Diplomarbeit

Assessment of Infusion Set Survival of a Novel Insulin Infusion Catheter in Type 1 Diabetes by glucose clamp technique (a Pilot Study)

eingereicht von

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Zusammenfassung

Einleitung und Fragestellung

Infusionssets sollten alle 2-3 Tage gewechselt werden um Lipohypertrophie, Schwankungen der Insulinabsorption und Katheter-Okklusionen zu vermeiden. PatientInnen würden allerdings eine längere Tragedauer bevorzugen, sollte dies unter stabiler Insulinzufuhr möglich sein. Der neu entwickelte Infusionskatheter mit Lantern-Technologie gewährleistet eine stabile Insulinabgabe über Schlitze im Kanülenschaft auch im Fall von Katheterokklusion oder Knickbildung. Die gegenwärtige Studie untersuchte die klinische Performance des Lantern-Infusionskatheters bei PatientInnen mit routinemäßiger Verwendung von Insulinpumpentherapie über eine verlängerte Tragedauer von sieben Tagen.

Material und Methoden

Es wurde eine kombinierte Studie bestehend aus Phasen am Forschungszentrum (euglykämische-hyperinsulinämische Glukose-Clamps an Tag 1, 4 und 7) sowie Heimstudienphasen (Insulinpumpentherapie über sieben Tage) durchgeführt, um die Performance und Tragedauer des Lantern-Infusionskatheters zu untersuchen. 16 C-Peptid negative PatientInnen mit Diabetes mellitus Typ 1 (Alter 44,2±15,4 Jahre, BMI 24,5±2,3kg/m2, HbA1c 55±8mmol/mol, Diabetesdauer 20±9 Jahre) absolvierten die 7-tägige Studienphase.

Ergebnisse

Alle Katheter konnten funktionstüchtig in den Probanden belassen werden. Während der Heimstudienphase kam es zu keiner schweren Hypoglykämie oder Ketoazidose. Der Glukose-Zielbereich von 70-180 mg/dl (3,9-10 mmol/l) in 24 Stunden war vergleichbar über die Heimstudienphase (d2: 60,8 ± 15,0 vs. d3: 66,5 ± 18,7 vs. d5: 55,8 ± 21,2 vs. d6: 53,5 ± 25,2%; mean ± SE). Zeit zum Erreichen von 50% der maximalen Glukoseinfusionsrate (GIR) war vergleichbar über die Tragedauer (31,5±1,6 min; 29,3±1,3 min; 27,3±1,3 min; p=0,51). Die Fläche unter der log-transformierten GIR-Kurve war vergleichbar für die ersten beiden Stunden über die Tragedauer (343,7±1,5; 421,3±1,6; 350,6±1,8 mg/kg; p=0,14); es zeigte sich jedoch ein Trend hinsichtlich einer reduzierten GIR-Kurve über acht Stunden (874,2±1,4 vs. 744,5±1,7 vs. 509,2±2,0 mg/kg; p<0,05).

Schlussfolgerungen

Der neue Lantern-Infusionskatheter konnte sicher über eine verlängerte Tragedauer von sieben Tagen verwendet werden. Es zeigte sich ein Trend in Richtung reduzierter Insulinwirkung über die Tragedauer. Die Studie wurde finanziert von ConvaTec.

Abstract

Objective

To evaluate the efficacy and safety of the new coated subcutaneous infusion set with Lantern Technology over seven days of wear and to determine whether the novel cannula design facilitates consistent insulin flow over extended wear time.

Method

16 type 1 diabetes patients (age 44.2±15.4 years, BMI 24.5±2.3 kg/m2, A1C 55±8 mmol/mol, diabetes duration 20±9 years) underwent a 7-day continuous subcutaneous insulin infusion (CSII) treatment combined with flash glucose monitoring (FGM). The patients participated in three 8h euglycemic clamp experiments (study days 1, 4, and 7) and spent the days between the experiments (study days 3, 4, 5, and 6) at home routinely managing diabetes with CSII and FGM.

Result

The catheter survival rate was 100%. There was no incidence of severe hypoglycemia or ketoacidosis during the study period. The percentage of time within the target range (70-180mg/dL) was similar over 24h (d2: 60.8 ± 15.0 vs. d3: 66.5 ± 18.7 vs. d5: 55.8 ± 21.2 vs. d6: 53.5 ± 25.2%; mean ± SE). Time to reach 50% of the maximum glucose infusion rate (GIR) was comparable between clamps (geo. mean 31.5±1.6 [20.0-49.49] vs. 29.3±1.3 [22.3-38.6] vs. 27.3±1.3 [20.4-36.7] min; p=0.51). The log-transformed AUC_{GIR} (area under the curve of GIR) did not significantly differ for the first 2h of the clamp (geo. mean 343.7 [228.6-516.7] vs. 421.3 [271.4-654.1] vs. 350.6 [200.3-613.6] mg/kg; p=0.14). Time to GIR_{MAX} was reduced with increasing wear time (median 137.50 [72.5-147.5] vs. 50.0 [40.0-80.0] vs. 45.0 [35.0-62.5] min; p<0.002). However, there was a reduction in AUC_{GIR} over 8h over time (geo. mean 874.2 [620.0-1232.7] vs. 744.5 [451.4-1228.0] vs. 509.2 [257.2-1008.2]mg/kg; p<0.05).

Conclusion

The coated infusion set with Lantern Technology could be safely used during extended wear. There was a shift of GIR_{MAX} profile towards faster onset and reduced insulin action over time. The findings need to be confirmed in a larger scale trial under routine conditions. The study was funded by ConvaTec.

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Glossary and Abbreviations

A1C	glycated hemoglobin
ACE	angiotensin-converting-enzyme
ADA	American Diabetes Association
AGE	advanced glycosylation endproducts
AUC	area under the curve
BACH2	transcription regulator protein
BG	blood glucose
BMI	body mass index
CD	cluster of differentiation
CRC	clinical research center
CSII	continuous subcutaneous insulin infusion
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTSH	gene that encodes cathepsin H
DAG	diacylglycerol
DCCT	Diabetes Control and Complication Trial
DM	diabetes mellitus
e.g.	exempli gratia
ECG	electrocardiography
EMA	endomysial autoantibodies
etc.	et cetera
FGM	flash glucose monitoring
Fiasp	Faster Insulin Aspart
FPG	fasting plasma glucose
GAD	glutamic-acid decarboxylase
GCP	good clinical practice
GIR	glucose infusion rate
HbA1c	Glykohämoglobin C des Hämoglobin A1
HLA	human leukocyte antigen
IAA	insulin auto antibodies
ICA	islet cell antibodies
IL-2R	interleukin-2 receptor
ISO	International Organization for Standardization

IU	international unit
LADA	latent autoimmune diabetes in adults
LFA-3	lymphocyte functional antigen-3
MAO	monoamine oxidase
MDI	multiple daily injections
MHC	major histocompatibility complex
Na-K-ATPase	sodium-potassium adenosine triphosphatase
NOD mice	non-obese diabetic mice
NPH	neutral protamin hagedorn
PKC	protein kinase C
PRKCQ	gene that encodes protein kinase C theta
PTPN	protein tyrosine phosphatase, non-receptor
SE	standard error
STAT3	signal transducer and activator of transcription 3
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TPO	thyroid peroxidase
TSH	thyroid stimulation hormone
tTG	tissue transglutaminase
WHO	World Health Organization
ZnT8	gene that codes for a zinc transporter related to insulin secretion

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1 Introduction

Diabetes mellitus (DM) is a group of chronic metabolic disorders with elevated blood glucose, which can – if not sufficiently treated – cause late complications over. The consequences are for example damage to blood vessels, to the heart, the nerves and other organs. (1) There are various etiological types of DM. The most common type of DM is diabetes mellitus type 2, also known as type 2 diabetes (T2D), which is associated with insulin resistance and elevated endogenous insulin levels, especially in the beginning. The second most frequent type is diabetes mellitus type 1 also known as insulin production failure or type 1 diabetes (T1D) (2). There is a third type, type 3 which is also named gestational diabetes, and additionally other rare types of diabetes exist. Epidemiologically, T2D is responsible for up to 90% of DM, followed by T1D responsible for five to ten percent. Type 1a diabetes is defined as an autoimmune disease against the beta cells in the pancreas beside the type 1b, where no autoimmune activity can be observed which results in an unknown etiology. Therefore, type 1b is called idiopathic diabetes mellitus. (3) The prevalence of DM has increased dramatically in the last years and will continue to do so according to various prognosis. (4–6)

1.1 Diabetes mellitus

1.1.1 Diabetes mellitus type 1

T1D is caused by the destruction of the pancreatic beta cells. Because those beta cells produce insulin, which is one of the hormones required for glucose hemostasis, over time insulin deficiency increases which results in an absolute insulin deficiency at the end stage and thus requires endogenous insulin substitution to establish normoglycaemia. If insulin is not substituted patients suffer from elevated blood glucose with all its consequences like increased urination, drinking, weight loss, etc. Additionally, diabetic ketoacidosis can occur in initial manifestations and in those cases the insulin deficiency leads to hyperglycemia and lipolysis. The hyperglycemia itself leads to hyperosmolarity with intracellular dehydration and diuresis (= extracellular dehydration). Through the lipolysis ketosis is stimulated and leads to a metabolic acidosis with Kussmaul breathing and smelling of aceton. If not treated, the hypovolemia and the metabolic acidosis could lead to death. (3, 7)

1.1.2 Latent autoimmune diabetes in adults (LADA)

LADA, also known as **l**ate onset **a**utoimmune **d**iabetes in **a**dults, is an apparent T2D in the beginning with an increasing insulin dependency over time because of autoantibodies directed against pancreatic beta cells antigens (e.g. ICA = islet cell antibodies and GAD65 = glutamic-acid decarboxylase isotope 65) or other antigens (for e.g. insulin IAA = insulin auto antibodies). LADA seems to be an in-between type of T1D and T2D. Patients with LADA are heterogeneous group with variable titers of antibodies, body mass index and even in the progression to the insulin dependence. (7, 8)

1.1.3 Diabetes mellitus type 2

T2D is the most common type of diabetes and causes about 90% of diabetes cases. T2D is caused by insulin resistance, which means that patients have sufficient or even elevated insulin levels, but due to down regulation of insulin receptors endogenous insulin cannot sufficiently shift blood glucose into the cells. In extreme cases a hyperglycemic hyperosmolar coma with severe hypovolemia can occur. Additionally, if beta cells are destroyed even a ketoacidosis can be observed because of insulin deficiency. Obesity is directly correlated to the prevalence of T2D, but it is not the only etiological factor. Genetic factors and environmental factors play a decisive role in initializing the pathophysiology of insulin resistance. Furthermore, hyperglycemia itself can induce insulin resistance. (7)

1.1.4 Gestational diabetes mellitus

Gestational diabetes occurs when the insulin secretion for mother and fetus is insufficient. On the one hand, this is caused on a higher insulin consumption and on the other hand a higher insulin resistance that is induced by anti-insulin hormones (e.g. estrogens, prolactin, cortisol, human chorionic somatomammotropin, etc.). The prevalence differs worldwide due to different diagnostic criteria and different ethnic groups but goes parallel to the percentage of T2D. The disease is a risk factor for T2D, cardiovascular disease in long term and a higher risk in fetal complications such as preeclampsia, macrosomia, fetal organomegaly, hydramnios etc. (3, 9)

1.2 Pathogenesis of diabetes mellitus type 1

The process of pathogenesis of T1D is a chronic process which usually takes over months or even years inside the patient without any symptomatic onset of hyperglycemia. Such hyperglycemic events occur at a point in time where already more than half of the beta cells are damaged seen in Figure 1.

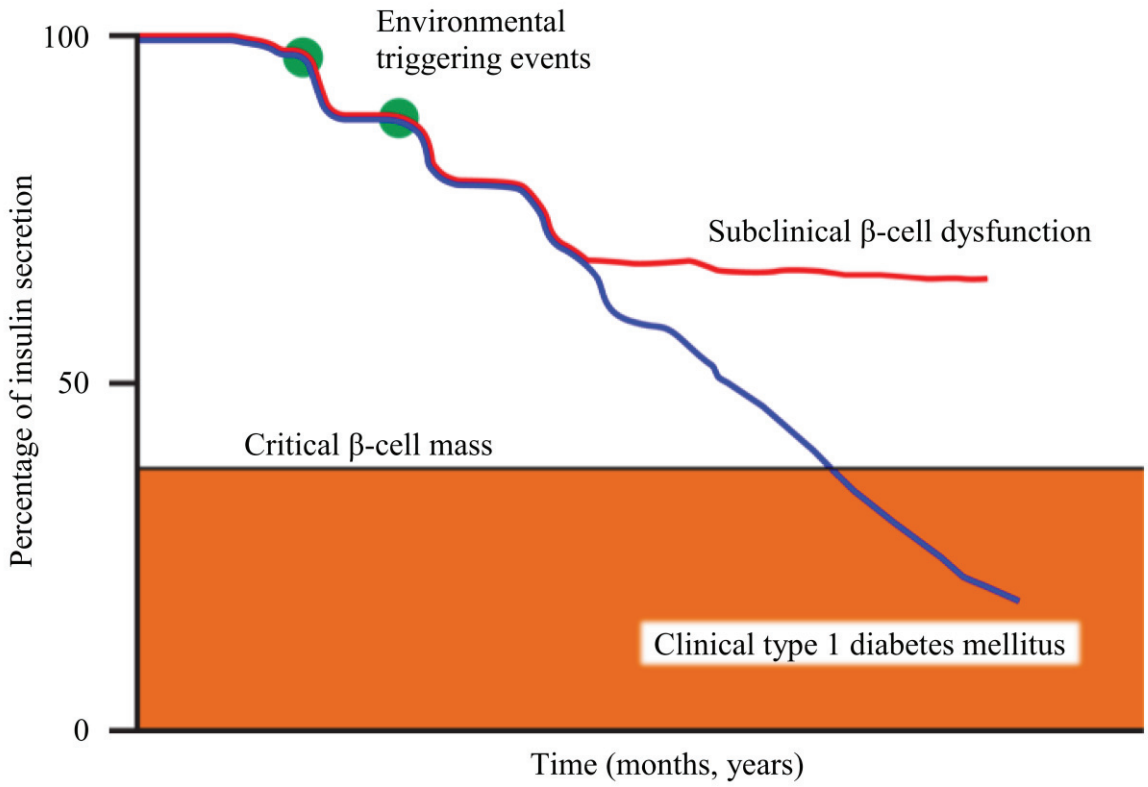

Figure 1: Progress of type 1 diabetes mellitus (10)

Given that the pathogenesis of T1D is only known for subtype 1a, solely this type will be described in greater detail. For subtype 1a an autoimmune process is responsible for performing the damage to the beta cells in the pancreas which is induced by genetical predisposition and environmental factors. Genetic factors can be observed from birth on, immune markers from the onset of the autoimmune process and metabolic markers can be detected even before the onset of hyperglycemia. Clinical symptoms can only be observed after the majority of insulin-producing beta cells are damaged. This shows that there is a chance to find the illness or the risk for T1D even before any obvious clinical symptoms are indicated. Even though T1D is named like T2D the pathophysiology is quite different and for e.g. there is no genetic overlapping between those two. (10)

1.2.1 Genetic susceptibility

Multiple genes (PTPN22, CTLA-4, BACH2, PRKCQ, CTSH, etc.) and various polymorphisms (HLA-DQalpha, HLA-DQbeta, HLA-DR, etc.) relate to the risk of diabetes mellitus type 1a. The greatest effect of multiple genes and various polymorphisms has human leucocyte antigen (HLA) followed by insulin gene polymorphism and PTPNN2. The lifelong risk for T1D is increased for relatives. Six percent in offspring, five percent in siblings, and 50 percent for homozygote twins suffer from T1D compared to the risk of 0.4 percent for people without a family history of diabetes. (10, 11)

1.2.1.1 MHC genes

In the HLA region on chromosome 6p genes for the expression of MHC II can be found. They are responsible for antigen-representing on cell surface of antigen-representing cells for e.g. on macrophages. T cells, recognizing the antigen through MHC II, have the main effect in the destructive autoimmune process (Figure 2).

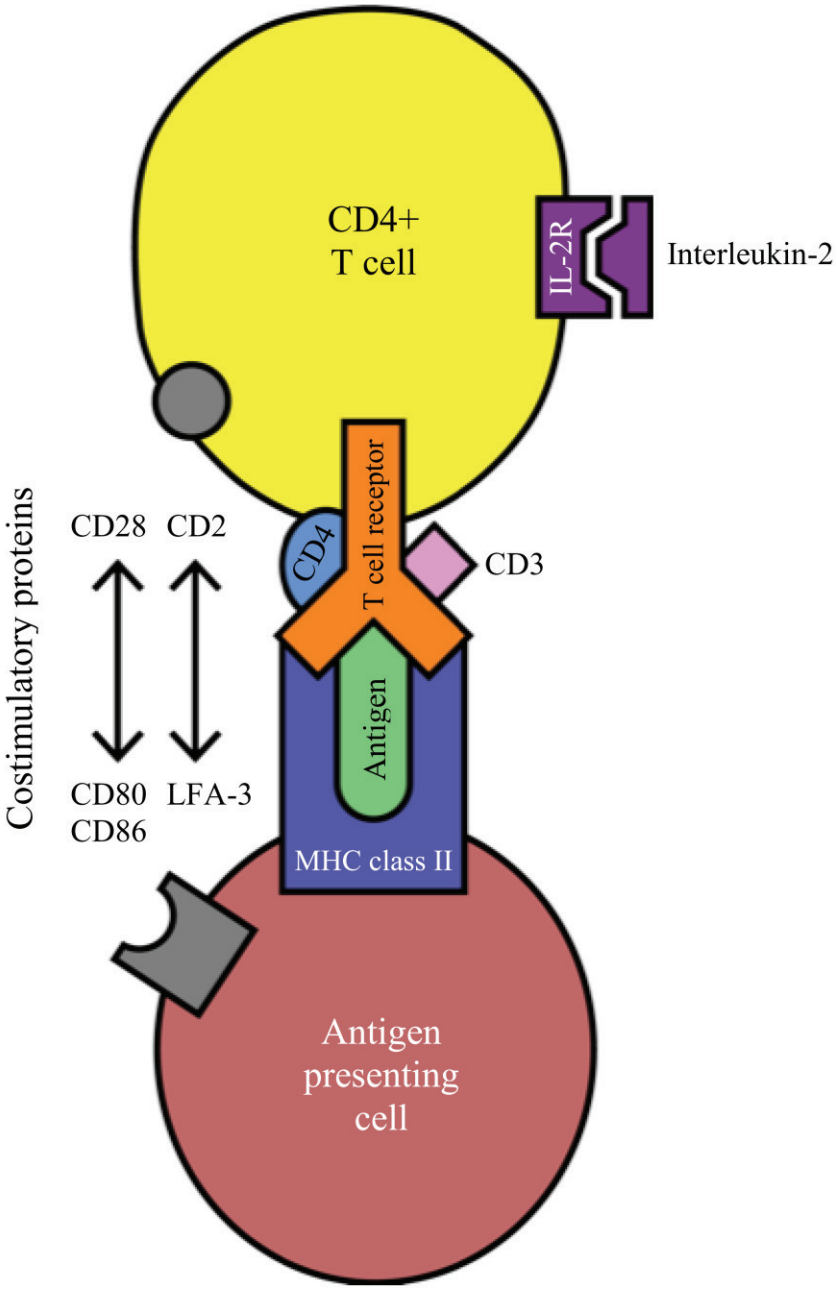

Figure 2: T cell activation (10)

Because MHC II structures are built upon an alpha and beta chain the susceptibility for T1D depends on those definitive setups which again rely on the HLA polymorphism of each person. The two most important HLA types for T1D are HLA-DR3, DBQ1*0201 (=DR3-DQ2) and HLA-DR4, DBQ1*0302 (=DR4-DQ8). In 90% of patients diagnosed with T1D, one of those two HLA types can be found. For instance, there is also an HLA allele DQB1*0602 which can reduce the risk of falling ill with T1D. (10, 12–14)

1.2.1.2 NON-MHC genes

The polymorphism of a promotor of the insulin gene is a risk factor in several populations. There is also a higher risk in one form of the protein tyrosine phosphatase in lymphocytes (PTPN22) which influences the T cell receptor signaling and is a risk factor for many autoimmune diseases. One other gene is known to be associated with T1D like a polymorphism of the cytotoxic T-lymphocyte-associated antigen-4 gene. It is important to mention that monogenetic reasons for T1D exist as well such as the mutation in the STAT3 gene, which is also accountable for many other autoimmune diseases. (10, 15–20)

1.2.2 Autoimmunity

The autoimmunity for T1D can be segmented within the humeral immune system into autoantibodies and autoantigens. Autoantibodies were found which are directed against the islet cells called ICAs that can be seen in 85 percent of patients at the time of diagnoses of T1D. (10, 21)

In the early stages of diabetes mellitus type 1a there is a phase called “epitope spreading” where autoantigens are increasing and a response through autoantibodies leads to progredience. There is also a theory that autoantibodies are not only directed to the islet cells itself but are directed to parts of the nervous system too. (10, 22, 23)

Autoantigens are primary proinsulin and insulin itself which was shown in the NOD mice model. In the NOD mice model diabetes can also be healed by changing a specific amino acid in insulin. Other important autoantigens have been found such as GAD, insulinoma-associated protein 2 (IA-2 and IA-2 beta) and the zinc transporter ZnT8. (10, 24)

1.2.2.1 Association with other autoimmune disease

T1D is associated with other autoimmune diseases, especially subjects having the genotype HLA-DR3. The most common diseases are autoimmune thyroiditis and celiac disease which will be mentioned shortly in the following paragraphs.

Autoimmune thyroiditis is found in up to 20 percent of patients with T1D but only two to five percent are hypothyroid. Girls and a later onset of T1D have a higher risk for

autoimmune thyroiditis and in case of subclinical hypothyroidism the risk for hypoglycemia symptoms is increased. TSH (thyroid stimulation hormone) is used for screening tests and if normal the screening should be repeated every one to two years and in special cases when abnormal thyroid function is assumed. The American Diabetes Association (ADA) recommends measuring TPO (thyroid peroxidase) antibodies and thyroglobulin at diagnosis. (10, 25–32)

The prevalence of celiac diseases in patients with T1D is about five percent with biopsy diagnosis. Up to ten percent have antiendomysial antibodies or transglutaminase antibodies. The risk for celiac disease increases in females, in patients with an earlier onset of diabetes or patients with an already present thyroid disease. Screening in newly diagnosed T1D patients is recommended by measuring tissue transglutaminase antibodies (tTG) and to run an assay for endomysial autoantibodies (EMA). To make sure there is no IgA insufficiency, because this could influence the test results, IgA quantity should be measured too. In case of a positive screening result, the test should be confirmed by a small bowel biopsy and in case of a positive histological result a gluten free diet should be started. Adherent patients profit from having less gastrointestinal symptoms, less severe episodes of hypoglycemia and less insulin requirement over time. A negative screening result is followed by a rescreening after two years and then after another five years. (25, 28, 32–38)

1.2.3 Environmental factors

One determinant in the pathophysiology in autoimmune diabetes are environmental factors. The fact that in some populations the incidence of T1D is increasing so fast shows the impact of environmental factors. (10, 39, 40)

Several different etiological factors like perinatal factors, viruses, diet are discussed to affect the incidence of T1D. Two of them will be explained shortly:

1.2.3.1 Perinatal factors

A study in Europe evaluated the perinatal risk factors in a research project with more than 300 children. The results showed an increased risk for older maternal age, maternal preeclampsia, neonatal respiratory disease, and jaundice caused on incompatible blood groups. An decreased risk could be found in firstborn children, children with low birthweight and in children with a short birth length. (10, 41)

1.2.3.2 Diet

There are divergent results in different studies according to the influence of cow's milk in diet. Studies who confirm an association between the consumption of cow's milk or beta casein (a specific protein in cow's milk) are based on epidemiological data or studies and where rolled out in up to ten different countries. They suppose an increased risk for T1D based on milk consumption in childhood. A higher T cell mediated immune response through proliferation after exposure to beta casein was found from a group in Rome. However, there are other prospective studies finding no evidence for an association between breast feeding and cow's milk for higher autoimmunity risk causing DM. (10, 42–47)

The supplementation of vitamin D seems to be protective according to a birth-cohort study published in 2001 after a case-controlled study had assumed a positive effect of vitamin D. In the birth-cohort study children with a regular daily supplementation of 2000IU had a decreased risk for T1D. (42, 48, 49)

1.3 Complications in patients with Diabetes mellitus type 1

Complications caused by T1D can be divided into two main groups: acute complications and chronic complications.

1.3.1 Acute glycemic complications

Hypo- and hyperglycemia are the acute complications of T1D. Hypoglycemia in healthy patients is prevented through counterregulatory hormones such as glucagon, epinephrine, cortisol and growth hormone. In T1D in contrast counterregulation can be reduced by an inappropriately low response of the pancreas through glucagon or other counterregulatory hormone responses. The response of such hormones gets blunted over time in T1D patients because of recent antecedent hypoglycemia. Therefore, recurrent existing of such hypoglycemic episodes leads to higher risk for hypoglycemia as there is a growing lack of possibilities to reregulate. (50–55)

Due to the lack of endogenous production of insulin hyperglycemia is obviously an acute glycemic complication which further implies ketoacidosis throughout time and ongoing impairment. Hypoglycemia and diabetic ketoacidosis can lead to neurological symptoms and if not treated to death. For prevention blood glucose should be measured regularly or continuous glucose monitoring systems should be used. (53, 56)

1.3.2 Chronic microvascular complications

The mechanism for vascular effects in T1D is not completely understood. For example, increased diacylglycerol and protein kinase C effect the endothelial permeability and the contractility in the vascular muscles (Figure 3). Higher activity of the aldose reductase leads to higher sorbitol. Then again, organ specific effects can be seen for instance in glomerular hypertension caused on high glycemic levels through a pathway. Duration of the T1D, glycemic control, genetics, gender and other factors like lifestyle influence the progression of vascular diseases. (53, 57, 58)

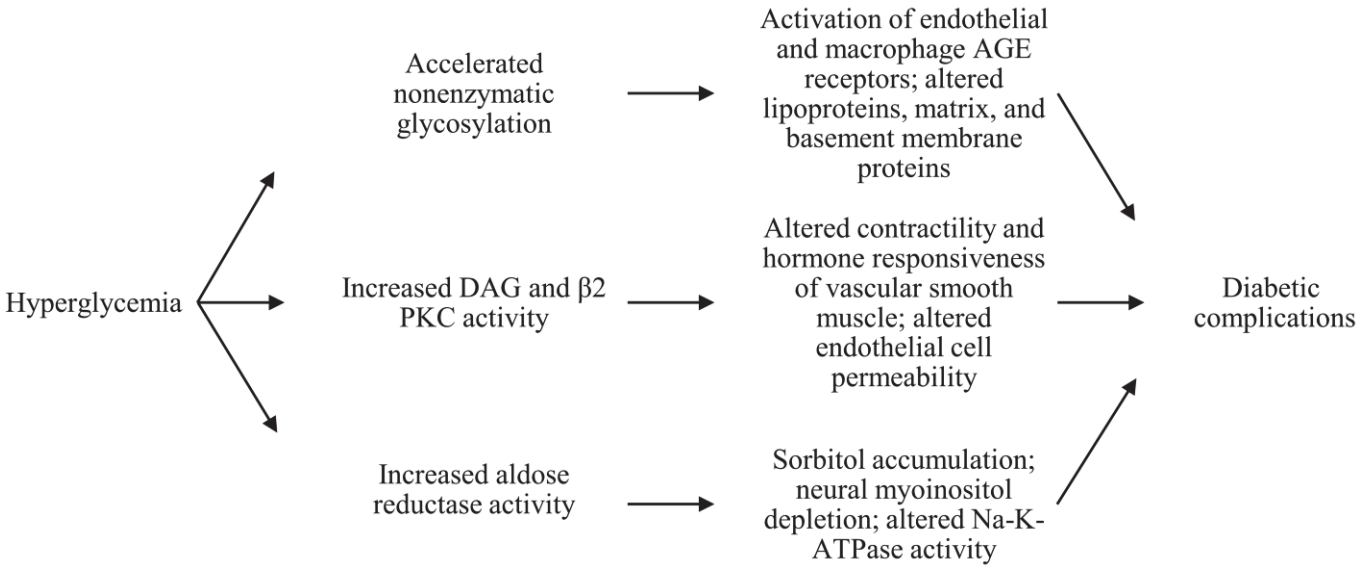

Figure 3: Vascular complications induced by hyperglycemia (57)

Diseases caused on microvascular complications with T1D increase rapidly over approximately 12% glycated hemoglobin and can be seen especially in nephropathy, retinopathy, neuropathy et cetera. Nephropathies earliest sign is microalbuminuria which can be seen in about 25 percent of patients with T1D after about 10 years and in about 50 percent of patients after about 20 years. Microalbuminuria correlates with the duration of diabetes and with glycemic control. The fact that 60 percent of patients in a cohort study with T1D ended up in end-stage renal disease after 50 years shows the importance of prevention for example by ACE inhibitors. (32, 53, 59–63)

Retinopathy can also be decreased through an intensive therapy from 54 percent to 12 percent after nine years. It can even be stopped from progression through DM if glycated hemoglobin is under seven percent in primary prevention. The effect of intensive therapy decreases with progression of retinopathy and is lost for advanced retinopathy. Only after about two years the first effect on intensive therapy can be seen. (57, 64–66)
Similar positive effects can also be viewed in neuropathologic clinical incidence reduction of 64 under intensive insulin therapy. There is also a decrease of abnormal nerve conduction of 44 percent and 53 percent of autonomic dysfunctions. (57, 67–69)
The results above emphasize the importance of glycemic control and as a consequence thereof a good glycated hemoglobin value. (57, 70)

1.4 Diagnosis of diabetes mellitus type 1

Diagnostic criteria for DM have been established - among other societies - by the ADA in 1997 and was updated in 2003 and 2010. These criteria include symptoms of diabetes and different chemical values like fasting plasma glucose (FPG), two hour plasma glucose values and A1C values.
Patients suffering from symptoms of diabetes such as thirst, polydipsia, polyuria, weight loss or blurry vision only require one additional random plasma glucose value to establish diagnosis of DM. Patients without symptoms require at least two different pathological values to establish diagnosis of DM. These values can be measured at the same time with two different methods or can be repeated on a subsequent day. Therefore, these three different values can be measured for diagnosis:

- Fasting plasma glucose: should be ≥ 126 mg/dl (≥7.0 mmol/l) for diagnosis
- 2 hours after oral glucose tolerance test: should be ≥ 200 mg/dl (≥11.1 mmol/l) for diagnosis
- A1C blood value: should be ≥ 6.5 % (≥ 48 mmol/l) for diagnosis

If there are two or more parameter measured and the interpretation is inconsistent because only one parameter exceeds the diagnostic cut off, the measurement should be repeated for the parameter above the cut off. These cut off values have been developed based on the incidence of retinopathy. The importance for a second evaluation on a subsequent day especially for measured plasma glucose values was found in a study where the prevalence significantly decreased about 24% if there was a second examination. The use of A1C (= glycated hemoglobin) to establish diagnosis was not recommended in the past but can be used nowadays because A1C assays got standardized. (7, 71–73)

After diagnosis of DM, it is necessary to distinguish between the types of diabetes through laboratory parameters to establish the diagnosis of T1D. Most importantly the insulin c-peptide needs to be measured. A degraded c-peptide value or even no measured c-peptide is necessary for diagnosis of T1D. To subclassify T1D autoantibodies like GAD65-autoantibodies, IA-2- autoantibodies, ICA, IAA, ZnT8 are measured and if detectable autoimmunity exists the subtype diabetes mellitus type 1a can be diagnosed. If only c-peptide is degraded the idiopathic diabetes mellitus type 1b will be diagnosed. (74)

1.5 Treatment of diabetes mellitus type 1

Intensive diabetes therapy is the standard therapy for T1D since the Diabetes Control and Complication Trial (DCCT) showed several benefits of this treatment. The target of this therapy is to achieve good glycemic control represented by a glycated hemoglobin value under 7% (53 mmol/l). The target could also be modified to higher levels in older patients, patients with short life expectancy or if there are other side effect caused on the intensive insulin therapy (especially hypoglycemia). For some motivated patients also <6% (<42 mmol/l) glycated hemoglobin could be a realistic target. (75, 76)

For optimal therapy a profound knowledge of the patients own condition is necessary and needs aligned training and education. Without the patient's commitment it is not possible to optimize therapy especially in the two key points beside insulin therapy: nutrition and exercise. The most crucial factor in nutrition consists of estimating the carbohydrates either in every intake or in every meal the patient takes. Additionally, the patient should know how much insulin he/she will need for a specific number of carbohydrates. And even then, the same meal can make a difference from one patient to the other for calculating the dose of insulin. Beside nutrition, exercise is important to reduce blood glucose levels too, especially because gaining weight is one risk factor in intensive diabetes therapy. To aim towards high compliance the activity should be enjoyable and the barriers for exercise should be eliminated or decreased. The blood glucose level could be affected in both ways, resulting potentially in hypo- or hyperglycemia, depending on day and time and the blood glucose baseline level before exercise. Because muscles glycogen stores are filled up even a few hours after exercise the blood glucose homeostasis can be affected through this time which affects the necessity for insulin. (75)

Insulin therapy aims to mimic the physiological insulin secretion by either mimicking physiology through a long acting insulin and a short acting insulin or by using an insulin pump with administration of basal rate and bolus insulin. The long acting insulin is supposed to cover the basal requirements and the short acting insulin to cover the blood

glucose excursions occurring because of meals, stress and other underlying physiologic processes. The meal-time insulin dose depends on the blood glucose level prior to meal, the carbohydrate content, the insulin sensitivity factor and the anticipated level of activity post meal. Stringent glycemic control however is associated with a threefold increased risk of hypoglycemia (77). (64, 75, 76, 78)

Stringent glycemic control, however, is associated with a threefold increased risk of hypoglycemia. To avoid this, patients need greater effort to adjust therapy. Without precise insulin administration erroneous insulin could easily be administered. To avoid hypoglycemia in case of insulin overdose patients need to counteract by carbohydrate intake that subsequently causes weight gain over time. Fear of hypoglycemia can also reduce patients' compliance and result in hyperglycemia and its late complications over time. Nevertheless, intensive diabetes therapy is recommended to most of patients because advantages outweigh the disadvantages. (64, 75, 77)

1.5.1 Blood glucose monitoring

For establishment of good glycemic control self- monitoring of (blood) glucose is recommended and should be performed four to seven times per day. Relevant time-points include measurements before meals and at bedtime, in-between if deemed necessary (e.g. when doing sports) and occasionally at 03:00 in the morning. Until recently determination of capillary blood glucose using a blood glucose meter has been state of the art. Continuous glucose monitoring (CGM) which measures glucose levels in interstitial fluid is used more frequently now. As a lot of CGM devices still need calibration through regularly capillary blood glucose measurements fingerstick measurement is still needed, but will probably lose importance for regular measurement in future. (64, 75, 76, 78)

Blood glucose can be measured through a blood sample or in the interstitial fluid. Patients with potential hypoglycemic episodes who receive blood glucose decreasing medication such as insulin, should be able to measure and interpret their blood glucose values on their own (79).

Frequent glucose monitoring is needed for every patient with T1D. For optimized glycemic control not only individual commitment and compliance of the patient is required but also the glucose measuring system must be reliable. To assess reliability and enable comparability of different CGM systems the International Organization for Standardization developed and adopted standards. According to ISO 15197:2013 measurements of glucose levels need to be within ±15 mg/dl for glucose values <100 mg/dl and ±15% for glucose values ≥100 mg/dl in 95% of all measurements. For consensus error grid 99% of

measurements need to be found in clinical acceptable zones A and B. In a recent study of Moser et al. 2018 the hypoglycemic range is still the bottle neck of accuracy with regard to sensor performance. (79–88)

CGM enables patients who are well trained in its use to optimize glycemic control whilst also reducing time in hypo- and hyperglycemia. The patients need to understand the principle of CGM and should be well educated and familiar with intensive insulin treatment. Additionally, the patient needs to use the CGM device frequently, not only occasionally. Additional fingerstick measurements might need to be performed for calibrating the CGM device (depending on the type of system). Insulin dose adjustment is needed for optimization of the insulin treatment to avoid hypo- and hyperglycemic episodes. Factors that can reduce glycated hemoglobin are good coping skills, adequate usage and analyzation of information-responders and involvement, participation, interest and encouragement of loved ones like partners. The recommendation for patient selection of the Endocrine Society Guidelines also include an A1C level under seven percent and a reliable daily use of the measurement device. Patients who are at higher risk of severe hypoglycemia for example people suffering from hypoglycemic unawareness profit most from CGM devices. (79, 89–94)

In Europe there are currently systems from three manufacturers on the market. Those devices measure the interstitial glucose with an electrochemical sensor which nearly correlates with the blood glucose level. Because of different perfusion resulting in a slower change of interstitial glucose level those systems are limited by rapid blood glucose changes. Further, the accuracy is lower than blood glucose fingerstick measurements, especially in hypoglycemic ranges. Patients who use medication that contains acetaminophen show, depending on the dose, erroneous glucose measurements (depending on the device). As costs for CGM devices are significantly higher than costs of capillary glucose monitoring they should be used in suitable candidates only to avoid increased cost for insurance companies. (79, 95–98)

1.5.2 Insulin Management

For insulin therapy there are basically two possible ways of insulin administration. Firstly, multiple daily insulin injections (MDI) and secondly insulin pumps can be used for continuous subcutaneous insulin infusion (CSII). Hypoglycemic phases can be seen in both therapies. Glycemic control can be handled easier and better under CSII therapy. The advantages and drawbacks need to be considered and a consent needs to be found between the physician and the patient for the appropriate type of therapy. In both categories two ways of insulin requirement coverage is planned: the basal insulin rate and bolus insulin. Basal insulin is used to cover the basal need of insulin over the day and is administered in MDI therapy usually twice a day with long acting insulin and in CSII therapy through a catheter which continuously operates with short acting insulin. The bolus insulin is applicated in MDI therapy for each meal with short acting insulin like in CSII therapy too. (64, 75, 99–103)

1.5.2.1 Types of insulin

Types of insulin could be separated according to the pharmacokinetic characteristics in fast-acting, short-acting, intermediate-acting, long-acting and ultralong-acting insulins. Another available type of insulin is premixed insulin which is mixed by the manufacturer and consists out of two categories mentioned above. One disadvantage in therapy using premixed insulins is less flexibility in dosage. (75, 104–106)

1.5.2.1.1 Short-acting insulin

Short acting insulin, also known as **regular insulin**, can be used like rapid acting insulin analogues but has also a longer effect up to twelve hours and through this it covers also partly the basal insulin need. The onset is only after 30 minutes to one hour and the peak, the time with the most effect of insulin, is about two to five hours. (75, 104–107)

1.5.2.1.2 Fast-acting insulin

Fast-acting insulin, or rapid-acting insulin, are used to cover insulin peaks which originate from meals. The onset is about ten to thirty minutes after dosing and has a peak after thirty minutes to three hours. The effect stops after about five hours. Examples for such insulins are lispro, aspart or glulisine. (75, 104–106)

The first ultra-rapid acting insulin analogue Fiasp (Faster Insulin Aspart) with an onset under five minutes has shown a greater reduction in hemoglobin A1C and could be administrated immediately prior to a meal or within 20 min following a meal. (108)

1.5.2.1.3 Intermediate-acting insulin

The onset of **intermediate acting insulin** is after about 1.5 hours to four hours and the peak after about four to twelve hours. The name for intermediate acting insulin is **n**eutral **p**rotamin **h**agedorn (NPH), which refers to the neutral pH, the protein protamin and to the inventor Hans Christian Hagedorn who created NPH for the first time in 1936. Because of the only intermediate duration of action of NPH insulin it needs to be administered twice a day to cover basal insulin requirements. (75, 104–106, 109)

1.5.2.1.4 Long-acting insulin

The sustained effect of **long acting insulin analogues** continues for up to 24 hours and onset of action is 0.8 to four hours after injection with only a minimal peak. Insulin detemir (Levemir®) and insulin glargine (Lantus®) can be used twice a day to cover the basal insulin need.

1.5.2.1.5 Ultra-long acting insulin

Insulin degludec is an **ultra-long acting insulin** and has special benefits for hypoglycemic episodes and overnight hypoglycemia although it only must be administered only once a day ± 3hours depending on the injection time of the prior day. Due to ultra-long action time way above 24 hours and missing peaks the action of insulin is stable and hypoglycemic events, especially overnight, occur less frequently. (75, 104–106)

1.5.2.1.6 Premixed insulins

Premixed insulins contain a fast- or short- and a long-acting insulin or insulin analog. NovoMix® 30 or Humalog® Mix 25 are examples for premixed insulins. The number shows the percentage of fast acting insulin. The residual percentage for 100 percent is a long acting insulin analog, typically NPH insulin. (110)

1.5.2.2 Multiple daily insulin injections

MDI therapy is built upon two types of insulins. The basal insulin requirements are covered by long acting insulin which are administered once or twice daily. If there is one application per day the time of application can be chosen by the patient. In most cases evening or morning are chosen though. Patients requiring two injections per day normally administer their insulin at breakfast and at bedtime. To cover peaks of the glucose level, boluses of fast acting insulin are administered. Due to a high need of insulin action after meal consumption fast acting insulins are administered immediately before the meal. (75, 107, 111–113)

1.5.2.3 Continuous subcutaneous insulin infusion - CSII

CSII is a way of insulin treatment over 24 hours on seven days a week with rapid- or short-acting insulin through an insulin pump which is connected to the patient. This is possible because a continuous administration of insulin can cover the basal insulin need and administered boluses before meals cover the peaks of blood glucose levels that can for example occur after intake of carbohydrates. For this treatment, preferably rapid acting insulin or ultra-rapid acting insulin is used because it is easier to keep track of the glycemic control. (75, 114)

Adjusting the initial CSII therapy of a patient who has been under MDI therapy before, the value of glycated hemoglobin is crucial for the first therapeutic proposal. Patients having an A1C level under seven percent need to be treated with a different total daily dose of about 90 percent of the previous MDI dose. Patients over seven percent A1C need about the same total daily dose as in their previous MDI regime. Because the needed basal rate differs from daytime to daytime and patient to patient it is important to adjust the basal insulin flow after the initial setting. As a result of the dawn phenomena during early morning hours it is necessary to increase the basal rate in these hours. Measuring during the night is terribly inconvenient which is why continuous glucose monitoring should be considered. If blood glucose levels are to adjust at time x because of a higher need of basal insulin rate, a delay of insulin administration for this time x should be contemplated. To reach a steady state at time x the basal rate of insulin infusion must be adjusted about three hours before time x. To estimate a typical need of basal insulin doses one could reckon with 0.01 IU per kg bodyweight per hour which can gain up to about 150 percent of it. For boluses administered before meal time the size of the meal containing a special amount of carbohydrates and the measured blood glucose just at that time influence the calculated bolus size. For precise calculation every patient has different calculation factors because the insulin sensitivity varies from patient to patient. (75, 115)

Advantages in CSII therapy are numerous and different from patient to patient. Especially children profit from the use of a CSII therapy without the need of hurting multiple daily insulin injections. Probably that is the main reason for increased CSII treatment among children. Studies showed an increasing number of patients with normal A1C value under continuous subcutaneous insulin infusion compared to the same patients who previously had MDI therapy. Simply said a lower A1C value could be achieved more easily under CSII therapy than under MDI therapy. In other studies, decreased nocturnal hypoglycemia could be observed. The therapy also enables a more flexible way of living due to meals in

two ways. Firstly, the basal rate of the pump therapy covers the basal need of insulin and is individually adjustable at every daytime according to the patient. Compared for example to the NPH therapy the peak time of the basal insulin could cause hypoglycemia. In NPH therapy, if administered in the morning, a meal at lunchtime is necessary but not in CSII therapy where it is possible to postpone lunch or even leave it out. Secondly the amount of dosing plays a key role for intensive therapy to achieve a low glucose value but not falling into hypoglycemia. Under CSII therapy it is possible to administer small precise amounts of insulin down to 0.05 units compared to at least 1 unit in MDI therapy. Thirdly, insulin absorption is more constant in CSII therapy than in MDI therapy due to the same location of administration within the time the same catheter is located and the small subcutaneous depot. (75, 116–120)

Sensor-augmented insulin pumps increase the benefits of bearing an CSII device because of a digital connection to the sensor device. This offers newly available functions like the threshold-suspend feature. With the feasibility to know the glycemic blood level at any time the pump can improve the release of the insulin to the body. The threshold-suspend feature offers the option to stop subcutaneous insulin delivery automatically for up to two hours if the measured sensor decreases below a specific configured threshold value. Studies, comparing the sensor-augmented insulin pump system to standard insulin pump systems with (no threshold-suspend feature) or without an additional continuous glucose monitoring system, showed a significant improvement for (nocturnal) hypoglycemia in sensor-augmented insulin pump systems. One of the studies compared two sensor-augmented insulin pumps with or without the threshold-suspend feature in 247 patients and showed a decrease of 31.8 percent of nocturnal hypoglycemic incidence by simultaneously no incident of ketoacidosis during study time. There was also no incident of ketoacidosis recorded in the control group that had no threshold-suspend feature. Another study compared the sensor-augmented insulin pump including the threshold-suspend feature to a standard insulin pump therapy without CGM sensor in patients with impaired awareness of hypoglycemia. In the sensor-augmented insulin pump group a 3.6 times lower incidence in hypoglycemic events could be observed. (75, 121, 122)

The latest technology for insulin pumps is automated closed loop pumps which perform the time in normoglycemic range for about ten percent and even more during nighttime. It is essential to distinguish between two systems: the bihormonal closed-loop system and the insulin-only hybrid closed loop system. The bihormonal closed-loop system works with two pumps, an insulin pump and an additional glucagon pump. Input of current blood

glucose levels are provided by CGM devices which are digitally connected to the pumps. Trails showed a benefit in bearing a bihormonal closed-loop system of 140.4 mg/dl (7.8 mmol/l) mean glucose compared with 162 mg/dl (9 mmol/l) conventional pump therapy in 43 adults due to eleven days of wear time each. Hypoglycemic incidence under 60 mg/dl (3.3 mmol/l) was also performed down to about a third of time. Another study with five days of wear time at a diabetes camp showed comparable results with 142 mg/dl (7.9 mmol/l) mean glucose level compared to 158 mg/dl (8.8 mmol/l) and hypoglycemic episodes under 60 mg/dl (3.3 mmol/l) occurred about 1.7 times rarer. Insulin-only hybrid closed loop systems are not fully automated and are therefore called partially automated-insulin closed-loop systems. Those systems consist only of a commercial pump and a CGM device connected to each other and are not fully automated because an intake of carbohydrates needs to be entered into the system and the following insulin bolus suggestion needs to be confirmed by the patient. A crossover random-order study comparing the hybrid insulin closed-loop system with a sensor-augmented pump therapy showed benefits in the hybrid system. The crossover study was performed for twelve weeks twice during normal daily life and without monitoring by the study-staff and showed an eleven percent increase of normoglycemic time between 70-180 mg/dl (3.9-10 mmol/l) in 33 adults during day and night. 25 children that were only observed during nighttime in the same study had an increase of 24.7 percent in normoglycemic time between 70 to 145 mg/dl (3.9-8 mmol/l). Therefore, also the mean glucose level reached 157 mg/dl (8.7 mmol/l) versus 168 mg/dl (9.3 mmol/l) in adults during 24 hours per day and 146 mg/dl (8.1 mmol/l) versus 176 mg/dl (9.8 mmol/l) in children over the nighttime. Additional hypoglycemic time was lower under hybrid insulin closed-loop therapy than under sensor-augmented pump therapy. Although this data is clearly showing the benefits of such systems, there is currently no closed-loop pump available on the European market. (75, 123–129)

There are at least three disadvantages involving pump therapy. Firstly, the costs need to be mentioned which are higher compared to the MDI therapy. A second disadvantage of having an insulin pump connected 24/7 to the body is that it disturbs patients when sleeping, having sexual intercourse etc. although it is possible to disconnect the pump for up to one hour without loss of blood glucose control. Some patients like to disconnect the pump for specific activities where it disturbs for example specific sports or also for special occasions over a few days. If the pump is disconnected more than one hour a bolus should be administered to cover the basal rate over this time. The dose for this “off pump” period

can go up to about two times of the basal rate, but it may also be needed to add some carbohydrate intake although no bolus for basal insulin is administered depending on the length and activities. Another very important disadvantage are some complications which can occur due to insulin delivery failure through the pump. This can be a leakage in the cable or proximal part of the catheter or more often a blockage in the cable, connections and especially the catheter. Such a delivery failure can easily trigger a hypoinsulinemia which causes a hyperglycemia which again could lead to diabetic ketoacidosis with all the possible complications. These symptoms can manifest faster if (ultra-) rapid acting insulin is used instead of regular insulin. Complications can also occur because of local inflammatory reactions around the administration area. (75, 130–133)

1.6 Infusion sets in CSII therapy

Insulin pumps where first invented in 1963 by Dr. Arnold Kadish for first CSII therapy. The pump was as big as a marine backpack and the first commercial pump was the so called “Big Blue Brick”. In the 1990s progress in medical technology enabled the development of smaller handhold pump devices which were the requirement for user-friendly devices resulting in a higher usage of this therapeutic method. (134, 135)

In CSII pump therapy the following components are required: First and foremost, the pump itself is needed with the controlling unit, processing unit, batteries and input/output interfaces. The insulin reservoir is normally found in the case of the pump too and should be disposable. The connection to the body is guaranteed by a tubing system which differs in length according to the patient’s requirements. The end of the tubing system is connected to the cannula carrying the insulin into the subcutaneous tissue. To ensure a good placement of the cannula special insertion devices are used for the cannula to avoid displacement, kinking and other causes for insulin delivery failures into the subcutaneous tissue.

Wear time is the bottleneck of catheters in CSII therapy as well as catheters in CSII therapy in general. The recommended wear time differs from two to three days depending on the manufacturer and the material the catheter is made of. Teflon catheters seem to have a slight benefit if the catheter was inserted correctly into the subcutaneous fat tissue. This advantage goes hand in hand with the disadvantage of a higher risk of kinking in Teflon catheters during the insertion. Steel catheters are easier to insert correctly but cause more irritation in the tissue which leads to higher risk of bleeding. In both catheters the rising inflammatory response is one of the main limitation factors for extended wear-time. Wear-time is also limited because of adverse events occurring more frequently in extended wear-

time over the recommended two to three days. 74.8% of such adverse events are attributed to hyperglycemic episodes which leads to an inefficient pump therapy with increased glycated hemoglobin values. Studies recommend sticking to the recommendations of the manufacturers to a wear-time of two to three days. On the other hand, a more frequent change of catheters leads to a higher number of insertions which result in a higher risk for unexplained hyperglycemia due to insertion failures which then end in increased glycated hemoglobin values. (136–139)

Therefore, if a longer wear-time could safely be ensured not only the glycemic control will improve, but patient's satisfaction and compliance will increase too. To match wear-time to continuous glucose monitoring systems, which can be worn up to one week, is a goal in research for automated closed-loop insulin delivery systems. One reason for adverse events in extended wear-time for catheters is catheter occlusion. This issue is probably easier to handle than inflammatory response mentioned above. Catheter occlusion seem to be conditional to different parameters like wear-time, temperature, type of insulin, insulin flow in the tube and cannula. There are probably even more parameters contributing to catheter occlusions which have yet to be researched. According to the study of Kerr at al the use of different insulin is taking effect only in extended wear-time over more than 72 hours. Three insulins where tested whereas insulin glulisine seems to have a higher risk in occlusions than insulin lispro and insulin aspart. Insulin lispro shows a slightly higher risk in occlusions than insulin aspart. Early occlusions have not occurred in the first 48 hours, which is an indication for no variation in early occlusion risk in the three insulins tested. The difference in insulins could probably be explained through insulin crystallization. However, the interpretation of the difference between the insulins should be made carefully because this study was carried out under laboratory conditions. Another point that could be observed is a higher occlusion risk at higher temperature which happened accidentally in the third run by an unnoticed temperature measure error. Another observed fact is that occlusions are highly associated to occur during boluses. Only three occlusions of a total of 48 occurred not during boluses. According to the hypothesis of Kerr, Morton at al aggregates associated loosely with the interior wall are detached when a bolus is in progress which could causes an occlusion. (138, 140–142)

The hypothesis of aggregates detaching during boluses which themselves causes silent occlusions seem to be a point for further research and improvement. A study by Gibney, Xue et al. (141) testing a new design of a catheter with an additional, proximal port in the wall of the catheter with a 90° angle to the normal distal port will probably be able to show

a reduction in catheter occlusions. The idea is to have an additional option for insulin leaving the catheter for the case that a distal occlusion occurs. Results of the study show a 92% reduction in silent occlusions in the new catheter with the additional port. Furthermore, reduced flow interruptions and reduced time with flow interruptions could be observed without a higher incidence of leakage at the insertion side. Although the study is limited to the use of insulin diluent and not original insulin, similar findings can be expected using original insulin. A lower incidence of occlusions for catheters with additional ports may help to improve catheters for a longer wear-time and also be a step in developing an automated closed-loop insulin delivery system. (140, 141)

2 Material und Methods

Modern insulin therapy aims to establish good glycemic control without relevant hypoglycemia in T1D and insulin-dependent T2D. Physiologic insulin secretion can best be mimicked by insulin pump therapy. (143–146) One of the bottle necks in insulin pump therapy is the catheter-tissue interface. Currently manufacturers of both Teflon and steel infusion sets recommend changes in infusion sets every two to three days to avoid lipohypertrophy, fluctuations in insulin absorption and occlusion. (147–151) However, most patients would prefer to use an infusion site over an extended wear time if stable insulin absorption could be achieved.

The novel Lantern catheter shall allow more stable insulin delivery via vertical slots cut into the shaft of the Teflon cannula even if kinking or clotting of the cannula occurs. The Lantern catheter has been tested in an animal setting and comparable tissue reaction was observed as compared to a conventional Teflon cannula. To date no clinical studies in patients have been performed. The aim of the present study is to investigate clinical performance of the Lantern catheter in patients with T1D using CSII over a period of up to seven days. It is expected that due to the specifications of the Lantern catheter insulin delivery is more stable over an extended wear time as compared to a conventional catheter. In this pilot study, a combined study design consisting of inpatient (euglycemic clamp) and outpatient phases (insulin pump therapy using the Lantern catheter) is chosen in order to allow assessment of performance and survival time of the Lantern catheter. The study period is set to seven days following catheter insertion to cover the maximum expected wear-time of the novel Lantern catheter. During the clamp visit, pharmacodynamics and pharmacokinetic properties will be assessed over time and will be compared to baseline data obtained with a regular Teflon infusion catheter. During the home treatment phase of the study, frequent blood glucose monitoring including flash glucose monitoring and ketone measurements will be performed. Additionally, insulin doses will be recorded to evaluate catheter performance over time.

The ethics committee of the Medical University of Graz approved the trial before start of the study which was performed under Good Clinical Practice (GCP) principles according to the Declaration of Helsinki. Before any study related activities were carried out every participant had to be informed about the planed study activities and additionally a printed consent paper had to be signed by each participant. Participants had to fulfill all inclusion criteria and none of the exclusion criteria for inclusion to the study.

The screening visit was done one to seven days before the first study visit. Then three visits were to be performed on days 1 to 2, 5 and 8 (day -1 to 1, 4 and 7 according to Lantern catheter wear-time). On those days an euglycemic clamp was executed which will be explained in detail below. On days 3, 4, 6 and 7 (day 2, 3, 5 and 6 according to Lantern catheter wear-time) patients lived under real life conditions at home. Seven days after the third visit a follow-up was scheduled for safety reasons. To enable a comparison to a conventional infusion-set (Inset IITM, Unomedical, Osted, Denmark) this system was used for the first clamp and thereafter the Lantern catheter was used. Figure 4 below shows the sequence of study days.

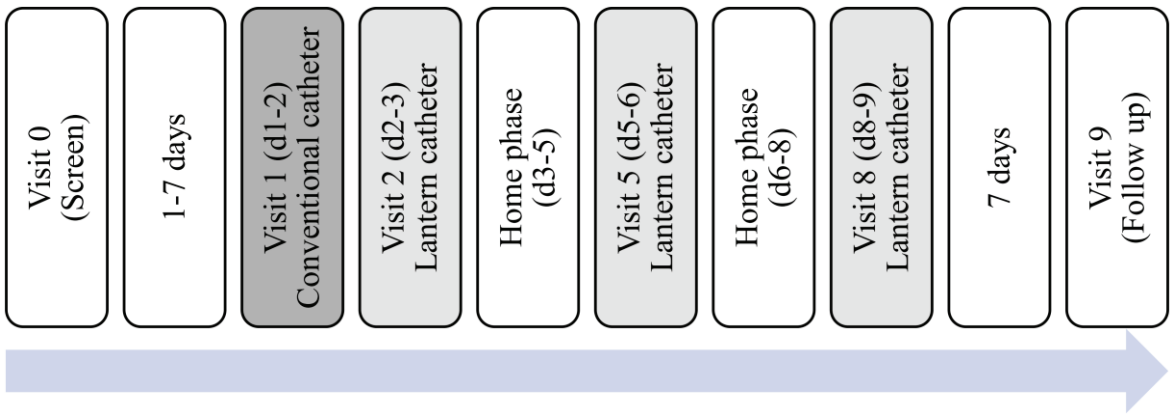

Figure 4: Study overview

2.1 Study design

This is an open, single-center, single-arm, controlled pilot trial investigating the efficacy and safety of an extended wear-time of the novel Lantern insulin infusion catheter on pharmacodynamics, pharmacokinetics and glucose control in subjects with T1D.

2.1.1 Subject Inclusion Criteria

1. Informed consent obtained after being advised about the nature of the study
2. Male or female aged ≥18 years
3. T1D for at least twelve months according to the WHO definition
4. Regular use of insulin aspart or glulisine for diabetes management
5. C-peptide <0.3nmol/L
6. Treatment with CSII for at least six months (an interruption of three months is allowed)
7. Body Mass Index (BMI) 20-28kg/m²

8. Willing and able to wear a CGM device and use the study specific insulin pump and study specific catheters for the duration of the study and undergo all study procedures
9. A1C ≤86 mmol/mol
10. Stable body weight in the last three months prior to study start (change in body weight under five percent)

2.1.2 Subject Exclusion Criteria

1. Non-insulin hypoglycemic agents
2. Regular use of insulin lispro for diabetes management
3. Diabetic ketoacidosis during the previous twelve months
4. Severe hypoglycemia requiring third party help, hospitalization or emergency room visit during the previous twelve months
5. Hypoglycemia unawareness
6. Female of childbearing potential who is pregnant, breast-feeding or intend to become pregnant or is not using adequate contraceptive methods
7. Skin pathology or condition prohibiting needle insertion/insulin administration as judged by the investigator (e.g. scar tissue)
8. History of bleeding disorder
9. Current participation in another clinical study
10. Significant acute or chronic illness that might interfere with subject safety or integrity of results as judged by the investigator
11. Smoker (> five cigarettes per day)
12. Lipodystrophy
13. Current treatment with systemic (oral or intravenous) corticosteroids, monoamine oxidase (MAO) inhibitors, non-selective beta-blockers, growth hormone, herbal products or non-routine vitamins. Furthermore, thyroid hormones are not allowed unless the use of these has been stable during the past three months.
14. Significant history of alcoholism or drug abuse or a positive result in urine drug/alcohol screen that in the opinion of the investigator would compromise the subject's safety or successful participation in the study
15. Known adrenal gland problem, pancreatic tumor, or insulinoma
16. Inability of the subject to comply with all study procedures
17. Inability of the subject to understand the patient information

2.1.3 Study day exclusion criteria

1. Strenuous exercise within the last 24 hours prior to dosing.
2. Non-fasting (i.e. consumption of food or beverages, other than water, later than 22:00 hours the evening before the visit) except if slight intake of rapidly absorbable carbohydrates has been necessary in order to prevent hypoglycemia.
3. Insulin bolus other than Actrapid later than 22:00 hours the night before the dosing visit
4. Pump infusion rate other than 0.1 IU/h later than 22:00 hours the night before Visit 5 and Visit 8
5. Positive result of alcohol breath test
6. Any medical condition that, in the opinion of the Investigator, could interfere with insulin pharmacokinetics and/or glucose metabolism.
7. Non-stable body weight between Visit 0 and Visit 1 (change in body weight over five percent)

2.1.4 Screening

After a screening visit (Visit 0), subjects fulfilling all inclusion and none of the exclusion criteria will be included into the study. Baseline assessments (ECG, vital signs, weight, height, safety lab) will be performed. Subjects not using the MiniMed 640G insulin pump will be switched to this system at the end of the screening visit and pump settings from their usual pump will be programmed. In between screening visit and first clamp visit subjects will be asked to perform insulin therapy using the MiniMed 640G insulin pump with their regular type of insulin and regular type of infusion catheter. Subjects will be provided with diabetes diaries and insulin pens (Actrapid®, NovoNordisk) for insulin application the night preceding clamp visits. In the night prior to the first clamp visit (Visit 1) subjects will be asked to stop insulin delivery via the insulin pump at 22:00. Correction insulin boli using Actrapid® can be administered until arrival at the clinical research center (CRC) and need to be documented in the diabetes diary.

2.1.5 Clamp visits (day 1 to 2, 5 and 8)

At Visit 1 the subject will be asked to attend the CRC at approximately 06:30 hours under fasting conditions. Study day exclusion criteria will be checked. The FGM sensor and venous lines for blood glucose sampling and glucose/insulin infusion will be inserted and the run-in phase will be started at 07:00 in the morning (Figure 5). The cartridge of the

insulin pump will be filled with insulin lispro, primed, the conventional catheter will be inserted and the pump will be immediately started on a constant basal rate of 0.1 IU/h which will be maintained throughout the clamp. During the run-in phase (3-5 hours, Figure 5) a variable intravenous infusion of human soluble insulin (40 IU Actrapid®, 100IU/ml in 99.6 mL saline) or glucose 20% will be initiated in order to obtain a plasma glucose level of 100 mg/dl (5.6 mmol/l). If insulin is infused, glucose infusion must be stopped and vice versa. Insulin and glucose infusion rate will be recorded. Plasma glucose should be within a range of 100mg/dl (5.6 mmol/l ± 20% (upper and lower limits included)) from -60 to -30 min and within a range of 100mg/dl (5.6 mmol/l ±10% [upper and lower limits included]) from -30 to 0 min before delivery of pump Bolus. At time point 0 min the pump Bolus (insulin dose of 0.15 IU/kg bodyweight of insulin lispro) will be administered via the insulin pump (Figure 5). After delivery of pump Bolus when only Actrapid® insulin is infused to maintain the glucose clamp target, the rate of Actrapid® insulin infusion will be tapered off as follows:

- Time-point +5min: 70% of infusion rate at time point 0min
- Time-point +10min: 40% of infusion rate at time-point 0min
- Time-point +15min: 10% of infusion rate at time-point 0min

Actrapid® insulin infusion will be ultimately completely terminated when plasma glucose has dropped 5mg/dl (0.3 mmol/l) relative to the baseline plasma glucose level. Baseline plasma glucose level is defined as mean plasma glucose at time points -10min, -5min, 0min.

At this time, a variable intravenous glucose infusion (glucose 20%) will be initiated to keep the plasma glucose concentration constant at the glucose clamp target of 100md/dl (5.6mmol/l).

Plasma glucose will be measured in 5-30min intervals using Super GL2 glucose analyzer until 8h post pump Bolus (time-point 0) or until persistent hyperglycemia >220mg/dl (>12.2 mmol/l) over 30min without glucose infusion occurs (i.e. early termination of clamp). Sampling or insulin analysis will be performed until 8h post-dosing irrespective of glycemia. If early termination of clamp occurs Actrapid® can be administered intravenous as judged by the investigator. After end of clamp subjects will receive a meal and resume their regular insulin regimen using the study specific pump. Subjects will stay at the research facility overnight. The conventional catheter will be removed at 22:00 and only bolus insulin using Actrapid® is allowed thereafter.

In the morning of Visit 2 new intravenous lines will be inserted if deemed necessary by the investigator. After appropriate priming with insulin lispro, the Lantern catheter will be inserted and will be started at a constant basal rate of 0.1 IU/h. The same procedures as described for the first clamp apply. Subjects will be discharged for the home treatment phase using the Lantern catheter as described below. Thereafter clamp visits will be performed on days 5 and 8 (i.e. days 4 and 7 of Lantern catheter wear-time) using the procedures as described above.

In the morning of day nine subjects will be discharged from the CRC and active participation in the study is completed.

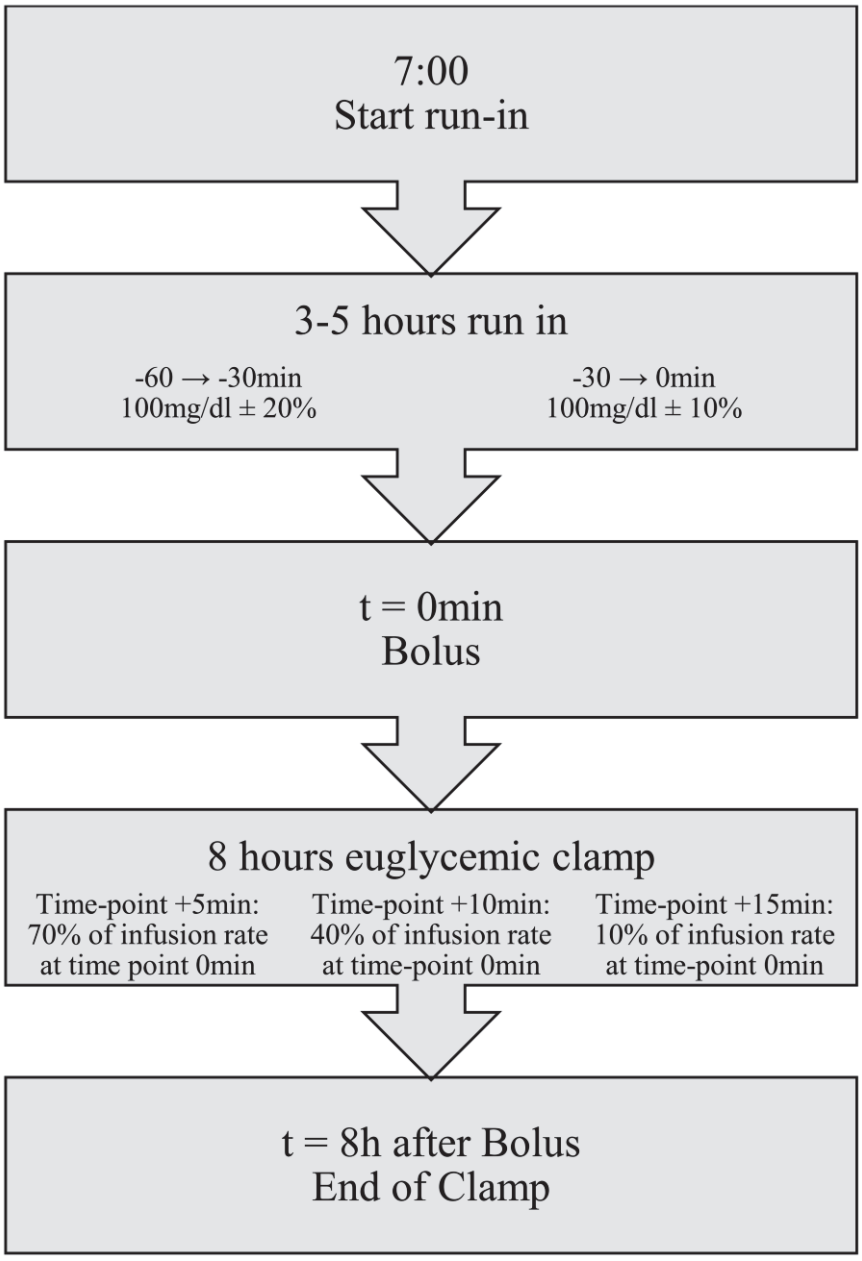

Figure 5: Clamp design

2.1.6 Home treatment phase under CSII (Days 3-5 and Days 6-8)

During the home treatment phase under CSII subjects will use the Lantern catheter in combination with the study specific insulin pump for diabetes management. Subjects shall follow their regular lifestyle, use the diabetes diary for documentation and will be contacted once daily by the study team to assess catheter performance. Subjects will be asked to regularly check glycemia using the FGM system. Additionally, subjects will be instructed to regularly measure capillary glucose values using the integrated blood glucose meter. In case the deviation of the measured glucose values exceeds 20%, the capillary blood glucose measurement will be repeated. In case of persistent deviation or sensor failure, the FGM sensor will be replaced. In case of persistent hyperglycemia, correction bolus insulin can be delivered manually using the disposable insulin pen (Humalog KwikPen) handed out to the subject. On days preceding clamp visits, basal rate of the pump must be switched to 0.1 IU/h and only Actrapid® is allowed from 22:00 onwards as described for Visit 1. Subjects are instructed to perform ketone testing in case of persistent hyperglycemia (blood glucose [= BG] >300mg/dl [>16.7mmol/l]). In case of hypoglycemia, rescue carbohydrates will be taken orally by the subject as under routine conditions. In case of suspected catheter failure subjects are instructed to contact the telephone hotline (24/7) and follow the instructions of the trial team. In case of infusion set failure as described above, participation for the subject is over and a follow-up visit will be scheduled. In case of accidental removal of the infusion set, a new Lantern catheter will be inserted and the clamp experiment will be continued on the clamp days as scheduled (ie 4 and/or 7 days after re-insertion).

2.1.7 Follow up

Seven days after the end of the final clamp visit, a telephone follow-up visit will be performed. Subjects will be asked if any insertion site reactions at the site of investigational catheter placement have occurred. In case no insertion site reaction is present, the subject is discontinued from the study. In case insertion site reaction is suspected by the investigator the subject will be asked to attend the clinical unit within one day. Physical examination incl. safety lab will be performed and the insertion site reaction will be documented as adverse event. The insertion site reaction will be followed-up until it is recovered.

2.2 Data analysis

Before data analysis all pharmacodynamic data were log-transformed. Normally distributed values were tested by the Shapiro-Wilk test ($p < 0.1$ indicate deviations from normality) to separate normally distributed data from not normally distributed data. A mixed-effect model ($p < 0.05$) was used for normally distributed data and was compared by means of paired t-test. For not normally distributed data the Wilcoxon signed rank test and for pairwise comparisons an adjusted Alpha-level of 0.0083 according to Bonferroni was used. The Software SAS 9.4 was used for analyses. Data is presented in figures as median values (25^{th} and the 75^{th} percentiles) if not otherwise declared.

3 Results

3.1 Study population

Study population included a total of 16 patients: five women and eleven men with an average age of 44.2 ± 15.4 years, from 21 to 64 years. The average BMI was 24.5 ± 2.3 kg/m^2, the average fasting C-peptide was 0.04 ± 0.1 nmol/L and the average A1C was 7.2 ± 0.7% (55.3 ± 7.8 mmol/mol). All patients were Caucasians.

3.2 Clinical phase - Clamps

In Figure 6 the glucose infusion rate after a subcutaneous bolus by insulin pump of insulin lispro is shown on the wear time day 1 for two different types of catheters: a conventional insulin catheter and the newly developed Lantern insulin catheter. In comparison for the two curves it can be said that the AUC_{GIR} (area under the curve of glucose infusion rate) was similar in both (1042.3 [692.5-1311.5] vs. 874.2 [711.2-1130.1] mg/kg; p=0.197, Student-t test, for log-transformed data shown in Table 1), although the mean of AUC_{GIR} for Lantern catheter was approximately 10-20% lower than the AUC_{GIR} of the conventional insulin catheter.

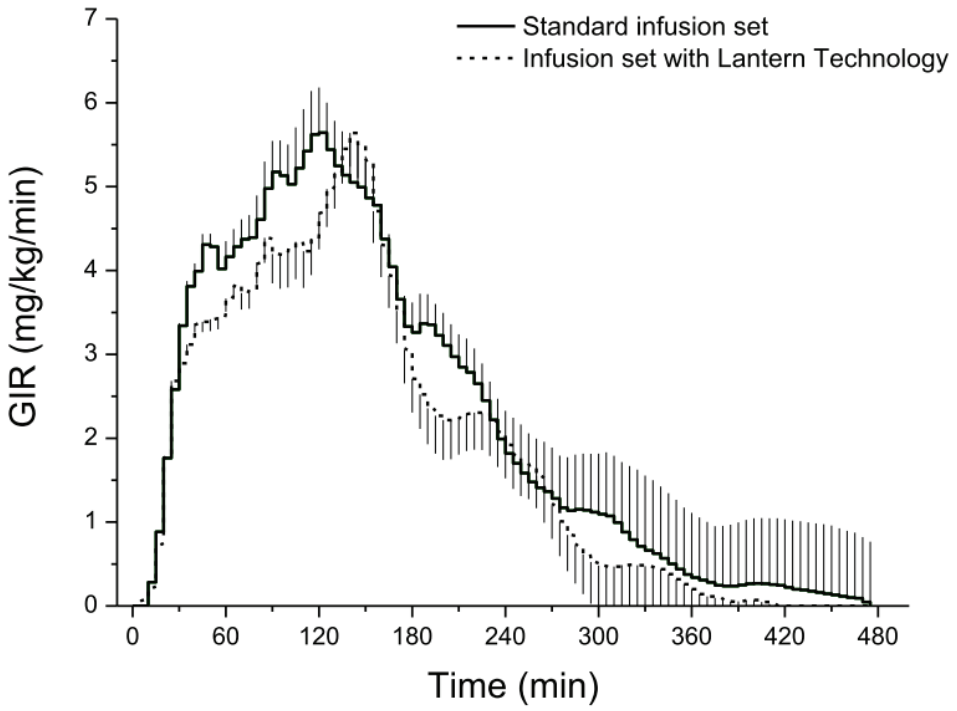

Figure 6: GIR of standard vs. Lantern infusion set

	conventional insulin catheter [mg/kg]	Lantern insulin catheter [mg/kg]	reached AUC_{GIR} compared to conventional insulin catheter in %	p-value of Student's t-test for log-transformed data (significant for p <0.0083)
mean $AUC_{GIR\ 0\text{-}1h}$	152.91 [109.46-182.95]	122.15 [84.48-122.15]	79.9	0.276
mean $AUC_{GIR\ 0\text{-}2h}$	396.73 [272.80-579.77]	339.83 [250.86-458.49]	85.7	0.279
mean $AUC_{GIR\ 0\text{-}4h}$	809.52 [567.45-1140.45]	734.02 [603.33-1009.06]	90.7	0.377
mean $AUC_{GIR\ 0\text{-}6h}$	1036.03 [692.52-1280.21]	872.08 [709.09-1122.40]	84.2	0.242
mean $AUC_{GIR\ 0\text{-}8h}$	1042.25 [692.5-1311.5]	874.2 [711.2-1130.1]	83.9	0.197

Table 1:AUC of GIR for standard vs. Lantern infusion set

Additionally, the time to reach GIR_{MAX} was higher for the Lantern catheter compared to the conventional insulin catheter (67.5 [45.0-115.0] vs.137.5 [72.5-147.5] min; p=0.046, Wilcoxon signed rank test), but the time to reach 50% maximum glucose infusion rate (TMAX50) was approximately the same for the Lantern catheter (32.50 [25.00-37.50] vs 27.50 [22.50-45.00] min; p=0.971, Wilcoxon signed rank test).

Figure 7 again shows the glucose infusion comparing the Lantern catheters on different days of catheter wear time. Lantern catheter wear-time is compared on day 1, 4 and 7, which is study day 2, 5 and 8. The AUC_{GIR} is comparable for the first two hours on all days (d1: 339.8 [250.9-458.5] vs. d4: 458.8 [280.4-592.7] vs. d7: 414.8 [228.2-540.8] mg/kg; p=0.142, mixed-effect model) but differs in a significant decrease afterwards in extended wear time for day 4 and 7 which was measured for up to eight hours after bolus (d1: 874.2 [711.2-1130.1] vs. d4: 856.3 [509.0-1074.4] vs. d7: 630.3 [328.3-814.0] mg/kg; p=0.02, mixed-effect model). Unexpected results have been recorded in a faster onset for GIR_{MAX} in extended wear time with a reduction of 67% (d1: 137.5 [72.5-147.5] vs. d7: 45.0 [35.0-62.5] min; p<0.0083, Wilcoxon signed rank test).

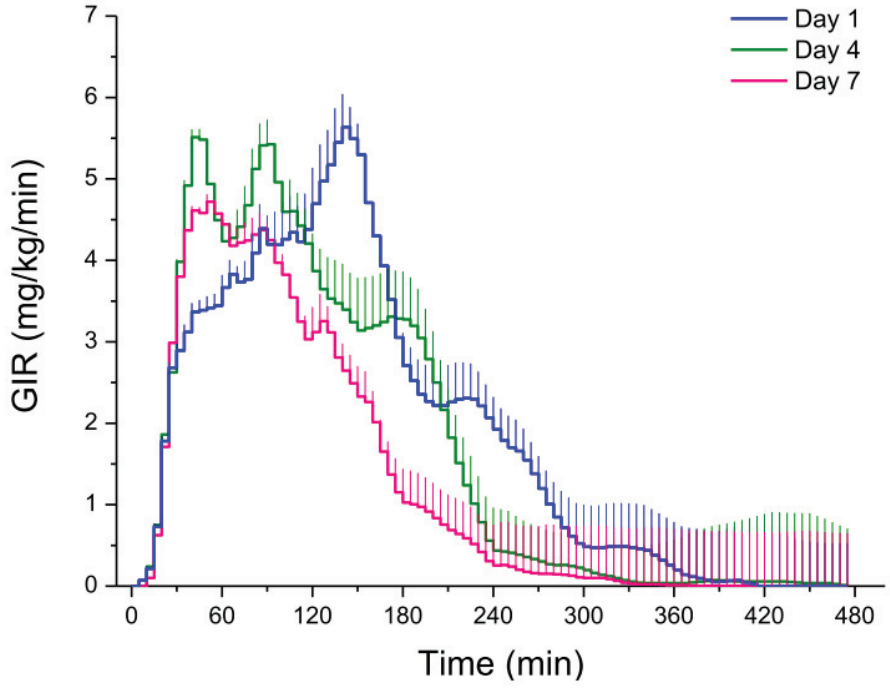

Figure 7: GIR of Lantern infusion set on day 1,4,7

3.3 Home treatment phase

3.3.1 Blood glucose

The blood glucose values measured with flash glucose monitoring devices during the home treatment phase (day 2, 3, 5 and 6 of Lantern catheter wear-time, this conforms study days 3, 4, 6 and 7) of the study included 64 days in total. For statistical analysis three days had to be excluded due to short sensor wear-time (<18 hours per day). Blood glucose target range (70-180 mg/dl - 3.9-10 mmol/l) was reached in 59.04 ± 15.26% of home treatment phase. Subjects had been in hyperglycemia >180 mg/dl (10mmol/l) in 32.74 ± 16.40% and in hypoglycemia <70mg/dl (3.9mmol/l) in 8.23 ± 7.06%.

Two main differences in blood glucose could be observed by separating the home treatment phase in individual days (Table 2 and Figure 8). Firstly, the time in blood glucose target range decreased slightly over time (d2: 60.8 ± 15.0 vs. d3: 66.5 ± 18.7 vs. d5: 55.8 ± 21.2 vs. d6: 53.5 ± 25.2%; mean ± SE). Secondly, the same could be observed for time in hypoglycemic range which results in an increase of time in hyperglycemic over Lantern-catheter wear-time. The highest increase in hyperglycemic range of 15.23% during daytime was between day 3 and 5 of Lantern catheter wear-time with a clamp day in between.

Lantern catheter wear-time	day 2	day 3	day 5	day 6
BG target range 70-180 mg/dl 3.9 – 10 mmol/l	60.83±14.96%	66.49±18.73%	55.81±21.16%	53.50±25.22%
hyperglycemia >180 mg/dl >10 mmol/l	25.68±14.25%	23.78±21.10%	39.01±23.26%	41.62±27.62%
hypoglycemia <70 mg/dl <3.9 mmol/l	13.49±11.28%	9.73±11.17%	5.18±6.76%	4.88±7.79%
in total	100%	100%	100%	100%

Table 2: Time in glycemic ranges during home treatment phase

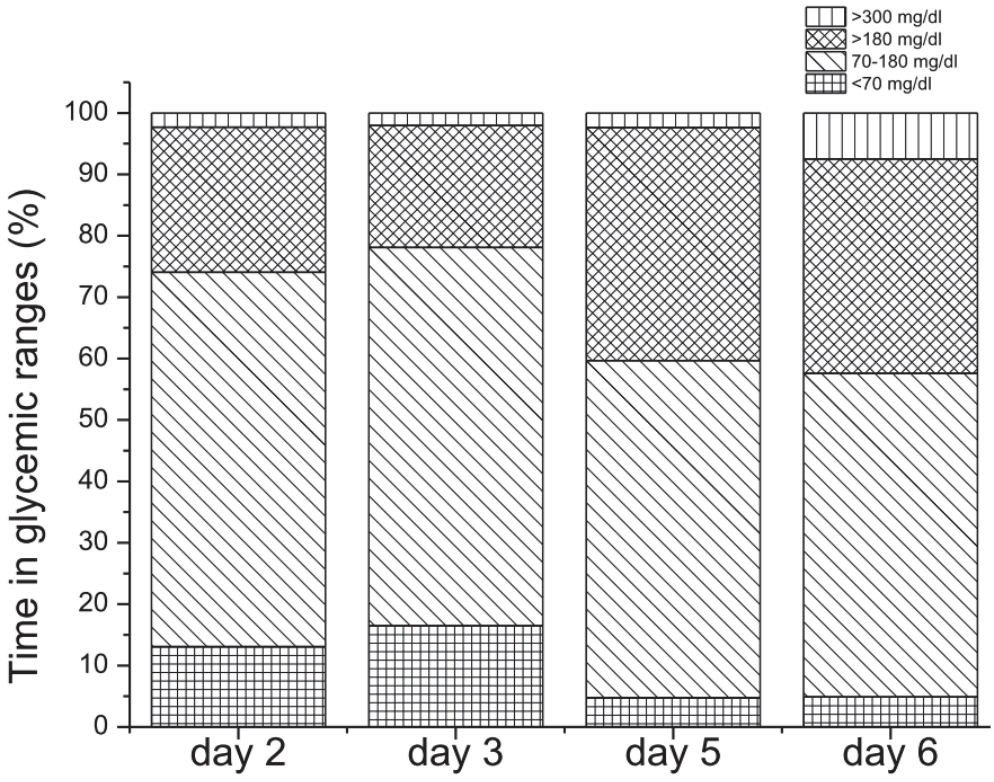

Figure 8: Time in glycemic ranges during home treatment phase

Comparing glucose variability from flash glucose monitoring over time shows an increase for the mean of variability after the second Lantern catheter clamp day (Table 3). The means of glucose variability during daytime decrease from day 2 to 3 of Lantern catheter wear-time. After the second clamp on day 4 of Lantern catheter wear-time an increasing tendency for the means of glucose variability were recorded from day 5 to 6 of Lantern catheter wear-time. The same tendencies could be observed for overall daytime, daytime and nighttime taken together. For the nighttime although an increase in blood glucose variability was recorded through all days of Lantern catheter wear-time during home treatment phase.

mean of blood glucose variability	all daytime 07:00 – 21:59	all nighttime 22:00 – 06:59	overall time 00:00 – 23:59
day 2 of Lantern catheter wear-time	247.73 ±36.75 mg/dl	114.67 ±53.37 mg/dl	251.13 ±38.92 mg/dl
day 3 of Lantern catheter wear-time	175.87 ±59.84 mg/dl	135.80 ±67.60 mg/dl	197.13 ±68.57 mg/dl
day 5 of Lantern catheter wear-time	199.80 ±49.03 mg/dl	140.00 ±58.42 mg/dl	221.87 ±43.47 mg/dl
day 6 of Lantern catheter wear-time	209.88 ±80.41 mg/dl	161.94 ±43.89 mg/dl	225.31 ±72.97 mg/dl

Table 3: Mean of blood glucose variability

Although mean glucose levels did increase from day to day according to Lantern catheter wear-time (d2: 142.29 ± 25.94 vs. d3: 143.14 ± 34.65 vs. d5: 165.51 ± 34.84 vs. d6: 176.19 ± 52.52mg/dl) none of the pairwise post-hoc t-test results, comparing each day of home treatment phase with each other day during home treatment phase, were statistically significant.

Sustained hyperglycemia >300 mg/dl (16.7 mmol/l) measured through flash glucose monitoring occurred 48 times. Those blood glucose values were between 303 – 471 mg/dl (16.8 – 26.1 mmol/l) and in mean 357.13 ± 40.47 mg/dl (19.8 ± 2.2 mmol/l). Duration of those sustained hyperglycemic episodes went from 15 – 590 minutes and mean duration was 105.15 ± 98.49 minutes. In total ten diary entries were recorded between 338-468mg/dl (18.8-26.0 mmol/l) with a minimal duration of 43 minutes and a maximum duration of 270 minutes.

During home treatment phase two hypoglycemic events <40 mg/dl (2.2 mmol/l) occurred. In both hypoglycemic events patients did not require third party help.

3.3.2 Insulin doses

Insulin doses administered via an insulin pump were recorded through the insulin pump and additional applicated insulin through insulin pens (correction boli) was recorded in patients' diaries. Due to implausible diary data three subjects had to be excluded from total daily insulin dose analysis (this includes diary data). For the total daily insulin dose an increase over time could be recorded (45.2 ± 13.9 - 52.8 ± 16.2 IU; mean ± SE; $p<0.05$) which is shown in Figure 9 and Table 4.

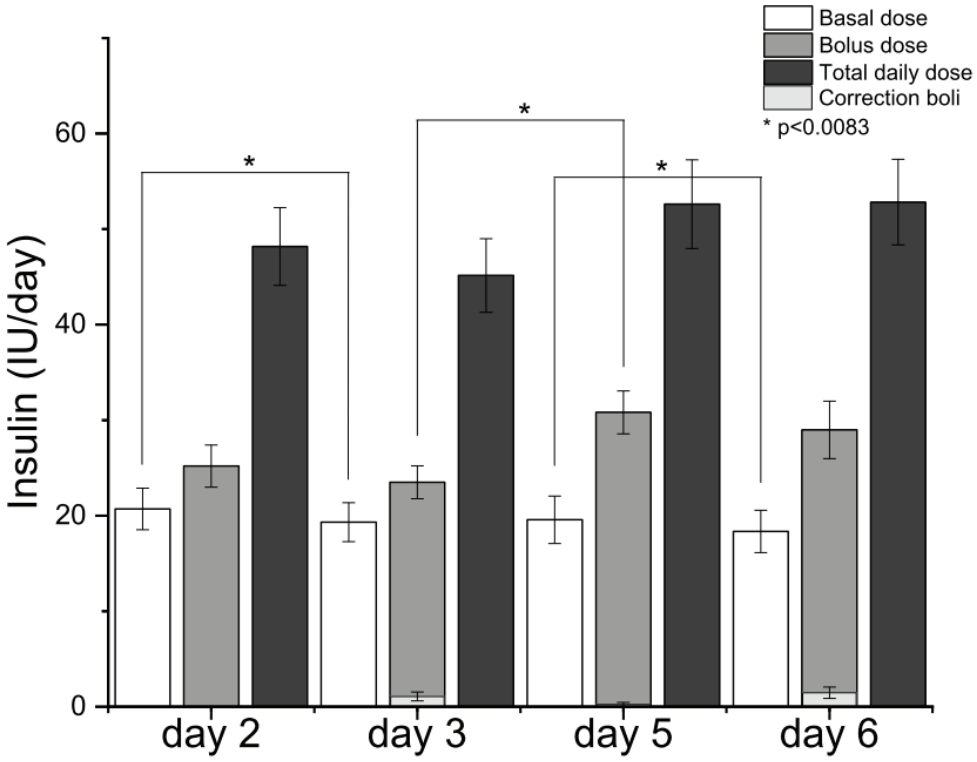

Figure 9: Insulin doses during home treatment phase

mean of insulin dose	basal dose by pump (IU)	bolus dose by pump (IU)	total daily dose by pump (IU)	total daily dose – combination of pump + pen (IU)
day 2 of Lantern catheter wear-time	20.71 ± 8.71	25.19 ± 8.84	45.90 ± 14.91	48.18 ± 14.68
day 3 of Lantern catheter wear-time	19.32 ± 8.14	23.50 ± 6.91	42.82 ± 13.46	45.15 ±13.89
day 5 of Lantern catheter wear-time	19.58 ± 9.95	30.82 ± 9.00	50.39 ± 16.52	52.61 ± 16.73
day 6 of Lantern catheter wear-time	18.34 ± 8.86	28.98 ± 12.06	47.32 ± 16.46	52.82 ± 16.16

Table 4: Mean of insulin dose during home treatment phase

A statistical small decrease in basal insulin dose comparing day 2 vs. 3 and day 5 vs. 6 of Lantern catheter wear-time was recorded (pairwise post-hoc t-test). Comparing day 3 vs. 5 of Lantern catheter wear-time a significant increase in administered insulin dose (both as bolus and via basal rate) could be seen (pairwise post-hoc t-test). However, no statistically significant changes in total daily insulin doses were found by pairwise post-hoc t-test comparing each day of Lantern catheter wear-time during home treatment phase.
When needed, correction boli with insulin pens could be administrated prior to the clamp visits due to study requirements or in case of persistent hyperglycemia during home treatment phase. During the whole study period twelve correction boli via insulin pens were recorded. Of those only three were administered due to persistent hyperglycemia, one bolus on day 6 and two on day 7 of Lantern catheter wear-time.

3.4 Safety

100% infusion-sets survival were observed in the study. During the whole study period no pump occlusion alarms or pump leakage alarms were recorded. Also, no severe hyperglycemia or ketoacidosis occurred. Hypoglycemia can occur in insulin therapy especially in patients thriving for good control. As mentioned above none of the two events required third-party help. No serious adverse event was recorded, and all recorded adverse events were of mild severity.

4 Discussion

The present study tested a novel insulin infusion catheter (= the Lantern catheter) for the first time in people with T1D. The catheter was investigated over an extended period of infusion set wear-time for up to seven days under clinical clamp conditions as well as in real-world use. The main findings of this study were as follows: Firstly, the Lantern catheter could safely deliver insulin to the subjects comparable to a conventional catheter. Secondly, the catheter seems to be able to deliver insulin safely to the patient also over an extended wear-time for up to seven days without causing severe hyperglycemic events, ketoacidosis or catheter occlusions. Additionally, faster insulin pharmacokinetics were observed with extended insulin catheter wear-time. These results are comparable to other studies with regard to achieved time in glucose target range (70-180 mg/dl or 3.9-10mmol/L) (124, 152).

In our pilot study we first compared the new Lantern catheter technology with a conventional catheter in a clamp procedure carried out on two consecutive days (which was day 1 of wear-time for both catheters). Subsequently the Lantern catheter was tested for a period of up to seven days of extended wear-time. The difference of the AUC_{GIR}, when comparing the conventional insulin infusion catheter and the Lantern insulin catheter, seems to show a slight disadvantage for the new Lantern insulin catheter on day 1 of wear-time. This ten to twenty percent lower AUC_{GIR} can be explained by the study design: due to the consecutive clamp day (i.e. day 1 of Lantern catheter wear-time) with little muscle activity during the first clamp day. Little muscle activity could lead to lower insulin sensitivity on the day where the Lantern insulin catheter was tested in a clamp setting (153, 154).

The onset of insulin action on day 1 of Lantern catheter wear-time assessed by time to reach GIR_{MAX} could also have been influenced by the mechanism described above. For conclusive information more data and another study design having at least several days in between clamps would be needed. According to Figure 6 similar onset of insulin action until 50% of GIR_{MAX} could be observed which is an argument for a similar effect on pharmacokinetics in both insulin catheters (153, 154).

Reduced insulin action and a faster onset of insulin action seems to be a phenomenon in extended wear-time not only in this study but also according to Hauzenberger et al and Swan et al. (155, 156). They discussed an inflammatory response as a cause for those effects. Swan et al. discussed a faster pharmacodynamic response in extended insulin catheter wear-time due to higher blood flow around the infusion set because of

microvascular changes. This observed effect for faster onset of insulin action and shorter duration of action could even be a positive effect for meal-related glucose excursion (155). We also argue for a better glycemic control due to this faster pharmacodynamic effect and due to missing other essential changes in AUC_{GIR} especially during the first two hours, which are mostly relevant to the meal-related glucose excursions.

During the home phase flash glucose monitoring was available for a total of 64 days. In our study participants had reached blood glucose target range (70-180 mg/dl - 3.9-10 mmol/l) in 59.04% ± 15.26 during home treatment phase. Others studies, including more participants, also observing time in the same blood glucose target range undergoing CSII therapy in adults, adolescents and children, had similar findings: 58.21% (152) and 56.8% ± 14.2 (124). Our similar results allow to argue sufficient insulin delivery over the Lantern insulin catheter during the first days of Lantern catheter wear-time, but also in extended wear time for up to seven days.

The highest increase of time in hyperglycemic range during daytime could be observed from day 3 to 5 including a clamp day in between. We hypothesis this increase is provoked due to hyperinsulinemia during the clamp day. The increased blood glucose variability over nighttime over the course of time during home treatment phases indicates a decrease in insulin action over extended wear-time. As insulin doses during home phases did not substantially increase one might speculate that patients who self-titrated their insulin dose might have been afraid of hypoglycemia and thus might have not sufficiently uptitrated. As the main focus for the Lantern catheter would be its use in the artificial pancreas setting with automated insulin dose adjustment this effect might not be observed in real-world application.

Almost all hyperglycemic events which required correction boli via insulin pen occurred in the pre-clamp phase when basal rate of CSII therapy was adjusted to 0.1 UI per hour and thus were related to study design and not to malfunction of the device. Only three correction boli via insulin pen to correct for persistent hyperglycemia were administered during regular use of Lantern catheter. Since those events occurred on days 6 and 7 of wear-time there may be a relation between persistent hyperglycemia and extended catheter wear time, although there were no complications like occlusions or leakage recorded afterwards in the same participants.

Due to the pilot study design the study was limited in the number of study participants and in comparability to the conventional catheter, because of a missing cross-over design. Other methodological weaknesses are missing tissue samples for histological analysis,

unphysiological clamp days including physical inactivity and hyperinsulinemia. The slow insulin basal rate of 0.1 UI/h in the pre-clamp phase may increase the risk of catheter occlusions compared to real-life conditions (140).

Instead of slits additional holes in the catheter wall could probably provide better insulin delivery in case of distal insulin catheter occlusion (141, 157). Further, in case of slits or holes, the stability of the insulin catheter needs to be ensured and compared to conventional catheters because of kinking or torn down material of the catheter which could be left behind in the subcutaneous tissue. Of note, in our study all catheters could be removed from the tissue without any complications and without any residues staying behind.

Finally, the study design can answer that insulin delivery over extended wear time of seven days is possible. The study design included real-life conditions on four days and study participants were part of the target group. Another methodical strength is the extended wear time of seven days which was not part of intense research yet.

For more information further investigations, including higher sample size and longer observational periods are needed. Other study designs in real-world settings and including other insulin pumps and insulin types would give conclusive information about the benefits and drawbacks of the novel insulin catheter.

To test the effectiveness of the slits cut into the insulin catheter wall, also a new trial with a new study design should be considered. The Lantern technology tries to deliver insulin through slits in case a distal insulin catheter occlusion occurs. The Lantern technology itself could not be tested with certainty, because of missing knowledge about the distal insulin catheter situation in the subcutaneous tissue of the participant. For testing the slits in the catheter wall a distal occlusion must be ensured and insulin boli need to be administrated in clamp environment for accurate data and participants safety reasons. A subsequent study to quantify the function of the slits alone is already planned. Our planed study design and other studies need to implicate duration of infusion set use according to others observation (155, 156) and our observation for consistent pharmacodynamic results.

5 Conclusion

Due to the study having no severe hypoglycemia or ketoacidosis nor catheter occlusions or leakages, the new Lantern catheter could be advocated for safe insulin delivery in extended wear-time for up to seven days.

Extended wear-time might help to improve quality of life in patients because of lower insertion frequency which causes pain each time. Especially children would benefit of this extended wear-time feature. In addition, patients using hybrid-closed loop systems can profit due to automatic adjustment of basal insulin rate over extended wear-time.

One might also speculate that better postprandial glycemic control can be achieved in extended wear-time because of a faster onset and shorter duration of insulin action is observed in our study and studies performed by others (154, 155).

Although the study is limited by the number of participants, the short and artificial study design and the lack of a control group it seems that the new infusion set may be able to preserve glycemic control over extended wear time for up to seven days. Further studies should be performed to address these gaps in current knowledge.

6 Literature Cited

1. WHO | Diabetes programme [cited 2018 Mar 4]. Available from: URL: http://www.who.int/diabetes/en/.

2. WHO | Diabetes [cited 2018 Mar 4]. Available from: URL: http://www.who.int/mediacentre/factsheets/fs312/en/.

3. Classification of diabetes mellitus and genetic diabetic syndromes - UpToDate [cited 2018 Mar 4]. Available from: URL: https://www.uptodate.com/contents/classification-of-diabetes-mellitus-and-genetic-diabetic-syndromes.

4. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018.

5. Skordis N, Efstathiou E, Kyriakides TC, Savvidou A, Savva SC, Phylactou LA et al. Epidemiology of type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century. Hormones (Athens) 2012; 11(1):86–93.

6. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014; 311(17):1778–86.

7. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010; 33(Suppl 1):S62-S69.

8. Schernthaner G, Hink S, Kopp HP, Muzyka B, Streit G, Kroiss A. Progress in the characterization of slowly progressive autoimmune diabetes in adult patients (LADA or type 1.5 diabetes). Exp Clin Endocrinol Diabetes 2001; 109 Suppl 2:S94-108.

9. Diabetes mellitus in pregnancy: Screening and diagnosis - UpToDate [cited 2018 Mar 21]. Available from: URL: https://www.uptodate.com/contents/diabetes-mellitus-in-pregnancy-screening-and-diagnosis.

10. Pathogenesis of type 1 diabetes mellitus - UpToDate [cited 2018 Mar 9]. Available from: URL: https://www.uptodate.com/contents/pathogenesis-of-type-1-diabetes-mellitus.

11. Cooper JD, Smyth DJ, Smiles AM, Plagnol V, Walker NM, Allen JE et al. Meta-analysis of genome-wide association study data identifies additional type 1 diabetes risk loci. Nat Genet 2008; 40(12):1399–401.

12. Pugliese A, Gianani R, Moromisato R, Awdeh ZL, Alper CA, Erlich HA et al. HLA-DQB1*0602 is associated with dominant protection from diabetes even among islet cell antibody-positive first-degree relatives of patients with IDDM. Diabetes 1995; 44(6):608–13.

13. Barker JM, Barriga KJ, Yu L, Miao D, Erlich HA, Norris JM et al. Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). J Clin Endocrinol Metab 2004; 89(8):3896–902.

14. Rowe RE, Leech NJ, Nepom GT, McCulloch DK. High genetic risk for IDDM in the Pacific Northwest. First report from the Washington State Diabetes Prediction Study. Diabetes 1994; 43(1):87–94.

15. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Allen HL, Franco E de et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nat Genet 2014; 46(8):812–4.

16. Almawi WY, Tamim H, Azar ST. Clinical review 103: T helper type 1 and 2 cytokines mediate the onset and progression of type I (insulin-dependent) diabetes. J Clin Endocrinol Metab 1999; 84(5):1497–502.

17. Rothe H, Jenkins NA, Copeland NG, Kolb H. Active stage of autoimmune diabetes is associated with the expression of a novel cytokine, IGIF, which is located near Idd2. J Clin Invest 1997; 99(3):469–74.

18. Kavvoura FK, Ioannidis JPA. CTLA-4 gene polymorphisms and susceptibility to type 1 diabetes mellitus: a HuGE Review and meta-analysis. Am J Epidemiol 2005; 162(1):3–16.

19. Smyth D, Cooper JD, Collins JE, Heward JM, Franklyn JA, Howson JMM et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. Diabetes 2004; 53(11):3020–3.

20. Bell GI, Horita S, Karam JH. A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. Diabetes 1984; 33(2):176–83.

21. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 1994; 331(21):1428–36.

22. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA et al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes 1996; 45(7):926–33.

23. Pietropaolo M, Towns R, Eisenbarth GS. Humoral autoimmunity in type 1 diabetes: prediction, significance, and detection of distinct disease subtypes. Cold Spring Harb Perspect Med 2012; 2(10).

24. Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D et al. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. Nature 2005; 435(7039):220–3.

25. Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus - UpToDate [cited 2018 May 2]. Available from: URL: https://www.uptodate.com/contents/associated-autoimmune-diseases-in-children-and-adolescents-with-type-1-diabetes-mellitus.

26. Kordonouri O, Klinghammer A, Lang EB, Grüters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 2002; 25(8):1346–50.

27. Kordonouri O, Hartmann R, Deiss D, Wilms M, Grüters-Kieslich A. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. Arch Dis Child 2005; 90(4):411–4.

28. Warncke K, Fröhlich-Reiterer EE, Thon A, Hofer SE, Wiemann D, Holl RW. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: a multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database. Diabetes Care 2010; 33(9):2010–2.

29. Spaans E, Schroor E, Groenier K, Bilo H, Kleefstra N, Brand P. Thyroid Disease and Type 1 Diabetes in Dutch Children: A Nationwide Study (Young Dudes-3). J Pediatr 2017; 187:189-193.e1.

30. Karavanaki K, Kakleas K, Paschali E, Kefalas N, Konstantopoulos I, Petrou V et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res 2009; 71(4):201–6.

31. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with Type 1 diabetes mellitus. Diabet Med 2002; 19(1):70–3.

32. 12. Children and Adolescents: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018; 41(Suppl 1):S126-S136.

33. Aktay AN, Lee PC, Kumar V, Parton E, Wyatt DT, Werlin SL. The prevalence and clinical characteristics of celiac disease in juvenile diabetes in Wisconsin. J Pediatr Gastroenterol Nutr 2001; 33(4):462–5.

34. Al-Ashwal AA, Shabib SM, Sakati NA, Attia NA. Prevalence and characteristics of celiac disease in type I diabetes mellitus in Saudi Arabia. Saudi Med J 2003; 24(10):1113–5.

35. Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F, Sacchetti C. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. Diabetes Care 2004; 27(6):1294–8.

36. Fröhlich-Reiterer EE, Hofer S, Kaspers S, Herbst A, Kordonouri O, Schwarz H-P et al. Screening frequency for celiac disease and autoimmune thyroiditis in children and adolescents with type 1 diabetes mellitus--data from a German/Austrian multicentre survey. Pediatr Diabetes 2008; 9(6):546–53.

37. Fröhlich-Reiterer EE, Kaspers S, Hofer S, Schober E, Kordonouri O, Pozza SB-D et al. Anthropometry, metabolic control, and follow-up in children and adolescents with type 1 diabetes mellitus and biopsy-proven celiac disease. J Pediatr 2011; 158(4):589-593.e2.

38. Abid N, McGlone O, Cardwell C, McCallion W, Carson D. Clinical and metabolic effects of gluten free diet in children with type 1 diabetes and coeliac disease. Pediatr Diabetes 2011; 12(4 Pt 1):322–5.

39. Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith G, Bloch C et al. Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth. Diabetes Care 2007; 30(3):503–9.

40. Gale EAM. The rise of childhood type 1 diabetes in the 20th century. Diabetes 2002; 51(12):3353–61.

41. Dahlquist GG, Patterson C, Soltesz G. Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group. Diabetes Care 1999; 22(10):1698–702.

42. Prevention of type 1 diabetes mellitus - UpToDate [cited 2018 May 4]. Available from: URL: https://www.uptodate.com/contents/prevention-of-type-1-diabetes-mellitus/print.

43. Virtanen SM, Saukkonen T, Savilahti E, Ylönen K, Räsänen L, Aro A et al. Diet, cow's milk protein antibodies and the risk of IDDM in Finnish children. Childhood Diabetes in Finland Study Group. Diabetologia 1994; 37(4):381–7.

44. Elliott RB, Harris DP, Hill JP, Bibby NJ, Wasmuth HE. Type I (insulin-dependent) diabetes mellitus and cow milk: casein variant consumption. Diabetologia 1999; 42(3):292–6.

45. Cavallo MG, Fava D, Monetini L, Barone F, Pozzilli P. Cell-mediated immune response to beta casein in recent-onset insulin-dependent diabetes: implications for disease pathogenesis. Lancet 1996; 348(9032):926–8.

46. Hummel M, Füchtenbusch M, Schenker M, Ziegler AG. No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German BABYDIAB Study. Diabetes Care 2000; 23(7):969–74.

47. Couper JJ, Steele C, Beresford S, Powell T, McCaul K, Pollard A et al. Lack of association between duration of breast-feeding or introduction of cow's milk and development of islet autoimmunity. Diabetes 1999; 48(11):2145–9.

48. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group. Diabetologia 1999; 42(1):51–4.

49. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001; 358(9292):1500–3.

50. Davis MR, Mellman M, Shamoon H. Further Defects in Counterregulatory Responses Induced by Recurrent Hypoglycemia in IDDM. Diabetes 1992; 41(10):1335–40.

51. Davis SN, Galassetti P, Wasserman DH, Tate D. Effects of antecedent hypoglycemia on subsequent counterregulatory responses to exercise. Diabetes 2000; 49(1):73–81.

52. Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993; 42(11):1683–9.

53. Complications and screening in children and adolescents with type 1 diabetes mellitus - UpToDate; 2018 [cited 2018 May 8]. Available from: URL: https://www.uptodate.com/contents/complications-and-screening-in-children-and-adolescents-with-type-1-diabetes-mellitus.

54. Hypoglycemia in children and adolescents with type 1 diabetes mellitus - UpToDate; 2018 [cited 2018 May 8]. Available from: URL: https://www.uptodate.com/contents/hypoglycemia-in-children-and-adolescents-with-type-1-diabetes-mellitus.

55. Tsalikian E, Tamborlane W, Xing D, Becker DM, Mauras N, Fiallo-Scharer R et al. Blunted counterregulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes. Diabetes Care 2009; 32(11):1954–9.

56. Lipton R, Good G, Mikhailov T, Freels S, Donoghue E. Ethnic differences in mortality from insulin-dependent diabetes mellitus among people less than 25 years of age. Pediatrics 1999; 103(5 Pt 1):952–6.

57. Glycemic control and vascular complications in type 1 diabetes mellitus - UpToDate; 2018 [cited 2018 May 9]. Available from: URL: https://www.uptodate.com/contents/glycemic-control-and-vascular-complications-in-type-1-diabetes-mellitus.

58. Maahs DM, Daniels SR, Ferranti SD de, Dichek HL, Flynn J, Goldstein BI et al. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation 2014; 130(17):1532–58.

59. Barzilay J, Warram JH, Bak M, Laffel LM, Canessa M, Krolewski AS. Predisposition to hypertension: risk factor for nephropathy and hypertension in IDDM. Kidney Int 1992; 41(4):723–30.

60. Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014; 37(7):2034–54.

61. Schultz CJ, Konopelska-Bahu T, Dalton RN, Carroll TA, Stratton I, Gale EA et al. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. Diabetes Care 1999; 22(3):495–502.

62. Amin R, Widmer B, Prevost AT, Schwarze P, Cooper J, Edge J et al. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. BMJ 2008; 336(7646):697–701.

63. Costacou T, Orchard TJ. Cumulative Kidney Complication Risk by 50 Years of Type 1 Diabetes: The Effects of Sex, Age, and Calendar Year at Onset. Diabetes Care 2018; 41(3):426–33.

64. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14):977–86.

65. Ramsay RC, Goetz FC, Sutherland DE, Mauer SM, Robison LL, Cantrill HL et al. Progression of diabetic retinopathy after pancreas transplantation for insulin-dependent diabetes mellitus. N Engl J Med 1988; 318(4):208–14.

66. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. Ophthalmology 1995; 102(4):647–61.

67. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993; 329(5):304–9.

68. Amthor KF, Dahl-Jørgensen K, Berg TJ, Heier MS, Sandvik L, Aagenaes O et al. The effect of 8 years of strict glycaemic control on peripheral nerve function in IDDM patients: the Oslo Study. Diabetologia 1994; 37(6):579–84.

69. The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 1995; 122(8):561–8.

70. Nathan DM, Bayless M, Cleary P, Genuth S, Gubitosi-Klug R, Lachin JM et al. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes 2013; 62(12):3976–86.

71. Clinical presentation and diagnosis of diabetes mellitus in adults - UpToDate; 2018 [cited 2018 May 8]. Available from: URL: https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-diabetes-mellitus-in-adults.

72. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2017; 40(Suppl 1):S11-S24.

73. Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycemia and implications for the classification of diabetes. Arch Intern Med 2007; 167(14):1545–51.

74. Diabetes mellitus [cited 2018 Nov 11]. Available from: URL: https://www.amboss.com/de/wissen/Diabetes_mellitus.

75. Management of blood glucose in adults with type 1 diabetes mellitus - UpToDate; 2018 [cited 2018 May 8]. Available from: URL: https://www.uptodate.com/contents/management-of-blood-glucose-in-adults-with-type-1-diabetes-mellitus.

76. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 1998; 128(7):517–23.

77. Egger M, Davey Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. Diabet Med 1997; 14(11):919–28.

78. Nathan DM, Cleary PA, Backlund J-YC, Genuth SM, Lachin JM, Orchard TJ et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353(25):2643–53.

79. Self-monitoring of blood glucose in management of adults with diabetes mellitus - UpToDate; 2018 [cited 2018 May 24]. Available from: URL: https://www.uptodate.com/contents/self-monitoring-of-blood-glucose-in-management-of-adults-with-diabetes-mellitus.

80. Kuo C-Y, Hsu C-T, Ho C-S, Su T-E, Wu M-H, Wang C-J. Accuracy and precision evaluation of seven self-monitoring blood glucose systems. Diabetes Technol Ther 2011; 13(5):596–600.

81. Brunner GA, Ellmerer M, Sendlhofer G, Wutte A, Trajanoski Z, Schaupp L et al. Validation of home blood glucose meters with respect to clinical and analytical approaches. Diabetes Care 1998; 21(4):585–90.

82. Trajanoski Z, Brunner GA, Gfrerer RJ, Wach P, Pieber TR. Accuracy of home blood glucose meters during hypoglycemia. Diabetes Care 1996; 19(12):1412–5.

83. Desachy A, Vuagnat AC, Ghazali AD, Baudin OT, Longuet OH, Calvat SN et al. Accuracy of bedside glucometry in critically ill patients: influence of clinical characteristics and perfusion index. Mayo Clin Proc 2008; 83(4):400–5.

84. Fineberg SE, Bergenstal RM, Bernstein RM, Laffel LM, Schwartz SL. Use of an automated device for alternative site blood glucose monitoring. Diabetes Care 2001; 24(7):1217–20.

85. Jungheim K, Koschinsky T. Glucose monitoring at the arm: risky delays of hypoglycemia and hyperglycemia detection. Diabetes Care 2002; 25(6):956–60.

86. Ellison JM, Stegmann JM, Colner SL, Michael RH, Sharma MK, Ervin KR et al. Rapid changes in postprandial blood glucose produce concentration differences at finger, forearm, and thigh sampling sites. Diabetes Care 2002; 25(6):961–4.

87. Jendrike N, Baumstark A, Pleus S, Mende J, Haug C, Freckmann G. Assessment of System Accuracy, Intermediate Measurement Precision, and Measurement Repeatability of a Blood Glucose Monitoring System Based on ISO 15197. J Diabetes Sci Technol 2019; 13(2):235–41.

88. Moser O, Pandis M, Aberer F, Kojzar H, Hochfellner D, Elsayed H et al. A head-to-head comparison of personal and professional continuous glucose monitoring systems in

people with type 1 diabetes: Hypoglycaemia remains the weak spot. Diabetes Obes Metab 2018.

89. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. Diabetes Care 2005; 28(5):1231–9.

90. Hirsch IB. Clinical review: Realistic expectations and practical use of continuous glucose monitoring for the endocrinologist. J Clin Endocrinol Metab 2009; 94(7):2232–8.

91. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018; 41(Suppl 1):S55-S64.

92. Ritholz MD, Atakov-Castillo A, Beste M, Beverly EA, Leighton A, Weinger K et al. Psychosocial factors associated with use of continuous glucose monitoring. Diabet Med 2010; 27(9):1060–5.

93. Klonoff DC, Buckingham B, Christiansen JS, Montori VM, Tamborlane WV, Vigersky RA et al. Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; 96(10):2968–79.

94. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018; 391(10128):1367–77.

95. Monsod TP, Flanagan DE, Rife F, Saenz R, Caprio S, Sherwin RS et al. Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? Diabetes Care 2002; 25(5):889–93.

96. Damiano ER, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors. Diabetes Care 2013; 36(2):251–9.

97. Damiano ER, McKeon K, El-Khatib FH, Zheng H, Nathan DM, Russell SJ. A comparative effectiveness analysis of three continuous glucose monitors: the Navigator, G4 Platinum, and Enlite. J Diabetes Sci Technol 2014; 8(4):699–708.

98. Maahs DM, DeSalvo D, Pyle L, Ly T, Messer L, Clinton P et al. Effect of acetaminophen on CGM glucose in an outpatient setting. Diabetes Care 2015; 38(10):e158-9.

99. Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia 2008; 51(6):941–51.

100. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 2002; 324(7339):705.

101. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab 2009; 94(3):729–40.

102. Yeh H-C, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012; 157(5):336–47.

103. Tsui E, Barnie A, Ross S, Parkes R, Zinman B. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabetes Care 2001; 24(10):1722–7.

104. Insulin Basics [cited 2018 May 24]. Available from: URL: http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html.

105. Insulin Types and Information; 2018 [cited 2018 May 24]. Available from: URL: https://www.diabetes.co.uk/insulin/insulin-types.html.

106. org JDCwj. Joslin Diabetes Center | Different Types of Insulin; 2018 [cited 2018 May 24]. Available from: URL: http://www.joslin.org/info/insulin_a_to_z_a_guide_on_different_types_of_insulin.html.

107. Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care 1999; 22(3):468–77.

108. Davis A, Kuriakose J, Clements JN. Faster Insulin Aspart: A New Bolus Option for Diabetes Mellitus. Clin Pharmacokinet 2018.

109. NPH insulin - Wikipedia; 2018 [cited 2018 May 24]. Available from: URL: https://en.wikipedia.org/w/index.php?oldid=823027114.

110. gebrauchsinformation_humalog_mix_25_100_eml_kwikpen [cited 2019 Feb 25]. Available from: URL: https://www.lilly-pharma.de/de/pdf/gebrauchsinformationen/endokrinologie/gebrauchsinformation_humalog_mix_25_100_eml_kwikpen.pdf.

111. Plank J, Siebenhofer A, Berghold A, Jeitler K, Horvath K, Mrak P et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. Arch Intern Med 2005; 165(12):1337–44.

112. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009; 180(4):385–97.

113. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. Cochrane Database Syst Rev 2016; (6):CD012161.

114. Colquitt J, Royle P, Waugh N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. Diabet Med 2003; 20(10):863–6.

115. Hildebrandt P, Birch K, Jensen BM, Kühl C. Subcutaneous insulin infusion: change in basal infusion rate has no immediate effect on insulin absorption rate. Diabetes Care 1986; 9(6):561–4.

116. Mecklenburg RS, Benson EA, Benson JW, Blumenstein BA, Fredlund PN, Guinn TS et al. Long-term metabolic control with insulin pump therapy. Report of experience with 127 patients. N Engl J Med 1985; 313(8):465–8.

117. Mecklenburg RS, Benson JW, Becker NM, Brazel PL, Fredlund PN, Metz RJ et al. Clinical use of the insulin infusion pump in 100 patients with type I diabetes. N Engl J Med 1982; 307(9):513–8.

118. Doyle EA, Weinzimer SA, Steffen AT, Ahern JAH, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin

infusion with multiple daily injections using insulin glargine. Diabetes Care 2004; 27(7):1554–8.

119. Kaufman FR, Halvorson M, Kim C, Pitukcheewanont P. Use of insulin pump therapy at nighttime only for children 7-10 years of age with type 1 diabetes. Diabetes Care 2000; 23(5):579–82.

120. Sindelka G, Heinemann L, Berger M, Frenck W, Chantelau E. Effect of insulin concentration, subcutaneous fat thickness and skin temperature on subcutaneous insulin absorption in healthy subjects. Diabetologia 1994; 37(4):377–80.

121. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013; 369(3):224–32.

122. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013; 310(12):1240–7.

123. Bekiari E, Kitsios K, Thabit H, Tauschmann M, Athanasiadou E, Karagiannis T et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ 2018; 361:k1310.

124. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME et al. Home Use of an Artificial Beta Cell in Type 1 Diabetes. N Engl J Med 2015; 373(22):2129–40.

125. El-Khatib FH, Balliro C, Hillard MA, Magyar KL, Ekhlaspour L, Sinha M et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet 2017; 389(10067):369–80.

126. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014; 371(4):313–25.

127. Automated Insulin Delivery; 2014 [cited 2018 May 31]. Available from: URL: https://diatribe.org/automated-insulin-delivery.

128. First Look at Lilly’s Automated Insulin Delivery System; 2018 [cited 2018 May 31]. Available from: URL: https://diatribe.org/sneak-peek-lillys-automated-insulin-delivery-system.

129. MiniMed 670G Insulin Pump System | World's First Hybrid Closed Loop System; 2018 [cited 2018 May 31]. Available from: URL: https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system.

130. Helve E, Pelkonen R, Koivisto VA. Overnight interruption of wearing insulin pump: substitution dose and injection site of insulin. Diabetes Care 1986; 9(6):565–9.

131. Mecklenburg RS, Benson EA, Benson JW, Fredlund PN, Guinn T, Metz RJ et al. Acute complications associated with insulin infusion pump therapy. Report of experience with 161 patients. JAMA 1984; 252(23):3265–9.

132. Mecklenburg RS, Guinn TS, Sannar CA, Blumenstein BA. Malfunction of continuous subcutaneous insulin infusion systems: a one-year prospective study of 127 patients. Diabetes Care 1986; 9(4):351–5.

133. Pein M, Hinselmann C, Pfützner A, Dreyer M. Catheter disconnection in type 1 diabetic patients treated with CSII: comparison of insulin lispro and human regular insulin. Diabetologia 1996; 39(suppl 1):847.

134. History of Pump Technology - Medscape [cited 2018 Aug 24]. Available from: URL: https://www.medscape.org/viewarticle/460365_2.

135. Insulin pump - Wikipedia; 2018 [cited 2018 Aug 24]. Available from: URL: https://en.wikipedia.org/w/index.php?oldid=856115663.

136. Hauzenberger JR, Münzker J, Kotzbeck P, Asslaber M, Bubalo V, Joseph JI et al. Systematic in vivo evaluation of the time-dependent inflammatory response to steel and Teflon insulin infusion catheters. Sci Rep 2018; 8(1):1132.

137. Ponder SW, Skyler JS, Kruger DF, Della Matheson, Brown BW. Unexplained hyperglycemia in continuous subcutaneous insulin infusion: evaluation and treatment. Diabetes Educ 2008; 34(2):327–33.

138. Pfützner A, Sachsenheimer D, Grenningloh M, Heschel M, Walther-Johannesen L, Gharabli R et al. Using Insulin Infusion Sets in CSII for Longer Than the Recommended Usage Time Leads to a High Risk for Adverse Events: Results From a Prospective Randomized Crossover Study. J Diabetes Sci Technol 2015; 9(6):1292–8.

139. Schmid V, Hohberg C, Borchert M, Forst T, Pfützner A. Pilot study for assessment of optimal frequency for changing catheters in insulin pump therapy-trouble starts on day 3. J Diabetes Sci Technol 2010; 4(4):976–82.

140. Kerr D, Morton J, Whately-Smith C, Everett J, Begley JP. Laboratory-based non-clinical comparison of occlusion rates using three rapid-acting insulin analogs in continuous subcutaneous insulin infusion catheters using low flow rates. J Diabetes Sci Technol 2008; 2(3):450–5.

141. Gibney M, Xue Z, Swinney M, Bialonczyk D, Hirsch L. Reduced Silent Occlusions with a Novel Catheter Infusion Set (BD FlowSmart): Results from Two Open-Label Comparative Studies. Diabetes Technol Ther 2016; 18(3):136–43.

142. Heinemann L, Fleming GA, Petrie JR, Holl RW, Bergenstal RM, Peters AL. Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting, and research needs: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetes Care 2015; 38(4):716–22.

143. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes Care 2003; 26(4):1079–87.

144. Pfützner A, Berger S, Spinas G. Aktueller Stellenwert der kontinuierlichen subkutanen Insulininfusion (CSII) mit Insulinpumpen in der Therapie des Diabetes mellitus. Schweiz Med Wochenschr 2000; 130(48):1854–61.

145. Pickup JC, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care 2008; 31 Suppl 2:S140-5.

146. Berthe E, Lireux B, Coffin C, Goulet-Salmon B, Houlbert D, Boutreux S et al. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. Horm Metab Res 2007; 39(3):224–9.

147. Bruttomesso D, Costa S, Baritussio A. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. Diabetes Metab Res Rev 2009; 25(2):99–111.

148. Hoogma RP, Schumicki D. Safety of insulin glulisine when given by continuous subcutaneous infusion using an external pump in patients with type 1 diabetes. Horm Metab Res 2006; 38(6):429–33.

149. Renner R, Pfützner A, Trautmann M, Harzer O, Sauter K, Landgraf R. Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Results of a multicenter trial. German Humalog-CSII Study Group. Diabetes Care 1999; 22(5):784–8.

150. Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P et al. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care 2005; 28(3):533–8.

151. Raskin P, Holcombe JH, Tamborlane WV, Malone JI, Strowig S, Ahern JA et al. A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. J Diabetes Complicat 2001; 15(6):295–300.

152. Weisman A, Bai J-W, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. The Lancet Diabetes & Endocrinology 2017; 5(7):501–12.

153. Stuart CA, Shangraw RE, Prince MJ, Peters EJ, Wolfe RR. Bed-rest-induced insulin resistance occurs primarily in muscle. Metab Clin Exp 1988; 37(8):802–6.

154. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. Metab Clin Exp 2011; 60(7):941–9.

155. Swan KL, Dziura JD, Steil GM, Voskanyan GR, Sikes KA, Steffen AT et al. Effect of age of infusion site and type of rapid-acting analog on pharmacodynamic parameters of insulin boluses in youth with type 1 diabetes receiving insulin pump therapy. Diabetes Care 2009; 32(2):240–4.

156. Hauzenberger JR, Hipszer BR, Loeum C, McCue PA, DeStefano M, Torjman MC et al. Detailed Analysis of Insulin Absorption Variability and the Tissue Response to Continuous Subcutaneous Insulin Infusion Catheter Implantation in Swine. Diabetes Technol Ther 2017; 19(11):641–50.

157. Edsberg B, Herly D, Hildebrandt P, Kühl C. Insulin bolus given by sprinkler needle: effect on absorption and glycaemic response to a meal. Br Med J (Clin Res Ed) 1987; 294(6584):1373–6.