Diploma thesis

Time in range for fully closed-loop systems versus current care during physical exercise in type 1 diabetes: a systematic review and meta-analysis

Submitted by

Benjamin Weilguni

in order to attain the academic degree

„Doctor medicinae universae“

(Dr. med. univ.)

at the

Medical University of Graz

conducted at the

Division of Endocrinology and Diabetology

under the supervision of

Univ.-Prof. Priv.-Doz. Mag. Dr. Othmar Moser

and

Dr. Max Lennart Eckstein, MSc

Graz, 06.09.2021

Statutory Declaration

I hereby declare that this diploma thesis is my own original work and that I have fully acknowledged by name all those individuals and organizations that have contributed to the research for this diploma thesis. Due acknowledgement has been made in the text to all other material used. Throughout this diploma thesis and in all related publications I followed the guidelines of "Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

Graz, am 06.09.2021 *Benjamin Weilguni eh.*

Acknowledgements

Ich möchte mich an dieser Stelle bei allen bedanken, die mich beim Verfassen dieser Diplomarbeit unterstützt haben.
Insbesondere möchte ich mich bei meinen beiden Betreuern Othmar Moser und Max Lennart Eckstein bedanken, die es mir ermöglichten, dieses Thema zu bearbeiten und mich immer mit viel Engagement begleitetet haben.
Ein weiteres großes Dankeschön gilt meiner ganzen Familie und vor allem meinen Eltern, die mir diese Ausbildung nicht nur ermöglichten, sondern mich auch zu jedem Zeitpunkt voll unterstützten.

Table of contents

Abbreviations

T1D	type 1 diabetes
T2D	type 2 diabetes
CLS	closed-loop system
HCL	hybrid closed-loop system
CGM	continuous glucose monitoring
ADA	American Diabetes Association
PZI	Protamine zinc insulin
NPH	neutral protamine Hagedorn
SMBG	self-monitoring of blood glucose
PLGS	predictive low-glucose suspend system
MDI	multiple daily injection
CSII	continuous subcutaneous insulin infusion
SAP	sensor-augmented pump therapy
LGS	low-glucose suspend
CI	confidence interval
AP	artificial pancreas
APX	AP with exercise dosing adjustments
DiAs	Diabetes Assistant
VO_{2max}	maximal oxygen consumption

Index of figures

Index of tables

Abstract [German]

Hintergrund und Ziele

Körperliche Aktivität geht oft mit unterschiedlichsten Reaktionen des Glukosestoffwechsels und damit schnellen Änderungen des Blutglukosespiegels einher. Dies ist auch der Grund warum es für Menschen mit Typ 1 Diabetes (T1D) so schwierig ist, den Blutglukosespiegel in diesen Phasen zu stabilisieren. Closed-loop Systeme (CLS) haben gezeigt, dass sie unter normalen Umweltbedingungen eine verbesserte Kontrolle der Blutglukosespiegel erreichen, doch wie gut diese Systeme während körperlicher Aktivität funktionieren, ist nach wie vor fraglich. Daher ist das Ziel dieser systematischen Übersicht und Metaanalyse zu untersuchen, ob CLS die Zeit in einem euglykämischen Bereich (70–180 mg/dL [3.9–10.0 mmol/L]) im Vergleich zu aktuell verwendeten Behandlungen bei Menschen mit T1D während körperlicher Aktivität verbessern.

Material und Methoden

Eine systematische Literaturrecherche wurde auf den Websites PubMed, Cochrane Central Register of Controlled Trials, ISI Web of Knowledge und EMBASE für den Zeitraum von 1950 – Jänner 2020 durchgeführt. Zwei Wissenschaftler wählten unabhängig voneinander relevante Studien aus, extrahierten die notwendigen Daten und bewerteten sie in Hinblick auf methodische Qualität und Evidenzniveau. Es wurden randomisiert kontrollierte Studien inkludiert, in welchen CLS zu aktuell verwendeten Behandlungen von Menschen mit T1D während körperlicher Aktivität verglichen wurden. Die Metaanalyse wurde mit Verwendung des „random effects“ Models und der „restricted maximum likelihood estimation“ Methode durchgeführt. Die Heterogenität wurde mittels Cochrane’s Q Test (T2) und I^2 Statistik erhoben.

Ergebnisse

Sechs randomisiert kontrollierte Studien, mit 153 Menschen mit T1D aus allen Altersgruppen wurden inkludiert. Aufgrund von Crossover-Testdesigns wurden Studien mit mehreren Interventions- oder Vergleichsgruppen mehrfach inkludiert (a-d). Durch Anwendung dieser Methode erhöhte sich die Anzahl an zu vergleichenden Proband*innen auf 266. CLS zeigten mit einem absoluten Mittelwertunterschied von 617%, 95% Konfidenzintervall [1.60, 10.75%] ($p<0.01$) eine signifikant verbesserte Zeit im euglykämischen Bereich während körperlicher Aktivität. T2 zeigte, dass die eingeschlossenen Studien keine gemeinsame Effektgröße aufwiesen ($p<0.10$). I2 (82%) und das Vorhersageintervall von -7.91, 20,26 deuteten auf eine hohe Variabilität in den Ergebnissen der inkludierten Studien hin.

Diskussion

Dies ist die erste systematische Übersicht und Metaanalyse, in der hervorgehoben wird, dass CLS bei Menschen mit T1D die Zeit in einem euglykämsichen Bereich, im Vergleich zu derzeitigen Behandlungsschemata, verbessert. Unsere Ergebnisse zeigen, dass CLS auch während glykämisch anspruchsvolleren Perioden eingesetzt werden können. Die Heterogenität der inkludierten Studien kann durch die Vielzahl an verwendeten Systemen, sportlichen Aktivitäten, Insulin Pumpen und Algorithmen erklärt werden. CLS zeigten sich als sehr sichere und effektive Behandlungsmethode, doch aufgrund der geringen Anzahl an inkludierten Studien und der Heterogenität der Ergebnisse, sind weitere Studien in diesem Bereich unbedingt notwendig, um ein fundiertes Ergebnis zu erhalten.

Abstract

Background and aims

Fully closed-loop systems (CLS) are an attempt to replace the physiological role of pancreatic ß-cells in people with type 1 diabetes (T1D). CLS have shown to improve glycemic control under environmental conditions, however, during physical activity the performance of these systems is questionable since high change rates in glucose and varying glucose responses during physical activity might be limiting factors. Therefore, the aim of this work is to perform a systematic review and meta-analysis, evaluating if CLS improve the time spent in an euglycemic range (70–180 mg/dL [3.9–10.0 mmol/L]) compared to current care during physical activity in people with T1D.

Materials and methods

A systematic literature search, from January 1950 until January 2020, was conducted in PubMed, Cochrane Central and Register of Controlled Trials, ISI Web of Knowledge and EMBASE. Studies were extracted, assessed for eligibility, methodological quality, and level of evidence by two independently working researchers. Fit for inclusion were randomized controlled trials in which CLS were compared against current care during physical activity in people with T1D. In order to perform the meta-analysis, the random effects model and restricted maximum likelihood estimation method were used. Heterogeneity of included studies was assessed using the I^2 statistics and Cochran's Q Test (T^2).

Results

Six randomized controlled trials with a total of 153 participants with T1D were included. By repeatedly including studies (a-d), which used different CLS or exercise interventions in crossover test designs, the comparisons were doubled to an overall number of 266.

With an absolute mean difference of 6.17%, (95% confidence interval (CI): 1.60, 10.75%; $p<0.01$), CLS showed a significantly higher TIR compared to current care.

The Cochrane's Q Test of $p<0.10$, showed, that the included studies did not share a common effect size. Further, the prediction interval of -7.91, 20.26 and I^2 (82%) indicated a significant variation in TIR across the included studies.

Conclusion

This is the first systematic review and meta-analysis conducted on this topic, showing superior performance of CLS compared to current care during physical activity in people with T1D. Our results prove that CLS are a safe and efficacious treatment option even during periods in which glucose responses are more unpredictable. Due to the heterogeneity of the study results, which can be explained by the variety in devices, exercise tasks, insulin pumps and algorithms, our results should not be seen conclusively, giving clear implications for the necessity of further research.

Publication:

Parts of this diploma thesis have been published as:

Eckstein, M.L.; Weilguni, B.; Tauschmann, M.; Zimmer, R.T.; Aziz, F.; Sourij, H.; Moser, O. Time in Range for Closed-Loop Systems versus Standard of Care during Physical Exercise in People with Type 1 Diabetes: A Systematic Review and Meta-Analysis. J. Clin. Med. 2021, 10, 2445. https://doi.org/10.3390/ jcm10112445

My contributions to this publication:

Starting with the systematic literature search, which was performed by myself in cooperation with my second supervisor Dr. Max Lennart Eckstein, MSc, I extracted all found records (in total 1476) into an excel sheet. All found studies were screened for eligibility on title, abstract and full-text level, by myself and my second supervisor, each working independently of the other. After the screening, disagreements were resolved by consensus between me and my second supervisor Dr. Max Lennart Eckstein, MSc and respectively after discussion with my primary supervisor Univ.-Prof. Priv.-Doz. Mag. Dr. Othmar Moser. For the studies included, I extracted all relevant information needed for our meta-analysis, performed the risk of bias assessment with the corresponding graphics, created the Prisma-flow diagram, Prisma 2009 statement, the tables for study characteristics and secondary outcomes. Always under the guidance and in close cooperation with my supervisors.
After conducting the statistical analysis (by statistician Aziz, Faisal, PhD), I independently interpreted the results and wrote this thesis, with approximate content specifications from my supervisors.

1 Introduction

The first written documentations of the disease nowadays known as “Diabetes mellitus” date back to 1500 B.C. (1). In antique Egyptian manuscripts the first clinical description of a polyuric conditions similar to diabetes mellitus is found, describing the symptoms as “too great emptying of urine” (1,2). A couple hundred years later, Indian physicians called the condition madhumeha (‘honey urine’), since they noticed that the sweet urine attracted ants (1,3). The term “diabetes” (Greek for siphon) was first mentioned by Aretaeus, a disciple of Hippocrates, in the first century A.D., who described the disease even more drastically: “… no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine” (1,4).

In those days, the pathophysiology behind diabetes was completely unclear and thought to be a very rare disease, however, the importance of exercise, life-style and diet were already promoted by Hippocrates as a concept of preventive medicine (4).

Diabetes mellitus was long thought to be a kidney disorder and has been correctly identified as a metabolic pathology in 1988 by Gerald M. Reaven during the Banting’s lecture (5). He first described the constellation of symptoms, nowadays called metabolic syndrome, combining diabetes, hypertension, central obesity, insulin resistance and impaired glucose tolerance (5).

In the so called “pre-insulin era”, the lack of understanding for the pathophysiology of diabetes mellitus and the limited therapeutic options resulted in various bizarre pharmacological treatments and dietary interventions trying to control the disease (5,6). For example, the use of opium as a treatment or based on the conviction that people with diabetes should compensate the urinary loss of calories, a French physician (Pierre Adolphe Piorry (1794-1879)) prescribed high-caloric diets in the 1850s (6).

However, some physician noticed that exactly the opposite of a high-caloric diet, namely fasting, resulted in the improvement of clinical symptoms of diabetes mellitus (5). Several different dietary approaches followed, for example, the so called “Allen diet”, by the American physician Frederick Madison Allen (1879– 1964). The Allen diet was based on a carbohydrate-restricted low-calorie diet or the so-called “starvation diet” by the American physician Elliott Proctor Joslin (1869–1962) who proposed a general prolonged fasting and under-nutrition or under-nourishment as a treatment for diabetes mellitus (5,7).

It was not until 1921, that Frederick Banting and Charles Best extracted the hormone insulin out of the islets of Langerhans of the pancreas and, for the first time in history, a truly

effective treatment for diabetes mellitus was available (5). Ever since this discovery 100 years ago, insulin has proven to be the most important medication for ensuring the survival of people with diabetes up until this day (8).

The exogenous insulin replacement and other technological developments made in the last century have led to diabetes becoming a well treatable disease. Long-term complications such as retinopathy, neuropathy, cardio-vascular diseases and acute hypoglycemia, however, still pose a challenge (8–10). The hope for the future is that the use of insulin analogues and mechanical technologies (e.g. insulin pumps, continuous glucose monitoring and (CGM) artificial pancreas (AP)) will more and more emulate the physiological role of the endocrine pancreas, hopefully, preventing complications and improving the quality life of people with diabetes mellitus (8–10).

1.1 Classification of Diabetes mellitus

In the last century, major advancements were made, not only regarding the treatment, but also in understanding the underlying pathophysiology of diabetes mellitus. Today, this allows us today to distinguish between different entities of the disease.

Type 1 Diabetes

Type 1 Diabetes (T1D) is defined as an absolute insulin deficiency due to an immune, if not autoimmune, mediated destruction of insulin producing β-cells in the Langerhans islets of the pancreas (11,12). Insulin itself is a peptide hormone which has the purpose of maintaining normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism, and further promoting cell division and growth through its mitogenic effects (13). Around 70-90% of people with T1D show immunological, self-reactive autoantibodies, leading to the proposed definition of type 1A (autoimmune) diabetes, whereas for the remaining, a specific pathogenesis remains unclear and is defined as type 1B (idiopathic) diabetes (14,15).

In 2014, T1D accounted only for 5% to 10% of the total population of people with diabetes (16). By the early 2000s studies have indicated a worldwide increase in both incidence and prevalence of T1D (17,18). While 15.000 new cases were estimated in Europe in 2005, the incidence in children under the age of five is predicted to nearly double by 2020, with a total of 24.400 new cases each year (17).

T1D has long been considered a disorder in children and adolescents. This opinion has changed over the past decades, so that the age of symptomatic onset is no longer a defining

factor in the diagnosis of T1D (19). The typical trio of symptoms associated with the disease onset are polydipsia, polyphagia, and polyuria together with overt hyperglycemia and ketonemia. These are primarily the diagnostic hallmarks in children and adolescents. In adults, in contrast, T1D shows a more gradual onset (20). Another characteristic of T1D is the need for immediate exogenous insulin replacement at disease onset and lifelong treatment due to the absolute lack of endogenously produced insulin (9). This is also the reason why "insulin-dependent diabetes mellitus" (IDDM) is often used as a synonym to T1D.

The diagnostic criteria of diabetes have historically included fasting blood glucose higher than 126 mg/dl (7 mmol/L), any blood glucose of 200 mg/dL (11.1 mmol/L) or higher with symptoms of hyperglycemia, or an abnormal 2h oral glucose-tolerance test (9,16). In 2009, the glycated hemoglobin (HbA_{1c}; representing the average glucose levels in the past 2-3 months) of 6.5% or higher has been included into the guidelines as a diagnostic criteria by the American Diabetes Association (ADA) (21).

Both, the absolute insulin deficiency and vice versa, the overdose of exogenous insulin, represent life-threatening situations. On the one hand, missing insulin leads to a lack of glucose uptake into the cells and therefore to hyperglycemia, dehydration, electrolyte imbalance and a compensatory ketoacidosis. On the other hand, an insulin overdose, if not compensated by carbohydrate intake, leads to hypoglycemia, again a life-threatening condition (9,22).

Besides these acute manifestations of diabetes, elevated blood glucose levels over a long period of time result in complications, which can be divided into the two categories of macro- and microvascular (9). Macrovascular complications are, for example, myocardial infarction, stroke or angina. The need for coronary artery revascularization is 10 times more likely to occur in people with T1D compared to the age-matched non-diabetic population (23). Microvascular complications include retinopathy, nephropathy, and neuropathy whose incidence is reduced by intensive insulin therapy (9).

This underlines once again the importance of fine-tuned glucose control, with the goal of keeping people with diabetes in an euglycemic range (blood glucose levels between 70-180 mg/dL (3.9-10 mmol/L)) and thereby not only preventing acute life-threatening situations but also long-term complications, which can be limiting factors on the quality of life of individuals with diabetes (9).

Other types of diabetes

The majority of people with diabetes (around 90%) suffer from type 2 diabetes (T2D), which is a heterogeneous and complex multi-systematic disorder (10). T2D can be described as a disease: "ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance" (24).

There is a variety of entities into which diabetes mellitus can be further classified. E.g., monogenic diabetes syndromes (e.g. neonatal diabetes and maturity-onset diabetes of the young), gestational diabetes: a glucose intolerance with onset or first recognition during pregnancy or diseases of the exocrine pancreas (e.g. pancreatitis). As these types of diabetes are not relevant for this thesis, they will not be discussed in further detail.

1.2 Advancements in treatment

Before the discovery and extraction of insulin, no effective pharmacological agents were available, ultimately leading to T1D being a deadly disease. In 1921, the first person to ever receive exogenous insulin was a 14-year-old boy called Leonard Thompson (25).

One of the problems in the early history of insulin was that only fast-acting insulin was available. To prevent long-term complications, e.g., ketoacidosis, reduction in growth of children, or diabetic dwarfism syndrome, multiple daily injections were required to keep the blood glucose level in an euglycemic range of 70-180 mg/dL (3.9-10 mmol/L). Therefore, the availability of an extended-action insulin was of utmost interest, resulting in the release of PZI (protamine zinc insulin), the first commercially available extended action insulin (25). In 1946, with the release of the second extended-action insulin, NPH (neutral protamine Hagedorn), the next major step in the development of insulin formulation was taken. The NPH insulin was shorter acting than PZI and could even be used in combination with regular (fast-acting) insulin (25).

In 1963, the first insulin pumps (portable systems to administer insulin subcutaneously) were introduced, however, only for research purposes. In the late 1970s first continuous subcutaneous insulin infusion (CSII) systems were commercially available (26,27). Advantages of the CSII systems compared to multiple-day insulin injections were e.g., the use of only one injection site for up to 72 hours, programmable insulin delivery, the use of short- or rapid-acting insulin and preventing peaks and absorption-related variability, which leads to a general improvement of glycemic control and quality of life (27).

In 1985, a pharma company introduced the first insulin pen delivery system; the NovoPen®. It offered a more convenient and quicker option for the administration of insulin than the previously used conventional syringes (28).

Before the 1980s, all available insulin preparations were derived from animal sources, mostly pigs and cows. This changed in the 1980s with the introduction of human insulin analogues. Due to their similarity to actual human insulin, these human insulin analogues were hoped to have the advantage of little or no immunogenicity in people with diabetes, ruling out rare cases of insulin resistance and insulin allergy. However, the available data on this topic does not seem to be conclusive (29).

Furthermore, the release of human insulin analogues allowed, firstly, genetic modifications in order to optimize the absorption, distribution, metabolism and excretion of insulin, and secondly, the introduction of the "basal-bolus" concept (5). The goal was to emulate the physiological insulin secretory patterns, having a constant but small release of insulin and prandial bolus insulin in an attempt to mimic the physiological insulin secretion after food intake (25,30).

In 1996, "Lispro" the first commercially available human rapid-acting insulin was released under the brand name Humalog (5).

Advancements in technology for self-testing of glucose levels in people with diabetes were continuously driven forward, especially during the second half of the 20th century. Starting with semi quantitative tests using urinary dry-reagents, followed by blood glucose dry-reagent tests, introduced in the 1960s, which used a drop of blood and changed color in relation to glucose levels. The first digital blood glucose meter "Ames Reflectance Meter" (ARM), weighing 1.2 kg, became available in 1970. The following decades were an active phase in the evolution of blood glucose meters, which were becoming easier to use, smaller in size, with more variation in design and more sophisticated software and measuring methods. These systems enabled people with diabetes to continuously monitor their blood glucose levels and administer insulin accordingly. Self-monitoring of blood glucose (SMBG) became the standard of care, especially for people with T1D. They, however, have the disadvantage of requiring multiple finger prick tests every day for the span of a lifetime (31,32).

In 1999, home glucose monitoring was revolutionized with the introduction of the first continuous glucose monitoring (CGM) system. A wearable system, using interstitial fluids, collected by a needle inserted into the skin that only needs to be changed every few days to continuously measure body glucose levels. In the following years, as the systems got more

and more sophisticated, various companies brought their products to the market, e.g. in 2004, the Guardian REAL-Time CGM system by Medtronic, which has the ability to notify users of hyperglycemia and hypoglycemia via alarms. In 2006, Medtronic also released the first integrated pump and sensor (32).

In 2013, the University of Cambridge presented the first commercially available system linking CGM and insulin pumps; the MiniMed 530G. The so-called sensor-augmented pump (SAP) provided glucose values from the CGM system. A low glucose suspend (LGS) feature is activated when sensor glucose reaches an actual or predicted glucose threshold set by the user ((pre-)hypoglycemia), stopping the insulin delivery (27). Initially, the goal was to prevent nocturnal hypoglycemia with insulin suspension, however, these systems have proven to improve glycemic control, reducing HbA_{1c} levels and reducing the risk and duration of hypoglycemia in hypoglycemia-prone people (33–35).

The next major step in mimicking the physiological role of the pancreas was made in September 2016 when the MiniMed 670G received FDA approval and was first commercially available in the US. Three years later, in June 2019, it was also available in Austria. This hybrid closed-loop system (HCL) or "artificial pancreas" is working with an even more sophisticated algorithm (36). The system is delivering insulin in a glucose-responsive fashion by automatically modifying the insulin infusion rate based on the sensor glucose levels, however, still giving the user the opportunity to intervene manually. Therefore, being a not a fully closed-loop system. Another possibility of the CLS-technology is the administration of not only insulin (single-hormone) but the combination with glucagon (increases blood glucose levels) or other hormones (dual-hormone) in a similar glucose-responsive manner (37). Studies have shown advancements in time spent in an euglycemic range 70-180 mg/dL (3.9-10 mmol/L) and reducing both hypoglycemia and hyperglycemia in people with T1D comparing CLS with SAP therapy during everyday-life and especially during the night (38,39). Despite these promising prospects, high rates of change in blood glucose, as they occur during physical exercise, might be a limiting factor to the performance of CLS.

1.3 Type 1 diabetes and physical activity

Physical activity has been controversially discussed for a long time in people with T1D. Studies have clearly shown beneficial effects of physical activity with respect to diabetes-related comorbidities and cardiovascular risk factors, however, associating physical activity with increased occurrence of severe hypoglycemia and coma (40,41). Several governmental and healthcare organizations acknowledge the importance of regular physical activity as an additionally beneficial factor for glucose management in people with T1D, nevertheless, the exercise participation rates remain low (40,42,43). During physical activity, various physiological difficulties in glucose metabolism lead to glycemic disturbances. Together with cardiorespiratory fitness and the fear of severe hypoglycemia, these reasons are cited as barriers to long-term participation in regular physical activity in people with T1D (44,45). Studies assessing the effects of physical activity on the overall glycemic control (measured with HbA_{1c} levels) have shown mixed results, with some demonstrating benefits (46,47) and others not (48,49). Fact is, for overall enhanced glycemic control, people with T1D are required to precisely balance insulin and food intake in a very individual way before, during and after physical activity (50).

Despite all pharmaceutical and technological improvements in the therapy of T1D, glycemic management during physical activity still poses a challenge. It even goes so far as preventing people with T1D to get engaged in regular physical activity, limiting the chances of positive effects on T1D related pathological complications (44).

Addressing the highly variable glucose responses during and after physical activity, closed-loop insulin delivery systems may present a solution. Continuously adapting insulin delivery in response to momentarily measured interstitial glucose levels may provide the necessary safety and efficacy in glycemic control, eliminating barriers for people with T1D to be physically active.

Despite these promising assumptions, CLS face several obstacles that still need to be addressed, e.g., studies have indicated a time lag between subcutaneous interstitial fluid and plasma glucose, which results in delayed CGM glucose measurements compared to the actual blood glucose level (51,52). This would subsequently lead to a delayed intervention of the CLS on rapidly changing glucose levels in the blood. The overall latency from physiologic and sensor-based glucose measurements may range at least from 8-10 min to above 20 min, which could detail a problem during physical activity where rapid changes in blood glucose levels are common (53,54).

Furthermore, despite the steadily improved precision and accuracy of CGM systems, these measurements still present limitations (55). Factors like the impact of the foreign body response or the influence of local effects such as skin temperature, movements and pressure may significantly influence the observed subcutaneous CGM sensor accuracy relative to blood glucose (56).

Another factor to be considered is the delayed onset of action of the insulin analogues used in insulin pumps. Due to their pharmacokinetic and pharmacodynamic properties, insulins need time from administration to their onset of action (57,58).

1.4 Aim of this systematic review and meta-analysis

As previously mentioned, glucose control can be particularly difficult for people with T1D during physical activity due to complex interactions between physical activity-induced effects on glucose metabolism and exogenously administered insulin.

The risk of physical activity-induced dysglycemia prevents many people with T1D from engaging in physical activity and, consequently from gaining long term beneficial effects like reduced cardiovascular disease risk or improved HbA_{1c} levels (40). While CLS have been proven to be a very reliable option for glycemic control in everyday life (59), the performance during physical activity still poses a challenge due to various reasons. This leads to the underlying question of my thesis; how reliable previously tested CLS regulate blood glucose levels during physical activity compared to (modern) current care.

This is the first comprehensive systematic review and meta-analysis performed on this this topic. Combining the findings of previous studies, conducted on closed-loop control during physical activity in people with T1D, in the form of a systematic review and meta-analysis represents the type of study with the highest validity in medical research. For clinicians as well as people with T1D, a well-founded answer to the efficacy of CLS during physical activity is of equally high interest. CLS might be the answer to mimic the physiological role of the pancreas. To do so, they are required to perform in a safe and efficacious way even during more challenging glycemic periods. Therefore, our results might have influence on ongoing and future research as well as therapy decisions. The aim of this systematic review and meta-analysis was to collect all currently available clinical studies comparing CLS in people with T1D during physical activity to (modern) current care. Specifically, assessing the time spent in an euglycemic range of 70-180mg/dL (3.9-10mmol/L) in order to answer the review question of whether CLS are superior to (modern) current care in reaching time in an euglycemic range during physical activity.

2 Materials and Methods

Systematic review and meta-analysis

Systematic reviews and meta-analysis are becoming increasingly important in health care. Due to the vast quantity of new publications, it has become more and more difficult for clinicians, therapists, healthcare managers and other people working in health care profession to keep up with primary research evidence (60,61). Addressing the problem of the overwhelming amount of new studies, systematic reviews help obtaining up-to-date high quality information concerning the effectiveness, meaningfulness, feasibility and appropriateness of a specific healthcare matter (62).

2.1 Method

This systematic review and meta-analysis was performed, based on a predefined study-protocol (Appendix 1). In order to meet the current recommendations on performing a high-quality systematic review and meta-analysis, the literature search as well as the screening for eligibility were performed based on the PRISMA 2009 statement (Appendix 2). Therefore, review question, hypothesis, inclusion and exclusion criteria for population, intervention, comparison, study types, as well as, primary- and secondary outcomes were defined before the literature search was conducted.

Null Hypothesis: We expect that there is no difference on time in range defined as XX when using a CLS compared to (modern) current care during physical activity in people with T1D

Alternative hypothesis: We expect that a CLS results in more time in range compared to (modern) current care during physical activity in people with T1D

2.2 Search strategy and selection criteria

Four databases/ platforms were predefined for the literature search: PubMed/ MEDLINE, EMBASE (1974 to 2020 January 20), Cochrane Central Register of Controlled Trials (Central) and Science Citation Index (Web of Science). Both, the search strategy and selection of search terms were aimed to achieve the highest possible sensitivity for relevant publications. The search strategy included a mix of MeSH and free text terms. Furthermore, various spelling and writing forms such as synonyms for each key concept were included in the search term. Additional to T1D, terms with respect to intervention, comparison and

physical activity were part of the search term (full search strategy shown in detail in Appendix 3).

The systems considered as intervention included CLS, single- and dual-hormone CLS.

The availability of a comparative intervention (standard of care) within the same study setting was another inclusion criterion. Systems and interventions considered as (modern) current care included predictive low-glucose suspend (PLGS) systems, sensor augmented insulin pumps, blood glucose measurement (SMBG) with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), flash glucose monitoring with MDI, continuous glucose monitoring with MDI, flash glucose monitoring with CSII and continuous glucose monitoring with CSII and HCL.

With respect to the included study population, no limitations were defined regarding age, BMI, c-peptide status, HbA_{1c} level, gender, levels of functional capacity or comorbidities. Trials in humans with clinically diagnosed T1D were the only determined inclusion criteria. For the type of physical activity or physical exercise, no limitations were set and included e.g. resistance, high-intensity and interval training. Concerning the criteria for included study types, crossover randomized trials, randomized controlled trials, randomized trials and observational controlled trials were eligible for inclusion. Further inclusion criteria were the minimum amount of three participants per group (intervention and comparison), the need for studies to have already been published and English as the language of publication.

2.3 Data extraction

All four databases/ platforms were searched on the same day (January 21, 2020). Initially, all limitations and filters were disabled and each single search term was entered into the database/ platform, noting the number of obtained publications (Appendix 3). This step was performed in order to ensure future traceability of the literature search. At last, the completed search term was entered, individual filters enabled, and all studies found were extracted, either in form of a word document or as a pdf. Limitations and filters used in the final search were "human" for MEDLINE/ PubMed, "Full Text" and "English Language" for both Embase (1974 to 2020 January 20) and Cochrane Central Register of Controlled Trials. For the platform Science Citation Index (Web of Science) the option to search all available databases and "English" as a filter were enabled.

As suggested by the PRISMA 2009 guidelines for systematic reviews and meta-analysis, the systematic screening for study eligibility was performed in several stages by two separately working investigators (Benjamin Weilguni and Max Lennart Eckstein). In a first step, all found records were screened for duplicates in order to remove them. All remaining records were then screened by title, abstract, and full texts for relevant studies meeting the eligibility criteria. In the screening process, exclusion criteria were applied in order to remove non-relevant studies, e.g. studies conducted on people without T1D, studies with no CLS as intervention, studies without physical activity, in-silico studies, reviews, studies conducted on people with T2D, studies without a control variable, conference abstracts or e-posters.

Disagreements were later resolved by consensus or following discussion with a senior reviewer (Priv.-Doz. Mag.rer.nat. Othmar Moser, PhD).

For potentially relevant studies, data was extracted for interventions, comparators, study baseline characteristics, participant baseline characteristics, and clinical outcomes by two individual working reviewers (Benjamin Weilguni and Max Lennart Eckstein) (the full data extraction form is shown in Appendix 4). Disagreements were again resolved by consensus or following discussion with a senior reviewer (Othmar Moser).

2.4 Outcomes

The primary outcome was defined as the time in an euglycemic range of 70-180 mg/dL (3.9-10mmol/L) given as percentage of total time during physical activity comparing CLS against (modern) current care. The reason for time in an euglycemic range being the primary outcome is its superior expressive value, regarding the evaluation of glycemic control, compared to other parameters. The time in hypoglycemia on its own, for example, would have no informative value on the quality of glycemic control since it does not give any information about the distribution between time spent in euglycemia or hyperglycemia. Therefore, little time in hypoglycemia could mask a high percentage of time spent in hyperglycemia and vice versa.

Secondary outcomes included the time spent in hypoglycemia <70mg/dL (<3.9mmol/L), hyperglycemia >180mg/dL (>10mmol/l) and number of hypoglycemic events <70mg/dL (<3.9mmol/L) during physical activity, as well as the time spent in an euglycemic range 70-180mg/dL (3.9-10mmol/L), in hypoglycemia <70mg/dL (<3.9mmol/L), in hyperglycemia >180mg/dL (>10mmol/L) and number of hypoglycemic events <70mg/dL (<3.9mmol/L) during the post exercise period (up to 24 hours post-physical activity).

2.5 Statistical analysis

The restricted maximum likelihood estimation method as well as the random effects model were used to perform the meta-analysis. Studies with multiple independent intervention and comparison groups were included in the meta-analysis several times and labeled with a, b, c,.. Subgroup analysis were conducted based on study population (children and adolescents (<18 years) or adults (>18 years)), type of exercise and type of trial. For studies providing only medians and interquartile ranges, appropriate formulas were used to calculate mean and variance, making no assumptions regarding the distribution of the given data (63). Statistical heterogeneity was assessed using I2 statistics and the Cochran's Q Test.

2.6 Assessment for risk of bias in individual studies and across studies

The quality assessment was carried out by two independent reviewers (Benjamin Weilguni, Max Lennart Eckstein), and any discrepancies were resolved by consensus. The Cochrane Risk of Bias 2 (RoB2) tool, which is an updated version to the original risk of bias tool that launched in 2008, was used. As a recommendation from the Cochrane Scientific Committee this is the go-to tool to assess the risk of bias in randomized trials (64). The tool is divided into a fixed set of domains of bias, considering different aspects of trial design, conduct, and reporting. Each domain contains a series of questions ('signaling questions') aiming to elicit information about features of the trial that are at risk of being biased. An algorithm uses the given information from the signaling questions and generates a proposed judgment about the risk of bias arising from each domain. The judgment for the risk of bias can vary from "Low-risk" to "Some concern" to "High-risk" (64).

The risk of bias across studies was further explored, both visually and formally, using a funnel plot, fail-safe N calculation, Kendalls Tau, Egger's Regression and the "trim and fill" method (65).

The 'fail-safe N' is "the number of additional 'negative' studies (studies in which the intervention effect was zero) that would be needed to increase the P value for the meta-analysis to above 0.05" (66).

Kendall's Tau is a non-parametric, statistical procedure and is used to check the bivariate relationship between two at least ordinally scaled characteristics by comparing two rank series (67).

Eggers' regression is "a test for asymmetry of the funnel plot and examines the correlation between the effect sizes and their corresponding sampling variances; a strong correlation implies publication bias. Egger's test regresses the standardized effect sizes on their precisions; in the absence of publication bias, the regression intercept is expected to be zero" (66).

The trim-and-fill method "aims at estimating potentially missing studies due to publication bias in the funnel plot and adjusting the overall effect estimate. The idea of the trim-and-fill method is to first trim the studies that cause a funnel plot's asymmetry so that the overall effect estimate produced by the remaining studies can be considered minimally impacted by publication bias, and then to fill imputed missing studies in the funnel plot based on the bias-corrected overall estimate" (66).

3 Results

3.1 Characteristics of included studies

As shown in Figure 1, our initial search retrieved 1474 records. Seventy-nine records were identified through Medline/ Pubmed, 882 records through EMBASE, 373 records through Web of Science, and 140 records through Cochrane (Central). Two additional records were identified through other sources resulting in a total number of 1476 records. After removing duplicates, the remaining 1034 records were screened, first on the level of titles, excluding 739 records, second on abstract level, removing 235 records, leaving 60 records for the full text assessment for eligibility. An additional 54 records were excluded from which six potentially viable studies for the meta-analysis had to be excluded because there was no data for time in an euglycemic range during physical activity available, despite having contacted the authors. This left six studies to be included in the meta-analysis. The search details are given in Figure 1.

Study characteristics

In Appendix 5, the detailed study characteristics and their participants baseline are shown for the six studies included in the systematic review and meta-analysis. They were also assigned the numbers 1 to 6.

Study 1: "Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial" - first author; Klemen Dovc, MD, PhD.

Study 2: "Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy" – first author; Peter G. Jacobs, PhD.

Study 3: "Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes" – first author; Daniela Elleri, MD.

Study 4**:** "Artificial Pancreas (AP) Ski Camp 2018: Successful use of the Tandem Control-IQ AP system in adolescents and children during winter sports and at home" – first author; Laya Ekhlaspour, MD.

Study 5: "Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: The artificial pancreas ski study" – first author; Marc D. Breton, PhD.

Study 6: "Randomized outpatient trial of single- and dual-hormone CLS that adapt to exercise using wearable sensors" – first author; Jessica R. Castle, MD.

The included studies were conducted in the years between 2013 and 2019, studies 2, 4, 5, 6 in North America, study 1 in Europe/ Slovenia and study 3 in the United Kingdom. Studies 1, 2, 3, 6 used a randomized controlled crossover design, whereas studies 4 and 5 were of parallel design.

The number of participants per study varied from 12 to 48. In all studies combined, 160 subjects were included. Seven participants did not complete the trials, leaving 153 participants for our analysis. Due to crossover test designs, using different CLS or exercise interventions, studies were included repeatedly in our meta-analysis. Applying this method, the comparisons double to a total number of 266. Studies 1, 3, 4, 5 were conducted on children/ adolescents and studies 2 and 6 on adults. The mean age of participants finishing the studies varied from 12.3 ± 3.2 years to 34.5 ± 4.7 years (interquartile range given).

All six studies used a CLS as intervention, studies 4 and 5 used the Diabetes Assistant (DiAs) system and algorithm, which uses a smartphone as a computational hub to run the CLS algorithm, including cloud-based remote monitoring, an AP user interface, and an automated alert system (68,69). Study 1 used the Glucositter fuzzy-logic algorithm, which uses a combination of control-to-range and control-to-target strategies in order to regulate individual glucose levels (70). Study 2 used a proportional-integral-derivative algorithm, a control algorithm that regulates the delivery of the hormones insulin and glucagon based on sensed glucose measurements and meal announcements by the patient (71). Study 3 used an algorithm based on model predictive control, which tries to predict the effect of current insulin infusion rates on future glucose concentrations (72). Study 6 used a modified fading memory-proportional-derivative algorithm, similar to the algorithm used in Study 2 (71). In study 2 as well as study 6, two different CLS were compared to a comparative intervention. In study 2, a CLS with exercise dosing adjustment (APX) and one without, and in study 6, a single-hormone and a dual-hormone CLS were compared to a comparative intervention. The insulin type used in the intervention group in study 2, 3 and 6 was Aspart. In study 2, Glucagon in form of a dual-hormone system was additionally used. The remaining studies did not report any information on the drug type used in their intervention system.

As a comparative intervention (modern current care), all six studies used a combination of insulin pump and CGM in form of an open-loop system. Study 2, 4, 5 used a sensor augmented pump system, study 6 used a PLGS and for study 1 and 3 the comparative intervention is reported as “normal pump therapy”. Study 6 also had the continuation of the participants’ current care as an additional comparative intervention.

The exercise in study 1 and 3 was performed on a cycle ergometer with, in study 1, two different intensities (55% of the maximal oxygen consumption ($VO_{2max)}$ and 55+80% of VO_{2max})) and, in study 3, moderate intensity (heartrate of 140 bpm). The exercise data for study 3 is divided into a morning and an afternoon exercise session. In studies 2 and 6, the exercise was performed on a treadmill ergometer, in study 2, with an intensity of 60% of maximum heartrate and, in study 6, with 60% of VO_{2max}. Studies 4 and 6 were performed during a winter ski camp without a defined exercise intensity. The exercise duration was 40 min in study 1, 45 min in study 2, 60 min in study 3, 240 min in study 4, 330 min in study 5 and 45 min in study 6, considering the cross-over designs, this results in approximately 480 hours of data during exercise.

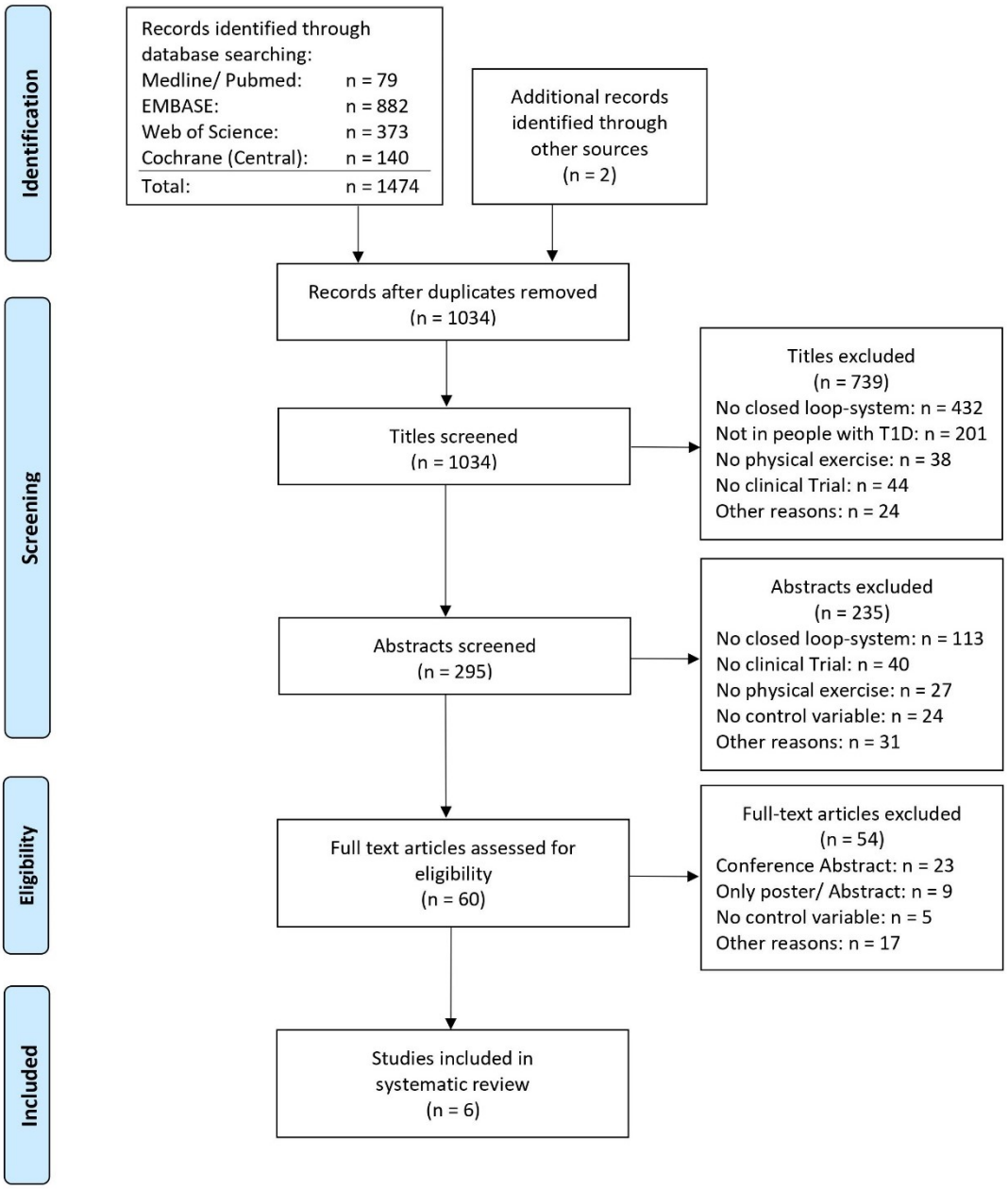


Figure 1: PRISMA Flow Diagram

3.2 Risk of bias and quality assessment

Figure 2 shows the risk of bias graph, stating the results of the Cochrane risk-of-bias tool presented as percentages across all included studies. In the randomization process, five studies (1, 2, 4, 5, 6) showed some concerns for bias. Referring to the overall risk of bias, four studies (3, 4, 5, 6) are described as low risk, only studies 1 and 2 show some concerns for publication bias. A detailed presentation of each risk of bias item for every included study is shown in Appendix 5.

Visual inspection of the funnel plot, stating the absolute mean difference of our primary outcome on the abscissa and the standard error on the ordinate, showing a slight heterogeneity in study results, indicated by single study arms leaving the proposed triangular area of the funnel plot (shown in Figure 3). In the formally assessment for publication bias, the 'fail-safe N' showed a value of 154 with a p=<0.001. The Kendalls Tau resulted in a value of -0.154 and a p=0.491. The Egger's regression showed a value of 0.377 with a p=0.706 and the 'trim and fill' method resulted in a value of 0.0. Table shown in Appendix 5.

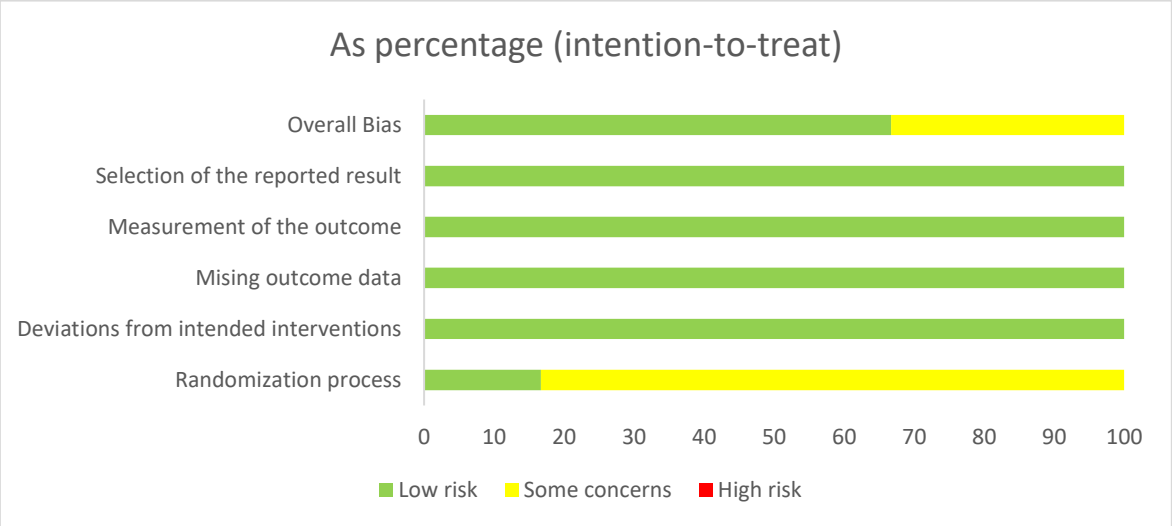


Figure 2: Risk of bias graph

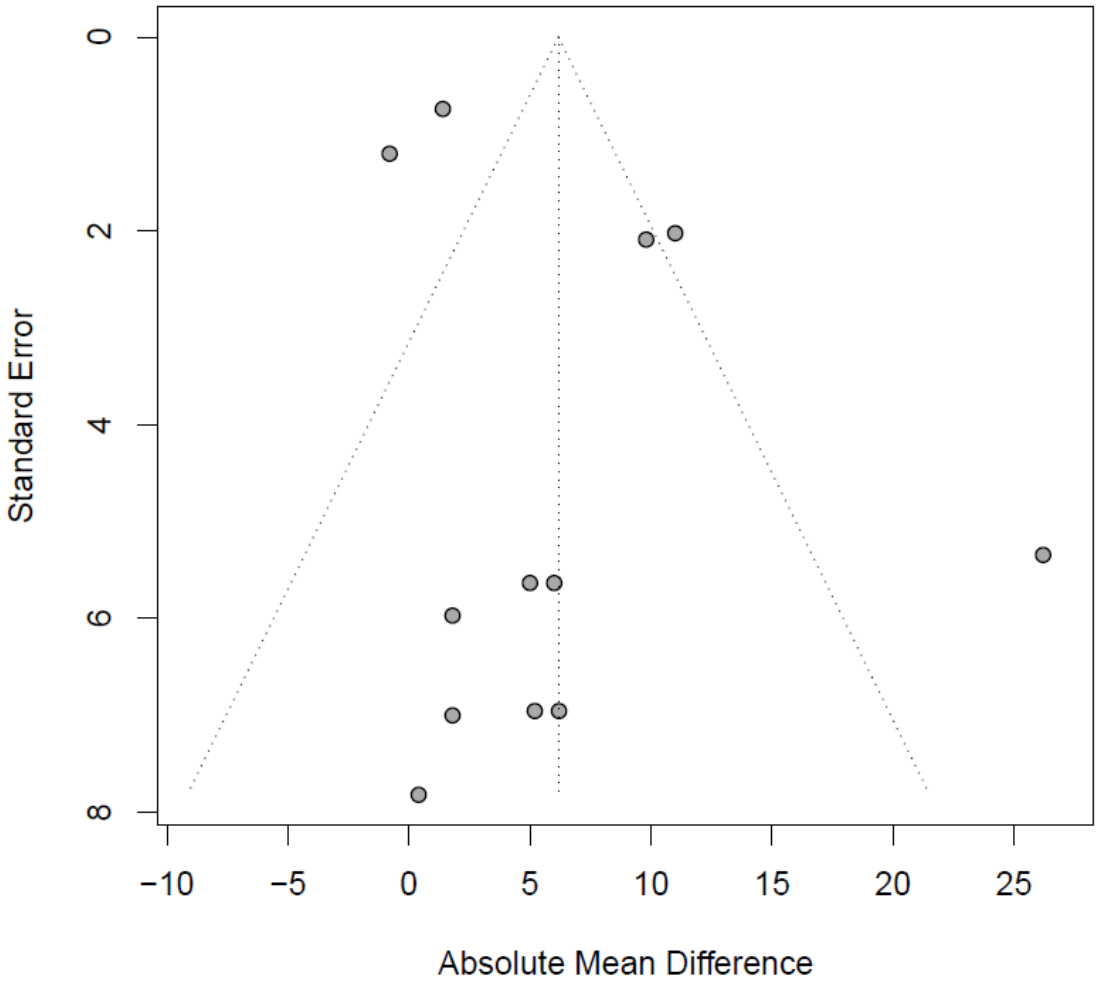


Figure 3: Funnel Plot of absolute mean difference

3.3 Primary outcome

All meta-analysis results are presented as the mean time spent in an euglycemic range of 70-180 mg/dl (3.9-10 mmol/L) given as percentage of total time during physical activity with the CLS labeled as “experimental” and the comparative interventions as “control”. Due to crossover designs and reported data for more than one intervention or comparison group, studies 1, 2, 3, and 6 were included in the meta-analysis repeatedly [a-d]. This resulted in 12 included study arms and doubled the total number of comparisons to 266. CLS compared to current care were associated with an increased time in an euglycemic range of 70-180mg/dl (3.9-10mmol/L) during physical activity with an overall weighted mean difference of 6.17% (95% CI 1.60% - 10.75%: $\tau 2 = 35.66$, I^2=82%, p<0.01).

τ2 showed that the included studies did not share a common effect size (p<0.01). I2 (82%) and the prediction interval of -7.91%, 20.26% indicated a significant variation in TIR, suggesting, that the intervention might not be beneficial in some settings.

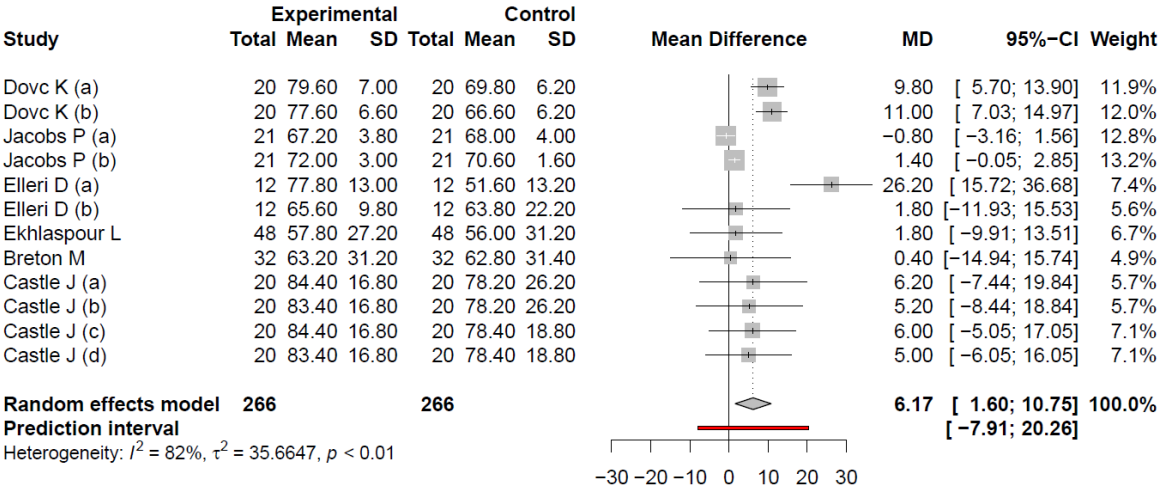


Figure 4: Meta-Analysis

3.4 Subgroup analysis

As shown in **Figure 5**, subgroup analysis regarding age of the study population showed a mean difference for TIR of 9.32% ((95% CI, -0.46% - 19.09%); I^2= 65%, τ^2= 66.25, 6 study arms, p= 0.01) for studies conducted in participants <18 years and a mean difference of 1.23% ((95% CI, -1.22% - 3.69%); I^2= 0%, τ^2= 2.89, 6 study arms, p= 0.45) for studies conducted in participants >18 years.

Subgroup analysis regarding type of exercise showed a mean difference for TIR of 12.34% ((95% CI, -2,60% - 27.27%); I^2= 70%, τ^2= 72.14, 4 study arms, p= 0.02) for studies using cycle ergometer as physical exercise, 1.23% ((95% CI, -1.22% - 3.69%); I^2= 0%, τ^2= 2.89, 6 study arms, p= 0.45) for studies using treadmill ergometer and 1.28% ((95% CI, -7.30% - 9.86%); I^2= 0%, τ^2= 0.01, 2 study arms, p= 0.89) for studies with skiing as physical exercise. Shown in detail in **Figure 6**.

Subgroup analysis regarding study type showed a mean difference for TIR of 6.88% ((95% CI, 1.52% - 12.23%); I^2= 85%, τ^2= 41.02, 10 study arms, p< 0.01) for studies performed as crossover randomized trials, and 1.28% ((95% CI, -7.3% - 9.86%); I^2= 0%, τ^2= 0.001, 2 study arms, p= 0.89) for studies conducted with a parallel design. Shown in **Figure 7**.

Residual heterogeneity varied between subgroup analysis, showing the following values for analysis divided into children and adolescents and adults: I^2= 47%, p= 0.04, analysis for type of exercise: I^2= 40%, p= 0.09 and for subgroup analysis regarding the type of trial: I^2= 83%, p< 0.01.

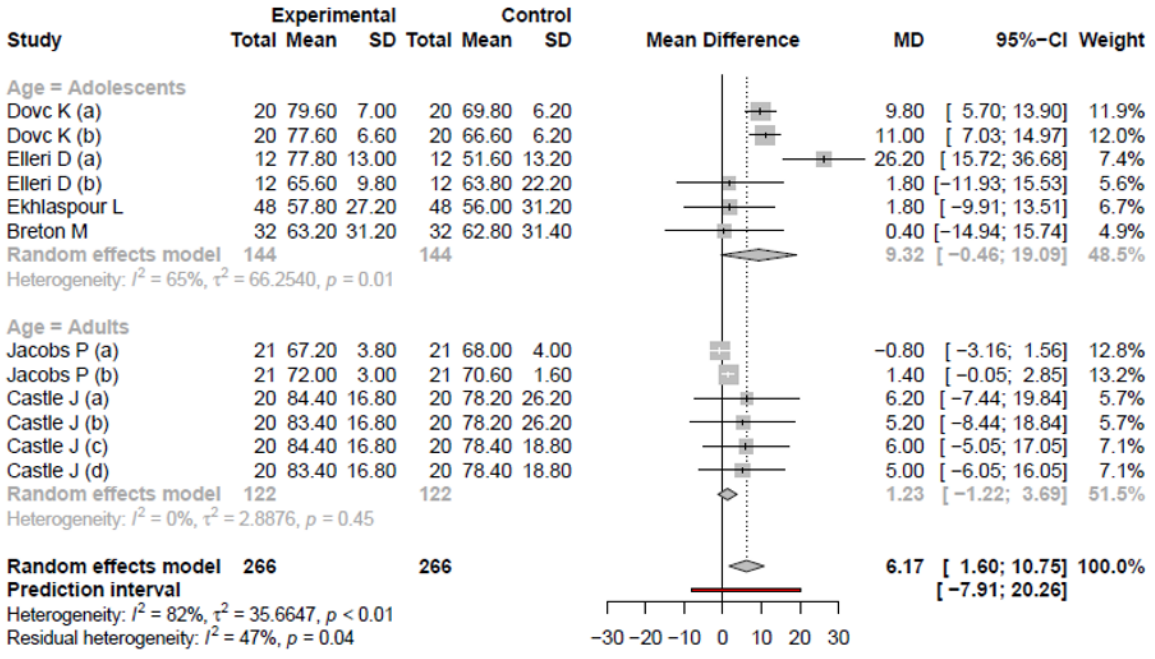


Figure 5: Subgroup Analysis I: split into children and adolescents (<18 years) and adults (>18 years)

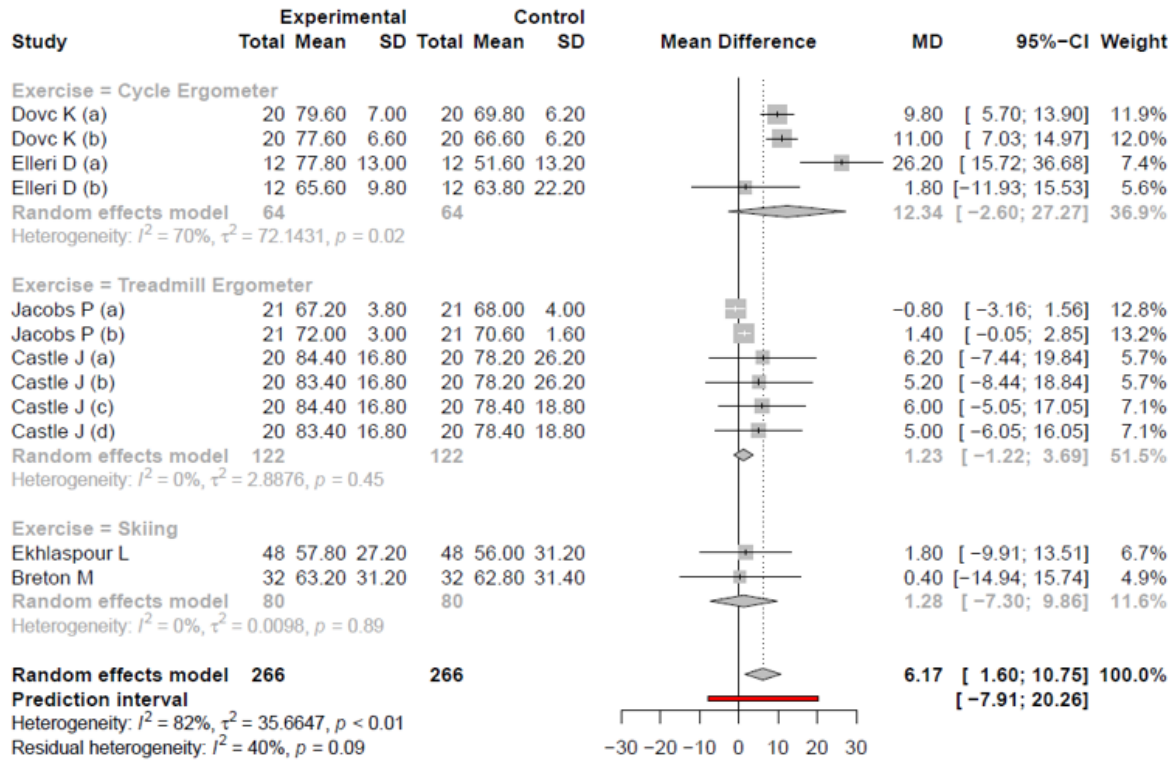


Figure 6: Subgroup analysis II: type of exercise

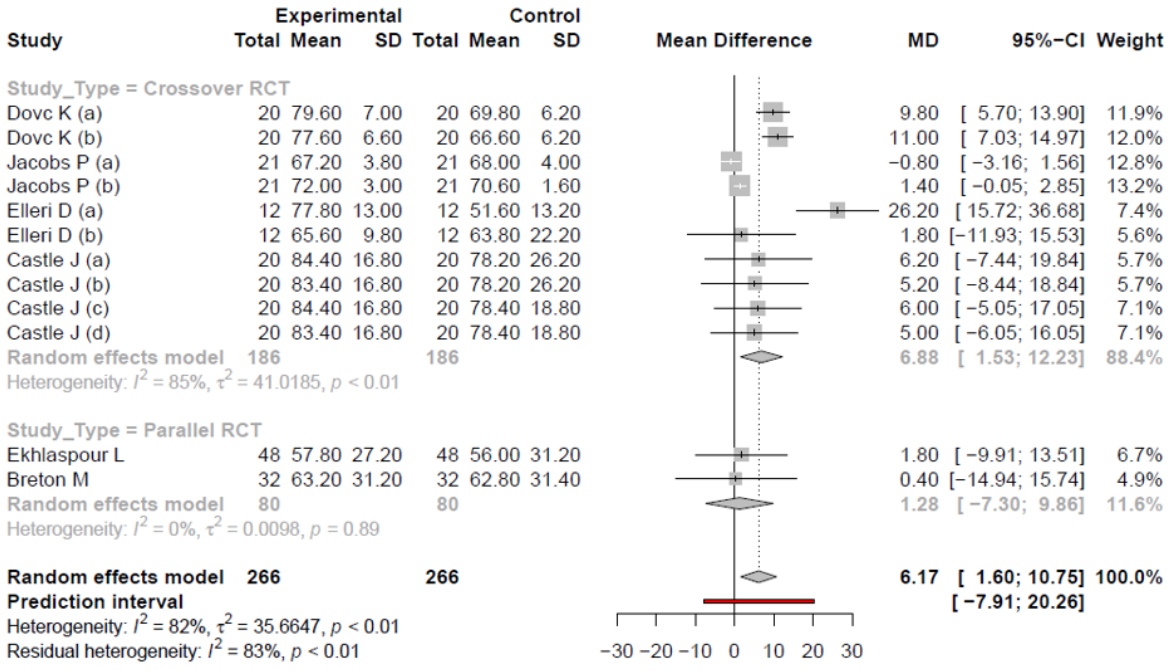


Figure 7: Subgroup analysis III: type of trial

3.5 Secondary outcomes

The studies included in our meta-analysis provided only little data on the predefined secondary outcomes. Due to the limited data reported and high variability of the given data, no statistical analysis were conducted, since very heterogenous and non-significant results were to be expected. Given in detail in **Appendix 7**.

In the intervention groups, time spent in hypoglycemia <70mg/dL (<3.9 mmol/L) during physical activity ranged from 0.0% (0.0-0.0%) in study 1a, to 8.3% (12.6%) in study 6. In the comparison groups, reported data ranged from 0.0% (0.0–3.3%) in study 1b, to 7.6% (8.0%) in study 6. Overall, the available data favors neither the intervention nor the comparison.

Five study arms reported data for time spent in hyperglycemia >180mg/dL (>10mmol/L) during physical activity. The given data points show large variances and interquartile ranges. The time spent in hyperglycemia in the intervention groups ranged from 17.1% (7.2–33.0%) in study 1a, to 41.4% ± 27.8% in study 4. In the comparison groups, time spent in hyperglycemia ranged from 25.2% (6.0–39.3%) in study 1a, to 41.5% ± 30.3% in study 4.

For two studies the number of hypoglycemic events <70mg/dL (<3.9 mmol/L) during physical activity was reported. Study arm 1b reported one hypoglycemic event during physical activity in the intervention group and four in the comparison group. Study 5 reported an average number of hypoglycemic events per study participant during physical activity of 0.3 ± 0.4 in the intervention group, and 0.3 ± 0.7 in the comparison group.

The time spent in an euglycemic range 70-180mg/dL (3.9-10 mmol/L) during the post-exercise period was reported for five study arms, considering the evening and/or night after physical activity as the post-exercise period. In all of them, the given data favored the intervention groups, however, showing large variances and interquartile ranges for both intervention and comparison groups. For example, in study 4, the time spent in an euglycemic range was 78.6% ± 20.3% in the intervention group and 50.9% ± 34.2% in the comparison group during the post-exercise period.

For the time spent in hypoglycemia <70mg/dL (<3.9 mmol/L) during the post-exercise period, data was reported in five study arms. Overall, only little time was spent in hypoglycemia during the post-exercise period, as most of the reported data points were close to 0.0%. Study 5 showed the highest values of 2.2% ± 2.3% in the intervention group and 2.5% ± 6.5% in the comparison group.

For the time spent in hyperglycemia >180mg/dL (>10 mmol/L) during the post-exercise period, data was reported in three study arms. Favoring the intervention group in all three study arms, however, showing large variances and interquartile ranges. E.g., study 4 reported 18.2% ± 21.4% time spent in hyperglycemia in the intervention group, and 44.5% ± 37% in the comparison group.

For two studies, the number of hypoglycemic events <70mg/dL (<3.9 mmol/L) during the post-exercise period was reported. Study arm 1a reported three hypoglycemic events during the post-exercise period in the intervention group and four in the comparison group. Study 5 reported an average number of hypoglycemic events per study participant during the post-exercise period of 0.1 ± 0.3 in the intervention group, and 0.1 ± 0.4 in the comparison group.

4 Discussion

4.1 Key findings

Regular physical activity is not only prerequisites for an overall healthy and balanced life, but also have proven beneficial effects on diabetes related comorbidities and cardiovascular risk factors in people with T1D (40). Various physiological difficulties in the glucose metabolism during physical activity, the difficulty to balance food and insulin intake before, during and after physical activity and fear of severe hypoglycemia are the main cited reasons preventing people with T1D from long-term participation in regular physical activity (43,44). CLS, as an attempt to mimic the physiological role of the pancreas, have proven to provide superior glycemic control compared to (modern) current care during everyday-life and especially during the night (38,39). Rapid changes in blood glucose levels during physical activity, combined with delayed display of actual blood glucose levels due to interstitial measurements, and delayed onset of action of the administered insulin are few examples why the efficacy of CLS for glycemic control may be limited (51,53,54).

In this systematic review and meta-analysis, comparing CLS to (modern) current care, use of CLS resulted in an increase of 6.17% (95% CI 1.60-10.75) time in an euglycemic glucose range of 70-180mg/dL (3.9-10 mmol/L). Reported values regarding the occurrence of hypoglycemic events and overall time spent in hypoglycemia were similarly low for both the intervention and comparison group during exercise. This suggests that the intervention as well as the comparative treatments were equally effective in terms of hypoglycemia prevention and therefore in their provided safety of glycemic control. As shown in previous studies (39,73,74), our data indicates superior glycemic control for CLS during night. In all study arms the TIR during the post-exercise period (night after exercise) was superior for CLS compared to the comparative groups (**Table 7**).

Time spent in hypoglycemia <70mg/dL (3.9mmol/L) and the number of hypoglycemic events <70mg/dL (3.9mmol/L) during the post-exercise period showed to be similarly low for both the intervention and comparative groups, underlining the provided safety in terms of hypoglycemia prevention of the systems used (**Table 7**). Reported data on hypoglycemic events <70mg/dL (3.9mmol/L) and overall time spent in hypoglycemia <70mg/dL (3.9mmol/L) showed to be similarly low for both the intervention and comparative groups during the post-exercise period.

Subgroup analysis split into adolescents (<18 years) and adults (>18 years) suggested the biggest improvement in TIR for studies conducted in adolescents 9.32% (95% CI; -0.46-

19.09) compared to studies conducted in adults 1.23% (95% CI; -1.23-3.69). Subgroup analysis for type of exercise showed the biggest improvement for TIR in studies using cycle ergometer 12.34% (95% CI -2.60-27.27) compared to studies using treadmill ergometer 1.23% (95% CI -1.22-3.69) and studies using skiing as physical exercise 1.28% (95% CI -7.30-9.86). Subgroup analysis for type of trial suggested greater improvement in TIR for studies with randomized-controlled crossover designs 6.88% (95% CI 1.53-12.23) compared to studies with randomized-controlled parallel designs 1.28% (95% CI -7.30-9.86).

Fast changes in glucose level are commonly seen during physical activity, due to the physiological delay between blood glucose level and interstitium, these fast changes may affect CGM accuracy and exogenous insulin requirements (75–77). Despite these potential difficulties, our meta-analysis indicates that CLS improve TIR compared to (modern) current care during physical exercise. Besides the improved overall mean difference of TIR for CLS, the fact, that our subgroup analysis showed favorable effects especially in studies conducted in children and adolescents might be surprising, since elevated glycemic variability is described in the younger population (78).

Clearly positive effects on TIR for CLS were seen when using cycle ergometer as physical activity, however, not for treadmill ergometer or skiing sessions. This might be caused by the different impact of physical exercises on metabolic processes due to different amounts of muscle mass used (79). Taking this into account, exercises engaging the whole body and using multiple muscle groups might deteriorate the performance of CLS.

In summary, our work indicates improved TIR for CLS during physical activity, during the post-exercise period and similarly low values for time spent in hypoglycemia and hypoglycemic events compared to (modern) current care. Allowing the conclusion, that CLS using an algorithm to administer insulin in a glucose responsive manner proved to be not only a viable option for glycemic control during periods with more unpredictable glucose responses but even surpasses the efficacy of (modern) current care.

4.2 Strengths and limitations of study

To ensure the validity of our results, the analyses were performed using the present guidelines for the conduct and reporting of systematic reviews and meta-analysis (PRISMA 2009 statement; Appendix 2). Based on a pre-specified protocol, the literature search, screening, and final inclusion of studies were performed by two separately working reviewers, allowing only minimal deviations. A comprehensive literature search on four databases was undertaken without imposing any restrictions based on study type, population, type of exercise or publications date. The literature search on all four databases was performed on the same day and the full search strategy is shown in Appendix 3, including the number of retrieved studies for each individual search term, providing full traceability and transparency of the performed literature search. Furthermore, the currently recommended tool (Cochrane Risk of Bias 2 (RoB2) tool) was used in order to assess the risk of publication bias in the included studies.

However, several limitations at the evidence and review level must be acknowledged. First, despite using broad inclusion criteria, maximizing the sensitivity for relevant studies, only six studies were included in our meta-analysis. Even after contacting the authors of potentially eligible studies, various studies did not report data for TIR during physical activity and had to be excluded. Further, most included studies had a small number of study participants and reported results with high heterogeneity. T^2 showed that the included studies did not share a common effect size ($p<0.10$). Further, I^2 (82%) and the prediction interval of -7.91, 20.26 indicated a significant variation in TIR. Differences in the systems used as intervention, e.g., different continuous glucose monitoring (CGM) systems, insulin pumps or algorithms, problems with sensor accuracy and performance e.g. due to interstitial reactions on the sensor, and different comparative systems used as control treatment might be contributing factors to the overall heterogeneity in the study results.

The small number of included studies and the heterogeneity in their reported results led to a statistically heterogeneous result and wide prediction interval of our meta-analysis, limiting the expressive power and the precision of our effect estimates.

The only subgroup stating a positive effect for CLS and a 95% CI in the positive range was shown for studies with randomized-controlled crossover designs. The two studies of parallel design were conducted during winter camps, with the participants engaging in physical activity in the form of skiing. Despite the fact that these two studies showed the highest numbers of study participants, the results showed to be very heterogeneous. A very

heterogeneous patient population, no defined exercise intensity and no standardized environment are few possible reasons for the disproportionate heterogeneity in the results of these two studies.

There are multiple potential explanations for the differences within the individual subgroup analysis in our meta-analysis. First, subgroup analysis primarily show the heterogeneity rather than differences between subgroups, further, the distribution of other study features can differ within each subgroup analysis, which are reasons, why our results should not be considered conclusive. Second, in all three individual subgroup analyses the groups with the greatest improvement in time in an euglycemic range 70-180mg/dL (3.9-10 mmol/L) showed the highest study heterogeneity within the subgroup analysis, e.g., in the subgroup analysis for type of exercise, studies using cycle ergometer showed a mean deviation of 12.34%, however with high heterogeneity parameters: 70%, τ^2=72.14, p=0.02. This results in confidence intervals down to the minus range, indicating, that the intervention might not be beneficial in some settings.

The included studies show a risk of bias in the randomization process, which is caused in the study settings and has its origin in the lack of masking of participants regarding their assigned intervention group. Since it would not be possible to mask the participants from their assigned intervention group, this is an unavoidable risk of bias, with probably little influence on the results.

4.3 Conclusion

This is the first systematic review and meta-analysis conducted on this topic. It has proven CLS as being a safe and efficacious treatment option for people with T1D during periods with more unpredictable glucose responses, like during physical activity. Our work even suggests improved glycemic control and time in an euglycemic range 70-180mg/dL (3.9-10 mmol/L) during physical activity for CLS compared to comparative interventions.

However, the expressive power of our meta-analysis is limited, due to the small number of included studies. Despite having the first commercially available hybrid CLS available since 2016, our work highlights a lack of studies conducted around the performance of these systems during physical activity, requiring further research before definitive conclusions can be made. Further research should also investigate possible differences between the individual components (CGM, algorithm, insulin pump, used insulin) determining their clinical relevance and how they influence the performance of CLS.

Our results highlight that CLS are a feasible and beneficial treatment option during physical activity and, as such, it is likely that CLS will change the management of T1D not only during everyday life but also during periods of more challenging glycemic responses.

5 References

1. Lakhtakia R. The history of diabetes mellitus. Vol. 13, Sultan Qaboos University Medical Journal. Sultan Qaboos University; 2013.
2. MacFarlane IA. Mathew Dobson of Liverpool (1735–1784) and the history of diabetes. Pract Diabetes Int. 1990 Nov;
3. Tipton CM. Susruta of India, an unrecognized contributor to the history of exercise physiology. J Appl Physiol. 2008;
4. Sanders LJ. From Thebes to Toronto and the 21st Century: An Incredible Journey. Diabetes Spectr. 2002 Jan 1;
5. Vecchio I, Tornali C, Bragazzi NL, Martini M. The discovery of insulin: An important milestone in the history of medicine. Vol. 9, Frontiers in Endocrinology. Frontiers Media S.A.; 2018.
6. Colwell AR. Fifty years of diabetes in perspective. Diabetes. 1968;
7. Mazur A. Why were "starvation diets" promoted for diabetes in the pre-insulin period? Nutr J. 2011 Dec 11;
8. Yaturu S. Insulin therapies: Current and future trends at dawn. World J Diabetes. 2013;
9. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;
10. Smushkin G, Vella A. What is type 2 diabetes? [Internet]. Vol. 38, Medicine. NIH Public Access; 2010.
11. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Vol. 464, Nature. 2010.
12. Todd JA. Etiology of Type 1 Diabetes. Vol. 32, Immunity. 2010.
13. Wilcox G. Insulin and Insulin. Clin Biochem Rev. 2005;
14. Eisenbarth GS. Update in Type 1 Diabetes. J Clin Endocrinol Metab. 2007 Jul 1;
15. Gianani R, Campbell-Thompson M, Sarkar SA, Wasserfall C, Pugliese A, Solis JM, et al. Dimorphic histopathology of long-standing childhood-onset diabetes. Diabetologia. 2010;
16. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014 Jan;
17. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G, Schober E, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009;

18. Tuomilehto J. The emerging global epidemic of type 1 diabetes. Curr Diab Rep. 2013 Dec;
19. Leslie RD. Predicting adult-onset autoimmune diabetes clarity from complexity. Vol. 59, Diabetes. 2010.
20. 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;
21. Nathan DM, Balkau B, Bonora E, Borch-Johnsen K, Buse JB, Colagiuri S, et al. International expert committee report on the role of the A1C assay in the diagnosis of diabetes. Vol. 32, Diabetes Care. 2009.
22. Evans Kreider K, Pereira K, Padilla BI. Practical Approaches to Diagnosing, Treating and Preventing Hypoglycemia in Diabetes [Internet]. Vol. 8, Diabetes Therapy. Springer Healthcare; 2017.
23. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Vol. 29, Diabetes Care. 2006.
24. Classification and diagnosis of diabetes: Standards of medical care in Diabetesd2018. Diabetes Care. 2018 Jan 1;
25. White JR. A brief history of the development of diabetes medications. Vol. 27, Diabetes Spectrum. American Diabetes Association Inc.; 2014.
26. Silverstein JH, Rosenbloom AL, Spillar R, Mccallum MH. Ambulatory Diabetes Management with Pulsed Subcutaneous Insulin Using a Portable Pump.
27. Mcadams BH, Rizvi AA. An Overview of Insulin Pumps and Glucose Sensors for the Generalist. 2016;
28. Rex J, Jensen KH, Lawton SA. A review of 20 years' experience with the NovoPen® family of insulin injection devices. Vol. 26, Clinical Drug Investigation. 2006.
29. Richter B, Neises G. ' Human ' insulin versus animal insulin in people with diabetes mellitus (Review). 2009;
30. Hirsch IB. Insulin Analogues. 2020;
31. Clarke SF, Foster JR. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus [Internet]. Vol. 69, British Journal of Biomedical Science. Step Publishing Ltd.; 2012.
32. Hirsch I, Battelino T, Peters A, Chamberlain J, Aleppo G, Bergenstal R, et al. Introduction: History of Glucose Monitoring. In: Role of Continuous Glucose

Monitoring in Diabetes Treatment. American Diabetes Association; 2018.
33. Denis R, Véronique S, Yves R, Bruno G, Eric R, Hélène H, et al. 11-Incremental Value of Continuous Glucose Monitoring When Starting Pump Therapy in Patients With Poorly Controlled Type 1 Diabetes. Diabetes Care. 2009;
34. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008 Jul;
35. Bergensta 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;
36. PMA P160017: FDA Summary of Safety and Effectiveness Data SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED).
37. Boughton CK, Hovorka R. Is an artificial pancreas (closed-loop system) for Type 1 diabetes effective? Diabet Med. 2019 Mar;
38. Ly TT, Buckingham BA, De Salvo DJ, Shanmugham S, Satin-Smith M, De Boer MD, et al. Day-and-night closed-loop control using the unified safety system in adolescents with type 1 diabetes at camp. Diabetes Care. 2016;
39. Brown SA, Breton MD, Anderson SM, Kollar L, Keith-Hynes P, Levy CJ, et al. Overnight closed-loop control improves glycemic control in a multicenter study of adults with type 1 diabetes. J Clin Endocrinol Metab. 2017 Oct 1;
40. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: A cross-sectional multicenter study of 18,028 patients. Diabetes Care. 2015 Aug 1;
41. Riddell MC, Perkins BA. Type 1 diabetes and vigorous exercise: Applications of exercise physiology to patient management. Can J Diabetes. 2006;
42. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. Vol. 39, Diabetes Care. American Diabetes Association Inc.; 2016.
43. Thomas N, Alder E, Leese GP. Barriers to physical activity in patients with diabetes. Postgrad Med J. 2004 May;
44. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care. 2008 Nov;

45. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, et al. Resistance versus aerobic exercise. Diabetes Care. 2013 Mar;
46. Cuenca-García M, Jago R, Shield JPH, Burren CP. How does physical activity and fitness influence glycaemic control in young people with Type1 diabetes? Diabet Med. 2012 Oct;
47. Aouadi R, Khalifa R, Aouidet A, Ben Mansour A, Ben Rayana M, Mdini F, et al. Aerobic training programs and glycemic control in diabetic children in relation to exercise frequency. J Sports Med Phys Fitness. 2011 Sep;
48. Ramalho AC, de Lourdes Lima M, Nunes F, Cambuí Z, Barbosa C, Andrade A, et al. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. Diabetes Res Clin Pract. 2006 Jun;
49. Åman J, Skinner TC, de Beaufort CE, Swift PGF, Aanstoot HJ, Cameron F, et al. Associations between physical activity, sedentary behavior, and glycemic control in a large cohort of adolescents with type 1 diabetes: The Hvidoere Study Group on Childhood Diabetes. Pediatr Diabetes. 2009;
50. Chu L, Hamilton J, Riddell MC. Clinical management of the physically active patient with type 1 diabetes. Phys Sportsmed. 2011 May;
51. Barry Keenan D, Mastrototaro JJ, Weinzimer SA, Steil GM. Interstitial fluid glucose time-lag correction for real-time continuous glucose monitoring. Biomed Signal Process Control. 2013 Jan;
52. Basu A, Dube S, Slama M, Errazuriz I, Amezcua JC, Kudva YC, et al. Time lag of glucose from intravascular to interstitial compartment in humans. Diabetes. 2013 Dec;
53. Coggan AR. Plasma Glucose Metabolism During Exercise in Humans. Vol. 11, Sports Medicine. 1991.
54. Schmelzeisen-Redeker G, Schoemaker M, Kirchsteiger H, Freckmann G, Heinemann L, Del Re L. Time delay of CGM sensors: Relevance, causes, and countermeasures. J Diabetes Sci Technol. 2015;
55. 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;
56. Helton KL, Ratner BD, Wisniewski NA. Biomechanics of the sensor-tissue interface - Effects of motion, pressure, and design on sensor performance and foreign body response - Part II: Examples and application. In: Journal of Diabetes Science and

Technology. SAGE Publications Inc.; 2011.
57. Czock D, Aisenpreis U, Rasche FM, Jehle PM. Pharmacokinetics and pharmacodynamics of lispro-insulin in hemodialysis patients with diabetes mellitus. Int J Clin Pharmacol Ther. 2003 Oct;
58. Haahr H, Heise T. Fast-Acting Insulin Aspart: A Review of its Pharmacokinetic and Pharmacodynamic Properties and the Clinical Consequences. Clinical Pharmacokinetics. Springer International Publishing; 2019.
59. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet. 2018 Oct 13;
60. Swingler GH, Volmink J, Ioannidis JPA. Number of published systematic reviews and global burden of disease: Database analysis. Vol. 327, British Medical Journal. 2003.
61. Oxman AD. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA J Am Med Assoc. 1994 Nov 2;
62. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;
63. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014 Dec 19;
64. Sterne J, Higgins J. Cochrane Scientific Committee Recommendation statement/report Review of the updated "Risk of bias" tool RoB 2.0. 2017;
65. Jin ZC, Zhou XH, He J. Statistical methods for dealing with publication bias in meta-analysis. Stat Med. 2015 Jan 30;
66. Soeken KL, Sripusanapan A. Assessing publication bias in meta-analysis. Nurs Res. 2003 Jan;
67. Ma Y. On inference for kendall's τ within a longitudinal data setting. J Appl Stat. 2012;
68. Keith-Hynes P, Mize B, Robert A, Place J. The Diabetes Assistant: A Smartphone-Based System for Real-Time Control of Blood Glucose. Electronics. 2014 Nov 14;
69. Keith-Hynes P, Guerlain S, Mize B, Hughes-Karvetski C, Khan M, McElwee-Malloy M, et al. DiAs user interface: A patient-centric interface for mobile artificial pancreas systems. In: Journal of Diabetes Science and Technology. Diabetes

Technology Society; 2013.

70. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-logic artificial pancreas system: A pilot study in adults with type 1 diabetes. Diabetes Care. 2010 May;
71. Jacobs PG, El Youssef J, Castle J, Bakhtiani P, Branigan D, Breen M, et al. Automated control of an adaptive bihormonal, dual-sensor artificial pancreas and evaluation during inpatient studies. IEEE Trans Biomed Eng. 2014 Oct 1;
72. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. In: Diabetes Technology and Therapeutics. 2005.
73. Haidar A, Rabasa-Lhoret R, Legault L, Lovblom LE, Rakheja R, Messier V, et al. Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. J Clin Endocrinol Metab. 2016 Jan 1;
74. 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;
75. Moser O, Eckstein ML, McCarthy O, Deere R, Pitt J, Williams DM, et al. Performance of the Freestyle Libre flash glucose monitoring (flash GM) system in individuals with type 1 diabetes: A secondary outcome analysis of a randomized crossover trial. Diabetes, Obes Metab. 2019 Nov 1;
76. Gargallo-Fernández M, Martín JES, Gómez-Peralta F, Moreno PR, Martínez AM, Botella-Serrano M, et al. Clinical recommendations for sport practice in diabetic patients (RECORD Guide). Diabetes Mellitus Working Group of the Spanish Society of Endocrinology and Nutrition (SEEN). Endocrinol y Nutr (English Ed. 2015 Jun;
77. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-Lhoret R, van den Boom L, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). Pediatr Diabetes. 2020 Dec 1;
78. Schreiver C, Jacoby U, Watzer B, Thomas A, Haffner D, Fischer D-C. Glycaemic variability in paediatric patients with type 1 diabetes on continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI): a cross-sectional cohort

study. Clin Endocrinol (Oxf). 2013 Apr 1;

79. Spendier F, Müller A, Korinek M, Hofmann P. Intensity Thresholds and Maximal Lactate Steady State in Small Muscle Group Exercise. Sports. 2020 May 28;

Appendices

Appendix 1: Study protocol

Title

Time in range for fully closed-loop systems versus current care during physical exercise in type 1 diabetes: a systematic review and meta-analysis

Short Title

ComeClose 1

Authors

Eckstein, Weilguni, Dietrich, Tauschmann, Sourij, Moser

Software

Excel, Rev Man 5.3, Meta-analysis software

Review Question

Is a closed loop system superior in reaching time in range than (modern) current care during physical exercise in people with type 1 diabetes?

Hypothesis

Alternative hypothesis: We expect that a CLS results in more time in range compared to (modern) current care during exercise in people with type 1 diabetes

Null Hypothesis: We expect that there is no difference when using a CLS compared to (modern) current care during exercise in people with type 1 diabetes

PICO

Population

- Human
- clinically diagnosed type 1 diabetes
- all ages
- all BMI
- c-pep positive and negative (0.03 nmol/L)
- all HbA_{1c}
- all genders
- all levels of functional capacity
- all comorbidities
- in-patient or outpatient

Intervention

- CLS

- Hybrid CLS (Medtronic 670 G)
- Single-hormone CLS
- Dual-hormone CLS

Comparison

(Modern) current care defined as:

- Blood glucose measurement (SMBG) with multiple daily injections (MDI) (pen therapy) or continuous subcutaneous insulin infusion (CSII) (pump therapy)
- Flash glucose monitoring with multiple daily injections (MDI) (pen therapy)
- Continuous glucose monitoring with multiple daily injections (MDI) (pen therapy)
- Flash glucose monitoring with continuous subcutaneous insulin infusion (CSII) (pump therapy)
- Continuous glucose monitoring continuous subcutaneous insulin infusion (CSII) (pump therapy)
- Sensor augmented insulin pump
- Predictive low-glucose suspend (PLGS) system

Primary Outcome

- Time in range (70-180 mg/dl) given as percentage of total time during physical exercise (all types of physical exercise and physical activity)

Secondary Outcome

- Time spent in hypoglycemia (<70 mg/dL) and hyperglycemia (>180 mg/dL) given as percentage of total time during physical exercise
- Time spent in hypoglycemia, time in range, hyperglycemia given as percentage of total time during the post-exercise period (up to 24 hours post-exercise)
- Time spent in hypoglycemia, time in range, hyperglycemia post-exercise period given as percentage of total time stratified for day and nighttime period (up to 24 hours post-exercise)
- Numbers of hypoglycemic episodes during physical exercise (<70 mg/dL)
- Numbers of hypoglycemic episodes in the post-exercise period (<70 mg/dL) (up to 24 hours post-exercise)

- Numbers of hypoglycemic episodes in the post-exercise period stratified also for day and nighttime (<70 mg/dL) (up to 24 hours post-exercise)
- Time spent in hypoglycemia, time in range, hyperglycemia during physical exercise stratified for single-hormone CLS or dual-hormone CLS
- Time spent in hypoglycemia, time in range, hyperglycemia in the post-exercise period stratified for single-hormone CLS or dual-hormone CLS (up to 24 hours post-exercise)
- Time spent in hypoglycemia, time in range, hyperglycemia in the post-exercise period stratified for single-hormone CLS or dual-hormone CLS stratified for day and nighttime (up to 24 hours post-exercise)

All outcomes are compared to (modern) current care

Types of Studies (minimum Number of Participants per group: 3)

- Crossover randomized trials
- Randomized controlled trials
- Randomized trials
- Observational controlled trials
- Minimum Number of Participants per group: 3
- Only Published Studies will be included
- English Language only
- No in silico studies

Database

- PubMED/MEDLINE
- EMBASE
- Cochrane Controlled Register of Trials (CENTRAL)
- Web of Science

Appendix 2: Prisma 2009 Statement

Appendix 2: Prisma 2009 Statement

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	9
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Appendix 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12-13
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	16
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17-18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	20-23
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24-25
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	26-27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

Appendix 3: Search Strategy

Table 1: Search Pubmed, January 2020

#	Term	Hits
#1	(diabetes mellitus, type 1 [mh])	74437
#2	(type 1 diabetes mellitus [tw])	77016
#3	(type 1 diabetes [tw])	38803
#4	("type i" diabetes mellitus [tw])	8600
#5	("type-i" diabetes mellitus [tw])	8600
#6	("insulin-dependent" diabet* [tw])	27696
#7	(Artificial pancreas [mh])	735
#8	(Bioartificial Organs [mh] AND (pancreas [tw] OR insulin [tw] OR diabet* [tw]))	75
#9	(Bionics [mh] AND (pancreas [tw] OR insulin [tw] OR diabet* [tw]))	8
#10	("synthetic pancreas" [tw] AND (insulin [tw] OR diabet* [tw]))	4
#11	("artificial endocrine pancreas" [tw] AND (insulin [tw] OR diabet* [tw]))	195
#12	(artificial beta cell* [tw] OR artificial b cell* [tw] OR artificial b-cell* [tw])	159
#13	(closed-loop* [tw] AND (pancreas [tw] OR insulin [tw] OR diabet* [tw]))	1124
#14	("closed loop*" AND (pancreas [tw] OR insulin [tw] OR diabet* [tw]))	1125
#15	("bioartificial pancreas" [tw] OR "bio-artificial pancreas" [tw])	269
#16	#1 - #15 OR	104067
#17	(insulin pump [tw])	2184
#18	(insulin delivery system* [tw])	488
#19	(insulin [tw])	406540
#20	(Infusion Pumps, Implantable [mh])	3616
#21	(Insulin Infusion System [mh])	5136
#22	(continuous subcutaneous insulin infusion [tw])	1935
#23	(csii [tw])	1492
#24	#17 - #23 OR	409716
#25	#16 AND #24	56261
#26	(glucose [tw] AND (sensor* [tw] OR sensing*))	13781
#27	("sensed glucose" [tw])	8
#28	(CGM [tw])	2135
#29	(CGMS [tw])	642
#30	(RTCGM [tw])	39
#31	(RTCGMS [tw])	3
#32	(ICGM [tw])	11
#33	(glucoWatch [tw])	54
#34	(medtronic [tw] AND diabet*)	423
#35	(dexcom [tw] AND diabet*)	154
#36	(abbott [tw] AND diabet*)	298
#37	(omnipod [tw] AND diabet*)	37
#38	(tandem [tw] AND diabet*)	2472
#39	(animas [tw] AND diabet*)	17
#40	(roche [tw] AND diabet*)	361

#41	#26 – #40 OR	18984
#42	#16 AND #24 AND #41	1943
#43	(Exercise [mh])	187953
#44	(Resistance Training [mh])	8109
#45	(High-Intensity Interval Training [mh])	850
#46	(high-intensity training [tw])	703
#47	(high intensity training [tw])	703
#48	(physical activity [tw])	104733
#49	#43 – #48 OR	253679
#50	#16 AND #24 AND #41 AND #49	92
#51	Limit: humans and english language	79

Table 2: Search Embase, January 2020

#	Term	Hits
#1	(diabetes mellitus, type 1).mp.	3186
#2	(type 1 diabetes mellitus).mp.	16025
#3	(type 1 diabetes).mp.	62482
#4	("type i" diabetes mellitus).mp.	2474
#5	("type-i" diabetes mellitus).mp.	2474
#6	("insulin-dependent" diabet*).mp.	340700
#7	(artificial pancreas).mp.	2906
#8	(Bioartificial Organs AND (pancreas OR insulin OR diabet*)).mp.	22
#9	(Bionics AND (pancreas OR insulin OR diabet*)).mp.	27
#10	("synthetic pancreas" AND (insulin OR diabet*)).mp.	7
#11	("artificial endocrine pancreas" AND (insulin OR diabet*)).mp.	276
#12	(artificial beta cell* OR artificial b cell* OR artificial b-cell*).mp.	210
#13	(closed-loop* AND (pancreas OR insulin OR diabet*)).mp.	2072
#14	("closed loop*" AND (pancreas OR insulin OR diabet*)).mp.	2072
#15	("bioartificial pancreas" OR "bio-artificial pancreas").mp.	391
#16	#1 - #15 OR	352561
#17	(insulin pump).mp.	7940
#18	(insulin delivery system*).mp.	759
#19	(insulin).mp.	765097
#20	(Infusion Pumps, Implantable).mp.	15
#21	(Insulin Infusion System).mp.	187
#22	(continuous subcutaneous insulin infusion).mp.	3371
#23	(csii).mp.	3418
#24	#17 - #23 OR	765224
#25	#16 AND #24	346428
#26	(glucose AND (sensor* OR sensing*)).mp.	22379
#27	("sensed glucose").mp.	11
#28	(CGM).mp.	4836
#29	(CGMS).mp.	1501
#30	(RTCGM).mp.	104

#31	(RTCGMS).mp.	9
#32	(ICGM).mp.	30
#33	(glucoWatch).mp.	193
#34	(medtronic AND diabet*).mp.	3001
#35	(dexcom AND diabet*).mp.	812
#36	(abbott AND diabet*).mp.	2774
#37	(omnipod AND diabet*).mp.	208
#38	(tandem AND diabet*).mp.	3323
#39	(animas AND diabet*).mp.	219
#40	(roche AND diabet*).mp.	3671
#41	#26 – #40 OR	37013
#42	#16 AND #24 AND #41	10448
#43	(Exercise).mp.	479276
#44	(Resistance Training).mp.	20024
#45	(High-Intensity Interval Training).mp.	2549
#46	(high-intensity training).mp.	860
#47	(high intensity training).mp.	860
#48	(physical activity).mp.	201470
#49	#43 – #48 OR	618491
#50	#16 AND #24 AND #41 AND #49	956
#51	Limit: human and english language	882

Table 3: Search ISY Web of Science, January 2020

#	Term	Hits
#1	TS= (diabetes mellitus, type 1)	220703
#2	TS= (type 1 diabetes mellitus)	220703
#3	TS= (type 1 diabetes)	250449
#4	TS= ("type i" diabetes mellitus)	17553
#5	TS= ("type-i" diabetes mellitus)	17553
#6	TS= ("insulin-dependent" diabet*)	167753
#7	TS= (artificial pancreas)	5821
#8	TS= (Bioartificial Organs AND (pancreas OR insulin OR diabet*))	298
#9	TS= (Bionics AND (pancreas OR insulin OR diabet*))	148
#10	TS= ("synthetic pancreas" AND (insulin OR diabet*))	4
#11	TS= ("artificial endocrine pancreas" AND (insulin OR diabet*))	328
#12	TS= (artificial beta cell* OR artificial b cell* OR artificial b-cell*)	28435
#13	TS= (closed-loop* AND (pancreas OR insulin OR diabet*))	1731
#14	TS= ("closed loop*" AND (pancreas OR insulin OR diabet*))	1722
#15	TS= ("bioartificial pancreas" OR "bio-artificial pancreas")	652
#16	#1 - #15 OR	353226
#17	TS= (insulin pump)	9641
#18	TS= (insulin delivery system*)	15831
#19	TS= (insulin)	738676
#20	TS= (Infusion Pumps, Implantable)	4399

#21	TS= (Insulin Infusion System)	25341
#22	TS= (continuous subcutaneous insulin infusion)	3830
#23	TS= (csii)	2280
#24	#17 - #23 OR	742532
#25	#16 AND #24	229761
#26	TS= (glucose AND (sensor* OR sensing*))	43648
#27	TS= ("sensed glucose")	10
#28	TS= (CGM)	4319
#29	TS= (CGMS)	1076
#30	TS= (RTCGM)	58
#31	TS= (RTCGMS)	4
#32	TS= (ICGM)	21
#33	TS= (glucoWatch)	119
#34	TS= (medtronic AND diabet*)	547
#35	TS= (dexcom AND diabet*)	229
#36	TS= (abbott AND diabet*)	381
#37	TS= (omnipod AND diabet*)	69
#38	TS= (tandem AND diabet*)	3395
#39	TS= (animas AND diabet*)	28
#40	TS= (roche AND diabet*)	553
#41	#26 – #40 OR	52534
#42	#16 AND #24 AND #41	6694
#43	TS= (Exercise)	711220
#44	TS= (Resistance Training)	43045
#45	TS= (High-Intensity Interval Training)	3993
#46	TS= (high-intensity training)	10682
#47	TS= (high intensity training)	23086
#48	TS= (physical activity)	694701
#49	#43 – #48 OR	1289571
#50	#16 AND #24 AND #41 AND #49	445
#51	#50 NOT (animal)	373
#52	Limit: english language	373

Table 4: Search Cochrane Controlled Register of Trials (CENTRAL)

#	Term	Hits
#1	(diabetes mellitus, type 1).mp.	5198
#2	(type 1 diabetes mellitus).mp.	1480
#3	(type 1 diabetes).mp.	5951
#4	("type i" diabetes mellitus).mp.	186
#5	("type-i" diabetes mellitus).mp.	186
#6	("insulin-dependent" diabet*).mp.	20400
#7	(artificial pancreas).mp.	274

#8	(Bioartificial Organs AND (pancreas OR insulin OR diabet*)).mp.	0
#9	(Bionics AND (pancreas OR insulin OR diabet*)).mp.	7
#10	("synthetic pancreas" AND (insulin OR diabet*)).mp.	0
#11	("artificial endocrine pancreas" AND (insulin OR diabet*)).mp.	21
#12	(artificial beta cell* OR artificial b cell* OR artificial b-cell*).mp.	6
#13	(closed-loop* AND (pancreas OR insulin OR diabet*)).mp.	474
#14	("closed loop*" AND (pancreas OR insulin OR diabet*)).mp.	474
#15	("bioartificial pancreas" OR "bio-artificial pancreas").mp.	0
#16	#1 - #15 OR	25261
#17	(insulin pump).mp.	1084
#18	(insulin delivery system*).mp.	95
#19	(insulin).mp.	57490
#20	(Infusion Pumps, Implantable).mp.	142
#21	(Insulin Infusion System).mp.	17
#22	(continuous subcutaneous insulin infusion).mp.	667
#23	(csii).mp.	672
#24	#17 - #23 OR	57598
#25	#16 AND #24	23374
#26	(glucose AND (sensor* OR sensing*)).mp.	1420
#27	("sensed glucose").mp.	1
#28	(CGM).mp.	1211
#29	(CGMS).mp.	308
#30	(RTCGM).mp.	24
#31	(RTCGMS).mp.	0
#32	(ICGM).mp.	1
#33	(glucoWatch).mp.	13
#34	(medtronic AND diabet*).mp.	283
#35	(dexcom AND diabet*).mp.	139
#36	(abbott AND diabet*).mp.	137
#37	(omnipod AND diabet*).mp.	13
#38	(tandem AND diabet*).mp.	174
#39	(animas AND diabet*).mp.	6
#40	(roche AND diabet*).mp.	133
#41	#26 – #40 OR	2987
#42	#16 AND #24 AND #41	1468
#43	(Exercise).mp.	86967
#44	(Resistance Training).mp.	8192
#45	(High-Intensity Interval Training).mp.	1435
#46	(high-intensity training).mp.	354
#47	(high intensity training).mp.	354
#48	(physical activity).mp.	27569
#49	#43 – #48 OR	102845
#50	#16 AND #24 AND #41 AND #49	209
#51	Limit: english language	140

Appendix 4: Data extraction form

For every trial with the necessary eligibility to be included into the meta-analysis the following information was extracted:

Trials characteristics:

NCT/ DOI

Source

Region

Design

Setting

Population

Intervention characteristics:

Intervention device

Algorithm used in the intervention device

Control Device/ System

Pump system

Insulin used

Type of exercise

Exercise duration

Exercise intensity

Baseline characteristics:

Patients(n)

Age (SD)

Male(n)/ Female(n)

We also extracted data for the following secondary outcomes:

- time spent in hypoglycemia (<3.9mmol/L) during exercise
- time spent in hyperglycemia (>10mmol/L) during exercise
- number of hypoglycemic events (<3.9mmol/L) during exercise
- time in range (3.9-10mmol/L) during the post-exercise period
- time spent in hypoglycemia (<3.9mmol/L) during the post-exercise period
- time spent in hyperglycemia (>10mmol/L) during the post-exercise period
- number of hypoglycemic events (<3.9mmol/L) during the post-exercise period

We also extracted information for the following parameters for assessment of risk of bias:

- Sequence generation (or randomized treatment order for cross-over studies)
- Allocation concealment
- Blinding
- Dropout rate per arm/intervention period
- Type of analysis (ITT, per protocol) and method of imputation
- Selective outcome reporting
- Appropriateness of cross-over design
- Carry-over effects
- Unbiased data

Appendix 5: Characteristics of included studies

	Study number	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Study Characteristics	Study title	Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial.	Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy.	Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes.	Artificial Pancreas (AP) Ski Camp 2018: Successful use of the Tandem Control-IQ AP system in adolescents and children during winter sports and at home.	Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: The artificial pancreas ski study.	Randomized outpatient trial of single- and dual-hormone CLSs that adapt to exercise using wearable sensors.
	First author	Dove K	Jacobs P	Elleri D	Ekhlaspour L	Breton M	Castle J
	Publication year	2017	2016	2013	2019	2017	2018
	Journal	Diabetologia	Diabetes, Obesity and Metabolism	Diabetes Care	Pediatric Diabetes	Diabetes Care	Diabetes Care
	Country	Slovenia	United States	United Kingdom	United States	United States	United States
	City	Ljubljana	Portland	Cambridge	Virgina, Stanford, Colorado	Virgina, Stanford, Colorado	Portland
	Continent	Europe	North America	Europe	North America	North America	North America
	Study Type	Randomised Controlled Crossover Trial	Randomized Controlled Crossover Trial	Randomized Controlled Crossover Trial	Randomized Controlled Trial	Randomized Controlled Trial	Randomized Controlled Crossover Trial
Population	Number of Participants	20	23	12	48	32	25
	Age range	10-17 years	18-45 years	12-18 years	6-18 years	10–16 years	21-45 years
	Participants completed the study	20	21	12	48	32	20
	Gender	11 male/ 9 female	9 male / 14 female	5 male/ 7 females	24 male/ 24 female	17 male/ 15 female	9 male / 16 female
	Age of participants that completed the study	14.2 ± 2.0 years	32 ± 7 years	15.0 ± 1.4 years	12.3 ± 3.2 years	13.2 ± 1.7 years	34.5 ± 4.7 years
	Anthropometrics	Available	Available	Available	Available	Available	Available
Outcome measures	Device Intervention	Paradigm Veo Medtronic; Enlite II sensor with MiniLink	Two Tandem t:slim pumps; Dexcom G4 CGM	Animas 2020 Pump; Dexcom Seven Plus CGM	Tandem t:slim X2; Dexcom G6 CGM	Tandem t:AP pump/ Roche-Accu-Check Spirit Combo pump; Dexcom G4 CGM	Tandem t:slim pump; Dexcom G5 CGM
	Device Control	Paradigm Veo Medtronic; Enlite II sensor with MiniLink	Sensor augmented pump with Dexcom G4 CGM	Animas 2020 Pump ,Dexcom Seven Plus CGM	Sensor-augmented pump; Dexcom G5 CGM	Remotely monitored sensor-augmented pump; Dexcom G4 CGM	Predictive low glucose suspend system: t:slim pump, Dexcom G5 CGM and current care

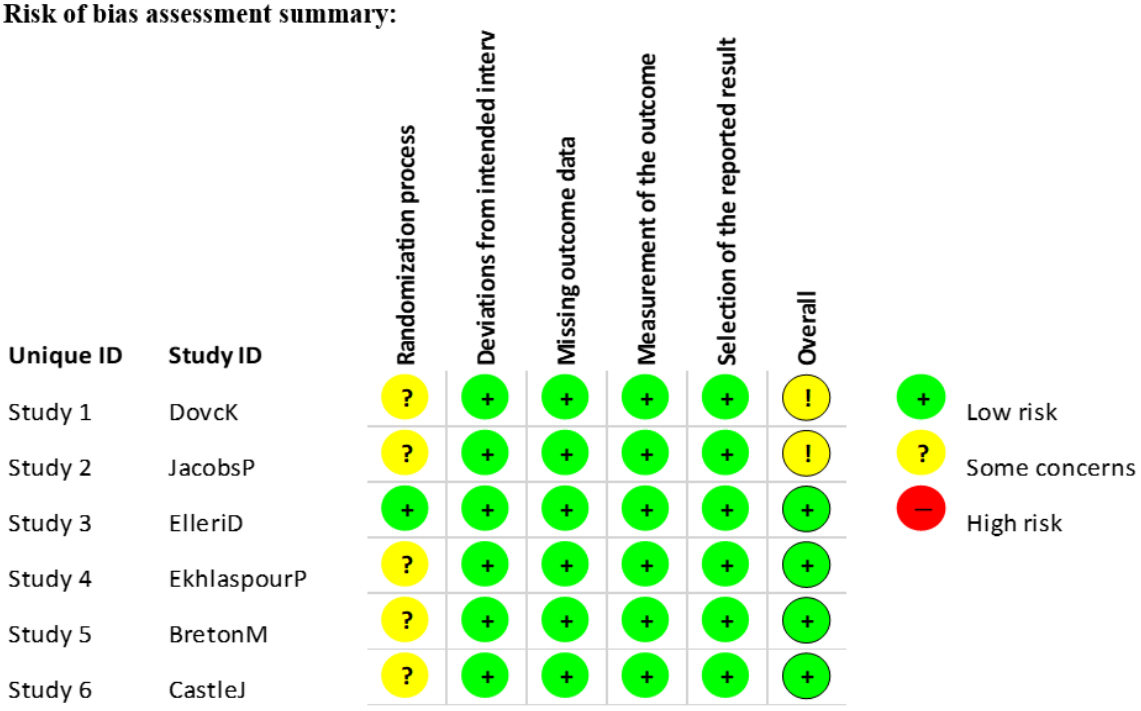
Outcome measures	**Drug type**	n/a		Novolog and glucagon		Aspart analog		n/a	n/a	Aspart	
	Algorithm	Glucositter, Israel, fuzzy-logic algorithm		Proportional-integral-deriative algorithm		Algorithm based on model predictive control		DiA algorithm / ControlIQ	DiA algorithm	Fading memory proportional-deriative algortihm	
	Time in range (70-180 mg/dL)* during physical exercise in the intervention group	55% VO2max: 80.9% (64.3–92.2)	55+80% VO2max: 75.3% (66.6–92.9)	With APX 67% (60-75)	Without APX 72% (66-78)	Morning exercise: 79% (54, 99)	Afternoon exercise: 60% (54, 88)	57.8% ± 27.3	63.2% ± 31.1	Dual-hormone AP: 84.3% (16.7)	Single-hormone AP: 83.3% (16.7)
	Time in range (70-180 mg/dL)* during physical exercise in the control group	68.1% (59.1–83.6)	68.4% (52.1–77.2)	68% (60-76)		56% (24, 70)	71% (18, 95)	55.9% ± 31.1	62.8% ± 31.4	78.3% (18.9)	78.2% (26.2)
Performance parameter	**Type of Exercise**	Cycle ergometer		Treadmill ergometer		Cycle ergometer		Skiing	Skiing	Treadmill ergometer	
	Exercise Duration	40 min		45 min		60 min		240 min	330 min	45 min	
	Exercise intensity	55% of VO2max and HIT 55/80% VO2max		60% of max. heart rate		Moderate-intensity (heartrate of 140 bpm)		n/a	n/a	60% VO2max	

***given as percentage of total time during physical exercise**

Table 5: Study baseline characteristics

Appendix 6: Risk of bias assessment

Risk of bias assessment summary:



Risk of bias formal assessment:

Test Name	value	p
Fail-Safe N	154.000	< .001
Kendalls Tau	-0.154	0.491
Egger's Regression	0.377	0.706
Trim and Fill Number of Studies	0.000	.

fi ùÍ Ƹ Fail-safe N Calculation Using the Rosenthal Approach

Appendix 7: Secondary outcomes

	Time spent <3.9mmol/L during exercise				Time spent >10mmol/L during exercise		Number of events <3.9mmol/L during exercise:	
	Closed-loop single hormone	Closed-loop dual-hormone	PLGS	Current care	Closed-loop	Current care	Closed-loop	Current care
Dovc K (1a)	0.0 (0.0–0.0)	n/a	n/a	0.2 (0.0–4.5)	17.1 (7.2–33.0)	25.2 (6.0–39.3)	n/a	n/a
Dovc K (1b)	1.1 (0.0–3.4)	n/a	n/a	0.0 (0.0–3.3)	20.8 (5.0–28.9)	29.6 (17.6–45.4)	n/a	n/a
Jacobs P (2a)	0.3 [-0.1, 0.7]	n/a	n/a	0.8 [0.1, 1.4]	32 [25, 39]	31 [24, 39]	n/a	n/a
Jacobs P (2b)	3.1 [0.8, 5.3]	n/a	n/a	n/a	25 [19, 30]	n/a	n/a	n/a
Elleri D (3a)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Elleri D (3b)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Ekhlaspour L (4)	0 (0.0, 0.8)	n/a	n/a	0 (0.0, 0.4)	41.4 ± 27.8	41.5 ± 30.3	n/a	n/a
BretonM (5)	1.4 ± 1.6	n/a	n/a	1.4 ± 1.6	n/a	n/a	0.3 ± 0.4	0.3 ± 0.7
CastleJ (6)	3.4 (4.5)	8.3 (12.6)	7.6 (8.0)	4.3 (6.8)	n/a	n/a	n/a	n/a

Table 6: Secondary outcomes: time in percentage below and above target range during exercise and events <3.9 mmol/L

	TIR during the post-exercise period:		Time spent <3.9mmol/L in the post-exercise period:		Time spent >10mmol/L during the post-exercise period:		Number of events <3.9mmol/L during the post-exercise:	
	Closed-loop	Current care	Closed-loop	Current care	Closed-loop	Current care	Closed-loop	Current care
Dovc K (1a)	92.8 (69.8–98.4)	73.3 (61.3–84.2)	n/a	n/a	7.2 (0.2–23.9)	22.7 (9.1–38.7)	3 (in total)	4 (in total)
Dovc K (1b)	n/a	n/a	0.0 (0.0–3.5)	0.0 (0.0–2.8)	n/a	n/a	n/a	n/a
Jacobs P (2a)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Jacobs P (2b)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Elleri D (3a)	94 (54, 100)	79 (34, 100)	0.0 (0.0, 1.0)	0.0 (0.0, 2.4)	1.0 (0.0, 13.9)	64.6 (1.6, 97.5)	n/a	n/a
Elleri D (3b)	96 (79, 100)	33 (2, 80)	0.2 (0.0, 4.7)	0.0 (0.0, 0.0)	n/a	n/a	n/a	n/a
Ekhlaspour L (4)	78.6 ± 20.3	50.9 ± 34.2	0 (0.0, 8.2)	0 (0.0, 6.4)	18.2 ± 21.4	44.5 ± 37	n/a	n/a
BretonM (5)	79.3 ± 29.8	68.8 ± 24.1	2.2 ± 2.3	2.5 ± 6.5	n/a	n/a	0.1 ± 0.3	0.1 ± 0.4
CastleJ (6)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Table 7: Secondary outcomes: time in percentage during the post-exercise period including number of events <3.9 mmol/L