Thesis

The effects of different doses of basal insulin on the cardiac and metabolic responses during exercise testing in people with type 1 diabetes

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 24.01.2023 *Ulrike Glatz m.p.*

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Abbreviations

T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 diabetes mellitus
HR peak	Peak heart rate
VO_{2peak}	Maximum oxygen consumption
CGM	Continuous glucose monitoring
MDI	Multiple daily injections
CSII	Continuous subcutaneous insulin infusion
CPX	Cardio-pulmonary exercise
IGlar U300	Insulin Glargine U300
IDeg U100	Insulin Degludec U100
CHO	Carbohydrate
FPG	Fasting plasma glucose
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
PG	Plasma glucose
OGTT	Oral glucose tolerance test
HR	Heart rate
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
IU	International unit
SD	Standard deviation

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Zusammenfassung

Ziel:

Das Ziel dieser Diplomarbeit war, die Unterschiede einer regulären (100%) im Vergleich zu einer 75% Dosis von Insulin Glargine U300 (IGlar U300) auf kardiale und metabolische Marker während mehrerer spontaner Sporteinheiten darzustellen.

Methoden:

Die Daten von 15 sportlich aktiven erwachsenen Teilnehmer*Innen (acht Männer, sieben Frauen) mit T1DM und guter glykämischer Kontrolle, wurden aus einer größeren Studie entnommen. Ultraflexi-1 ist eine randomisierte, crossover-kontrollierte, monozentrische Studie, bestehend aus vier Phasen (IGlar U300, IDeg U100 jeweils in der Dosierung 100% und 75%). Pro Phase wurden 6 Trainingseinheiten innerhalb zwei aufeinanderfolgender Wochen durchgeführt, in welchen die Teilnehmer*Innen jeweils ein 60-minütiges Training auf einem Fahrradergometer, davon 54 Minuten bei einer VO_{2max} von ca. 66% (moderate Intensität), absolvierten. Für diese Diplomarbeit wurden nur Daten zu IGlar U300 (100% und 75%) berücksichtigt. Von den während der Trainingseinheiten durchgeführten Messungen, wurden Herzfrequenz, Blutdruck, Blutglukose und Laktat erhoben. Zudem wurden die Kohlenhydratzufuhr während des Trainings und die durchschnittliche tägliche Bolusinsulin-Gesamtdosis über die jeweilige 14-Tages-Periode analysiert. Die Daten wurden mittels Shapiro-Wilk-Normalitätstest auf Normalverteilung geprüft und die Parameter mittels t-Test für verbundene Stichproben, sowie nicht-normalverteilte Daten mittels nicht-parametrischem Friedman-Test, verglichen ($p \leq 0,05$).

Ergebnisse:

Die Unterschiede in der Herzfrequenz (122,88 ± 15,91 vs. 122,94 ± 12,72; p = 0,91), dem systolischen (148,9 ± 15,3 vs. 147,34 ± 15,32; p = 0,18) und diastolischen Blutdruck (77,08 ± 5,04 vs. 77,37 ± 6,22; p = 0,93), Laktat (2,03 ± 0,8 vs. 1,95 ± 0,61; p = 0,82), der Blutglukose (141,79 ± 17,69 vs. 141,4 ± 20,09; p = 0,61), der CHO-Supplementierung (27,48 ± 20,97 vs. 25,26 ± 18,29; p = 0,44) sowie die durchschnittliche tägliche Bolusinsulin-Gesamtdosis (16,6 ± 10,66 vs. 15,7 ± 9,32; p = 0,28) im Vergleich zwischen der 100% und 75% Dosierung von IGlar U300 zeigten keine statistische Signifikanz.

Schlussfolgerung:

In der metabolischen und kardialen Reaktion wurden keine Unterschiede zwischen einer 100% und 75% Dosierung von IGlar U300 festgestellt. Diese Ergebnisse könnten darauf hindeuten, dass eine Reduktion um 25% von Basalinsulin IGlar U300 für sportliche Betätigung, keine unmittelbaren negativen Auswirkungen auf das Herz-Kreislauf-System (Blutdruck und Herzfrequenz) sowie den Stoffwechsel (Blutglukosespiegel und Laktat) während eines Trainings hat.

Abstract

Aim

The aim of the thesis was to compare the effects of a regular (100%) vs. 75% dose of insulin Glargine U300 (IGlar U300) on the cardiac and metabolic markers during several spontaneous exercise sessions.

Material and methods

Data from 15 physically active adult participants (eight male, seven female) with T1DM in good glycemic control were obtained from a larger study. Ultraflexi-1 is a randomized single-center four period cross-over trial (IGlar U300, IDeg U100 each in the dosage 100% and 75%). In each period, six training sessions were conducted within two consecutive weeks, in which the participants performed 60 minutes of exercise on a cycle ergometer, including 54 minutes at a VO_{2max} of around 66% (moderate intensity). For this thesis, only data regarding IGlar U300 (100% and 75%) were included. Various measurements were performed during the exercise sessions, of which heart rate, blood pressure, blood glucose, and lactate were obtained for this thesis. In addition, CHO intake during exercise and the average total daily bolus insulin dose were analyzed over the respective 14-day period. Data were tested for normal distribution using Shapiro-Wilk normality test and parameters were compared using paired t-test ($p \leq 0.05$). For non-normally distributed data the non-parametric Friedman test was used ($p \leq 0.05$).

Results

There was no statistically significant difference in heart rate (122.88 ± 15.91 vs. 122.94 ± 12.72; $p = 0.91$), systolic (148.9 ± 15.3 vs. 147.34 ± 15.32; $p = 0.18$) and diastolic (77.08 ± 5.04 vs. 77.37 ± 6.22; $p = 0.93$) blood pressure, lactate (2.03 ± 0.8 vs. 1.95 ± 0.61; $p = 0.82$), blood glucose (141.79 ± 17.69 vs. 141.4 ± 20.09; $p = 0.61$), CHO intake (27.48 ± 20.97 vs. 25.26 ± 18.29; $p = 0.44$) as well as the average total daily bolus insulin dose over the respective 14-day period (16.6 ± 10.66 vs. 15.7 ± 9.32; $p = 0.28$) between the 100% and 75% dosing scheme of IGlar U300.

Conclusion

No differences were observed in cardiac and metabolic response between 100% and 75% dosing of IGlar U300. These results may indicate that a reduction by 25% in basal insulin IGlar U300 has no immediate negative effects on the cardiovascular system, represented by blood pressure and heart rate, and the metabolism, represented by blood glucose levels and lactate during exercise.

1 Introduction

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease that presents with hyperglycemia. The etiology is considered as a multifactorial interaction between environmental factors, microbiome, metabolism, genome, and the immune system, which differs between the individuals (Figure 1.1) (1). The disease results from an autoimmune process which destructs the pancreatic β cells, with the consequence of complete or near-total insulin deficiency (2). This destruction is caused by the presence of autoantibodies that are directed against the autoantigens on the insulin-secreting pancreatic β cells (3). There are no prevention ways defined for the occurrence or progression of T1DM (2,4).

1.1 Epidemiology

T1DM makes up 5 to 15% of the group of diabetes diseases. Incidence rates between the continents vary widely. The incidence of T1DM is 15 per 100 000 in the European population, same as in Asia with 15 per 100 000, 8 per 100 000 in Africa, while the highest incidence, 20 per 100 000, is in America. The prevalence of T1DM is 12.2 per 10 000 in Europe (4). The global increase of the prevalence of T1DM is about 3-5% per year worldwide. The reason for this increase is not exactly known, but it is noticeable that the diagnosis made at younger ages is increasing (2). T1DM is a disease that can affect life expectancy and quality. Therefore, it is important to perform research and get more knowledge about disease management. Research in a Scottish cohort could show a decreased estimated life expectancy about 11 years for men and 13 years for women (5).

1.2 Etiology

There are various theories about the etiology. Primary β cell abnormalities could be a cause that leads to purported β cell suicide (1). Other theories say that the overexpression of HLA class I antigens on the β cells is a homing signal for cytotoxic T lymphocytes (6). There are also other trigger mechanisms discussed, that consider the cause of the β cell destruction as a response, for example to a viral infection or stress in the endoplasmic reticulum of the β cell (1). Most people with T1DM have evidence for islet-directed autoimmunity, while

other individuals develop the disease without the presence of the immunologic markers, who are indicative for the autoimmune process against the β cells and the genetic markers of T1DM (2). There are four major humoral autoantibodies against specific β cell proteins detected, which are specific for the disease. These antigens are insulin, glutamate decarboxylase, islet antigen 2 and zinc transporter 8 (7). The hormone secreting cells, for example, the glucagon secreting α cells, somatostatin producing δ cells or the pancreatic polypeptide producing PP cells, are not affected by the disease, therefore the immune system selectively attacks the β cells. Mainly CD8+ T cells can be found in the insulitis lesions. Furthermore, macrophages (CD68+), CD4+ T cells, B- lymphocytes (CD20+) and plasma cells (CD138+) are involved in the autoimmune destruction of the pancreatic β cells (3).

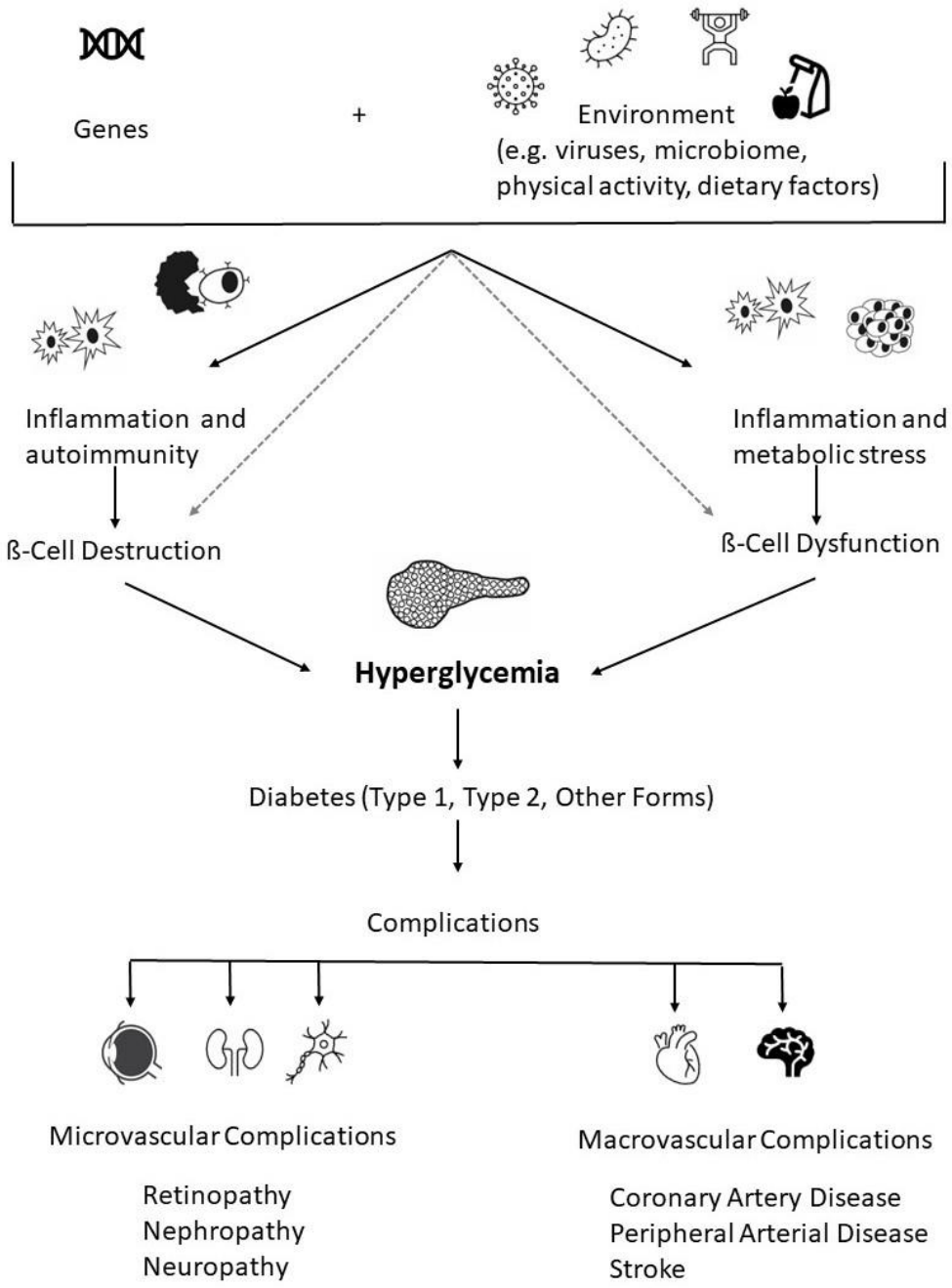

Figure 1.1 – "Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress. These states affect β-cell mass and/or function such that insulin levels are eventually unable to respond sufficiently to insulin demands, leading to hyperglycemia levels sufficient to diagnose diabetes. In some cases, genetic and environmental risk factors and gene-environment interactions can directly impact β-cell mass and/or function" (8). This figure is reproduced from Skyler et al. 2017 (8).

1.3 Diagnosis

T1DM can occur at any age, but in most cases, it develops before the age of 20 years (2). Children show more often the classic symptoms polyuria, polydipsia and weight loss, also called the classic trias, while the presentation in adults can be more variable (1). Nearly one-third of all youth with T1DM are presenting with diabetic ketoacidosis (9). Other possible symptoms beside the classic trias can initially manifest as constant hunger, vision changes and fatigue (10).

The diagnosis of diabetes mellitus is based on one of the following criteria:

- fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) (fasting means no caloric intake for at least 8 h)
- 2 h plasma glucose (PG) ≥ 200 mg/dL (11.1 mmol/L) during a 75 g oral glucose tolerance test (OGTT)
- A1C ≥ 6.5% (48 mmol/mol)
- a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), if there is a typical clinical manifestation of hyperglycemia or hyperglycemic crisis

If no definite hyperglycemia is detected in the FPG, the 2 h PG or the A1C, two test results obtained from the same sample or from two different samples must be abnormal to confirm the diagnosis (11).

Three stages of T1DM have been defined. Stage 1 diagnostic criteria include the presence of multiple islet autoantibodies (two or more) without impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The autoimmune markers implicated here are zinc transporter 8, tyrosine phosphatases islet antigen 2 (IA-2) and IA-2β, insulin, islet cell autoantibodies and autoantibodies to GAD (glutamic acid decarboxylase, GAD65). The diagnostic criteria of stage 2 include the presence of islet autoantibodies (usually multiple), dysglycemia (IFG and/or IGT), FPG between 100-125 mg/dL (5.6-6.9 mmol/L), 2 h PG between 140-199 mg/dL (7.8-11.0 mmol/L), and an A1C of 5.7-6.4% (39-47 mmol/mol) or an increase in A1C ≥ 10%. In stage 3, it is possible that the autoantibodies are no longer present and the standard criteria for the diagnosis of diabetes apply as a further criterion (11).

1.4 Physical activity in people with T1DM

The positive effect of regular exercise includes cardiovascular risk reduction, amelioration of blood pressure values, lower plasma glucose values during and after exercise, an increase of insulin sensitivity, as well as the impact to the physique including build-up of muscle mass, reduction of body fat and weight loss (2). Furthermore, exercising on a regular basis reduces the total daily need of insulin (12). Complications like retinopathy and microalbuminuria are less prevalent in adult people with T1DM who are physically active (12). Exercising on a regular basis is generally advised for people with T1DM, because of the multitude of beneficial effects to the body. However, this can be challenging for people with T1DM due to the risk of hypoglycemia and hyperglycemia. During exercise, multiple hormones including insulin, glucagon, catecholamines, growth hormone and cortisol regulate the fuel metabolism and maintain the homeostasis of glucose between the glucose consumption of the exercising muscle and the sugar release of the liver (13). Maximum oxygen consumption (VO_{2peak}) is a measure of a person's fitness. This parameter represents the capacity of the lungs, the heart and large muscle groups and expresses aerobic capacity (14). VO_{2peak} is described to be a strong predictive value for the risk of cardiovascular complications (15). There are several studies that showed reduced VO_{2peak} values in people with T1DM (14–17). Furthermore, an association between poor glycemic control and lower VO_{2peak} values was found (18).

1.5 Hormone response to exercise

In people with T1DM, there is no normal glucoregulatory mechanism compared to healthy people. Physiologically, insulin levels decrease, and glucagon levels increase during physical activity in healthy individuals (2). If the onset of T1DM was more than five years ago, the glucagon response to hypoglycemia is either lost or significantly impaired (19). In individuals with T1DM, insulin does not decrease and as well glucagon does not rise when glucose concentration falls during exercise, compared to healthy individuals (2). Hence, the body can only react to a decreasing blood glucose by releasing catecholamines (19).

There is an increased consumption of glucose by the skeletal muscle during exercise. So, there is a proneness for hyperglycemia or hypoglycemia during physical activity impacted

by the plasma glucose level right before the exercise, the current insulin level and the catecholamines (2). Studies have shown that depending on the mean intensity, the hormone response to exercise is a significant increase of adrenalin, noradrenaline and dopamine until exercise is completed. A slight but nonsignificant increase in cortisol and IGF-1, but not glucagon, was detected. No differences could be shown in the hormone response between aerobic short high intensity interval exercise and moderate continuous exercise (20,21). Increased insulin concentrations during exercise come along with an increased glucose disposal (12). Once insulin levels decrease too far, there is a risk of a catecholamine increase, which results in excessively high plasma glucose and ketone production with a possible complication of ketoacidosis. On the other side, too high insulin levels could lead to an inhibition of the glucose production in the liver by inhibiting glycogenolysis and gluconeogenesis and, furthermore, the excessive insulin level results in an increased consumption of the working muscle which both leads to hypoglycemia (2).

1.6 Metabolic response to exercise

1.6.1 Lactate metabolism during exercise

Based on glucose availability, physical exercise can be categorized into aerobic and anaerobic (= lactic acid) (22). Continuous exercise is based on aerobic energy supply (12). The metabolic response to exercise in the metabolism regarding lactate changes is described by three phases, divided by two thresholds, which can be seen in continuous and intermittent exercise. The difference between these three individual phases lies in the energy supply. When exercise is started, the active muscles begin to produce lactate. The first phase is described to lie between resting and the lactate turnpoint 1 (LTP1). During this phase, the produced lactate can be aerobically eliminated in the muscle. The homeostasis of production and elimination leads to a balance, which is called lactate steady state. Once LTP1 is attained, phase 2 lasts until lactate turnpoint 2 (LTP2) is reached. In this phase the produced lactate is at a level, at which it cannot be oxidized in the working muscle in total, so it partly reaches the blood stream, from where organs can metabolize the lactate. This phase is also a steady state based on a balance by a systemic compensation through the body system. Phase 3 is beyond the LTP2. In this phase the lactate production in the active muscle exceeds the

degradation process of the muscle and the organs, so the lactate accumulates in the circulating blood (23).

1.6.2 Blood glucose during exercise

There are multiple ways physical training impacts the blood sugar system, as for example through the amplification of exercise effects on insulin sensitivity, an increase of glucose utilization and storage. Physical exercise leads to an upregulation of insulin, stimulated insulin receptor substrate 1 and Akt Ser473 phosphorylation, which enhances the glucose elimination after insulin stimulation (22). In muscles that were just active, the insulin efficacy and in the same way the glucose uptake are locally improved. Insulin stimulates the translocation of glucose transporters, more accurate the GLUT4 in the muscle membrane after physical activity. This mechanism gets improved by physical training because of the influence of exercise on the insulin signaling pathway to GLUT4 translocation and therefore an improved insulin response (22).

People with T1DM are at increased risk for hypoglycemia about 7-11 hours (up to 24 h (12)) after physical exercise, also called the “lag effect” of exercise. Therefore, it is suggested to have a blood glucose level of minimum 100 mg/dL (5.6 mmol/L) or higher pre-exercise (13). Suggested glycemic range during physical exercise is around 108-144 mg/dL (6-8 mmol/L) (12).

There is a multitude of factors influencing the glycemic response to exercise. The modality of exercise depending on intensity and duration, the insulin application localization, the dose of insulin, the blood glucose level pre-exercise, the last oral intake, and the training condition are some important influences. In particular, there is a risk of nocturnal hypoglycemia if the sport is practiced in the afternoon (12). The increased risk for hypoglycemia during and after exercise is caused by several mechanisms that coincidence. Basal insulin concentrations in the blood as well as increased insulin sensitivity and, furthermore, possibly blunted glucose counter regulations are considered as contributing factors. The insulin concentration in the blood cannot decline sufficiently fast when aerobic exercise is started. Furthermore, there might be a risk of an increase of the insulin level due to an enhancement of the blood flow to the tissue (12). Most individuals with T1DM develop hypoglycemia around 45 minutes after exercise commencement. The glucose consumption of the muscle declines directly after aerobic exercise is completed, but in order to refill the glycogen storage blood sugar consume

remains increased (12). Basal and bolus insulin dose adjustment is an important part of the glycemic management, beside regularly blood glucose control and an adjusted intake of carbohydrates. Dosage reductions of long-acting basal insulin before exercise results in a risk reduction of hypoglycemia, but hyperglycemia could occur time-delayed as a possible consequence (12). The response of the blood glucose concentration to the different modalities of exercise are very distinct from person to person, but also intra-individually as well. Aerobic exercise basically tends to lead to reductions in glucose concentrations, while anaerobic exercise can be associated with intermittent increments of glucose levels. However, for both types of sport, there is a risk of hypoglycemia during exercise and in the recovery period (12).

1.6.3 Hypoglycemia

The main cause of death for people with either T1DM or type 2 diabetes mellitus (T2DM) is cardiovascular disease. Hypoglycemia is seen as a contributing factor in the pathophysiological mechanism of cardiovascular disease. As shown in multiple studies, 0.5 to 5 severe hypoglycemic events occur on average every year in people with T1DM, and it is therefore seen as a common complication. There are several processes provoked by hypoglycemia in the human body like the sympathetic nervous system response, enhanced pro-coagulant state, altered t-wave morphology, pro-atherothrombotic responses, inflammation, and endothelial dysfunction (19).

Hypoglycemia can acutely lead to various cardiovascular changes. The release of catecholamines, provoked by hypoglycemia, results in several hemodynamic changes such as an enhancement of myocardial contractility, stroke volume, and cardiac output (19). Although the exact mechanism of the “dead in bed” syndrome is not known for certain, the current shared understanding is that severe nocturnal hypoglycemia causes fatal cardiac arrhythmias (19). People with T1DM who are unaware of hypoglycemia have impaired responsiveness to endogenous catecholamines. This seems to be associated with an impaired β-adrenergic sensitivity (24).

1.7 Impact of T1DM on the heart rate during exercise

The rise in the heart rate during exercise is considered to be caused by parasympathetic withdrawal and sympathetic activation. The decline of the heart rate directly after exercise might be due to the reactivation of the parasympathetic tone (25). Cardiac autonomic neuropathy (CAN) is described as a common complication, affecting one quarter of people with T1DM. Clinical symptoms include a reduced heart rate variability, an increased resting heart rate as well as a reduced heart rate response to exercise amongst others (26). Some studies showed a reduced peak heart rate in people with T1DM compared to healthy people (14,17,27), while other studies showed no differences (15,16). Reductions in maximum heart rate might be caused by dysregulation in central and peripheral hemodynamic response during exercise. So far, reductions in catecholamine levels and a reduced sympathetic activation are some possible explanations amongst others for these findings (28). Furthermore, the relationship between the quality of glycemic control and heart rate dynamics during exercise was investigated, and it was shown that those with poorer glycemic control had slower increases in heart rate during the early stages of cardio-pulmonary exercise (CPX) testing (29). The heart rate performance curve constitutes the relationship between heart rate and work and can be assessed based on CPX testing (30). Most individuals show a heart rate turn point in the heart rate performance curve, which refers to an upward or downward alteration in the slope. The deflection is described as most common (found in about 85% of healthy adults), while there is also evidence for inverse deflections or increases in the heart rate performance curves (30,31). Results of CPX testing in healthy people and people with chronic diseases showed that only a small part of the examined participants had a linear or inverted heart rate response. This finding was interpreted as a possible first sign of functional alterations in the myocardium (17). Study results have shown that heart rate dynamics, represented as heart rate-to performance curve, exhibits a linear progression with increasing intensity of exercise in people with T1DM towards people without diabetes (17,27). However, while these differences in the response of heart rate during cardiopulmonary exercise testing could be found there is little evidence regarding moderate intensity exercise comparing the differences in heart rate patterns between people with T1DM and healthy subjects.

1.8 Blood pressure changes in people with T1DM during exercise

Blood pressure is regulated by cardiovascular adjustments as well as neural mechanisms, which are responsible for hemodynamic fine-tuning to compensate for the reduced systemic vascular resistance caused by exercise-induced muscle vasodilatation (28). The metaboreflex is presumed to deliver feedback about the metabolic status of the working muscles to the cardiovascular control areas. The accumulation of the products of the metabolism leads to the activation of the afferent part of this reflex and consecutively increments the sympathetic tone. The hemodynamic adaptations resulting from this reflex affect cardiac performance, systemic vascular resistance, and heart rate changes, leading to a blood pressure change. Blood pressure increase is the consequence of systemic vascular resistance and cardiac output increments, so blood pressure can rise due to arteriolar vasoconstriction and/or due to flow-mediated mechanisms. These mechanisms are both controlled by the autonomic nervous system (32). Autonomic modulation is distinguished by a fine adjustment of the sympathetic and parasympathetic tone. In order to prevent exorbitant increases in the sympathetic tone, a baroreflex controls this autonomic activity (28). These autonomic adjustments, which are affected by the motor cortex, metabolic and mechanical status, working muscle as well as blood pressure level, can be detracted by T1DM (28). In people with T1DM, there has been shown a blunted mean blood pressure response compared to a healthy control group. Furthermore, a reduced capacity to increase the systemic vascular resistance in response to metaboreflex was shown. Stroke volume was shown to be higher compared to the control group. These findings were interpreted as an altered cardiovascular regulation due to T1DM and the reduced capacity to elevate the sympathetic tone that is associated with the disease (32).

It is not yet fully understood if the underlying pathophysiological mechanism of chronic increased blood pressure is a primary decline of renal function that primarily affects small vessels which consecutively leads to a secondary damage of large arteries through renal injury. In this scenario circulating toxins like urea or other metabolic waste products are thought to be associated with the worsening of kidney function. In another scenario, the stiffening of large arteries is the underlying cause for a gradual enhancement in blood pressure which leads to rapid perfusion and pressure waveforms and consecutively damages the renal arterial bed and the afferent glomerular arterioles. This results in more and more increasing glomerular damage (33).

1.9 Insulin therapy

1.9.1 Insulin regimens

The usual insulin dosage for people with T1DM ranges between 0.4 to 1.0 units/kg/day with 50% applied as basal insulin (2). Insulin regimens include multiple-component insulin regimens, multiple daily injections (MDI), or continuous subcutaneous insulin infusion (CSII) (2). In MDI management, a combination of basal insulin and bolus insulin (preprandial short-acting insulin) is used, while in CSII management, pre-prandial insulin is emitted by the insulin infusion device, and the patient can create an individualized algorithm. Both systems provide advantages. MDI therapy offers more flexibility in daily life and there is no need to carry an insulin pump attached to the body. The time and dose of short-acting insulin can be adjusted as required to current blood glucose levels, food intake, and exercise. CSII can emit very small insulin doses (microliters per hour). In CSII therapy variable insulin basal infusion rates that differ between night and daytime, or different bolus insulin waveforms can be programmed as needed (2). The same amount, type, and dose of insulin in subcutaneous injections can result in different metabolic effects because of the intra- and inter-individual variability, which is higher in intermediate and long-acting insulin than in regular insulin. This difficulty often is the cause of the day-to-day variability of blood glucose levels. Another reason for the day-to-day fluctuation of the blood glucose values is the influence of the dosing on the absorption of intermediate and long-acting insulins. Higher dosages of these types of insulin lead to poorer absorption rates (34).

1.9.2 Types of insulin

Insulin types can be classified depending on the onset and the duration of the effect as well as the onset of the peak of the effect. The different types can be divided into different strengths for example U100, U200, or U300. Rapid acting insulin has its onset of action about 15 minutes post-dose and the peak effect is one to two hours afterward with a duration about two to four hours. Active substances are insulin Aspart, insulin Glulisine or insulin Lispro. Regular or short-acting insulin takes about 30 minutes until it reaches the blood circulation post-injection with a peak effect of about two to three hours post dose and a duration of the effect of about three to six hours. Human Regular is a substance of this type

of insulin. Intermediate-acting insulin, like NPH, is one of these insulin types with an onset two to four hours post-dose, develops the peak effect four to 12 hours afterward and lasts for 12 to 18 hours. Long-acting insulin enters the blood circulation a few hours after the subcutaneous injection and has a duration of the effect of up to 24 hours. Insulin Degludec, Detemir, and Glargine are representatives of this type of insulin. Ultra-long-acting insulins, like insulin Glargine U300, enter the blood circulation six hours after administration. This type of insulin does not show any peak effect and has an effective duration of about 36 hours or more (35). Insulin Glargine 300 units/mL (IGlar U300) and insulin Degludec (IDeg U100 or IDeg U200) are second-generation basal insulin analogues. Compared with earlier generation basal insulins, they have a more prolonged duration action over 24 hours, a flatter profile, reduced variability which comes closer to physiological insulin, and the risk of hypoglycemia is lower. They are both more prolonged and stable in pharmacodynamic and pharmacokinetic profiles compared to earlier basal insulin analogues (36). IGlar U300 showed a steady-state plateau-like insulin profile for up to 16 hours after injection, followed by a slow decrease, while IDeg U100 increased continuously post dose and reached the maximum concentration at hour ten, followed by a slow decrease (36). An euglycemic clamp study showed a lower pharmacodynamic fluctuation in IGlar U300. Compared to IDeg U100, IGlar U300 showed a more evenly distributed pharmacokinetic profile and 20% less within-day variability in the pharmacodynamic profile. This less day variability has been demonstrated at least at the 0.4 units/kg/day dose. It may be assumed that smaller fluctuations in blood glucose levels lower also the risk of hypoglycemia (37). IGlar U300 rapidly precipitates in the area of application because of its low solubility at physiological pH value. Therefore, it reaches the bloodstream at a slower rate compared to insulin Glargine U100 which has a lower concentration (38). IDeg U100 becomes a soluble multihexamer depot in the area of injection because these insulin molecules are acylated with a long-chain fatty acid. When it leaves the tissue, it reversibly binds to albumin as a next step, and this results in a very low concentration of free active insulin (38).

1.9.3 Insulin therapy around physical exercise

Currently, no nationwide validated guideline exists for the approach of glycemic management around exercise in people with T1DM. Usually, people with T1DM receive information from health care professionals, books, or the internet. However, these sources mainly provide information that is valid for the public and is not tailored to individual needs

(39). Based on clinical experience as well as clinical, albeit limited, experimental data, a consensus statement for exercise management in type 1 diabetes declared that a reduction of long-acting basal insulin concentrations before exercise reduces the risk of hypoglycemia around exercise. This may promote hyperglycemia at other times of the day (12). For this reason, the consensus statement could not make a general recommendation for basal insulin dose reduction, however, it is recommended as a therapeutic option for those who carry out exercise more premeditatedly (12). Further research is still needed to determine optimal recommendations for insulin dose adjustments and the management of glycemia after exercise to prevent post-exercise hypoglycemia (12).

2 Methods

2.1 Trial design

All data presented in this thesis was obtained from a larger trial (Ultraflexi-1). The study is investigating the flexibility of the second-generation ultra-long-acting basal insulin Glargine U300 (IGlar U300) versus insulin Degludec U100 (IDeg U100) around multiple spontaneous exercise sessions in people with T1DM.

Ultraflexi-1 is a randomized, single-center, four-period cross-over trial, performed at the Clinical Research Center (CRC) of the Medical University of Graz, Austria. The trial has been approved by the ethics committee of the Medical University of Graz (31-551 ex 18/19). The trial was conducted in accordance with the principles of Good Clinical Practice (GCP) and followed the declaration of Helsinki. Potential participants have been provided in advance with oral and written information about the trial. Before starting any trial-related activities, written informed consent was obtained. Participants could terminate their participation in the study at any time and for any reason. The trial consisted of 27 visits in total. Two screening visits, 24 exercise visits, and a final visit. In the exercise visits, participants performed moderate-intensity cycle ergometer exercise sessions, lasting 60 minutes. This thesis will exert data from 12 exercise visits regarding the effect of different dosing of basal insulin Glargine U300 with respect to the cardiac- and metabolic responses of 15 participants of the trial. For this purpose, heart rate, blood pressure, lactate, and glucose measurements performed every six minutes at 13 time points in total throughout each of the 12 exercise visits were of main interest for this thesis.

During visit 1, participants were screened for eligibility for the trial. A physical examination including the recording of vital signs, and a 3- and 12- lead ECG were performed. Several laboratory tests for infectious parameters (HIV screening, HBV, HCV) HbA_{1c}, C-peptide, blood count (including RBC, WBC, including differential populations and platelets), biochemistry (electrolyte status, renal function parameters, liver enzymes, iron status, cholesterol, and triglycerides), and coagulation parameters were conducted. A urinalysis and pregnancy test were performed, as well as an alcohol breath test. Anthropometric parameters including height and weight were measured, and body mass index was calculated. The diagnosis of diabetes, diabetes treatment history, medical history, concomitant illnesses, and

concomitant medication of each participant were assessed at the screening visit. A maximum incremental cardiopulmonary exercise (CPX) test was performed to assess the peak oxygen uptake (mass specific VO_{2max}), the first and second lactate turnpoint (LTP1 & LTP2), as well as maximum heart rate and midpoint heart rate, were calculated amongst other cardiorespiratory markers (e.g., first and second ventilatory threshold, power output, oxygen pulse). Inclusion and exclusion criteria were evaluated. The eligible participants for this trial were randomized to one of the two possible types of basal insulin in the first place. In a second step, participants were randomized to the dosing (75% or 100%) of the basal insulin. Next, participants were titrated to their randomized basal insulin (IGlar U300 or IDeg U100).

During the titration period, each participant was called by the clinical research team regularly in order to guarantee a safe and fast titration process. Independent of the type of basal insulin or the type and dose of insulin previously used the first dose given was 0.3 IU/kg bodyweight. The titration criteria of morning fasting blood glucose concentration between 80 to 130 mg/dL had to be fulfilled over a period of three consecutive days in order to be admitted to the following training sessions. In accordance with the same method, the other basal insulin type was titrated in phase 3. All trial participants received a CGM (Dexcom G6, Dexcom, San Diego, California, United States) from the trial investigator. They also received insulin from the trial investigator as well. The two study drugs Insulin Glargine U300 (Toujeo® 300 U/mL) in 3 mL SoloStar® and Insulin Degludec (Tresiba® 100 U/mL) in 3 mL FlexTouch® were used. There were no changes in the type of bolus insulin therapy. Insulin was injected into a skin fold on the surface of the abdomen or thigh. During the whole trial duration participants were blinded to the sensor glucose readings. Participants managed their own bolus insulin dosage using additionally the FreeStyle Libre 1 (Abbott, Lake Bluff, Illinois, USA) for interstitial glucose monitoring device or blood glucose measurements. The interstitial glucose levels were tracked using the continuous glucose monitor (CGM Dexcom) during the whole duration of the trial, starting at the screening visit until the final visit.

The participants were allocated to four periods of two consecutive weeks each and consisting of three exercise sessions per week. So, there were six exercise sessions in each of the four trial arms (100% IGlar U300, 75% IGlar U300, 100% IDeg U100 and 75% IDeg U100), which resulted in a total of 24 training units. The days on which the exercise sessions took place were randomly assigned and the participants were blinded to the information on which days the exercise takes place. Thus, the participants were informed via phone call in the

morning of an assigned training day and were asked to exercise in the evening at the Clinical Research Centre. Furthermore, the participants were reminded in this phone call whether to inject the regular (100%) or the 75% basal insulin dose. These conditions were created in order to mimic the spontaneous wish of exercising under real life-like conditions. Participants in the 75% dosing group reduced their basal insulin dose by 25% on the days of exercise. On all remaining non-exercise days participants kept injecting the 100% dose of the basal insulin. The second trial arm was subsequently followed by the same basal insulin in the remaining dose. Before each exercise session, inclusion-, exclusion- and withdrawal criteria were evaluated. The last carbohydrate ingestion and the last insulin injection (incl. dosing) of the participants were documented. Right before the beginning of each exercise blood glucose from a fingertip, CGM data, and body weight were assessed. For the blood glucose concentration measurement from the fingertip (0.3 µl) FreeStyle Precision Neo Abbott Diabetes Care Ltd and FreeStyle precision Abbott UK diabetes care blood sugar stripes were used.

If pre-test blood glucose was not within the predefined values 7 mmol/L-16.7 mmol/L, the exercise test was not performed. The exercise session was only started if the blood glucose concentration was above 126 mg/dL (7 mmol/L). In case of a blood glucose level lower than 7 mmol/L (126 mg/dL) 15 minutes before the exercise started, 15-30 grams of carbohydrates (CHO) were supplemented by oral intake (juice or gel). After a period of 15 minutes, blood glucose concentration was checked again and if it was still below 7 mmol/L, the same procedure was repeated as often as needed. When blood glucose concentration was above 16.7 mmol/L (330 mg/dL) a ketone measurement was performed, and in case of a blood ketone level below 1.5 mmol/L, the exercise testing started. If blood ketone levels were above 1.5 mmol/L, it was not possible to perform the exercise session, and it had to be canceled. Participants ate the same type and amount of meals at the same time points on the days of exercise. In order to maintain real-life conditions, this differed slightly due to intra-individual variability. After the phone call in the morning, the basal insulin injection was made at 10 a.m. A lunch with 1 gram per kg CHO and a bolus insulin dose between 12 a.m. and 2 p.m., a small brunch with 15-30 grams CHO and a regular bolus dose between 3-4 p.m. - was intended. The exercise sessions always took place in the evening at 6 p.m.

2.1.1 Continuous moderate-intensity testing

The exercise testing was performed using the following bicycle ergometers: Ergoline (Type ergoselect 4, Germany) or crane circular (s10 studio, Austria) ergometer. The session started with a 3-minute resting period, sitting quietly on the cycle ergometer (0 watts (W)), followed by a warmup period with a workload of 20 W for another 3 minutes. Participants continued the exercise for 54 minutes in the target workload. The target workload was calculated based on the data obtained from the incremental cardiopulmonary exercise test, representing the midpoint between LTP1 and LTP2 corresponding to around 66% of the maximum oxygen uptake (VO_{2max}), which is moderate exercise intensity. The exercise in the target workload was followed by a 3-minute cool-down period with 20 W, ensued by another 3-minute resting period, sitting quietly on the cycle ergometer (0 W).

The measurements were performed every 6 minutes including measurements in the resting periods at the start and the end of the session. These included the collection of capillary blood samples from the earlobe for the lactate and glucose measurement, capillary blood samples from a fingertip for the measurement of blood glucose concentration, interstitial blood glucose level measurements from Dexcom and FreeStyle Libre including trend (arrow) of both CGM systems, measurement of blood pressure, heart rate, and the rating of perceived exertion (RPE) on the Borg scale. For the capillary blood glucose measurement from the fingertip, the same glucose measuring device as mentioned above was used (FreeStyle Precision Neo Abbott Diabetes Care Ltd.). The capillary blood sample taken from the earlobe for determining lactate and glucose concentrations was measured by filling a 20 µl capillary tube. The filled tube with the sample was placed into the glucose/lactate hemolyzing solution cup and gently shaken to release the sample into the solution (1:50 dilution). These samples were analyzed with EKF Diagnostics Biosen C-Line glucose/lactate analyzer by an enzymatic-amperometric method. For the determination of the heart rate, participants wore a Polar H10 (Polar in Malaysia) Electro T61 chest heart rate monitor (Polar Inc, Lake Success, New York, United States). Blood pressure was measured using the cuff/stethoscope auscultation method, using the blood pressure cuff, boso, model, Germany. In order to prevent hypoglycemia, carbohydrates were provided if blood glucose was falling to a level ≤ 3.9 mmol/L (70 mg/dL) during exercise. Blood glucose value was measured 10 minutes after the glucose administration and if blood glucose concentration was still ≤ 3.9 mmol/L, this procedure was repeated as many times as necessary.

2.2 Trial population

Eight male and seven female participants with T1DM participated in the trial.

Inclusion criteria:

1. Signed informed consent obtained
2. Male or female in the age between 18-65 years (both inclusive)
3. Type 1 diabetes mellitus, clinically diagnosed ≥ 12 months ago
4. Treated with multiple daily injection insulin therapy (MDI) ≥ 12 months
5. Body mass index between 18.0-29.9 kg/m² (both inclusive)
6. Performing regular physical cardiorespiratory activity in the last 3 months prior to screening
7. $HbA_{1c} \leq 10\%$ (86 mmol/mol)
8. Mass-specific peak oxygen consumption (VO_{2peak}) > 20 ml/kg/min

Exclusion criteria:

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Receipt of any investigational medicinal product within one month prior to screening in this trial
3. Hemoglobin < 8.0 mmol/L (12.9 mg/dL) (male) or < 6.8 mmol/L (11 mg/dL) (female)
4. Systemic (oral or i.v.) corticosteroids, monoamine oxidase inhibitors, non-selective beta-blockers, growth hormones, non-routine vitamins, and herbal products. Thyroid hormones are not allowed unless a stable use has been provided in the past 3 months.
5. Currently existing/ history of a life-threatening disease (i.e., cancer judged not to be in full remission except basal cell skin cancer or squamous cell skin cancer), or clinically severe diseases that directly influence the study results, as judged by the investigator. This does not prohibit the participation of patients taking medication that influences the metabolism (e.g., statin) or cardiorespiratory system (e.g., asthma spray) as long as the therapy is stable and is not adapted throughout the run of the trial. Participants with celiac disease (similar diseases or allergies) are not excluded, if the disease is stable, and participants are able to stay on their specific (e.g.) gluten-free diet.

6. Participants with a heart rate < 35 beats per minute (bpm) at screening (after resting for 5 minutes in a supine position).
7. People with decompensated heart failure (New York Heart Association class III and IV) at any time and/or angina pectoris within the last 12 months and/or acute myocardial infarction at any time.
8. Supine blood pressure at screening (after resting for 5 minutes in a supine position) outside the range of 90-150 mmHg for systolic or 50-95 mmHg for diastolic (excluding white-coat hypertension; therefore, if a repeated measurement on a second screening visit shows values within the range, the participant can be included in the trial). This exclusion criterion also pertains to participants being on anti-hypertensives.
9. Clinically significant abnormal ECG at screening, as judged by the investigator.
10. Severe retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the investigator.
11. Any chronic disorder or severe disease which, in the opinion of the investigator might jeopardize the participant's safety or compliance with the protocol.
12. History of multiple and/or severe allergies to drugs or foods or a history of a severe anaphylactic reaction.
13. Significant history of alcoholism or drug/chemical abuse as per investigator's judgment or a positive result in the urine drug/alcohol screen at the screening visit.
14. Smoker (defined as a participant who is smoking more than 5 cigarettes or the equivalent per day).
15. Not able or willing to refrain from smoking or use of nicotine substitute products during the inpatient period.
16. Recurrent severe hypoglycemia (more than one severe hypoglycemic event during the past 12 months).
17. Hypoglycemic unawareness as judged by the investigator or hospitalization for diabetic ketoacidosis during the previous 12 months.
18. Participants with mental incapacity or language barriers precluding adequate understanding or cooperation, as individuals who, in the opinion of the primary care physician or the investigator, should not participate in the study.
19. Potentially non-compliant or uncooperative during the trial, as judged by the investigator.
20. Any condition that would interfere with trial participation or evaluation of results, as judged by the investigator.

21. Pregnancy, breast-feeding or female of childbearing potential, who intend to become pregnant, or who are not using adequate contraceptive methods (adequate contraceptive measures include sterilization, hormonal intrauterine devices, oral contraceptives, sexual abstinence or vasectomized life partner).
22. Using a real-time CGM device, which allows to individually set glycemic thresholds (e.g., Dexcom G4/5/6, Medtronic Guardian, or FreeStyle Libre 2 systems). That does not exclude using FreeStyle Libre 1.
23. Renal function eGFR (CKD-EPI) < 50 mL/min/1.73 m².

2.3 Objectives

Primary objectives:

The aim of the thesis was to compare the impact of a regular (100%) vs. 75% of the regular basal insulin dose on cardiac- and metabolic markers around multiple spontaneous exercise sessions. The parameters analyzed for this purpose are the blood glucose concentration measured from the fingertip, the lactate measured from the earlobe, the blood pressure, and the heart rate.

The null hypothesis implies, that there is no difference between the two dosages of insulin regarding the cardiac- and metabolic response during exercise. The alternative hypothesis states, that the different dosages of insulin would reach different results in the cardiac- and metabolic response.

Secondary objectives:

The secondary objective was to compare the amount of carbohydrates administered during exercise to avoid hypoglycemia and the average total daily bolus insulin dose within the respective 14-day total period between the 100% and 75% basal insulin dosing regimens.

2.4 Statistical analysis

All data were tested for normal distribution using the Shapiro-Wilk normality test. The parameters, lactate, blood glucose, blood pressure, heart rate, and the CHO supplementation investigated throughout the 12 exercise sessions and the bolus insulin administration were compared between 100% and 75% dosing of IGlar U300 using a paired t-test ($p \leq 0.05$). For non-normally distributed data the non-parametric Friedman test was used ($p \leq 0.05$). Descriptive statistics with the calculation of mean and standard deviation were performed to determine the characteristic data of all participants regarding anthropometric properties as well as performance data and diabetes-specific data. Analysis was performed using GraphPad Prism® software version 8.0.2 for Windows, GraphPad Software, San Diego, California USA.

3 Results

To investigate the cardiac and metabolic response of different dosages of basal insulin, blood pressure, heart rate, glucose, and lactate were analyzed. Carbohydrate (CHO) supplementation and the average total daily bolus insulin dose within the respective 14-day period of exercise were analyzed as well.

Table 3.1 Baseline characteristics. Values are given as mean ± standard deviation (SD).

Age (years)	**41.4 ± 9.9**
Sex	**7 female, 8 male**
Weight [kg]	**77 ± 15.4**
BMI [kg/m2]	**24.2 ± 2.9**
HbA_{1c} [%]	**7.3 ± 0.7**
HbA_{1c} [mmol/mol]	**56.3 ± 7.3**
Diabetes duration [years]	**17.7 ± 9.8**
VO_{2max} [l/min]	**2.8 ± 0.84**
C-peptide (nmol/L)	**0.03 ± 0.07**
TDD [IU]	**39.7 ± 15.4**

3.1 Primary objective

The results of the primary objective are presented in **table 3.2**. There was no statistical significance in the comparison of the parameters between the 100% and 75% dosing scheme of basal insulin Glargine U300. Thus, the null hypothesis is confirmed.

Table 3.2 Parameters comparing 100% vs. 75% IGlar U300 dosing scheme during exercise given as mean ± SD

	100% IGlar U300	**75% IGlar U300**	**p- value**
Heart rate [beats/minute(bpm)]	122.88 ± 15.91	122.94 ± 12.72	0.91
Lactate [mmol/L]	2.03 ± 0.8	1.95 ± 0.61	0.82
Systolic blood pressure [mmHg]	148.9 ± 15.3	147.34 ± 15.32	0.18
Diastolic blood pressure [mmHg]	77.08 ± 5.04	77.37 ± 6.22	0.93
Blood glucose [mg/dL]	141.79 ± 17.69	141.4 ± 20.09	0.61

3.1.1 Lactate

The difference observed between the 100% vs. 75% dosing scheme regarding the blood lactate level was not statistically significant ($p = 0.82$). Mean value and standard deviation (SD) of the 15 participants of all six training sessions for the 100% dosing scheme of

IGlar U300 was 2.03 ± 0.8 mmol/L vs. 1.95 ± 0.61 mmol/L for the 75% dosing scheme of IGlar U300.

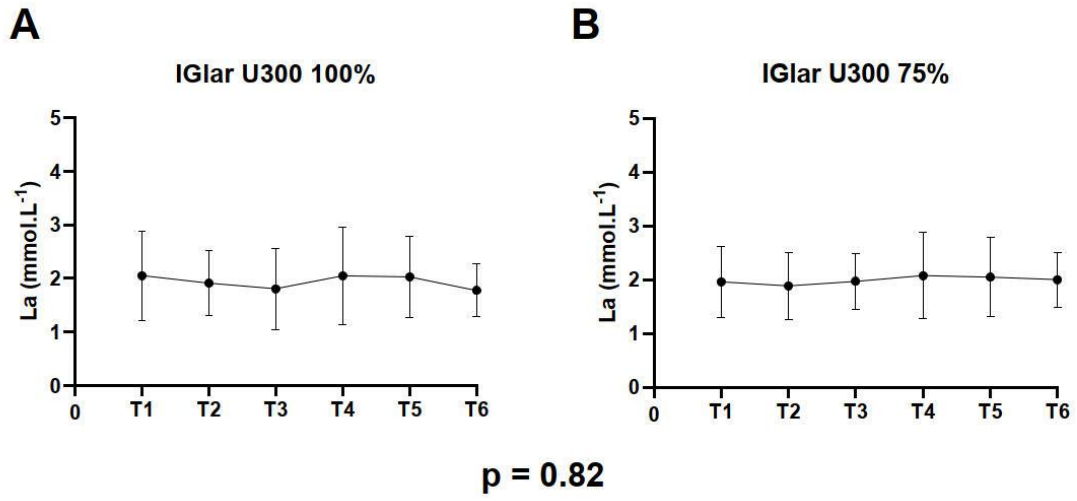

Figure 3.1 lactate (La) values IGlar U300 100% vs. IGlar U300 75%

Figure 3.1 shows lactate levels given as mean and SD over the course of the six training sessions in comparison for each dosing scheme IGlar U300 100% (A) vs. IGlar U300 75% (B). T1-6 stands for the six training sessions.

The graphical representation of the lactate values over the six training units in the respective dosage shows comparatively similar curves. The mean values are constant from training unit to training unit within the respective dosage, and also in comparison between the two dosages they are in a narrow range. Furthermore, a relatively large SD can be seen in both curves, which remains almost constant for all values.

3.1.2 Heart rate

There was no statistically significant difference between the 100% and the 75% dosing regarding the heart rate (p = 0.91). The data, expressed as mean and SD of the 15 participants during all six training sessions at the respective dosage of IGlar U300, showed a heart rate of 122.88 ± 15.91 bpm at the 100% dosing scheme, compared to 122.94 ± 12.72 bpm at the 75% dosing scheme.

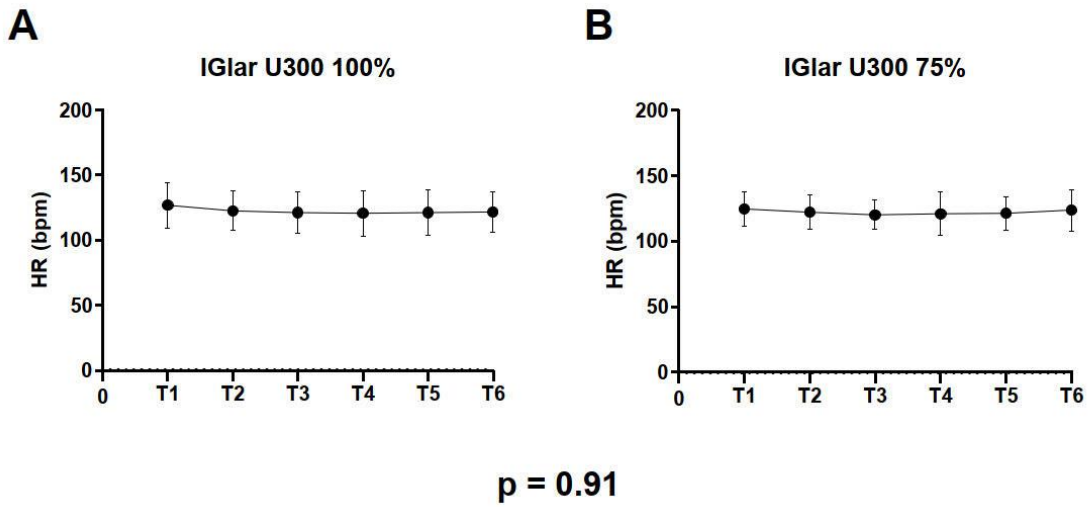

Figure 3.2 heart rate (HR) values IGlar U300 100% vs. 75%

Figure 3.2 shows a graph depicting the heart rate values as mean and SD. The graph shows a constant curve in each dosing scheme (100% and 75%) over the course of the six training sessions (T1-6). The mean values of the heart rate are very close to each other and show a constant behavior, which makes the course of the curve very straight. This applies to each graph for the 75% and 100% dosages as well as for the comparison between the two dosages, there are almost no differences between these two graphs. The SD also shows a constant behavior for all values.

3.1.3 Blood pressure

For systolic blood pressure (p = 0.18) and diastolic blood pressure (p = 0.93), there was no significant difference between the two dosing schemes. The mean and SD of the systolic blood pressure values of the 15 participants of all six training sessions in the 100% dosing scheme of IGlar U300 was 148.9 ± 15.3 mmHg, compared to 147.34 ± 15.32 mmHg in the 75% dosing scheme. With respect to the diastolic blood pressure values of the 15 subjects of all six training sessions, the mean and SD at the 100% dosing scheme of IGlar U300 was 77.08 ± 5.04 mmHg vs. 77.37 ± 6.22 mmHg at the 75% dosing scheme.

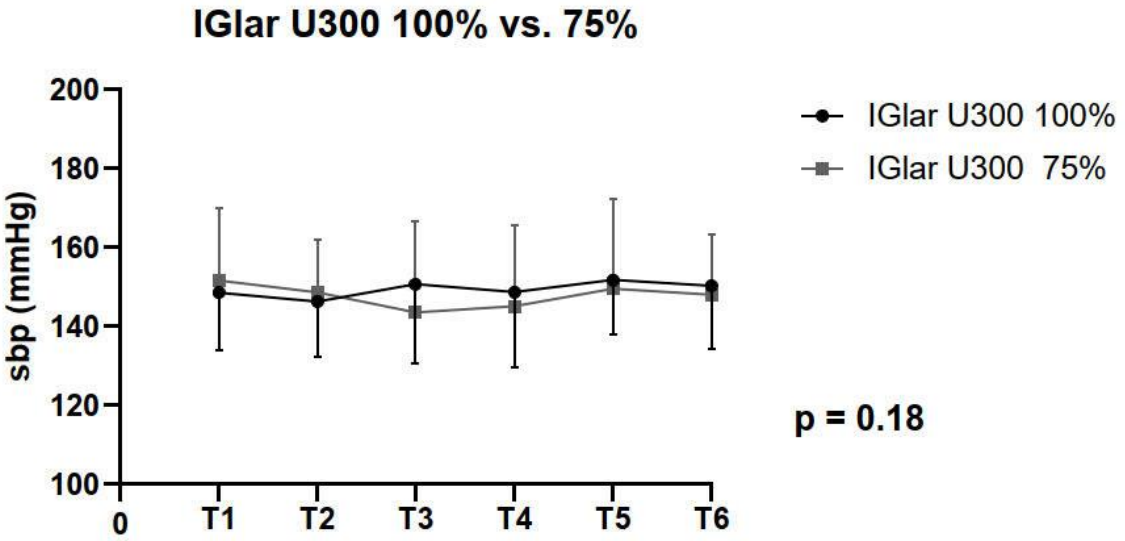

Figure 3.3 systolic blood pressure (sbp) IGlar U300 100% vs. 75%

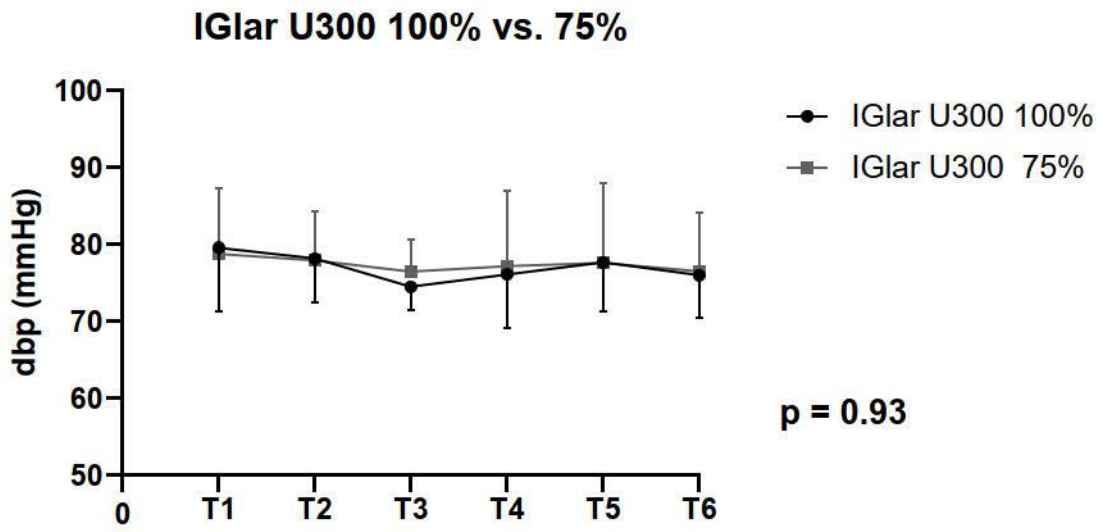

Figure 3.4 diastolic blood pressure (dbp) IGlar U300 100% vs. 75%

In figure 3.3 the mean values and SD of the systolic blood pressure (sbp) and in **figure 3.4** mean values and SD of diastolic blood pressure (dbp) of the 15 participants during the six training sessions (T1-6) are shown as graphs, without any differences in the comparison between the two dosing regimens of IGlar U300 100% vs. 75%.

The graph in **figure 3.3** shows slight fluctuations of the mean values of the 75% as well as the 100% dosage in a relatively narrow fluctuation range. The mean values of the 75% and 100% dosages do not show any significant difference in relation to each other, so no distinct trend can be recognized. Also, slight variances of the standard deviations can be seen. In **figure 3.4**, the mean values of diastolic blood pressure show slight fluctuations, but not as extensively as in **figure 3.3,** and the mean values are closer to each other here. With very constant mean values of diastolic blood pressure, a rather straight course of the curves results for both dosing regimens. The variance between the standard deviations is more distinct than in **figure 3.3**.

3.1.4 Blood glucose

The difference in blood glucose levels between the 100% and 75% dosing during exercise was not statistically significant (p = 0.61). The mean and the SD of blood glucose values from all six training sessions was 141.79 ± 17.69 mg/dL in the 100% IGlar U300 dosing group vs. 141.4 ± 20.09 mg/dL in the 75% IGlar U300 dosing group.

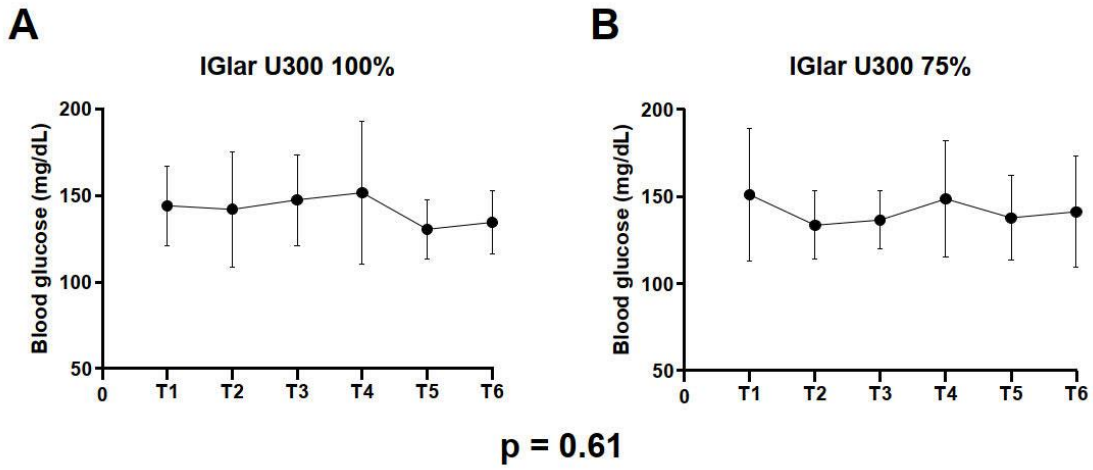

Figure 3.5 blood glucose values IGlar U300 100% vs. 75%

The mean values and SD of blood glucose during the six training sessions are shown as graphs in **figure 3.5** comparing the two dosing regimens IGlar U300 100% (A) vs. IGlar U300 75% (B). The graph shows relatively constant mean values with slight fluctuations over the course of the six training units in both dosage groups. Both graphs show a slight increase up to T4 and lower values at T5 and T6, but overall, no distinct trend is discernible. A comparatively larger variance of the SD can be seen in both graphs.

3.2 Secondary objective

The results of the secondary outcome are presented in **table 3.3**. The comparison of the investigated parameters did not show statistical significance between the 100% and 75% dosing scheme of IGlar U300.

Table 3.3 Parameters comparing 100% vs. 75% IGlar U300 dosing scheme given as mean ± SD

	100% IGlar U300	**75% IGlar U300**	**p-value**
CHO supplementation [g]	27.48 ± 20.97	25.26 ± 18.29	0.44
Total daily bolus insulin dose [IU]	16.6 ± 10.66	15.7 ± 9.32	0.28

3.2.1 CHO supplementation

Carbohydrate (CHO) supplementation administered as juice or gel during the exercise for prevention of hypoglycemia over the six training sessions expressed in grams of glucose did not show statistical significance between the 75% or 100% dosing scheme of IGlar U300 ($p = 0.44$). On average 25.26 ± 18.29 grams of glucose were supplemented per exercise in the 75% IGlar U300 dosing scheme vs. 27.48 ± 20.97, respectively, in the 100% IGlar U300 dosing scheme (values each given as mean ± SD).

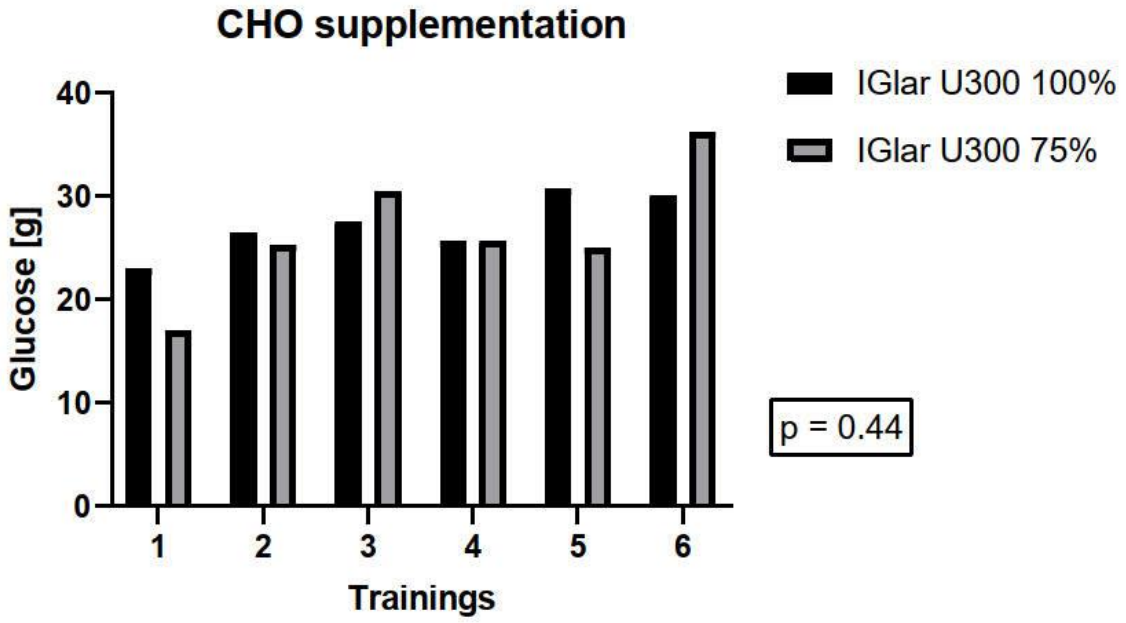

Figure 3.6 carbohydrate (CHO) supplementation IGlar U300 100% vs. 75% (g=gram)

Figure 3.6 shows the mean values of the carbohydrate (CHO) supplementation expressed in grams of glucose given during each of the six training sessions comparing the IGlar U300 100% vs. 75% dosing regimen.

3.2.2 Total daily bolus insulin dose

The comparison of the average total daily bolus insulin dose calculated from the bolus insulin administration of the respective 14-day period showed no difference between the 75% vs. 100% dosing scheme of basal insulin IGlar U300 ($p = 0.28$). 15.7 ± 9.32 IU bolus insulin during 75% IGlar U300 period and 16.6 ± 10.66 IU bolus insulin during 100% IGlar U300 period were administered on average per day during the respective 14-day period (values each given as mean ± SD).

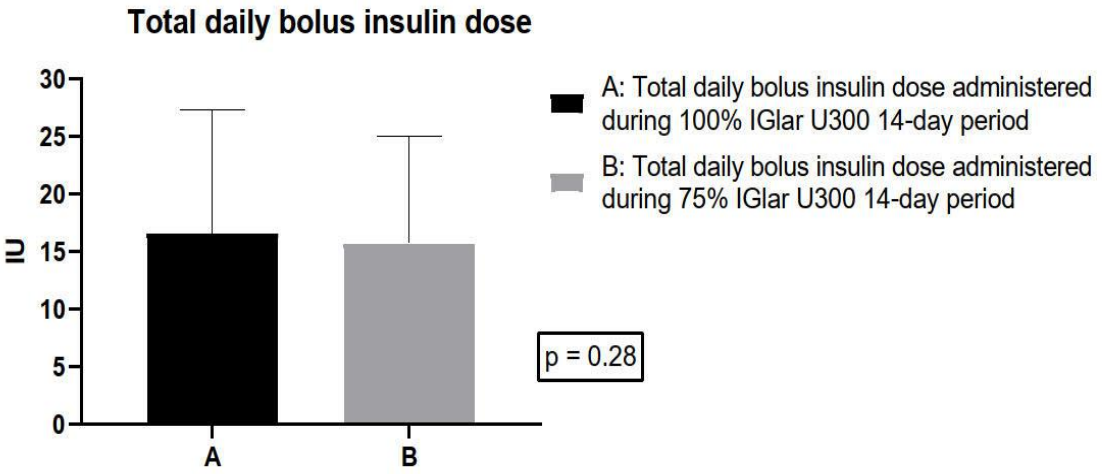

Figure 3.7 total daily bolus insulin dose administered in the respective 14-day period of IGlar U300 100% vs. 75% (IU= international units)

Figure 3.7 shows mean, and SD of the average total daily bolus insulin dose calculated from the bolus insulin administration over the respective 14-day period given in international units (IU) in the comparison of IGlar U300 100% (A) vs. IGlar U300 75% (B).

4 Discussion

People with T1DM have an increased cardiovascular risk (40), which is one of numerous reasons why regular exercise is highly recommended (12). The American Diabetes Association recommends at least 150 minutes of moderate-intensity exercise per week (41). One major cause why people with T1DM are more cautious to follow this recommendation is the fear of exercise-induced hypoglycemia (42). Hypoglycemia following moderate-intensity exercise occurs in up to 66% of people with T1DM according to several studies (43). The risk of nocturnal hypoglycemia is increased for exercising in the evening because blood glucose levels are likely to decrease during sleep. Therefore, basal insulin adjustments prior to exercise play an important role in the improvement of glycemic control (44). The recommendations for basal insulin reductions from 2018 clinical practice consensus guidelines for children and adolescents with diabetes advocate a 20% basal analogue reduction on the day of physical activity and, in addition, a carbohydrate bedtime snack. This recommendation applies mainly to insulins such as Neutral Protamine Hagedorn (NPH), Glargine, or Detemir, whereas for more stable and more prolonged acting insulins such as Degludec and IGlar U300, a dose reduction is recommended depending on the duration of action prior to exercise. Reductions by 30-50% of long-acting insulin the night before and on the day of exercise are recommended for activities such as skiing, water sports, or similar (45). An online survey for people with T1DM questioned 502 adults about their glycemic management around exercise. 10% of the participants who exclusively self-measure their blood glucose level (without using CSII or CGM) and 25% of those using CGM only, reported adjusting long-acting basal insulin for exercise. Basal insulin adjustments related to exercise were more frequently performed the night before and the night after exercising in subjects who used only self-monitoring blood glucose or only CGM. Half of the participants in this study reported that they sometimes or often reduce the meal bolus insulin prior- or post-exercise. The occurrence of hypoglycemia after exercise is still a problem that affects the majority of people with T1DM even if they make adjustments to carbohydrate intake and insulin use (42). The majority of people using multiple daily injections do not yet incorporate basal insulin adjustments into their routine management around exercise (46), while 55% of people using insulin pump therapy in combination with continuous glucose monitoring reported reducing the basal rate of insulin around exercise (42).

Most studies that investigated the safety of basal insulin were conducted under conditions of acute exertion (43). To date, only a few studies examined the effects of basal insulin reductions and their impact on glycemic control around physical exercise (12,43,44,46). So far, the limited amount of data in this regard already reports results with good prospects concerning an improvement of the glycemic control (43,44). In a study by Moser et al., a reduction of basal insulin by almost 50% on the day before and the day of a running competition was shown to be sufficient to prevent further dysglycemia (47). Results published by Campbell et al. state that the combination of a reduction in basal insulin by 20% in combination with bolus insulin reductions and additional low glycemic index carbohydrate supplementations prevent hypoglycemia for 24 hours after moderate-to-vigorous intensity running in people with T1DM. In this study participants received either 100% or 80% dosing of basal insulin Glargine U100 or insulin Detemir (44). In a further study, Moser et al. showed that a reduction of insulin Degludec by 25% in advance and during a period of five consecutive days of moderate-intensity exercise in the evening significantly improved the time of euglycemia in people with T1DM (43). Both studies could show more time spent in euglycemic ranges post-exercise (43,44).

A study investigating the differences between the long-acting basal insulins Degludec U100 and Glargine U100, showed that the risk of hypoglycemia during and after moderate-intensity exercise was similar between these two insulins. Pre-exercise bolus dose reduction, but no basal insulin reduction was performed in this study. Heise et al. made the influence of counterregulatory hormones responsible for hampering the examination of the impact of different basal insulin dosing schemes (48). Similar processes may also be influential for the results in this thesis and further examination in this regard would be revealing. Many previous studies investigated the effects of bolus insulin reductions prior- as well as post-exercise on glycemic control. In this context, some studies investigated conditions of high-intensity sports, but also moderate-intensity sports (9,49–52). The aforementioned consensus guidelines for clinical practice in children and adolescents recommend a 25-50% reduction in the pre-exercise meal bolus dose for continuous moderate to vigorous aerobic exercise lasting 30-45 minutes and a 50-75% bolus dose reduction for exercise durations greater than 45 minutes. For the bolus insulin injected at meals after exercise a reduction of up to 50% is recommended (45). Recommendations for bolus insulin reduction as a function of exercise intensity, expressed by VO_{2max}, were compiled (53). Bolus insulin reductions have reduced

the risk of hypoglycemia during and immediately after exercise (51), but do not prevent late-onset hypoglycemia post-exercise (52).

The majority of the studies that focused on the adjustments in basal components of insulin therapy has been conducted in the setting of continuous subcutaneous insulin infusion (CSII) therapy to address basal rate reduction. However, a substantial part of people with T1DM uses MDI, making further studies in this area imperative (44).

As shown in Figure 3.5, there was no significant difference between the blood glucose values when comparing a regular (100%) vs. a reduced (75%) dose of IGlar U300. These results are also consistent with the conclusion of the above-mentioned study by Campbell et al., reporting that a reduction in basal insulin by 20% and additional bolus insulin adjustments does neither affect acute glycemic control nor lead to other metabolic disturbances after exercise. The study demonstrated that moderate-intensity exercise resulted in similar decreases in blood glucose with both dosing regimens. In the study by Campbell et al., the study population consisted of a small sample size of ten physically active and well diabetes-controlled males performing a single bout of aerobic exercise. As there are currently few studies examining the effects of basal insulin reductions, comparisons with other outcomes are currently limited (44). In the study by Moser et al., no significant differences in glycemic ranges were found when comparing the 100% vs. 75% dosing scheme of Degludec within the first and last 48 hours of the five-day training intervention (43).

The effects of basal insulin reductions in different exercise modalities were examined by a study performing evening basal insulin reductions by 10%, 20%, and 30% on the evening after high-intensity intermittent exercise (HIIE) as well as basal insulin reduction by 20% on the evening after moderate-continuous exercise. Results did not demonstrate the expected differences between exercise modalities on glucose profiles, but only eight hypoglycemic events occurred over sixty study nights, which proved to be a very low number of nocturnal hypoglycemic events. Additional management for hypoglycemia prevention included a reduction of bolus insulin at dinner after exercise by 25% and a bedtime snack in this study. In addition, for ethical reasons, this study did not include a comparison group that would not have received basal insulin reduction, which underpins the importance of basal dose adjustments (54).

Lactate represents a metabolic parameter that is the end product of the anaerobic metabolism of glucose (55). Lower lactate levels in response to exercise were observed in people with T1DM (56). Available data seem to indicate that exercise results in less activation of glycolysis and glycogenolysis in people with T1DM compared to healthy people (57). Since insulin is known to inhibit glycogen breakdown, the persistently high plasma insulin levels could potentially contribute to the blunted glycogenolytic response (56,57). Therefore, the examination of the impact of insulin reductions on lactate levels might be of interest.

Reduction of basal insulin dose by 25% on the day of exercise resulted in similar values of lactate during exercise compared with the use of a regular (100%) dose, as shown by the data of this thesis (Figure 3.1). These results are consistent with other studies which have shown that a reduction of bolus and/or basal insulin did not result in differences in lactate levels during or after exercise (43,44,49–51,58). A study by Vartak et al. examined the effects of reduced bolus insulin dosing prior to performing aerobic exercise on lactate levels in people with T1DM and found no risk for lactatemia (58). Bracken et al. demonstrated a similar increase in blood lactate following running (aerobic exercise c. 70% VO_{2peak}) at full or reduced (75%, 50%, or 25%) pre-exercise bolus insulin doses (50). Mauvais-Jarvis et al. demonstrated that a 50-90% bolus insulin reduction before moderate exercise did not lead to a worsening of metabolic control. The changes in plasma lactate values were not statistically significant in both groups with and without bolus insulin reduction (49). In a further study Campbell et al. examined the effects of administering reduced rapid-acting insulin before and after an intensive bout of prolonged running exercise and it was found that this likewise does not lead to metabolic disturbances. Peak lactate levels were similar with and without insulin reduction (51). Moser et al. reported similar lactate values at a 100% and 75% doses of basal insulin Degludec during exercise (43). In the study by Campbell et al., in which the reduction of basal insulin by 20% in combination with pre- and post-exercise prandial bolus insulin and additional low glycemic carbohydrate intake was examined, no differences in metabolic parameters up to 60 minutes after exercise with no significant differences in lactate values were reported as well (44). The current data is consistent with the results of the thesis as they show no differences in lactate values when performing basal insulin reductions. Since blood lactate levels can be used to determine training intensity, the similar values between the groups shown here may indicate that training intensity was similar between the groups (59).

The comparison of the cardiac response (heart rate and blood pressure) showed no differences between the two groups (Figure 3.2, Figure 3.3, Figure 3.4). The results regarding the heart rate are consistent with the study data in Moser et al., comparing the mean heart rate values between 100% and 75% dosing of long-acting insulin Degludec during exercise. Moser et al. interpreted these results as being caused by biological variability (43). In addition, there were no differences in pre-and post-exercise heart rates in the comparison between the two long-acting insulins Degludec 100 units/ml and Glargine 100 units/ml during moderate-intensity exercise, although no dose reductions were made here (48). Campbell et al. compared heart rate peaks between the group receiving regular (100%) basal insulin dose and those receiving the 20% reduced basal insulin dose during exercise of similar intensity in people with T1DM and reported no difference between the groups (44). Although blood pressure was measured presumably for safety reasons, the values and the effects of the dosing reductions on blood pressure were not reported in the results of most studies that examined basal insulin reductions around exercise (43,44,48,58). However, further research could use this parameter for the comparability of training intensity between groups comparing different basal insulin dosing schemes and the effects on the cardiovascular system.

The carbohydrate intake between both groups showed no significant difference (Figure 3.6). This may support the theory that the non-significant differences shown between the two dosing schemes in the previously discussed parameters (glucose, lactate, heart rate, and blood pressure) were not a consequence of compensatory carbohydrate supplementation. Comparable results could be found in Moser et al. and Campbell et al. (43,44). Campbell et al. reported no differences in total energy intake in comparison of the two dosing regimens (44). Moser et al. reported a statistically nonsignificant but numerically higher value of correction carbohydrate supplementation in participants receiving the 100% insulin Degludec dosing regimen (43). Similar values were shown for the concomitant average total daily bolus insulin dose within the respective 14-day period in the comparison of IGlar U300 100% and 75% (Figure 3.7). It may be assumed that the reduced dose was not compensated with an increased administration of bolus insulin. Similar outcomes were obtained in Moser et al. when comparing the two dosing regimens of insulin Degludec during exercise (43).

Limitations

For this thesis, the main limitation was that data were only obtained from 15 participants, which is a relatively small number of subjects to extrapolate the validity of the data to the general population with T1DM. Furthermore, this study cohort is a relatively homogenous population that is physically active and has no severe comorbidities. All participants are in good glycemic control, and it would be of further interest to examine participants with suboptimal glycemic control. In addition, only one type of sport was examined and the effects of other sports and intensities of exercise would be of further interest as well.

The strength of the study was the combination of a well-controlled setting, keeping blood glucose levels within the recommended limits pre-exercise, but at the same time mimicking more real-life-like situations.

5 Conclusion

No difference in cardiac and metabolic response was shown between the 100% and the 75% dosage of IGlar U300. This thesis demonstrates that a reduction of basal insulin prior to exercise does not result in statistically significant differences in heart rate, blood pressure, lactate, or blood glucose during exercise. These results align with previous study results (43,44). It might be assumed that the intensity at which the subjects exercised was well regulated and the results are similar between the two groups due to these conditions. The similar values for carbohydrate intake may indicate that the non-significant differences in the cardiac and metabolic parameters shown between the two dosing schemes were not a consequence of compensatory carbohydrate intake during exercise. The hypothesis may be strengthened that a reduction in IGlar U300 by 25% on a day when moderate-intensity exercise is performed in the evening, has no immediate negative effects on the cardiovascular system, represented by blood pressure and heart rate, and metabolism, represented by blood glucose levels and lactate levels during exercise. A reduction of ultra-long-acting basal insulin may increase time spent in hyperglycemia and could therefore have an impact on overall glycemic control (12). Chronic hyperglycemia increases the cardiovascular risk (60), but the long-term effects of hypoglycemia may also increase this risk as well (61). Considering the potentially serious consequences of hypoglycemia (19), it's important to weigh up these risks. However, further research on basal insulin reduction in the context of exercise and its impact on human physiology including cardiovascular, metabolic, counter-regulatory hormonal, and inflammatory effects is particularly important to ensure improved glycemic management around physical activity for the safety of people with T1DM using MDI.

6 Bibliography

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. The Lancet. 2018;391(10138):2449–62.

2. Jameson JL; Fausi AS et al. Harrison's Principles of Internal Medicine, 20e. McGraw-Hill. 2018.

3. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. The Lancet. 2014.

4. Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Fard HH, Ghojazadeh M. Prevalence and incidence of type 1 diabetes in the world: A systematic review and meta-analysis. Health Promot Perspect. 2020;10(2):98–115.

5. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N, et al. Estimated life expectancy in a scottish cohort with type 1 diabetes, 2008-2010. JAMA - Journal of the American Medical Association. 2015;313(1).

6. Richardson SJ, Rodriguez-Calvo T, Gerling IC, Mathews CE, Kaddis JS, Russell MA, et al. Islet cell hyperexpression of HLA class I antigens: a defining feature in type 1 diabetes. Diabetologia. 2016;59(11).

7. McLaughlin KA, Richardson CC, Ravishankar A, Brigatti C, Liberati D, Lampasona V, et al. Identification of tetraspanin-7 as a target of autoantibodies in type 1 diabetes. Diabetes. 2016;

8. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017.

9. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: The search for diabetes in youth study. Pediatrics. 2014;

10. World Health Organization. Global Report on Diabetes. Isbn. 2016;

11. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022;45.

12. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: a consensus statement. Vol. 5, The Lancet Diabetes and Endocrinology. 2017.

13. 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.

14. WR K, MAL G, ML C, GL S, AR C, TLB N, et al. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. Pediatr Diabetes. 2005;

15. Rissanen APE, Tikkanen HO, Koponen AS, Aho JM, Peltonen JE. Central and peripheral cardiovascular impairments limit VO2peak in Type 1 diabetes. Med Sci Sports Exerc. 2015;47(2).

16. Wilson LC, Peebles KC, Hoye NA, Manning P, Sheat C, Williams MJA, et al. Resting heart rate variability and exercise capacity in Type 1 diabetes. Physiol Rep. 2017;5(8).

17. Eckstein ML, Farinha JB, McCarthy O, West DJ, Yardley JE, Bally L, et al. Differences in Physiological Responses to Cardiopulmonary Exercise Testing in Adults With and Without Type 1 Diabetes: A Pooled Analysis. Diabetes Care. 2021;44(1).

18. Niranjan V, McBrayer DG, Ramirez LC, Raskin P, Hsia CCW. Glycemic control and cardiopulmonary function in patients with insulin- dependent diabetes mellitus. American Journal of Medicine. 1997;103(6).

19. Davis IC, Ahmadizadeh I, Randell J, Younk L, Davis SN. Understanding the impact of hypoglycemia on the cardiovascular system. Vol. 12, Expert Review of Endocrinology and Metabolism. 2017.

20. Moser O, Tschakert G, Mueller A, Groeschl W, Pieber TR, Obermayer-Pietsch B, et al. Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. PLoS One. 2015;

21. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: Effects on acute and late glycaemia in athletes with Type1 diabetes mellitus. Diabetic Medicine. 2011;28(7).

22. Banfi G, Colombini A, Lombardi G, Lubkowska A. Metabolic markers in sports medicine. In: Advances in Clinical Chemistry. 2012.

23. Tschakert G, Hofmann P. High-intensity intermittent exercise: Methodological and physiological aspects. International Journal of Sports Physiology and Performance. 2013.

24. Korvtkowski MT, Mokan M, Veneman TF, Mitrakol A, Cryer PE, Gerich JE. Reduced β-adrenergic sensitivity in patients with type 1 diabetes and hypoglycemia unawareness. Diabetes Care. 1998;21(11).

25. Georgoulias P, Demakopoulos N, Valotassiou V, Orfanakis A, Zaganides A, Tsougos I, et al. Long-term prognostic value of heart-rate recovery after treadmill testing in patients with diabetes mellitus. Int J Cardiol. 2009;134(1).

26. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. Vol. 4, Journal of Diabetes Investigation. 2013.

27. Moser O, Tschakert G, Mueller A, Groeschl W, Eckstein ML, Koehler G, et al. Different heart rate patterns during cardio-pulmonary exercise (CPX) testing in individuals with type 1 diabetes. Front Endocrinol (Lausanne). 2018;9(OCT).

28. Roberto S, Crisafulli A. Consequences of Type 1 and 2 Diabetes Mellitus on the Cardiovascular Regulation During Exercise: A Brief Review. Curr Diabetes Rev. 2016;13(6).

29. Moser O, Eckstein ML, McCarthy O, Deere R, Bain SC, Haahr HL, et al. Heart rate dynamics during cardio-pulmonary exercise testing are associated with glycemic control in individuals with type 1 diabetes. PLoS One. 2018;

30. Bodner ME, Rhodes EC. A review of the concept of the heart rate deflection point. Vol. 30, Sports Medicine. 2000.

31. Binder RK, Wonisch M, Corra U, Cohen-Solal A, Vanhees L, Saner H, et al. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. Vol. 15, European Journal of Preventive Cardiology. 2008.

32. Roberto S, Marongiu E, Pinna M, Angius L, Olla S, Bassareo P, et al. Altered hemodynamics during muscle metaboreflex in young type 1 diabetes patients. J Appl Physiol. 2012;113(8).

33. Cameron JD, Cruickshank JK. Glucose, insulin, diabetes and mechanisms of arterial dysfunction. Vol. 34, Clinical and Experimental Pharmacology and Physiology. 2007.

34. Toni S, Reali MF, Barni F, Lenzi L, Festini F. Managing insulin therapy during exercise in Type 1 diabetes mellitus. In: Acta Biomedica de l'Ateneo Parmense. 2006.

35. https://www.diabetes.org/healthy-living/medication-treatments/insulin-other-injectables/insulin-basics. 2021.

36. Owens DR, S Bailey T, Fanelli CG, Yale JF, Bolli GB. Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) – a review of evidence and clinical interpretation. Vol. 45, Diabetes and Metabolism. 2019.

37. Bailey TS, Pettus J, Roussel R, Schmider W, Maroccia M, Nassr N, et al. Morning administration of 0.4 U/kg/day insulin glargine 300 U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100 U/mL in type 1 diabetes. Diabetes Metab. 2018;44(1).

38. Schiavon M, Visentin R, Giegerich C, Sieber J, Dalla Man C, Cobelli C, et al. In silico head-to-head comparison of insulin glargine 300 U/mL and insulin degludec 100 U/mL in type 1 diabetes. Diabetes Technol Ther. 2020;22(8).

39. Narendran P, Quann N, Nagi D, Gallen I, Gorton J, Daly H, et al. Rationale and methods for the Exercise for Type 1 Diabetes Education program: A pilot randomized controlled trial of an education program to support adults with type 1 diabetes mellitus (T1DM) to undertake exercise. BMJ Open Diabetes Res Care. 2019;7(1).

40. Schofield J, Ho J, Soran H. Cardiovascular Risk in Type 1 Diabetes Mellitus. Vol. 10, Diabetes Therapy. 2019.

41. 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. 2016.

42. Pinsker JE, Kraus A, Gianferante D, Schoenberg BE, Singh SK, Ortiz H, et al. Techniques for Exercise Preparation and Management in Adults with Type 1 Diabetes. Can J Diabetes. 2016;40(6).

43. Moser O, Eckstein ML, Mueller A, Birnbaumer P, Aberer F, Koehler G, et al. Reduction in insulin degludec dosing for multiple exercise sessions improves time spent in euglycaemia in people with type 1 diabetes: A randomized crossover trial. Diabetes Obes Metab. 2019;21(2).

44. Campbell MD, Walker M, Bracken RM, Turner D, Stevenson EJ, Gonzalez JT, et al. Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: A randomized controlled trial. BMJ Open Diabetes Res Care. 2015;3(1).

45. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2018;19.

46. McCarthy O, Bain SC, Deere R. Basal insulin reductions in anticipation of multiple exercise sessions in people with type 1 diabetes—a clinical perspective. Ann Transl Med. 2018;6(S2).

47. Moser O. Improved glycaemic variability and basal insulin dose reduction during a running competition in recreationally active adults with type 1 diabetes—A single-centre, prospective, controlled observational study. PLoS One. 2020;15(9 September).

48. Heise T, Bain SC, Bracken RM, Zijlstra E, Nosek L, Stender-Petersen K, et al. Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: A randomized cross-over trial. Vol. 18, Diabetes, Obesity and Metabolism. 2016.

49. Mauvais-Jarvis F, Sobngwi E, Porcher R, Garnier JP, Vexiau P, Duvallet A, et al. Glucose response to intense aerobic exercise in type 1 diabetes: Maintenance of near euglycemia despite a drastic decrease in insulin dose [5]. Vol. 26, Diabetes Care. 2003.

50. Bracken RM, West DJ, Stephens JW, Kilduff LP, Luzio S, Bain SC. Impact of pre-exercise rapid-acting insulin reductions on ketogenesis following running in Type 1 diabetes. Diabetic Medicine. 2011;28(2).

51. Campbell MD, Walker M, Trenell MI, Luzio S, Dunseath G, Tuner D, et al. Metabolic implications when employing heavy pre- and post-exercise rapid-acting insulin reductions to prevent hypoglycaemia in type 1 diabetes patients: A randomised clinical trial. PLoS One. 2014;9(5).

52. Campbell MD, Walker M, Trenell MI, Jakovljevic DG, Stevenson EJ, Bracken RM, et al. Large pre-and postexercise rapid-acting insulin reductions preserve glycemia and prevent early- but not late-onset hypoglycemia in patients with type 1 diabetes. Diabetes Care. 2013;36(8).

53. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care. 2001;24(4).

54. Lee AS, Way KL, Johnson NA, Twigg SM. High-intensity interval exercise and hypoglycaemia minimisation in adults with type 1 diabetes: A randomised cross-over trial. J Diabetes Complications. 2020;34(3).

55. Kruse JA, Carlson RW. Lactate Metabolism. Crit Care Clin. 1987;3(4).

56. Turinese I, Marinelli P, Bonini M, Rossetti M, Statuto G, Filardi T, et al. "Metabolic and cardiovascular response to exercise in patients with type 1 diabetes." J Endocrinol Invest. 2017;40(9).

57. Brugnara L, Vinaixa M, Murillo S, Samino S, Rodriguez MA, Beltran A, et al. Metabolomics approach for analyzing the effects of exercise in subjects with type 1 diabetes mellitus. PLoS One. 2012;7(7).

58. Vartak V, Chepulis L, Driller M, Paul RG. Comparing Two Treatment Approaches for Patients with Type 1 Diabetes During Aerobic Exercise: a Randomised, Crossover Study. Sports Med Open. 2021;7(1).

59. Billat LV. Use of blood lactate measurements for prediction of exercise performance and for control of training. Recommendations for long-distance running. Vol. 22, Sports Medicine. 1996.

60. Sousa GR, Pober D, Galderisi A, Lv HJ, Yu L, Pereira AC, et al. Glycemic control, cardiac autoimmunity, and long-term risk of cardiovascular disease in type 1 diabetes mellitus A DCCT/EDIC cohort–based study. Circulation. 2019;139(6).

61. Yang SW, Park KH, Zhou YJ. The Impact of Hypoglycemia on the Cardiovascular System: Physiology and Pathophysiology. Vol. 67, Angiology. 2016.