ovat sormenpäämittaukset ja manuaaliset insuliinipistokset. Datan siirto kotimittauksista terveydenhuoltoon on edelleen usein riippuvaista datan manuaalisesta siirrosta mittalaitteelta ensin tietokoneelle ja sitten terveydenhuoltoon. Työn toinen osa keskittyy telelääketieteen tulevaisuuteen. Tällä alueella suurimmat kehitysaskeleet keskittyvät parempiin keinohaimoihin ja laitteiden yhteentoimivuuteen.

Tutkimus osoittaa, että diabeteksen hoidossa on olemassa suuri tarve paremmille telelääketieteen ratkaisuille. Ottaen huomioon sen, että pelkästään Suomessa ainoastaan diabeettisten jalkahaavojen hoidon kustannukset saattavat vuosittain kohota 250 miljoonaan euroon, mitkä tahansa säästöt alalla ovat kansantaloudellisesti merkittäviä. Tämän hetken suurin trendi telelääketieteessä on yhteentoimivuuden kehittäminen. Tällä alueella on paljon kehitettävää, sillä tiukka lainsäädäntö estää yrityksiä kehittämästä yhteentoimivia laitteita.

Avainsanat: diabetes, telelääketiede, etäseuranta, keinohaima, jatkuva-aikainen glukoosinseuranta

Tämän julkaisun alkuperäisyys on tarkastettu Turnitin OriginalityCheck –ohjelmalla.

PREFACE

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Tampere, 17th of 9th 2020

Kerttu Ojala

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LIST OF SYMBOLS AND ABBREVIATIONS

T1D	Type 1 diabetes
T2D	Type 2 diabetes
CGM	Continuous glucose monitoring
AP	Artificial pancreas
HONK	Hyperosmolar non-ketotic syndrome
BGM	Blood glucose monitoring
ISF	Interstitial fluid
BG	Blood glucose
HbA1c	Glycated haemoglobin
WHO	World Health Organisation
ATA	American Telemedicine Association
eHealth	Electronic health
mHealth	Mobile health
FDA	Food and Drug Administration
DiAs	Diabetes Assistant
MDR	Medical Device Regulation
EHR	Electronic health record
PHR	Personal health record
HIPAA	Health Insurance Portability and Accountability Act
BV	Blood viscosity
PPG	Photoplethysmography
iAPS	Interoperable Artificial Pancreas System

1. INTRODUCTION

Diabetes mellitus is a group of chronic diseases that cause problems with the pancreas insulin production and elevated blood sugar in the long term. Diabetes is defined by the reduction of insulin production, insulin resistance or both. Diabetes is often indicated by the patient's unexplained weight loss and polyuria and polydipsia, meaning the constant need to urinate and to drink. The diagnosis is confirmed by hyperglycaemia, meaning dangerously high blood sugar. [1] Diabetes is divided into several subtypes, which cannot always be clearly separated from each other. [2]

In diabetes the insulin production of the pancreas is non-existent (Type 1) or severely lowered (Type 2). This increases the risk of an early death and the possibility of additional diseases, such as ulcers or neuropathy. Diabetes is treated with the combination of monitoring the blood glucose level with dietary choices and balanced eating schedule, and additional insulin treatment. In Type 1 diabetes (T1D) insulin treatment is always needed. Type 2 diabetics can often go without extra insulin, just by balancing their diet to minimize severe changes in the glucose level and eating oral medication. [2, 3] In this work, the focus is on these two most common types of diabetes, although most of the described solutions are perfectly usable with other types, such as gestational diabetes as well.

The Finnish Current Care guidelines [2] for Type 2 diabetes (T2D) treatment hold life quality as one of the most important goals in diabetes treatment. Life quality has a strong effect on treatment options: if the patient's life quality is low, they likely cannot commit to self-care as well as patients with better life quality. The care plan must therefore be individualised and planned around each patients' resources. It has also been clearly shown that the possibilities of the patient to affect their own treatment has a direct effect on the motivation of the patient to commit to their self-care plan. In Finland as many as 500 000 individuals are affected, so diabetes has a considerable impact on national health. [2]

In diabetes the patient has a much larger responsibility for their own health and treatment than in many other common chronic diseases. This is due to the variance in the insulin dosage and the need to watch the amount of carbohydrates eaten. The carbohydrate number is used to calculate the insulin dose, and even though nowadays there are digital tools to help with this, the basis of the calculation relies on the patient's ability to do the calculations by hand. The large responsibility of the patient carries some problems, as treatment fatigue is fairly common among diabetes patients. Fatigue causes the patient to neglect their care, which can lead to worse therapeutic equilibrium. This does not only mean less tight control of blood glucose but can for example show in the worsening of additional diseases, such as not bothering to take care of one's feet, which in diabetes is very important to avoid foot ulcers. Fatigue leads to worse health outcomes in patients, so taking it seriously and trying to develop easier and lighter care solutions is of paramount importance. Digital solutions should be offered to the patient in a way that best supports their individual care. [3]

Modern telehealth applications offer more options for the patient and the healthcare provider and can therefore aid in giving the patient more agency and in improving the life quality by making treatment and communication with the care provider easier. This can be achieved with for example with continuous glucose monitoring (CGM) or with applications where the patient and the care provider can view the patient's blood glucose level history. There are also automated insulin pumps, called artificial pancreases (AP), but their use is strictly regulated due to the risks associated with device failure. Telehealth can also lead to savings in healthcare costs, because the disease is in tighter control and the patient stays in better health. The aim of this literary review was to investigate the telehealth solutions available for diabetes patients and the challenges associated with modern telehealth. Some possible future solutions for these issues are also investigated.

In Chapter 2 diabetes and its treatment in the present day is presented. In Chapter 3 telemedicine is presented and some of its applications in diabetes treatment are investigated. The focus is on devices and software that are already on the market. Chapter 4 focuses on the future of telemedicine and on things to expect in the coming years. Finally, Chapter 5 presents the conclusions that can be drawn from the literature review.

2. TREATMENT OF DIABETES IN THE PRESENT DAY

Type 1 diabetes is an autoimmune disease, where the body's own processes destroy the beta cells of the pancreas. It typically presents already in childhood, although it can present for the first time at any point of life. Type 2 lacks clear diagnostic criteria, as it is a group of diseases. In this form of diabetes, the patient suffers from insulin resistance and insulin secretion can be defective [1]. The typical patient is an overweight adult with metabolic syndrome. Around 10-15 % of the diabetes patients in Finland have Type 1 and about 75 % have Type 2. The rest are diagnosed with rarer diabetes types or their diagnosis is unclear. [3]

Type 1 diabetes is typically diagnosed when symptoms such as unexplained weight loss and constant need to urinate drive the patient to see a doctor. Other symptoms, such as blurred vision may be present. Despite experiencing these symptoms, a 5-10 % portion of patients will only go to a doctor once diabetic ketoacidosis symptoms start. [1] Diabetic ketoacidosis is a life-threatening state where the patient is nauseous and vomiting, their consciousness is lowered, and they are dehydrated despite the continuous need to drink water. It is caused by fatty acids being released from body fat due to insulin deficiency. This leads to ketosis and eventually to ketoacidosis. Ketoacidosis is rare in Type 2 diabetics but can happen for example if a difficult infection raises the need for insulin. [3]

Type 2 diabetes diagnosis can happen when the patient has no symptoms at all to them presenting with hyperosmolar non-ketotic syndrome (HONK). Many patients diagnosed with T2D have been living with unnoticed hyperglycaemia for many years before diagnosis. This carries the risk of tissue damage. It is estimated that in the United Kingdom 50 % of people with T2D are undiagnosed. [1]

Insulin and glucagon are the two hormones that influence blood glucose. They are produced by the beta and alpha cells of the Langerhans islets of the pancreas. Insulin controls the absorption of glucose from the blood into muscles and liver. Glucagon causes the liver to convert glycogen into glucose and release it into the bloodstream. It also stimulates the release of insulin, so that the glucose can be taken into the insulin dependent tissues and used. [1]

While diabetes is a disease mainly affecting the functions of the pancreas, it also causes several additional diseases, such as diabetic retinopathy, nephropathy, and peripheral neuropathy. In retinopathy, the blood vessels of the fundus of the eye are growing abnormally and proliferating. The fundus is the part of the eye opposite of the lens. Retinopathy can lead to vision impairment and even blindness. Nephropathy usually starts with microalbuminuria, which means excess albumin secretion into urine. It can eventually lead to insufficient kidney filtration and need for dialysis treatment. In neuropathy, the nervous system experiences changes. The most well-known and common symptom is the loss of feeling in the legs or the feeling of pins and needles. This in turn can lead to foot ulcers. Good control of blood glucose helps prevent these illnesses. [3]

2.1 Blood glucose monitoring and management

Blood glucose monitoring (BGM) is an intrinsic part of the treatment of every type of diabetes. It can be measured at certain times or nowadays also continuously. It is a hugely important topic in the health technology world, and this is highlighted by the fact that 80% of all biosensors currently in use in the world measure blood glucose [4] Body glucose is not always measured from blood. Especially with continuous glucose monitoring, the glucose measured is interstitial fluid (ISF) glucose. [5]

The goal glucose values for diabetic patients are under 7 mmol/l in general and under 10 mmol/l after meals, and HbA_{1c} (glycated haemoglobin, used to measure long term glucose values) should be under 53 mmol/mol or under 7 % [2]. Blood glucose (BG) levels need to be strictly monitored and cared for, because high BG can cause osmotic pressure to the cells and lead to cell dehydration, or in the worst case, diabetic ketoacidosis, which can be lethal. High BG also has a negative effect on wound healing, as it can interfere with neutrophil function. On the other hand, low BG carries the risk of hypoglycaemic coma, which can lead to brain damage and even death. [6]

Traditionally, BG has been monitored with capillary glucose measurements by pricking the skin and collecting a blood sample to a glucose strip. The strip is then inserted to a measurement device that displays the BG level, as demonstrated in Figure 1. This method is inconvenient, because the patient needs to be in a space where they are comfortable with performing the measurement and because recording continuous trends in BG is impossible with test strips. It is also not sustainable, because the glucose strips are single use. However, the results acquired this way are accurate and are received immediately. The method is easy to use. Finger-prick testing remains both widely in use and the gold standard of BG measurement. It is used to ensure the validity of data achieved by other methods [7, 8].

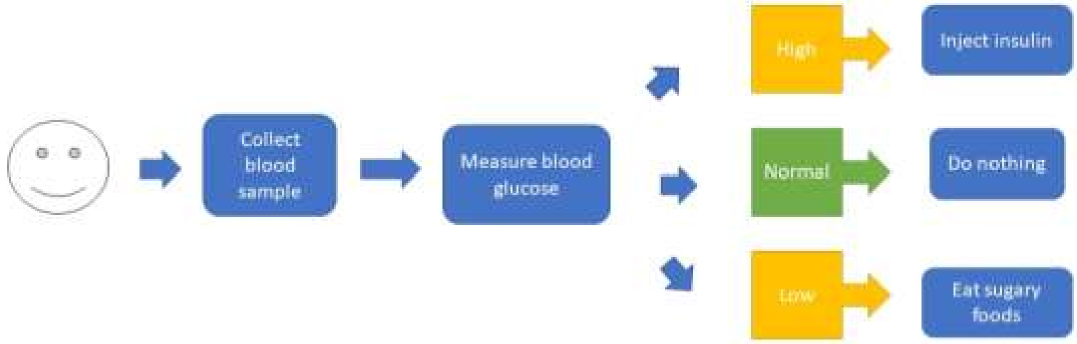

Figure 1. *A traditional view to controlling blood sugar*

Insulin administration is done by injecting it to the stomach, on the outer side of the thigh or on the buttocks. The injection site must be changed every time to avoid the development of lipohypertrophy, meaning excess growth of the fatty tissue. The needles used to inject insulin are also single use. [3]

Insulin pumps have also been available for patients for some time now. The most basic pump models inject a set level of basal insulin all the time, but more advanced ones may have for example a low glucose suspend functionality. This means that the pump stops injecting insulin if the patient's BG is too low and continues only once the BG level is deemed to be on a safe level again. Insulin pumps mimic the body's own insulin production more closely than traditional insulin injection. Pump therapy is most beneficial for patients with additional diseases, insufficient therapeutic equilibrium, irregular schedule, or for patients who exercise a lot. Conversely, patients who cannot commit to their own care usually should not be treated with insulin pumps. [3]

Insulin therapy is always needed in the treatment of T1D. Many Type 2 diabetics can eventually go without, but often it is needed immediately after diagnosis to treat hyperglycaemia. Different types of insulin and insulin analogues are used to provide effective treatment for a variety of situations. They have different durations of effect, which ensures that the patient stays in the normal BG level range during the night and after meals. [3]

The most widely used insulin analogues in Finland are presented in the Table 1. From there we can see that the effects of different insulins are very different from each other. In insulin pump treatment the long-acting insulin analogues are passed over entirely, and the basal insulin effect they provide in traditional injection therapy is replaced by continuous administration of rapid acting insulins. Glargines 100 and 300 differ from each other only in concentration. This shows that by varying the dosage, different lengths of effect can be achieved. [2]

Table 1. *Types of commonly used insulin analogues and their differences [3]*

Type	**Rapid acting insulin analogues**	**Long-acting insulin analogues**	**Overly long-acting insulin analogues**
Names	Aspart-, glulis- and lisproinsulin	Detemir Glargine 100	Glargine 300 Degludekinsulin
Speed of effect felt	10-20 min	-	-
Effect peak felt	1-2 h	-	-
Duration of effect	3-5 h	Detemir: 12-24 h Glargine 100: 20-30 h	Glargine 300: over 30 h Degludekinsulin: 33-42 h
Usage	Meal insulin Correction of high BG Insulin pumps	Basal insulin	Basal insulin

Table 1 omits some of the other insulins used in Finland, such as short-acting human insulins and medium range NPH-insulins (Neutral Protamin Hagedorn). This is because these types have fallen out of favour due to the listed insulin analogues being better and safer to use. For example, human insulins used to be used as meal insulin, but since they act slower than modern rapid acting insulin analogues, they have fallen out of use except in special cases. NPH-insulin carries a stronger hypoglycaemia risk than long-acting insulin analogues. [3]

In the treatment of T2D, oral medicines are most commonly used. These include metformin, gliptins, sulfonylureas, glinides, GLP-1-analogues, SGLT-2 inhibitors and glitazones. Metformin is recommended as the first medicine to start treating T2D. It inhibits the glucose production of the liver. Gliptins and GLP-1 analogues are suitable for post-meal hyperglycaemia treatment, because they raise the levels of gut enzymes GLP-1 and GIP. These improve the glucose dependant insulin secretion. Sulfonylureas and glinides block the potassium channels of the beta cells of the pancreas, which causes the release of insulin into the bloodstream. SGLT-2 inhibitors increase the secretion of glucose into urine, which lowers the daily calorie intake. Glitazones sensitize fat and other tissue to insulin. [2]

2.2 Ulcer treatment

Diabetic foot ulcers, that is chronic wounds, are a serious health issue affecting 2–5 % of diabetes patients every year [9, 10]. Diabetic neuropathy is the most important reason for ulcer development, as it can lead to loss of feeling and to faulty walking postures. These in turn lead to small and insignificant looking wounds, that however easily become chronic, as the diabetic cannot feel that the wound is irritated. Nephropathy, issues with peripheral blood circulation, high blood glucose level and smoking also increase the risk of ulcers. [10]

Diabetic foot infections cause more hospital days than any other diabetes complication and multiply the risk of foot amputation. People most at risk of ulcers require regular check-ups with medical professionals. Diabetics who are determined to be low risk still need to take care of their feet. Diabetic foot care is arranged by a team of a diabetes doctor, a diabetes nurse, a foot therapist and an assistive technician or a physiotherapist, if necessary. [10]

Treatment of diabetic ulcers is very costly. The multisectoral teams and hospital stays add up to costs averaging 10,000 € per year per patient when patients from 10 different European countries were analysed. The cost of amputation climbed to 25,000 € per year per patient. It is possible that the treatment costs associated with foot ulcers could be as high as 10 billion euros in Europe. [10, 11] From these numbers it can be calculated that the yearly cost of ulcer treatment in Finland comes up to 100–250 million € per year. Even a minor reduction in these figures would be significant for the public economy.

The most effective ways of reducing patient harm and therefore lowering treatment costs are prevention and early recognition and treatment of ulcers. Patient self-care and monitoring are an essential part of treatment. This includes daily washing and inspection of feet, keeping nails short, well-fitting and comfortable shoes, and frequent moisturising. If a change or wound in the skin is detected, the foot must be put to rest immediately, and healthcare professionals must be contacted within a few days, if the wound does not heal. [10]

3. CURRENTLY USED TELEMEDICINE SOLUTIONS

The definition of telemedicine is central to this work. No single all-encompassing definition exists. The following is the World Health Organisation (WHO) definition from the year 1998 [12]:

> “The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities” [12].

The American Telemedicine Association (ATA) [13] defines telehealth as

> “Technology-enabled health and care management and delivery systems that extend capacity and access.”

This definition is much wider, as it does not restrict the definition to only healthcare providers and professionals. For the purpose of this work, this definition is used, as it is more patient oriented. This is important in the context of diabetes, because as has been established, the responsibility of the patient for their own care is notable.

Telemedicine encompasses such fields as electronic health (eHealth) and mobile health (mHealth). EHealth means the delivery of healthcare services via internet connection and therefore mHealth generally falls under it. MHealth is defined as advancing health using mobile phones and other mobile technology. This can mean for example using the phone to connect and control other devices. The use of machine learning in the healthcare context also falls under the telemedicine umbrella. [13]

3.1 Blood glucose and insulin level monitoring

Continuous glucose monitoring covers all methods that allow for continuous measurement of BG. This includes minimally invasive methods, such as microneedle patches, and implantable devices. These methods usually measure BG from interstitial fluid. CGM marks an improvement from prick testing, as it allows for longer trends of BG to be followed and also reduces the need for waking up in the middle of the night to find out if the patient has nightly hypoglycaemia [3]. The measurements are either sent to a terminal device, for example a mobile phone, every few minutes or read by taking the terminal device close to the sensor in so-called flash-devices. However, these devices still need to be frequently calibrated with finger-prick tests, for example in the case of Dexcom G5, twice a day. The newest Dexcom sensor, the G6, no longer needs calibration, and finger-prick tests are only required in the case where the patient's symptoms do not match with the glucose level reading. [8]

There is evidence that CGM improves the condition of the patient and possibly their life quality. This is especially true in certain patient groups, for example ones not able to care for themselves, the care is not balanced, or more accurate monitoring is needed to ensure occupational safety. These groups include children and teens, pregnant people, patients prone to hypo- or hyperglycaemia, patients with severe fear of needles and patients with jobs where hypoglycaemia could cause dangers. [3]

In children it has been demonstrated that CGM reduces parental stress and fear of hypoglycaemia, as it is easier for the parent to follow their child's BG values, as there are applications that allow the guardian to remotely view the patient's BG level [14]. The first commercial one in use is the Dexcom G5 Mobile app, which allows the readings to be shared with up to 5 people and works on both Apple and Android devices. [8]

Happy Bob is an iPhone app developed by Harald AI Oy that reads your CGM data and displays it with funny comments, such as "[your] blood sugar is lower than a rapper's pants". The user can also collect stars from staying in the designated BG range. [15] The app is an example of gamification, meaning the application of game design elements and principles to non-game contexts. The goal varies, but gamification is usually applied to increase engagement. In the context of Happy Bob, the goal is to make children with T1D engage better with their care and to make BG monitoring, a necessary but not an exciting activity, fun.

Real-time CGM also improves the therapeutic equilibrium when used at least 80% of the time, even in patients whose control of their diabetes is very good. In some cases, it is advised to use a real-time device instead of a flash-device. These include strong changes in BG without warning symptoms and severe hypoglycaemia instances. The ability of the sensor to warn about hypoglycaemia can help to avoid it. [3]

It should be noted that despite the progress in GCM in the 2010s, not everyone has been perfectly happy. The #WeAreNotWaiting movement is a group of people who first got fed up with scattered platforms, competing products not communicating with each other and not being able to monitor their children's BG remotely. The tagline is their core idea: they should not have to wait for the control of their own bodies. What this means in action is that they build open software that allows one to hack one's glucose monitor and to display the data online. [16]

Their frustration was largely borne out of the fact that all the technology required to share BG measurements already existed in the early 2010s, but it was not commercially available. Nowadays this has partially been relieved, as noted for example by the Dexcom mobile app. Despite these advances, devices generally are not interoperable, and smartphone connectivity remains a rarity.

The development of CGM devices has been rapid during the last ten years. Despite the advances in the area, manual work is needed with measurement calibration and insulin pumps. Automated devices are being developed and some are already available, but due to costs and tight regulation the movement to market has been slow.

3.2 Insulin pumps and artificial pancreases

In recent years in addition to CGM devices, artificial pancreas devices, sometimes called bionic pancreases, have entered the market. These advanced insulin pumps adjust the insulin levels automatically based on the patient's previous reactions to insulin and on trends of BG development. It has been shown that these devices improve the BG and HbA_{1c} levels in the patients, and that the benefit is especially strong in the challenging patient population of teenagers and young adults. [17] Regular insulin pumps as such do not necessarily fall under any definition of telemedicine, unless when coupled with a CGM functionality or device. The patients who most benefit from these advanced insulin pumps are typically those who have a high motivation to commit to their care and the required technical skills to use the pump. Pumps with low glucose suspend functionality are especially useful for patients with nightly hypoglycaemia. [3]

The first of such devices to enter the market is the MiniMed 670G produced by Medtronic. This device also employs real-time CGM by coupling with a Guardian CGM sensor, and gives automated alerts on too high or too low BG. It employs so called closed-loop technology where it automatically administers basal insulin based on its readings of BG. It is not fully automated as the user still needs to enter meal insulin manually. [7] It also has an open-loop mode where the user can modify all parameters of insulin delivery, whereas in Auto mode the user only has to enter the meal insulin. The user can also up the glucose target level temporarily for sports or driving. The pump leaves the Auto mode quite often as a result of hyperglycaemia or other reasons, such as issues with sensor connectivity. [17] The pump’s functionality is presented in Figure 2. This graphic omits the CGM device for clarity.

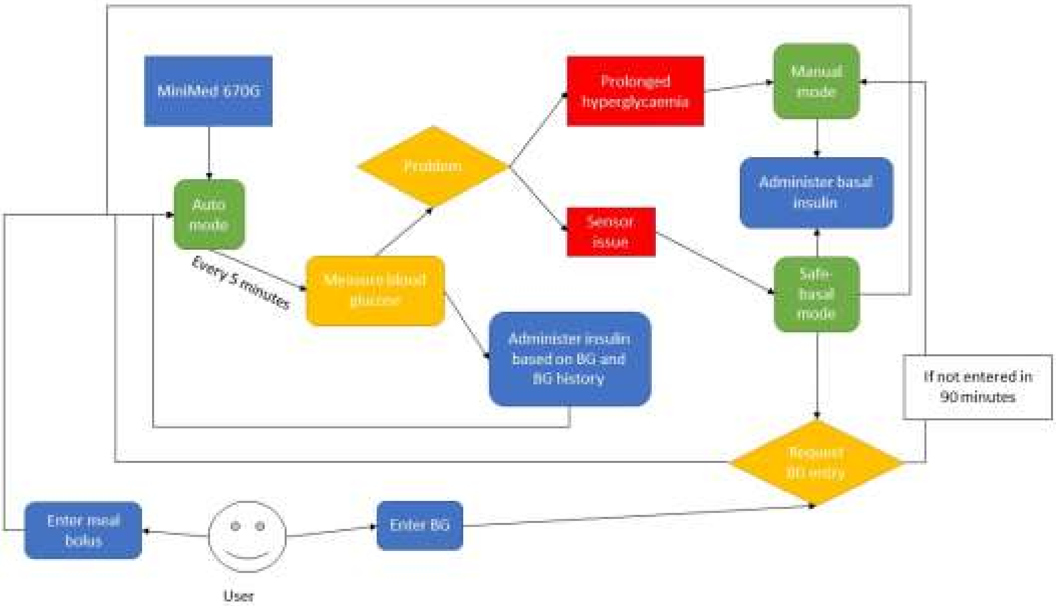

Figure 2. *How MiniMed 670G controls the patient’s blood sugar*

The only other device to be approved by the Food and Drug Administration (FDA) to this date is the t:slim X2 pump with Control-IQ technology developed by Tandem Diabetes Care. It was cleared for release in December 2019 [18]. The pump works with the G6 CGM sensor. The pump can also be fitted with Basal-IQ software: it then functions as a regular insulin pump with a low-glucose suspend functionality. With Control-IQ, it is a full-fledged AP system. In addition to low glucose suspend, it can administer automated insulin correction boluses. It also has extra functionalities for sleep and exercise. [19]

The pump can be used with a smartphone application, the t:connect, also developed by Tandem. The application is only a display for the pump data and the pump cannot be controlled through it. However, the application uploads the pump data wirelessly to the t:connect web application, through which it can be shared to healthcare providers. [19] The inability to control the pump through a smartphone is an unfortunate lack, but even being able to see the data on a phone can be counted as an advancement.

The Control-IQ software is a product of a decade of product development. In 2011, the University of Virginia developed the mobile DiAs (Diabetes Assistant). It used a smartphone to run an AP system. Its second-generation form was the inControl, developed by TypeZero Technologies. The inControl is also a mobile algorithm, and it was used extensively in clinical trials, including large-scale ones. The Control-IQ uses the same algorithm embedded in the t:slim X2 pump. [20]

The efficacy of the t:slim X2 pump and the Control-IQ have been extensively shown in clinical studies. In children and adolescents its safety and efficacy even in rougher situations was proved in a study [21] taking place in a high-altitude ski camp. Despite several hours of exercise every day, high altitude and cold temperature, the participants' time in range was significantly improved (66.4 ± 16.4 vs 53.9 ± 24.8%). The increase averaged to about 3 hours a day. The study group also had a 15 % reduction in time spent hyperglycaemic, and this reduction was even more significant overnight. This was achieved without increasing insulin usage; the mean daily insulin amount was the same in both the study and the control group.

The Control-IQ has not yet been cleared for sale in the EU, whereas Medtronic 670G has been. In addition to these devices, a French company called Diabeloop has its own AP system called DBLG1. This device received a CE marking in 2018 but has yet to be commercially released anywhere. Diabeloop is planning on releasing it in France and Germany in the near future. [22]

The DBLG1 is a hybrid closed-loop system, like the Medtronic 670G. Unlike it though, it is not an insulin pump, but an algorithm hosted in a dedicated handset, that connects to a CGM device and an insulin pump. One of the promised features of the system is better compatibility with devices compared with other options on the market, but as of now that is not yet true. Currently it is only compatible with the Kaleido pump by ViCentra and the Dexcom G6 CGM device, but Diabeloop is attempting to bring in more options. [23]

The efficacy of the DBLG1 has been extensively studied. In a 12-week study [24] the time the study group spent in the glucose target range (3.9 -10.0 mmol/L) was 9 % more than the control group (68.5 ± 9.4 vs. 59.4 ± 10.2 %). Similarly, hyper- and hypoglycaemia were reduced in the study group. No adverse events caused by the algorithm were identified during the study.

These devices pose a very high risk to the patient in the event of a device failure. Due to this they are classified as Class IIb medical devices under the Medical Device Regulation (MDR) of the European Union and as Class 3 by the FDA. Due to the great risks associated with automation, the development of these devices is slow and highly regulated. The regulation is also one of the main reasons as to why the connectivity of these devices is so restricted. As the development of new connections is highly regulated, it is both safer for the company and more economically reasonable to limit the connectivity.

The prevalence of automated insulin administration will continue to rise, as it provides solutions to the difficulties of diabetes treatment especially in children and adolescents. It is a well-known problem that diabetic patients omit insulin boluses, most often in an attempt to lose weight [25]. It has also been demonstrated that some young patients administer extra insulin to facilitate hypoglycaemia. There are varying reasons for this, but access to extra treats and to parental attention have been cited. [26, 27] Despite the fact that these problems can partially be addressed by automated insulin delivery, mental health care and therapy is advised to treat the underlying problems.

3.3 Other telemedicine solutions

The use of remote doctor examinations has been slowly gaining popularity, but the CoViD-19 pandemic could be the event to catapult them to more widespread use. One problem that has slowed the spread of video visits has been the cybersecurity of videoconferencing software, but nowadays there are programs designed for medical use.

Online telehealth services can take on many forms. There are video conferencing options for remote doctor examinations, chat services, personal health records and symptom and health surveys. All these applications can be applied to diabetes treatment.

The electronic health record (EHR) system Kanta is in use in every level of the Finnish healthcare system. It contains several subsystems, such as the electronic prescription service Resepti, the health and symptom survey service OmaOlo, and the MyKanta service, where the patient can access their data and apply for prescription renewal. The patient can also upload their personal health data to Omatietovaranto, a personal health record (PHR). Omatietovaranto is an example on how legislation can slow the progress of telehealth: the Finnish law currently does not allow the patient to share this data with their healthcare provider or with third-party companies, which reduces the Omatietovaranto to a data storage. When it was developed, the idea was that the user can share data from their smartwatches and other devices and companies could develop apps to process and use this data for the user’s benefit. Kanta also includes services aimed at health and social care professionals, such as the Kelain service, which allows doctors to prescribe medication, and the patient health and social data archives. [28]

In a Norwegian study [29] about the application of telemedicine intervention to foot ulcer care it was found that the program helped the diabetes nurses and podiatrists to feel more secure with their professional expertise and also gave a clear guide on how to proceed with the patient in an outpatient clinic appointment. The program, developed by

Dansk Telemedisin AS, is a web-based portal where a healthcare professional can add their comments about the patient and include pictures of the feet to make the following of wound progress easier. The application also allows all healthcare professionals working with the patient to access the information, making the care more comprehensive. [29]

The intervention worked very well in a clinic setting, but in the busy home care setting, where lack of light and of appropriate space were an issue, the results were not as good. Nevertheless, the home care nurses felt that the system improved their work. The biggest challenge was the inability to access the system from the patient's home. It was discussed if this could be resolved by giving the nurses laptop computers. [29]

It has been demonstrated that telemedicine interventions can make healthcare more equal in remote areas. In a study set in the Lower Eastern Shore of Maryland, USA, a multidisciplinary team was formed of diabetes specialists, nurses, and other medical professionals. When a diabetic child arrived at the clinic, a nurse obtained their physical measurements and laboratory results and uploaded them to an electronic medical record. These were then accessible to a diabetes physician situated elsewhere, with whom a two-way videocall was held. The parents of the patients fulfilled a questionnaire on their satisfaction with the telemedicine approach. Overall, the parents were very happy with it and one commented on how a trip to a tertiary care centre takes all day whereas the visit to the clinic close by only took an hour. The patients were also able to see a diabetes doctor sooner than they would have been able to in normal circumstances. [30]

There are many different web portals through which a patient can share their BG level data to their care providers. One such platform used in Finland is Diasend by Pharmanova. Through Diasend, the patient can upload data from many different BGM devices, both traditional and continuously working. [31] Another Finnish company, Sensotrend, also offers this kind of service, the Sensotrend Connect. Their applications allow the user to upload data from many different devices to for example the Kanta system or to an EHR. [32] Medtronic offers another such service under the name CareLink [33]. For the Diasend and the Medtronic systems, the patient needs an external connectivity device between the BG meter or insulin pump and the computer. The data cannot be therefore viewed in real-time, or on a mobile device.

The Nightscout project, originally developed by parents with Type 1 diabetic children, aims to solve this accessibility problem. They offer a way to hack ones CGM device so that its data can be uploaded to cloud in real-time, and viewed through almost any device, from smartphones and PCs to smartwatches. Nightscout's website offers guidance on setup and all the code needed. The project relies completely on volunteer work. [34]

What should be noted about Nightscout and other similar projects is that they do not have the approval of FDA or other regulatory bodies. This is in part intentional: a large part of the reasons why the existing systems do not communicate is the strictness of regulation. Nevertheless, if a hacked device should fail, there is no warranty and the entire fault lies with the user. The Nightscout website displays various disclaimers denying the use of the program for medical purposes. It should also be noted that the data the user uploads to the internet is readable by anyone, and that Nightscout is not and is not attempting to become a Health Insurance Portability and Accountability Act (HIPAA) covered entity. [34]

Despite Nightscout apps not officially qualifying as medical devices, the data collected there by the patient is valuable and usable in their treatment. Sensotrend offers a service for the patient to view and upload Nightscout data into Omatietovaranto, via a medical application called Nightscout Connect Kanta PHR. They also offer a related service, Nightscout Connect EHR, which allows medical professionals to view their patients' Nightscout data in their EHR system. Because many of Sensotrends systems work with Nightscout, they allow the data to be followed in real-time. [32]

These applications are currently not utilised to their fullest extent in the treatment of diabetes. The first steps in this process should be to update the laws governing the usage of data to allow a patient to share their personal BG measurements to healthcare providers and companies of their choosing.

3.4 Challenges

3.4.1 Issues with telehealth

The use of mobile phone images as diagnostic tools in diagnosing of food ulcers posed challenges with image quality [35]. Admittedly, mobile phone image quality has greatly improved since iPhone 4, which was used in the study. It was also demonstrated that mobile phone images are valid for ulcer development follow up, when taken by professionals [29]. It may be that if the patient were trained in taking photos of their ulcer and the camera used was good enough, these images could be used in diagnostics and development monitoring.

Cybersecurity is an important topic when it comes to telehealth. An attacker taking advantage of a vulnerability could lead to patients' personal health information leaking, or even device malfunction, which could in the worst-case scenario lead to patient death.

Medtronic has had cybersecurity issues especially during the year 2019. There have been reports of their insulin pumps being able to connect to wrong devices in the vicinity, which could lead to someone else controlling the pump, with potentially disastrous consequences. This led to the FDA recalling the MiniMed 508 and MiniMed Paradigm series insulin pumps. These are older models and the FDA emphasized the need to move on to newer and better protected pumps. [36]

However, these same pumps are favoured among the #WeAreNotWaiting movement, partially because of the cybersecurity flaws. They are easier to modify on your own to work as artificial pancreases, because of the mentioned flaws. As they are older, used models are available cheaply on internet marketplaces. [37] This is one of the reasons why the arrival of new pumps with better interoperability and cybersecurity is eagerly anticipated.

3.4.2 Problems associated with continuous glucose monitoring

CGM devices can have an approximately 15-minute delay in the BG reading. This is caused by ISF glucose having a slight delay in glucose level changes when compared to blood. This means that if a patient using a CGM device is displaying hypoglycaemia symptoms the BG level may need to be confirmed by a fingertip test, as BG can occasionally drop very fast [3]. This requires diabetics to carry prick tests with them even though they are using a CGM device. This same issue is present in every device that mainly measures ISF glucose [5].

Another factor with an effect on CGM devices is acetaminophen, or as it is commonly known, paracetamol. Acetaminophen interferes with the sensors of the CGM devices and produces a false reading, making the glucose value seem higher than it is. BG measurement does not have this issue. It was demonstrated that the variation from the actual body glucose value could be as high as 61 mg/dL or 3.39 mmol/L after two hours of ingesting 1,000 mg of acetaminophen. [38] This can potentially be dangerous, as the patient can think they are suffering from hyperglycaemia and administer extra insulin. As insulin is not actually needed, the risk of hypoglycaemia is increased.

The microneedle patch flash CGM device FreeStyle Libre has been known to cause allergic contact dermatitis [39] as shown in Figure 3. The patient developed the allergy to isobornyl acrylate, which is an ingredient in the adhesive that glues the sensor to the skin. [40] Similar issues have also been reported about the Dexcom G4® Platinium Sensor. In the latter case the allergy was caused by 2-ethyl cyanoacrylate. [41] It has also been regularly reported that these devices often cause mild rash or reddening of the skin even when there is no allergic reaction [3]. This is also often the case with insulin pumps, because they use the same glues to attach.

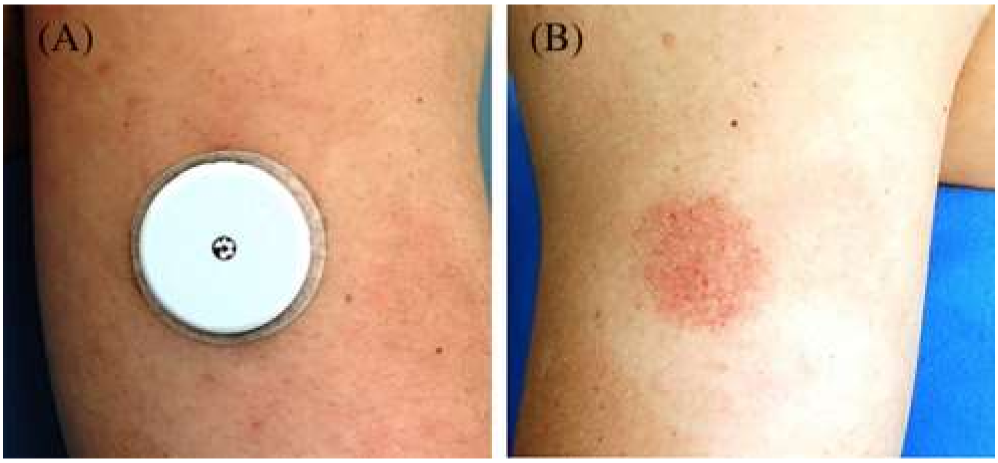

Figure 3. *Chronic eczema on the upper part of the arm where Freestyle Libre was applied [40]*

Rash can be somewhat avoided by switching up the arm or the spot on the stomach on which the device is attached to every time the device needs to be changed.

4. PREDICTIONS FOR THE FUTURE AND RISING TRENDS

4.1 Non-invasive monitoring of blood glucose

As has been demonstrated earlier in this work, even minimally invasive BGM methods have problems. The development of a non-invasive, reliable CGM method has long been a goal of diabetes research, to the point where it is dubbed the “Holy Grail” of research breakthroughs. There are several obstacles on the way, starting from the slower response time of ISF glucose levels. Other problems include unreliable sensors, slow fluid collection time for sweat-based sensors and difficulty of separating the inherent glucose level from saliva in mouth-based sensors [42].

It has been demonstrated that high BG causes blood viscosity (BV) to also be higher. It has been hypothesized that this causes lower transmission of oxygen and nutrients to the extremities, and that BV influences diabetic retinopathy. [43] However, this also allows for an indirect way of measuring blood glucose.

Photoplethysmography (PPG) has long been used to measure blood oxygenation and heart rate. As BG variations change BV, it also changes the PPG pulse profile in a way that can be measured and estimated. A wearable wristband using visible near-infrared spectroscopy was demonstrated to accurately measure subjects’ blood glucose when compared to the values acquired from a traditional prick test. The created model also predicted the behaviour of a subject’s BG for a full day based on 2 hours of data. [42] These kinds of sensors could in the future be integrated into smartwatches or other wearable devices.

Another proposed method of non-invasive BG measurement is the utilization of Raman spectroscopy. Utilising near-infrared laser to cause Raman scattering, it was possible to measure glucose from interstitial fluid. The problems with this method are that BG measurement is difficult due to the penetration depth being low and strong interference. Due to the shallow penetration depth, the measured glucose is mainly ISF glucose. [5]

4.2 Artificial pancreas development

A recognised problem with current diabetes technology is the lack of interoperability. In addition to projects like Nightscout, there is continuous research being performed in the area. Researchers from Harvard University developed an Interoperable Artificial Pancreas System (iAPS) that works through the user's smartphone and that communicates wirelessly with insulin pumps, CGM devices and decision-making algorithms. The user can control the devices through the app, for example for administering a meal bolus, and log events, such as exercise. [44]

The iAPS turns the separate devices into a system that works as an artificial pancreas. It gives out notices, alerts, and alarms for the user in the case of adverse events and according to event severity. For example, a notice might be given for loss of internet connection, an alert for pump insulin running low and an alarm for impending hypoglycaemia. Alarms are also sent as text messages for extra safety. During the study, the researchers placed considerable stress on the system with their test subjects, including heavy restaurant meals, unannounced meals and exercise, and deliberately caused connectivity issues. Despite these imposed challenges, the test patients seemed to spend an improved time in target glucose range. [44]

A 2018 study [45] showed that artificial pancreases improve the time spent in goal glucose range over sensor augmented pumps. The study used Medtronic Minimed 640G pumps, augmented with a smartphone operated control application. 86 people in total from the United States and the UK completed the study. Participants lived their lives normally during the study.

After the 12-week study period, the closed-loop group showed 10 % more time in range than the control group (65 % vs. 54 %). The improvement was seen in all age groups enrolled in the study. Both groups saw an improvement in their HbA_{1c} values, which were significantly lowered during the study period. The reduction was greater in the closed-loop group than in the control group. Closed-loop therapy also significantly reduced the time when BG was under 3.9 mmol/L. The occurrence of hypoglycaemic episodes in both groups was not different. No severe hypoglycaemia was experienced in either group. These results were achieved without increasing the total amount of daily glucose compared to the control group. [45]

In addition to the Minimed 670G described in chapter 3.1, there are many other commercially aimed devices in development. The iLet, developed by Beta Bionics is especially interesting, because it administers glucagon in addition to insulin. This allows for tighter control of BG as the device resembles the natural pancreatic control of BG more closely. Also administering glucagon allows the patient to raise their blood sugar level without needing to consume carbohydrates. [46]

The device requires the user to only input their body weight to being using it. Then it utilises a machine learning algorithm to learn the user's habits and bodily reactions. What is also different from devices such as the MiniMed 670G, the user does not need to enter meal boluses. [47] Meals are instead announced as meal types, for example breakfast, snack or dinner, and the user chooses whether they ate only a little, a normal amount or more than usually. The user does not have to calculate their meals carbohydrate content. [48] These things in combination make the iLet a truly artificial and autonomous pancreas and can possibly lead to great improvement in the patient's life quality.

Several studies have shown the promise of the iLet. The latest published study [48] from 2016 demonstrated that the device performs well in the home setting, and truly initially only requires the patient's body weight. It was demonstrated that the patients time in range improved when compared to the comparator period. All participants completed two 11-day study periods: the actual study period with the iLet and another with their usual treatment.

The device received a Breakthrough Therapy Designation from the FDA in December 2019 [49]. Treatments that receive this designation are seen to be great advances in treatment of serious diseases, and their development and approval is fast-tracked in every possible way [50].

In Table 2 different AP devices and algorithms are compared. The conclusions that can be drawn from here are that the technology has already advanced from the MiniMed 670G. The iLet and the Control-IQ administer correction boluses automatically, and the iLet does not require carbohydrate counting. The starting requirements for the iLet and the Control-IQ are also minimal when compared to the MiniMed 670G.

Table 2. *Comparison of different released and oncoming artificial pancreases*

Device	Beta Bionics iLet	t:slim X2 with Control-IQ	DBLG1 with Kaleido pump	Medtronic MiniMed 670G
Release year	Unreleased	2020	CE marked in 2018, not commercially released	2017
Hormone products	Insulin and glucagon	Insulin	Insulin	Insulin
Automation	Closed loop	Hybrid closed-loop	Hybrid closed-loop	Hybrid closed-loop
Correction boluses	Automated	Automated	-	Manual
Meal boluses	User chooses meal type and amount of food eaten	Manual carbohydrate or insulin dosage input	-	Manual insulin input
Initiation data	Body weight	Body weight, total daily insulin	-	At least 48 hours of continuous usage in manual mode

The validity of artificial pancreases has been shown in many studies and also in action. These devices improve the therapeutic equilibrium and the quality of life of diabetes patients. As more of these devices enter the market, the competition will hopefully lead to new innovations that help the field progress.

5. CONCLUSIONS

The goal of this thesis was to get a general view on the current state of telehealth in diabetes management, and to present future trends and challenges to be solved. As has been demonstrated, the future of diabetes telehealth applications looks bright. This is achieved by ever shrinking and smarter electronics and cheaper data transmission. Nevertheless, the work is far from done. Systems by different vendors do not communicate with each other without hacking, and data transfer is occasionally still done manually. The tightness of the regulation governing high-class medical devices guarantees patient safety, but it comes at the cost of limited connectivity.

It has been shown that the care of diabetes patients in the present day is still dependent on methods that have been in use for decades, such as measuring blood glucose by finger-prick tests and injecting insulin by hand as opposed to automated pumps. Strong support for new solutions continues to be required. Nevertheless, the rapid development in the area during the last decade provides hope for the future.

The Nightscout movement has influenced the diabetes medical community outside of its users too. The popularity of Nightscout apps and devices has shown companies in the field that this kind of service is both wanted and needed, and therefore likely to be profitable. Nowadays Dexcom's CGM devices communicate with a smartphone app and there are projects developing APs that started as attempts of worried parents to improve the life of their diabetic children.

It is likely that interoperability will increase in the coming years. One possible way for this to develop is through mobile applications that communicate with insulin pumps and CGM sensors and with cloud services. For this to happen safely and effectively, strong cybersecurity and laws and regulation concerning interoperability is needed.

In the near future there are several next-generation artificial pancreases entering the market, such as the Beta Bionics iLet and the DBLG1 by Diabeloop. The need for these is recognised on a governmental level, as the iLet has been designated as a Breakthrough Therapy by the FDA. This means that it is possible to fast-track the release of new therapies, if there is a recognised need for it.

The development of new, more effective therapies can have a significant effect on public economy. As has been shown, the treatment of diabetes is vastly expensive, so even small reductions can mean millions in savings. This only has upsides, because the saved costs come from patients being healthier and therefore needing less medical care.

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