Diplomarbeit

Association of diabetes-specific markers and functional capacity in people with type 1 diabetes

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr.^{in} med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Klinischen Abteilung für Endokrinologie und Diabetologie

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Graz, am 17.01.2022

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Danksagungen

An dieser Stelle möchte ich mich bei allen jenen bedanken, die mich während der Erstellung dieser Diplomarbeit und während meines gesamten Studiums unterstützt haben.
Ich bedanke mich bei meinen Betreuern, Othmar Moser und Felix Aberer, sowie Alexander Müller für die Ermöglichung dieser Arbeit und für den in die klinische Forschung gewonnenen Einblick und die dadurch erworbenen Kenntnisse.
Allen voran möchte ich allerdings meiner gesamten wundervollen Familie Dank aussprechen, die stets an mich glaubt und mich in allen meinen Vorhaben bestärkt und ermutigt. Ich könnte mir keine bessere Familie vorstellen.
Außerdem möchte ich mich noch bei meinen unglaublichen Freund*innen (ihr wisst, wer ihr seid!) inner- und außerhalb der Uni sowie jenen, die aus meinem Erasmus-Aufenthalt resultieren, bedanken, ohne die die letzten 6 Jahre niemals zu dem geworden wären, was sie waren.

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Abbreviations

BMI……body mass index
CPX……cardiopulmonary exercise
CRF……..cardiorespiratory fitness
CSII……....continuous subcutaneous insulin infusion
DD……diabetes duration
ECG……....electrocardiogram
HR……...heart rate
HRPC……...heart rate performance curve
HRTP……....heart rate turn point
IPAQ……..International Physical Activity Questionnaire
LTP_1……..first lactate turn point
LTP_2……..…..second lactate turn point
MLSS……maximal lactate steady state
P……..……power output
$P_{ET}O_2$…..……..end-tidal partial pressure of oxygen
$P_{ET}CO_2$…..……..end-tidal partial pressure of carbon dioxide
RER……..……respiratory quotient
rpm……...revolutions per minute
RR……respiratory rate
SD……standard deviation
T1D.....type 1 diabetes
VE……minute ventilation
VE/VO_2…….respiratory equivalent for carbon dioxide
VE/VO_2……..respiratory equivalent for oxygen
VCO_2……carbon dioxide output
VO_2…….....oxygen uptake
VO_2/HR……oxygen pulse
VT……..ventilatory threshold or tidal volume
VT_1……first ventilatory threshold
VT_2……..…..second ventilatory threshold

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Zusammenfassung

Hintergrund:

Diabetes mellitus Typ 1 (T1D) stellt eine chronische Erkrankung dar, die schwerwiegende kurz- und langfristige (v.a. mikro- und makrovaskuläre) Komplikationen hervorrufen kann. Neben einer suffizienten Blutzuckereinstellung stellt regelmäßige physische Aktivität einen wichtigen Eckpfeiler in der Prävention von diabetesassoziierter Morbidität und Mortalität dar. Obwohl allgemein bekannt ist, dass körperliche Bewegung ein wirksames therapeutisches Instrument ist, ist nicht vollkommen geklärt, ob und wie diabetesspezifische Marker, speziell das HbA_{1c}, die funktionelle Leistungsfähigkeit beeinflussen. Ziel dieser Arbeit war es daher, die Zusammenhänge zwischen diabetesspezifischen Markern (HbA_{1c}, Diabetesdauer, C-Peptid-Status, anthropometrische und demografische Daten) und funktioneller Leistungsfähigkeit sowie kardiorespiratorischen Markern im Rahmen kardiopulmonaler Ausbelastungstests (CPX-Tests) zu untersuchen.

Methoden:

Im Rahmen einer randomisierten kontrollierten Cross-Over-Studie, welche an der Medizinischen Universität Graz durchgeführt wurde, wurde die Effizienz von zwei verschiedenen ultra-langwirksamen Basalinsulinen bei spontanen 60-minütigen Trainingseinheiten am Ergometer bei 15 Personen mit T1D untersucht. Die daraus gewonnenen Labor- und kardiorespiratorischen Marker wurden auf Korrelationen sowie Subgruppen-Unterschiede bezüglich 1. Laktatschwelle (LTP_1), 2. Laktatschwelle (LTP_2) und Maximalbelastung in Abhängigkeit von HbA_{1c}, Diabetesdauer, C-Peptid, Alter, Body-Mass-Index (BMI) und Geschlecht der Proband*innen analysiert.

Ergebnisse:

Es konnten keine signifikanten Korrelationen zwischen HbA_{1c} und maximaler Sauerstoffaufnahme (VO_{2max}) gefunden werden, weder für die absolute VO_{2max}

(Gruppe „niedriges“ HbA_{1c} [≤ 7.5%]: R = 0.40, p = 0.33, Gruppe „hohes” HbA_{1c} [> 7.5%]: R = 0.15, p = 0.75) noch für die relative VO_{2max} („niedriges“ HbA_{1c}: R = 0.24, p = 0.565, „hohes” HbA_{1c}: R = 0.10, p = 0.828). Auch im Vergleich der Untergruppen („niedriges“ vs. „hohes“ HbA_{1c}) zeigten sich keine signifikanten Unterschiede zwischen absoluter VO_{2max} (2.71 ± 0.93 vs. 2.82 ± 0.86 L/min, p > 0.999) und relativer VO_{2max} (37 ± 9 vs. 34 ± 10 ml/min/kg, p = 0.532). Bei Personen mit erhaltener Insulinrestfunktion (C-Peptid positiv) wurden signifikant höhere relative VO_{2max}-Werte beobachtet als bei C-Peptid-negativen Personen (41 ± 10 vs. 31 ± 5 ml/min/kg, p = 0.032*). Jüngere Proband*innen (≤ 41 Jahre) zeigten signifikant höhere relative VO_{2max}-Werte im Vergleich zu älteren (> 41 Jahre) (41 ± 9 vs. 31 ± 6 ml/min/kg, p = 0.030*) sowie Korrelationen für absolute VO_{2max} (R = 0.66, p = 0.074) und relative VO_{2max} (R = 0.84, p = 0.008**). Bezüglich Diabetesdauer und BMI wurde kein signifikanter Einfluss auf absolute und relative VO_{2max} beobachtet.

Conclusio:

Die Qualität der Blutzuckereinstellung hatte in dieser Studie keinen Einfluss auf die maximale Leistungskapazität. Teilnehmer mit erhaltener Insulinrestfunktion und jüngerem Alter erreichten eine höhere VO_{2max}. Die Diabetesdauer und der BMI waren keine signifikanten Prädiktoren für die Leistung.

Abstract

Background:

Type 1 diabetes (T1D) is a chronic condition that implicates serious short-term and long-term complications, above all microvascular and macrovascular disease, which contribute to the major morbidity and mortality associated with T1D. Physical activity poses an important cornerstone in the prevention of cardiovascular disease. However, even though it is well established that physical exercise is an effective therapeutic tool, it is not entirely clear whether and how diabetes-specific markers, especially HbA_{1c}, affect functional capacity in people with T1D. Therefore, the objective of this thesis was to focus on the relations between diabetes-specific markers (HbA_{1c}, diabetes duration, C-peptide, anthropometric and demographic measurements) and functional capacity as well as cardiorespiratory markers during cardiopulmonary exercise (CPX) testing.

Methods:

Data was collected at the Medical University of Graz from 15 individuals with T1D participating in a randomized controlled cross-over trial investigating two different ultra-long-acting basal insulins' performance around multiple spontaneous 60-minute exercise sessions, during which CPX tests were performed. The laboratory and cardiorespiratory markers obtained from the CPX tests were analyzed for correlations as well as between-group differences regarding the first lactate turn point (LTP_1), the second lactate turn point (LTP_2) and maximum exertion depending on the participants' HbA_{1c}, diabetes duration, C-peptide status, age, body mass index (BMI) and sex.

Results:

No significant correlations were found between HbA_{1c} and maximum oxygen uptake (VO_{2max}), neither for absolute VO_{2max} ("good" HbA_{1c} [≤ 7.5%] group: $R = 0.40$, $p = 0.33$, "poor" HbA_{1c} [> 7.5%] group: $R = 0.15$, $p = 0.75$) nor relative VO_{2max}

(“good” HbA_{1c}: R = 0.24, p = 0.565, “poor” HbA_{1c}: R = 0.10, p = 0.828). Also between-group comparisons (“good” vs. “poor” HbA_{1c}) for mean absolute VO_{2max} (2.71 ± 0.93 vs. 2.82 ± 0.86 L/min, p > 0.999) and relative VO_{2max} (37 ± 9 vs. 34 ± 10 ml/min/kg, p = 0.532) showed no significant differences. Significantly higher relative VO_{2max} values were observed in people with residual pancreatic beta cell function (positive C-peptide) vs. people with negative C-peptide (41 ± 10 vs. 31 ± 5 ml/min/kg, p = 0.032*). Also younger (≤ 41 years) individuals showed significantly higher relative VO_{2max} compared to older (> 41 years) subjects (41 ± 9 vs. 31 ± 6 ml/min/kg, p = 0.030*) as well as correlations for absolute VO_{2max} (R = 0.66, p = 0.074) and relative VO_{2max} (R = 0.84, p = 0.008**). Diabetes duration and BMI did not demonstrate significant influence on absolute and relative VO_{2max}.

Conclusion:

In this study, blood sugar control had no influence on functional capacity. Participants with residual pancreatic beta cell function and younger participants achieved higher VO_{2max}. Diabetes duration and BMI were no significant performance predictors.

1 Introduction

Type 1 diabetes (T1D) is a chronic condition in which immune-mediated or idiopathic pancreatic beta cell destruction usually results in an absolute loss of insulin-secretory reserve, leading to chronic hyperglycemia (1,2).
Although T1D accounts for only approximately 5-10% of all cases of diabetes its incidence is increasing, implicating serious short-term and long-term complications, above all microvascular (diabetic nephropathy, retinopathy and neuropathy) and macrovascular (cardiovascular, cerebrovascular and peripheral vascular) disease, which contribute to the major morbidity and mortality associated with T1D. To avoid these complications, adequate diabetes management is vital. The major components of T1D management include appropriate insulin delivery via continuous subcutaneous insulin infusion systems (CSII) or multiple daily injections (MDI) comprising a basal-bolus approach, consistent monitoring of blood glucose concentrations, nutritional knowledge, and physical activity (2). The latter poses an important cornerstone in the prevention of metabolic syndrome and cardiovascular disease, hence people with T1D are highly encouraged to engage in regular physical activity due to its beneficial effects on glycemic control, diabetes-related comorbidities, cardiovascular risk factors and, of utmost importance, quality of life (3).
However, even though it is well established that physical exercise is an effective therapeutic tool to improve glycemic control and further markers of metabolism, it is not entirely clear whether and to which extent diabetes-specific markers are associated with functional capacity in people with T1D. While some studies have reported lower peak and sub-maximal cardiorespiratory fitness in people with T1D compared to healthy individuals, others did not confirm these findings, raising the question for potential causality (1,3,12–20,4–11).

Therefore, the objective of this thesis is to focus on the relations between diabetes-specific markers (HbA_{1c}, diabetes duration, C-peptide, anthropometric and demographic measurements) and functional capacity as well as cardiorespiratory markers assessed by cardiopulmonary exercise (CPX) testing. From a clinical point of view, such information might reveal additional insight into

the effects of T1D on the functioning of the cardiovascular and respiratory system and could be useful in providing exact recommendations for people with T1D. Hence exercise prescription can go forward the route to be personalized depending on patients' needs and individualized diabetes management.

In order to understand the dynamics of T1D and its effects on the cardiovascular and pulmonary system during physical activity, this thesis will provide information regarding diabetes-specific markers and cardiorespiratory parameters obtained from CPX testing.

1.1 Diabetes-specific markers

1.1.1 Diagnosis of T1D and HbA_{1c}

Criteria for diabetes diagnosis do not differ between the types of diabetes and comprise:

- a fasting blood glucose higher than 126 mg/dL (7 mmol/L),
- any random blood glucose of 200 mg/dL (11.1 mmol/L) or higher with symptoms of hyperglycemia
- or an abnormal 2-hour oral glucose tolerance test.
- In 2009, the American Diabetes Association also included glycated hemoglobin (HbA_{1c}), which represents the average blood glucose concentrations over the last 3 months, of 6.5% (48 mmol/mol) or higher in the guidelines (21,22).

1.1.2 C-peptide and diabetes duration

C-peptide is a routinely applied measure of pancreatic beta cell function and may help in the differentiation of diabetes type and therefore in the diagnosis of T1D. It is an amino acid and a byproduct of the enzymatic cleavage of proinsulin to insulin. After insulin and C-peptide are split from the prohormone in the pancreatic beta cells they are secreted into the blood stream in equimolar concentrations.

Since C-peptide is eliminated more slowly than insulin, it can be a useful indicator of insulin secretion and permits discrimination of diminished insulin secretion, as in insulin-dependent diabetes like T1D, or suppressed insulin secretion, as a normal response to exogenous insulin. Interestingly, many individuals with long-standing T1D still produce clinically meaningful amounts of insulin, as reflected by preserved C-peptide production (23–26). However, by the nature of the autoimmune process, with increasing diabetes duration the chance of beta cell survival is smaller, even though residual insulin-producing cells can be found in most individuals with T1D (27,28). Nonetheless, residual beta cell function has been linked to a reduced risk of retinopathy, nephropathy and severe hypoglycemia with even small amounts of detectable C-peptide leading to better clinical outcomes (26). Currently it is not known, though, if C-peptide and diabetes duration independently influence also functional capacity and other cardiorespiratory parameters and might therefore benefit cardiorespiratory fitness.

1.2 Cardiopulmonary exercise testing

In order to assess functional capacity, cardiopulmonary exercise (CPX) testing is performed. CPX testing has become a significant clinical, non-invasive tool involving measurements of respiratory oxygen uptake (VO_2) and carbon dioxide production (VCO_2), minute ventilation (VE) and other ventilatory measures such as ventilatory thresholds (29) during exercise.

There are different methods to measure ventilation and respiratory gas parameters during CPX testing; most systems use breath-by-breath analysis techniques since they display the metabolic response to exercise most accurately (29).

CPX testing is usually conducted on a motorized treadmill or a stationary cycle ergometer; within the framework of this thesis assessment of functional capacity took place on the latter one. There are several advantages and disadvantages in choosing one mode of exercise over the other, VO_{2peak} is typically 5-10% higher on a treadmill than on a cycle ergometer due to early quadriceps fatigue in untrained subjects; furthermore, cycle ergometry requires the individual to uphold constant pedal speed. On the other hand, cycle ergometry might be safer and more suitable

for patients with severe obesity, gait instability, orthopedic and other limitations (29,30).

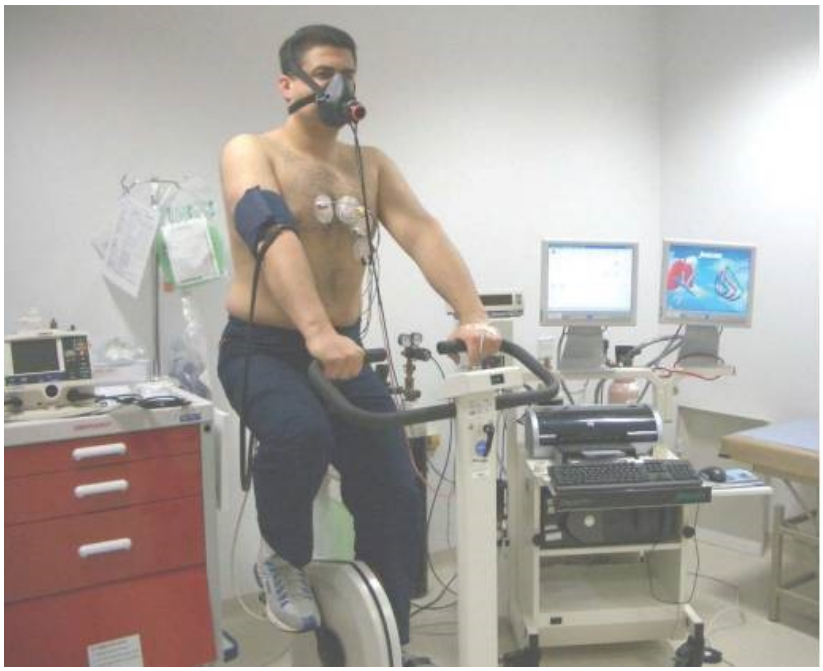

Figure 1. CPX testing using the cycle ergometer, copied from (29).

When assessing functional capacity it is of crucial importance to choose an adequate exercise test protocol, particularly when VO_{2max} is estimated, since test protocols with large stage-to-stage increments usually have a poorer relationship between measured VO_2 and workload. Therefore, exercise test protocols with moderate increases in workload or so-called “ramp” protocols, in which small increments in work rate happen at intervals of <10 to 60 seconds, should be used. Furthermore, the test protocol should be individually tailored so that the exhaustion-limited exercise duration is approximately 8-12 minutes, regardless of the specific test protocol selected. If the test duration is below 6 minutes a non-linear relationship between VO_2 and workload might be observed, even if the exercise test protocol is appropriate. Vice versa, if the exercise duration exceeds 12 minutes individuals might terminate exercise due to muscle fatigue or e.g. orthopedic circumstances instead of cardiopulmonary end points (30,31).

Often times, there will be also be continuous ECG monitoring as well as frequent blood pressure measurements, especially in patients with pre-existing conditions such as heart disease (29).

1.3 Cardiorespiratory and metabolic markers during cardiopulmonary exercise testing

1.3.1 Functional capacity and VO_{2max}

Functional capacity is determined by the pulmonary, cardiovascular and skeletal muscle systems and refers to the ability of a person to perform aerobic work, which is defined by the maximal oxygen uptake (VO_{2max}). VO_{2max} subsequently is defined as the product of cardiac output and arteriovenous oxygen difference (a-VO_2; which refers to the amount of oxygen extracted from the blood by the tissues) at physical exhaustion, as described in the Fick equation (30,32):

$$\dot{V}O_{2max} = (HR \times SV) \times a\text{–}\dot{V}O_2diff,$$

Figure 2. The Fick equation, copied from (30). Abbreviations: HR (heart rate), SV (stroke volume), a-VO_2 (arteriovenous oxygen difference).

Even though VO_{2max} is quantified in liters of oxygen per minute, it is commonly expressed in milliliters of oxygen per minute per kilogram of body weight (ml/min/kg) in order to simplify interindividual comparisons.

It is important to distinguish between measured and estimated VO_{2max}. Measurement of VO_{2max} implies that a maximal cardiopulmonary exercise test has been conducted and that the subject has achieved its physiological limit by giving maximal effort, which has been determined as a plateau in VO_{2max} between the final two exercise workloads. However, since people with cardiovascular or pulmonary disease but also apparently healthy individuals might not reach a plateau in VO_2, the term peak VO_2 can be used instead. In individuals who are not able to perform maximal activities estimated VO_{2max} might be applied using one of a variety of tests.

Aerobic capacity is influenced by various parameters, such as age, gender, conditioning status and medications that interfere with its components. VO_{2max} can reach up to 80 ml/min/kg in young male professional endurance athletes, whilst 15 ml/min/kg represents an average value for a sedentary but healthy 80-year-old woman. VO_{2max} decreases by approximately 10% per decade in non-athletic

individuals. However, this rate of decline does not seem to be linear but instead appears to accelerate significantly with increasing age: While young individuals between their 20s and 30s experience a decline in VO_{2max} of approximately 3-6%, individuals aged 70 and older may exceed 20% per decade. These changes in functional capacity are attributable to physiological processes such as a reduction in stroke volume, maximal heart rate, perfusion to the skeletal muscle, and skeletal muscle function, all of which determine VO_{2max} (30,33–35).

In terms of gender-specific differences in aerobic capacity, VO_{2max} is 10-20% greater in men than in women regardless of age due to higher hemoglobin concentration, larger percentage of muscle mass as well as greater stroke volume in men. As a result, it is vital to take into account these population specificities when interpreting aerobic capacity with regard to a percentage of an age-predicted VO_{2max} (30). Table 1 and 2 categorize VO_{2max} values for adult females and males of various ages.

Table 1. Relative VO_{2max} norms [ml/min/kg] for females aged 20 to 65 years, modified from (36).

Age [years]	Very poor	Poor	Fair	Average	Good	Very good	Excellent
20-24	<27	27-31	32-36	37-41	47-51	47-51	>51
25-29	<26	26-30	31-35	36-40	45-44	45-49	>49
30-34	<25	25-29	30-33	34-37	38-42	43-46	>46
35-39	<24	24-27	28-31	32-35	36-40	41-44	>44
40-44	<22	22-25	26-29	30-33	34-37	38-41	>41
45-49	<21	21-23	24-27	28-31	32-35	36-38	>38
50-54	<19	19-22	23-25	26-29	30-32	33-36	>36
55-59	<18	18-20	21-23	24-27	28-30	31-33	>33
60-65	<16	16-18	19-21	25-27	25-27	28-30	>30

Table 2. Relative VO_{2max} norms [ml/min/kg] for males aged 20 to 65 years, modified from (36).

Age [years]	Very poor	Poor	Fair	Average	Good	Very good	Excellent
20-24	<32	32-37	38-43	44-50	51-56	57-62	>62
25-29	<31	31-35	36-42	43-48	49-53	54-59	>59
30-34	<29	29-34	35-40	41-45	46-51	52-56	>56
35-39	<28	28-32	33-38	39-43	44-48	49-54	>54
40-44	<26	26-31	32-35	36-41	42-46	47-51	>51
45-49	<25	25-29	30-34	35-39	40-43	44-48	>48
50-54	<24	24-27	28-32	33-36	37-41	42-46	>46
55-59	<22	22-26	27-30	31-34	35-39	40-43	>43
60-65	<21	21-24	25-29	29-32	33-36	37-40	>40

The importance of this knowledge about functional capacity becomes clear when one considers that cumulative epidemiological and clinical evidence has firmly assessed that cardiorespiratory fitness (CRF) is a strong and independent marker for risk of cardiovascular disease, all-cause mortality, and mortality rates ascribable to several cancers. These findings have been observed in healthy men and women, those with suspected or known cardiovascular disease, and those with comorbidities, such as obesity, type 1 and type 2 diabetes, arterial hypertension, and hyperlipidemia (37).

Various studies have demonstrated that CRF might even be a stronger predictor of mortality than traditional risk factors like smoking, hypertension, high cholesterol, and T2D as well as other exercise test variables, including ST-segment depression and hemodynamic responses. An analysis by Blair et al. showed that age-adjusted mortality rates were lowest among the most fit and highest among the least fit females and males, as displayed in figure 3 (37).

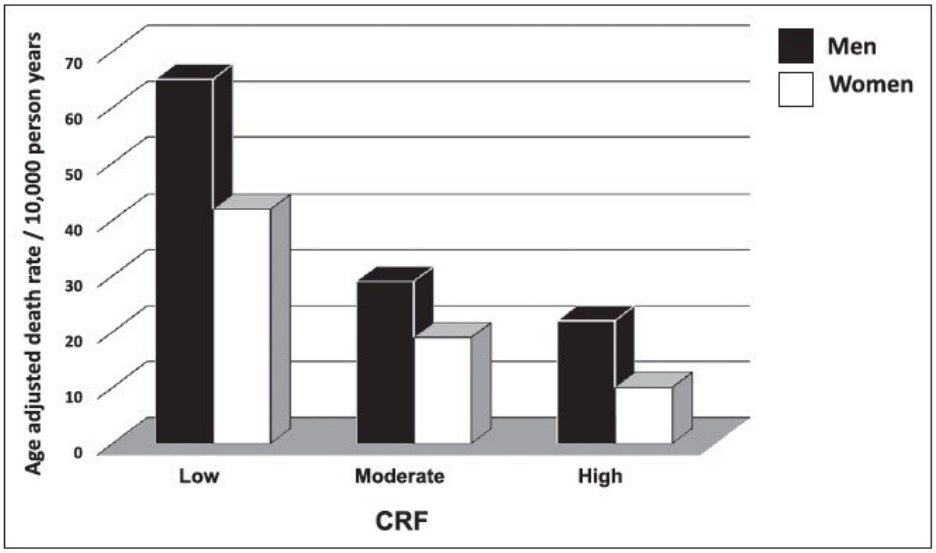

Figure 3. All-cause death rates across categories of cardio- respiratory fitness (CRF) in 3120 women and 10224 men, copied from (37).

Vice versa and very importantly, increased CRF (which can be obtained via endurance training primarily by augmenting stroke volume and arteriovenous oxygen difference) is associated with reduced risk of death, with even small increases leading to considerably (10-30%) lower rates of adverse cardiovascular events, which highlights the importance of regular physical exercise (30,37,38).

1.3.2 Lactate turn points

Apart from the maximal oxygen uptake, cardiopulmonary exercise testing also allows the determination of aerobic performance markers like thresholds, which are recommended for individualized physical fitness estimation or training prescription (39).

This is possible since at given intensity rates, lactate is produced in exercising muscles via anaerobic glycolysis and can be utilized as a source of fuel in other tissues, such as the heart and the kidney, that can take up lactate from the blood and metabolize it into ATP via aerobic metabolism. During exercise, glucose is broken down to and oxidized to pyruvate to generate energy. However, when the demand for energy is high, the oxygen supply to the muscle can be insufficient and pyruvate is converted to lactate. Therefore, when exercise increases in intensity, lactate is shifted out of the cells and into the blood. Initially, the increase in blood lactate levels is usually small since other tissues can eliminate the lactate. However, once the intensity reaches a certain level, blood lactate concentrations begin to rise significantly. In exercise physiology, this point is called first lactate turn point (LTP_1) or lactate threshold and translates to the incapacity of the muscle to completely oxidize produced lactate within the cell and is consequently partly transported into the blood. However, the LTP_1 represents a threshold in which there is still a metabolically steady state, but in a systemic context (40,41).

The LTP_1 corresponds with the first ventilation threshold (VT_1), using noninvasive measures of respiration instead of taking blood samples (40).

The second lactate turn point (LTP_2) then represents the second threshold, in which the working muscles cannot keep up anymore with the cellular or systemic elimination of the produced lactate, leading to a blood lactate accumulation and a metabolically imbalanced state. As before, the LTP_2 corresponds with the second ventilatory threshold (VT_2) (41).

Up until the LTP_2 the body is still able to maintain a metabolically steady state, therefore the LTP_2 can be used to estimate the maximal lactate steady state (MLSS), representing the critical lactate clearance rate that defines the maximum power output at which the subject can hold its blood lactate levels constant (42). Figure 4 summarizes the phases of lactate metabolism during CPX testing.

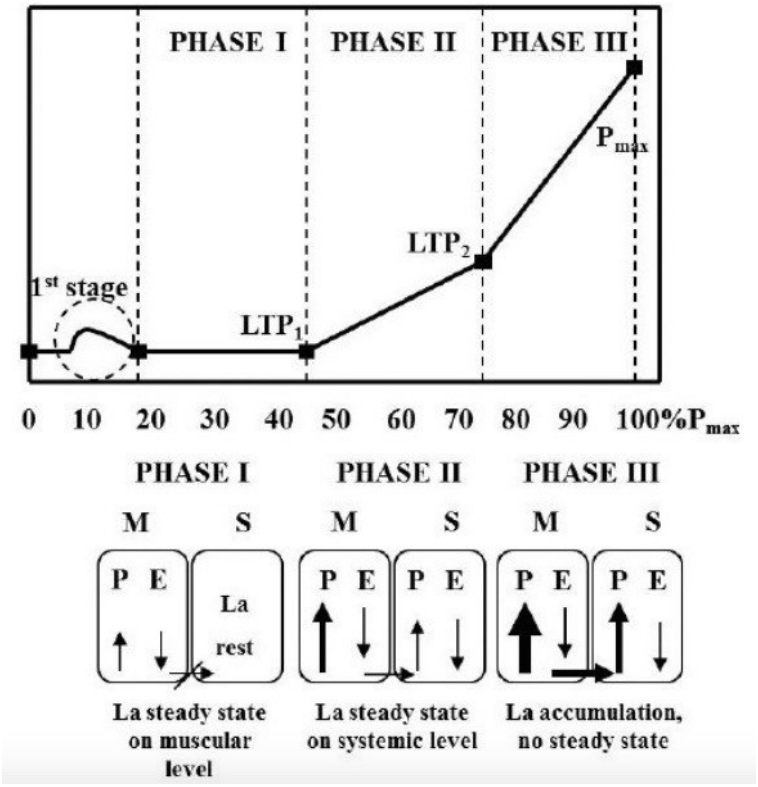

Figure 4. Phases of lactate (La) metabolism during CPX testing. Abbreviations: LTP_1 (first lactate turn point), LTP_2 (second lactate turn point), P_{max} (maximal power output), M (working muscle), S (system), P (lactate production), E (lactate elimination), copied from (43).

These thresholds relativized to the VO_{2max} are important parameters since they allow the sensitive analysis of physical exercise performance in both healthy subjects and patients (44).

1.3.3 Heart rate turn point and heart rate dynamics

Other information obtainable from CPX testing is the heart rate turn point (HRTP) and heart rate dynamics. The HRTP refers to a downward or upward deviation from the heart rate (HR)-power relationship observed during CPX testing. It is not always found, though, since the heart rate performance curve (HRPC) can also show a linear time course (39,45).

A deflection of the HRPC to the right at a specific power output is seen in approximately 85% of young, healthy individuals and is referred to as a regular, S-shaped heart rate response pattern, whereas about 15% of young and healthy

subjects show non-regular heart rate curves, meaning linear or even inverted HRPC (41,42,46). Figure 5 shows a schematic model of the HRPC with regular downward reflection, linear time course and upward deflection.

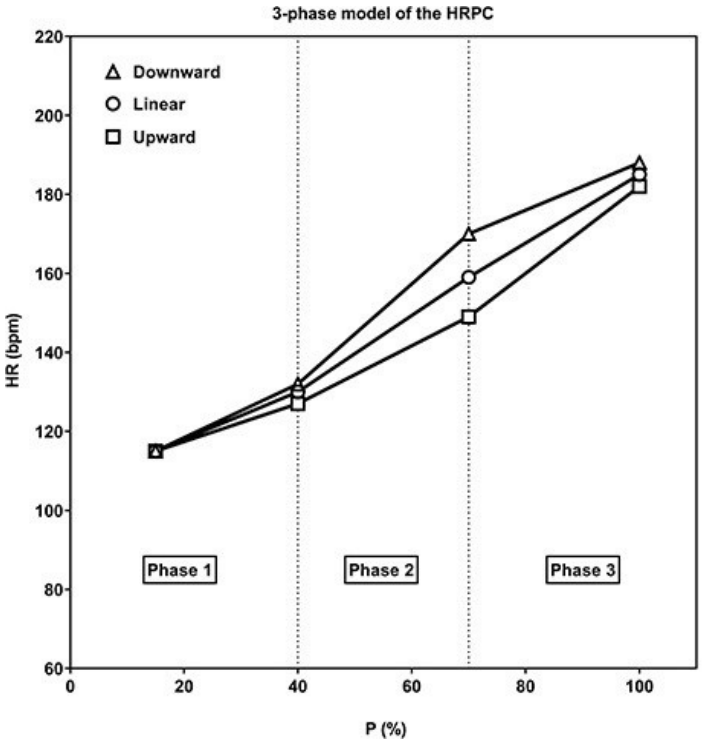

Figure 5. Schematic model of the HRPC from CPX testing with regular downward reflection, linear time course and upward deflection, copied from (47).

The physiological mechanisms that regulate the HRTP have not been fully elucidated. However, especially older and cardiac patients but also people with T1D show higher rates of irregular HRPC, which has been associated to reduced left ventricular ejection fraction and β_1-adrenoceptor insensitivity and therefore also lower maximum heart rates (HR_{max}). Impairment of β_1-adrenoceptor sensitivity might be ascribed to chronically elevated HbA_{1C} and associated elevated catecholamine levels as well as inflammatory processes (41,46,48–52).

It has been suggested that individuals with regular HR response patterns show a significant increase in HR between the LTP_1 and the LTP_2 when catecholamine concentrations are still low and might therefore be referred to as “early responders”. However, when reaching the LTP_2 receptors might become saturated due to a marked increase in catecholamine levels, resulting in a deflection of the HRPC.

On the other hand, individuals with non-regular HRPC display slow increases in HR up to the LTP_2. When reaching the LTP_2 though, a sharp increase in catecholamine levels leads to an augmented HR reaction. Therefore, subjects with linear or inverted HRPC may be referred to as “late responders” (46).
If the test protocol during CPX testing has adequate stage-to-stage increments the power at the HRTP is significantly associated to the power at the LTP_2 and the VT_2 (42,46). This also applies to people with T1D (53).

1.3.4 Ventilatory equivalents

The ventilatory equivalent for oxygen (VE/VO_2), assessed by evaluation of the rise in minute ventilation (VE) relative to the respiratory oxygen production (VO_2), represents the number of liters of ventilation required to consume 1 L of oxygen. It is a good marker of breathing efficiency during physical activity since high values suggest inefficient ventilation (54–56).
The ventilatory equivalent for carbon dioxide (VE/VCO_2), assessed by evaluating the rise in minute ventilation (VE) relative to the respiratory carbon dioxide production (VCO_2), represents the number of liters of ventilation per 1 L of CO_2 output and is another marker of ventilatory efficiency (54,55). There is a linear relationship between VE and VCO_2 during exercise since VE is tightly adapted by the metabolic and anaerobic production of CO_2 (54,57). VE/VCO_2 values <30 are considered normal without adaptation for age and gender. In specific populations, such as patients with chronic obstructive pulmonary disease, pulmonary hypertension and heart failure, VE/VCO_2 can far surpass this normal threshold, with values >60 in patients with progressed disease (54). Pathophysiologically, elevated VE/VCO_2 values have been linked to increased ventilation-perfusion mismatching (adequate ventilation and poor perfusion), elevated chemoreceptor and ergoreceptor sensitivity (which lead to an excessive ventilatory response to physical activity), decreased cardiac output, increased pulmonary pressures, diminished alveolar-capillary membrane conductance and decreased heart rate variability (54,58,59).
In people with T1D, only very limited research has been conducted on the ventilatory response to cardiopulmonary exercise testing, though such data might

reveal additional insights on the impact of glycemic control on the functioning of the cardiovascular and respiratory system.

1.3.5 Respiratory exchange ratio

The respiratory exchange ratio (RER), defined by the ratio of carbon dioxide production to oxygen consumption (VCO_2/VO_2), provides information about which metabolic source the energy is mainly obtained from. An RER of 1.0 indicates metabolization of mainly carbohydrates. In case of fat metabolism, the RER is around 0.71. At rest, the muscle receives its energy from approximately 40% carbohydrates and 60% fat, which results in an RER of about 0.80. During exercise, energy is increasingly obtained from carbohydrates. However, in good physical condition, more fat is burned even under physical exertion. An RER exceeding the value of 1.00 indicates metabolic stress since more carbon dioxide is exhaled than oxygen is absorbed due to metabolic acidosis (60).

The RER also serves as an accurate marker of sufficient subject effort during CPX testing in healthy subjects as well as patients, since the maximal HR response to exercise, which is a well-recognized measurement for that very purpose, shows great variability in the general population and is further complicated by the widespread use of ß-blocking agents. A maximum RER of ≥1.10 indicates outstanding subject effort during CPX testing, while attainment of a maximum RER of <1.00 in a CPX test that is ended by participant request, is ascribable to submaximal cardiovascular effort but might also be seen in subjects with pulmonary limitations to physical activity (54,61).

In terms of T1D, only very limited research has been done regarding its influence on RER. One study has reported lower peak RER and lactate values during CPX testing in individuals with T1D compared to healthy subjects, suggesting greater lipid substrate utilization in diabetic people (1,62). Since constantly elevated blood insulin levels may impair the glycolytic response in patients with T1D, substrate production in the tricarboxylic acid cycle might be inhibited, which is very important for early energy production during exercise, though (1,12,63). However, due to the lack of data, further investigation might be useful in gaining insights on the impact of T1D on the RER.

1.3.6 Oxygen pulse

The oxygen pulse (VO_2/HR) is defined by the amount of oxygen taken up with each heartbeat and can be used to indirectly estimate the heart's stroke volume. Under physiological conditions it should increase steadily during physical activity to a value over 10 ml per heartbeat and might also further rise during the recovery phase. Low O_2-pulse values might indicate low cardiac output due to heart disease or pulmonary circulation dysfunction. However, low oxygen pulse should not be over-interpreted if maximum VO_2 is normal (64).

It is currently unknown whether T1D is associated with lower stroke volume. In some studies no differences could be detected for stroke volume in individuals with T1D versus their healthy counterparts during CPX testing (7,65). However, when subdividing patients with T1D into a high- and a low-HbA_{1c} group, one study could demonstrate higher stroke volume in subjects with low HbA_{1c} (7). Another study has reported higher stroke volume in individuals with diabetes with higher insulin sensitivity versus individuals with lower insulin sensitivity during maximal incremental exercise testing (66). All in all, there is a lack of information regarding T1D and its effects on stroke volume by means of oxygen pulse determination.

1.3.7 End-tidal partial pressure of oxygen and carbon dioxide

End-tidal partial pressure of oxygen ($P_{ET}O_2$) is the PO_2 at the end of exhalation, while end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) refers to the PCO_2 at the end of exhalation. The incapacity of $P_{ET}CO_2$ to decrease or a rise indicates limited ventilatory capacity or neuromuscular impairment (55).

In cardiac patients it has been shown that $P_{ET}CO_2$ is lower during exercise compared to their healthy counterparts, which was correlated with lower cardiac output and cardiac index at peak exercise in individuals with heart failure (67–69).

However, no information currently exists on the influence of T1D on these parameters, even though such data might be useful in further understanding the mechanism of T1D and its impact on the respiratory and cardiovascular system.

1.4 Association of glycemic control and aerobic capacity in people with T1D

As mentioned earlier, T1D has been linked to an increased risk of cardiovascular disease, which is why individuals with T1D are encouraged to exercise regularly (3,70). Nonetheless, physical inactivity remains high within the diabetes population, which can be attributable to factors such as low fitness level, fear of exercise-induced hypoglycemia and loss of control over diabetes, serving as barriers to initiate or maintain regular physical exercise (3,71,72).

T1D as well as glycemic control per se in terms of HbA_{1c} have been suggested of being a limiting factor regarding functional capacity and therefore maximum/peak VO_2 in people with T1D. There is a variety of studies that observed lower peak VO_2 values in individuals with T1D versus their healthy counterparts (1,4,16–19,73,8–15), while others did not confirm these findings in similarly trained subjects with and without diabetes (5,7,51).

However, limited evidence currently exists on the independent influence of HbA_{1c} on functional capacity. Previous research inversely associated HbA_{1C} and peak aerobic capacity, with lower VO_{2peak} values in poorly controlled groups (7,10,20). When individuals with T1D were stratified into groups based on HbA_{1C} levels, and cardiorespiratory markers such as VO_2 were set in relation to sub-maximal markers, other studies demonstrated that higher HbA_{1C} levels correlated with higher rates of O_2 use at sub-maximal work rates, indicating reduced exercise economy (3). In contrast to these findings, other studies could not find any correlation between HbA_{1C} and aerobic capacity (1,4,9,15,73).

The cumulative data may be indicative of impaired exercise performance in people with T1D, which raises the question for potential causality. A possible explanation for the divergence in previous findings might be the independent influence of glycemic control on peak VO_2, which is why the primary aim of this study was to investigate the association between HbA_{1c} and functional capacity in people with T1D during cardiopulmonary exercise testing. Furthermore, relationships to C-peptide, diabetes duration, anthropometric, demographic and other cardiorespiratory parameters were explored.

2 Materials and methods

The empiric data were collected and analyzed at the Medical University of Graz, Austria, from a randomized cross-over trial investigating ultra-long-acting basal insulins' flexibility around multiple spontaneous exercise sessions in people with type 1 diabetes. Backgrounds of this study and its relevance to the current research question are explained in the following part.

2.1 Trial design

Within this thesis all data was obtained from a randomized, single-center, four-period, cross-over trial at the Medical University of Graz, Austria, investigating ultra-long-acting basal insulins' flexibility around multiple spontaneous exercise sessions in people with type 1 diabetes.
As part of the study, screening visits were conducted, in which participants performed a maximum incremental cardiopulmonary exercise test on a cycle ergometer to determine the peak oxygen uptake (VO_{2peak}) and the first and second lactate turn points (LTP_1 and LTP_2) as well as other cardiorespiratory markers such as maximum heart rate (HR_{max}), first and second ventilatory threshold (VT_1 and VT_2), power output (P), oxygen pulse (VO_2/HR), respiratory equivalents for oxygen and carbon dioxide (VE/VO_2 and VE/VCO_2), respiratory quotient (RER), ventilation (VE), tidal volume (VT), respiratory rate (RR) as well as end-tidal partial pressure of oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$), which were of main interest for this thesis.

Prior to the screening visit, participants were provided with oral and written information about the trial and informed consent was obtained.
At the screening visit, the following information was assessed and documented in a case report form: check of signed and dated informed consent, inclusion and exclusion criteria, demography (age, sex, ethnicity, race), abuse of drugs, abuse of alcohol and smoking habits, confirmation of diabetes diagnosis, diabetes treatment history, medical history (any relevant illness in the past), concomitant illness,

concomitant medication, hypoglycemic episodes and hypoglycemic symptoms assessment, glucose measurements, body measurements (body weight, height and body mass index, physical examination, vital signs (blood pressure and heart rate), 3- and 12-lead electrocardiogram, alcohol breath test, dependence-causing substances screen, laboratory examination (HbA_{1C}, C-peptide, hematology, biochemistry, coagulation, hepatitis B/C screening, HIV screening), urine analysis, exercise physiological markers, blood glucose, ketones, pregnancy test (in women of childbearing potential), IPAQ, CPX testing for the assessment of mass specific VO_{2peak} and vasculature response to CPX testing.

The CPX test was performed using a standardized CPX testing protocol to ensure maximal exhaustion during exercise testing, which was initiated by 3 minutes of sitting passively on a cycle ergometer (Ergoline Type Ergoselect 4, Germany), followed by a 3-minute warm-up period applying 20 watts in trained or 10-15 watts in untrained participants, followed by 1-minute incremental steps of 20 watts in trained or 10-15 watts in untrained participants until exhaustion occurred. Throughout CPX testing cadence had to be maintained above 60 revolutions per minute (rpm). Exhaustion was defined as a cadence below 50 rpm for longer than 3 seconds. The termination of the CPX test was followed by a 3-minute cool-down period applying 40 watts in males and trained females or 20 watts in females and untrained males, followed by 3 minutes of sitting passively on the cycle ergometer.
During CPX testing, respiratory parameters including oxygen (VO_2), carbon dioxide (VCO_2) and ventilation (V) were measured continuously (Metamax 3B spiroergometry), as were the heart rate (Polar heart rate monitor) and the cardiac response (ECG). For safety reasons blood glucose from the fingertip (0,3 µl) (FreeStyle Libre, Abbott) was measured as often as needed but at least every 5 minutes. Blood glucose and blood lactate from the earlobe (20 µl) (Biosen S line, EKF Diagnostics) were taken at the end of every workload and after warm-up and cool-down to assess exercise-induced effects. Blood pressure was measured every 2 minutes.
CPX testing was only started if the blood glucose concentration was above 7 mmol/L (126 mg/dl) 15 minutes prior to the start. If the blood glucose concentration was below 7 mmol/L (126 mg/dl) 15-30 grams of carbohydrates (gel or juice) were administered. If the blood glucose was still below 7 mmol/L (126 mg/dl) after 15

minutes this procedure was repeated as often as needed.

The laboratory and cardiorespiratory markers obtained from the CPX tests were then analyzed for correlations as well as differences regarding LTP_1, LTP_2 and maximum exertion depending on the participants' HbA_{1c}, diabetes duration, C-peptide status, age, BMI and sex, as described in the results section of this thesis.

2.2 Trial population

15 participants with T1D were included in the trial.

2.2.1 Key inclusion criteria

- Males or females aged 18-65 years (both inclusive)
- Type 1 diabetes mellitus (as diagnosed clinically) ≥ 12 months
- Treated with multiple daily insulin injections ≥ 12 months
- Body mass index 18,0-29,4 kg/m^2 (both inclusive)
- Mass-specific peak oxygen consumption (VO_{2peak}) > 20 ml/min/kg
- HbA_{1c} ≤ 10% (86 mmol/mol)
- Participants performing regular physical cardiorespiratory activity during the last 3 months prior to screening

2.2.2 Key exclusion criteria

- Recurrent severe hypoglycemia (more than one severe hypoglycemic event during the past 12 months)
- Hypoglycemia unawareness as judged by the Investigator
- Hospitalization for diabetic ketoacidosis during the previous 12 months

2.3 Objectives

The primary objective of the study was the investigation of performance of two different commercially marketed basal insulins (insulin degludec and insulin glargine U300) during moderate exercise sessions lasting 60 minutes conducted on a cycle ergometer performed 3 days per week for a total of 8 weeks (24 exercise visits).

One of the secondary objectives and serving as the primary objective of this thesis was to obtain information regarding the influence of HbA_{1c} on VO_{2max} in people with T1D.

Secondary objectives included evaluating potential associations of other diabetes-specific markers, anthropometric and demographic data, and functional capacity as well as other cardiorespiratory parameters in people with T1D.

2.4 Statistical analyses

The 15 participants included were divided into two subgroups, each regarding their HbA_{1c}, diabetes duration, C-peptide status, age, BMI and sex. To do so, the respective values less than or equal to the median formed one group, the respective values above the median formed another group, as displayed in table 3.

Table 3. Subgroups: cut-off values for HbA_{1c}, diabetes duration, C-peptide, age, BMI and sex.

Subgroups	**Cut-off**
"Good" HbA_{1c}	≤ 7.5%
"Poor" HbA_{1c}	> 7.5%
"Short" diabetes duration	≤ 21 years
"Long" diabetes duration	> 21 years
C-peptide negative	0.00 pmol/L
C-peptide positive	> 0.00 pmol/L
"Young"	≤ 41 years
"Old"	> 41 years
"Good" BMI	≤ 24.0 kg/m^2
"Poor" BMI	> 24.0 kg/m^2

Subsequently, the following cardiorespiratory parameters (obtained from the CPX tests) were set in relation to each participant's individual thresholds for LTP_1, LTP_2 and maximum exertion: absolute VO_2, relative VO_2, VO_2/HR, HR, P, VE/VO_2, VE/VCO_2, RER, VE, VT, RR, $P_{ET}O_2$ and $P_{ET}CO_2$.

All groups were then analyzed for differences in the above-mentioned parameters for lactate thresholds and at maximum exertion. To do so, all data were tested with Shapiro-Wilk normality test and evaluated for normal distribution. Subsequently, unpaired students' t-test was applied to determine significant differences in normally distributed groups, Mann-Whitney-U-test was used to compare non-normally distributed groups.

In order to determine the thresholds for LTP_1 and LTP_2, for this thesis, though ventilatory thresholds and HR curves were available, lactate curves were applied. Linear regressions were performed to detect possible significant correlations between diabetes-specific, anthropometric and demographic data in regard to specific cardiorespiratory markers (absolute VO_2, relative VO_2, VO_2/HR, HR, P, VE/VO_2, VE/VCO_2, RER, VE, VT, RR, $P_{ET}O_2$, $P_{ET}CO_2$ at LTP_1, LTP_2 and maximum exertion). Descriptive statistics included mean and standard deviation for the before-mentioned participants' characteristics. A confidence interval of 95% was chosen for all calculations. All statistics were performed with Prism® Software version 8.2.1 (GraphPad, USA).

3 Results

3.1 Baseline characteristics of the study cohort

Data was obtained from a total of 15 physically active individuals with T1D with an overall healthy lifestyle and without major concomitant illnesses or medication apart from insulin treatment. Out of the 15 participants 7 were females, 8 were males. Baseline characteristics of the population are displayed in table 4.

Table 4. Baseline characteristics of the study cohort.

	n	**mean ± SD**
Age [years]	15	40.6 ± 10.1
BMI [kg/m^2]	15	24.3 ± 2.9
HbA_{1c} [%]	15	7.3 ± 0.7
Hba_{1c} [mmol/mol]	15	56.3 ± 7.6
Diabetes duration [years]	14	18.4 ± 10.1
C-peptide (pmol/L)	15	0.1 ± 0.2

Furthermore, above-mentioned demographic, anthropometric and diabetes-related data were stratified by sex, with no significant differences being detected between females and males, see table 5.

Table 5. Baseline characteristics stratified by sex. Values are given as mean ± SD.

	female (n = 7)	**male (n = 8)**	**p-value**
Age [years]	43.7 ± 7.3	37.9 ± 11.8	0.278
BMI [kg/m^2]	24.1 ± 3.2	24.5 ± 2.9	0.825
HbA_{1c} [%]	7.3 ± 0.7	7.3 ± 0.7	0.943
Hba_{1c} [mmol/mol]	56.3 ± 8.0	56.3 ± 7.8	0.993
Diabetes duration [years]	18.1 ± 11.6	18.7 ± 9.3	0.921
C-peptide (pmol/L)	0.1 ± 0.2	0.1 ± 0.2	0.563

3.2 Subgroup analyses: participant characteristics versus cardiorespiratory makers

3.2.1 HbA_{1c}

In the following table a comparison of performance data and physiological data during CPX testing between both groups is shown, with no significant differences being detected:

Table 6. Values are given as mean ± SD.

	"good" HbA_{1c} (n = 8)	**"poor" HbA_{1c} (n = 7)**	**p-value**
Age [years]	38.3 ± 9.1	43.3 ± 11.1	0.352
Absolute $VO_{2\ LTP1}$ [L/min]	0.99 ± 0.23	0.99 ± 0.21	0.991
Absolute $VO_{2\ LTP2}$ [L/min]	1.75 ± 0.55	1.77 ± 0.48	0.694
Absolute VO_{2max} [L/min]	2.71 ± 0.93	2.82 ± 0.86	>0.999
Relative $VO_{2\ LTP1}$ [ml/min/kg]	14 ± 2	12 ± 3	0.255
Relative $VO_{2\ LTP2}$ [ml/min/kg]	24 ± 5	24 ± 9	0.429
Relative VO_{2max} [ml/min/kg]	37 ± 9	34 ± 10	0.532
VO_2/HR_{LTP1} [ml/b/min]	9 ± 2	10 ± 3	0.298
VO_2/HR_{LTP2} [ml/b/min]	12 ± 3	13 ± 3	0.444
VO_2/HR_{max} [ml/b/min]	15 ± 4	16 ± 4	0.499
HR_{LTP1} [/min]	111 ± 17	101 ± 19	0.313
HR_{LTP2} [/min]	152 ± 21	138 ± 15	0.155
HR_{max} [/min]	183 ± 18	177 ± 10	0.694
P_{LTP1} [W]	54 ± 22	46 ± 18	0.474
P_{LTP2} [W]	132 ± 50	125 ± 40	0.933
P_{max} [W]	209 ± 83	201 ± 63	0.977
$VE/VO_{2\ LTP1}$	23.0 ± 4.0	22.5 ± 2.5	0.779
$VE/VO_{2\ LTP2}$	25.6 ± 3.9	24.9 ± 3.8	0.890
VE/VO_{2max}	36.3 ± 6.0	36.3 ± 7.3	0.986
$VE/VCO_{2\ LTP1}$	29.0 ± 3.3	27.7 ± 2.1	0.359
$VE/VCO_{2\ LTP2}$	27.1 ± 2.6	25.8 ± 3.4	0.843
VE/VCO_{2max}	32.6 ± 4.4	31.5 ± 6.0	0.791
RER_{LTP1}	0.80 ± 0.05	0.81 ± 0.03	0.080
RER_{LTP2}	0.96 ± 0.05	0.96 ± 0.05	0.940
RER_{max}	1.12 ± 0.04	1.15 ± 0.07	0.388
VE_{LTP1} [L/min]	25.6 ± 3.1	25.0 ± 4.2	0.975
VE_{LTP2} [L/min]	48.0 ± 10.6	47.0 ± 11.6	0.965
VE_{max} [L/min]	102.7 ± 28.2	107.1 ± 33.8	0.773
VT_{LTP1} [L]	1.44 ± 0.62	1.36 ± 0.26	0.631
VT_{LTP2} [L]	2.04 ± 0.72	2.27 ± 0.83	0.420
VT_{max} [L]	2.52 ± 0.68	2.84 ± 1.10	0.420

RR_{LTP1} [/min]	20 ± 4	20 ± 5	0.969
RR_{LTP2} [/min]	25 ± 5	22 ± 5	0.272
RR_{max} [/min]	41 ± 6	40 ± 9	0.623
$P_{ET}O_{2\ LTP1}$ [mmHg]	96 ± 6	95 ± 4	0.985
$P_{ET}O_{2\ LTP2}$ [mmHg]	101 ± 5	98 ± 6	0.516
$P_{ET}O_{2max}$ [mmHg]	113 ± 4	112 ± 7	0.650
$P_{ET}CO_{2\ LTP1}$ [mmHg]	37 ± 3	38 ± 2	0.525
$P_{ET}CO_{2\ LTP2}$ [mmHg]	39 ± 3	41 ± 5	0.670
$P_{ET}CO_{2max}$ [mmHg]	32 ± 4	34 ± 8	0.976

When exploring the relationship between HbA_{1c} and absolute VO_2 a correlation could be found only within the "good" HbA_{1c} group at LTP_1, though without statistical significance (n = 8, R = 0.53, p = 0.17174), as displayed in figure 6.

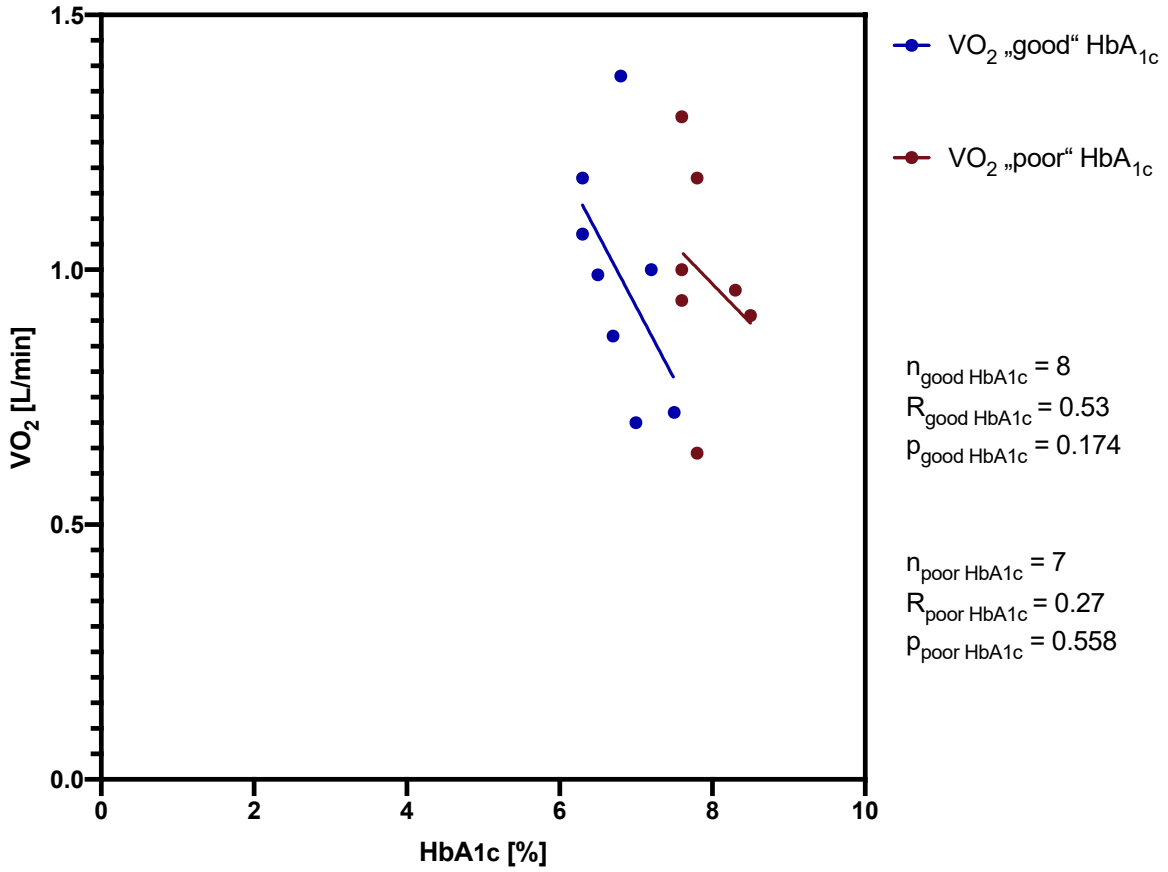

Figure 6. "Good" vs. "poor" HbA_{1c}: absolute VO_2 at LTP_1.

At LTP_2 and maximum exertion no significant correlations could be found in neither group, as shown in figure 7.

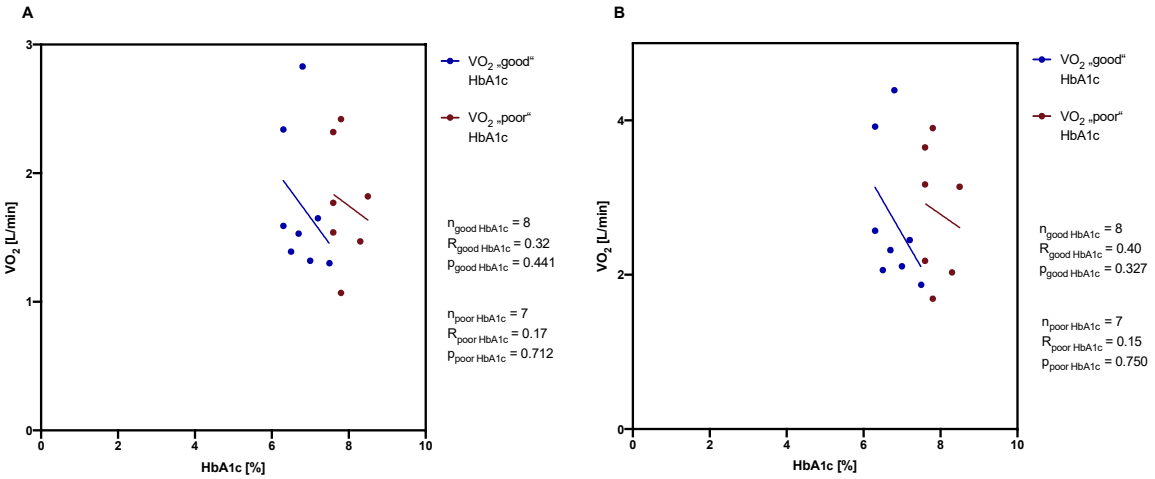

Figure 7. Comparison of absolute VO_2 between both groups. **(A)** "Good" vs. "poor" HbA_{1c}: absolute VO_2 at LTP_2, **(B)** "good" vs. "poor" HbA_{1c}: absolute VO_{2max}.

When analyzing the correlation between HbA_{1c} and relative VO_2, no significant correlations were found, see figure 8.

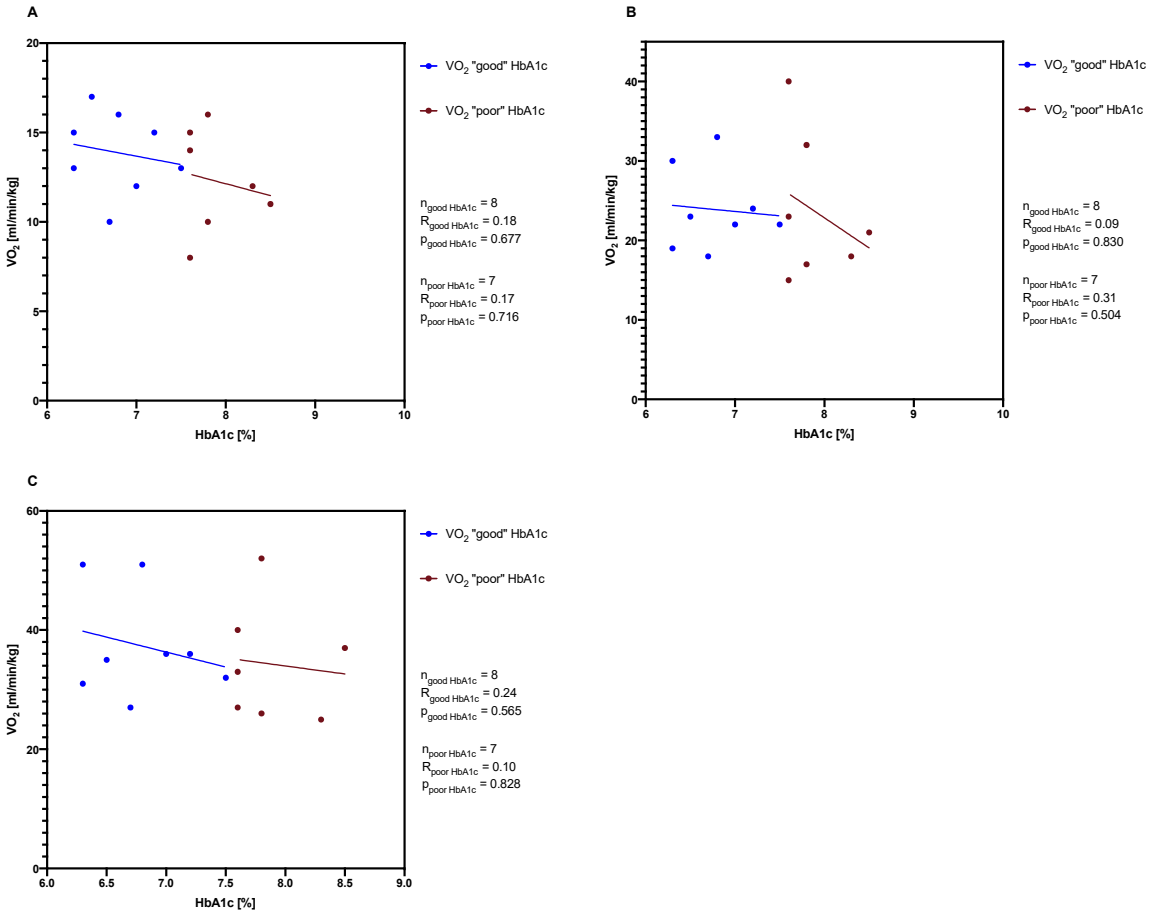

Figure 8. Comparison of relative VO_2 between both groups. **(A)** "Good" vs. "poor" HbA_{1c}: relative VO_2 at LTP_1, **(B)** "good" vs. "poor" HbA_{1c}: relative VO_2 at LTP_2, **(C)** "good" vs. "poor" HbA_{1c}: relative VO_{2max}.

A correlation could be found between “good” HbA_{1c} and HR_{max} (n = 8, R = 0.62, p = 0.100), however without statistical significance (figure 9). At LTP_1 and LTP_2 no significant correlations could be found in either group.

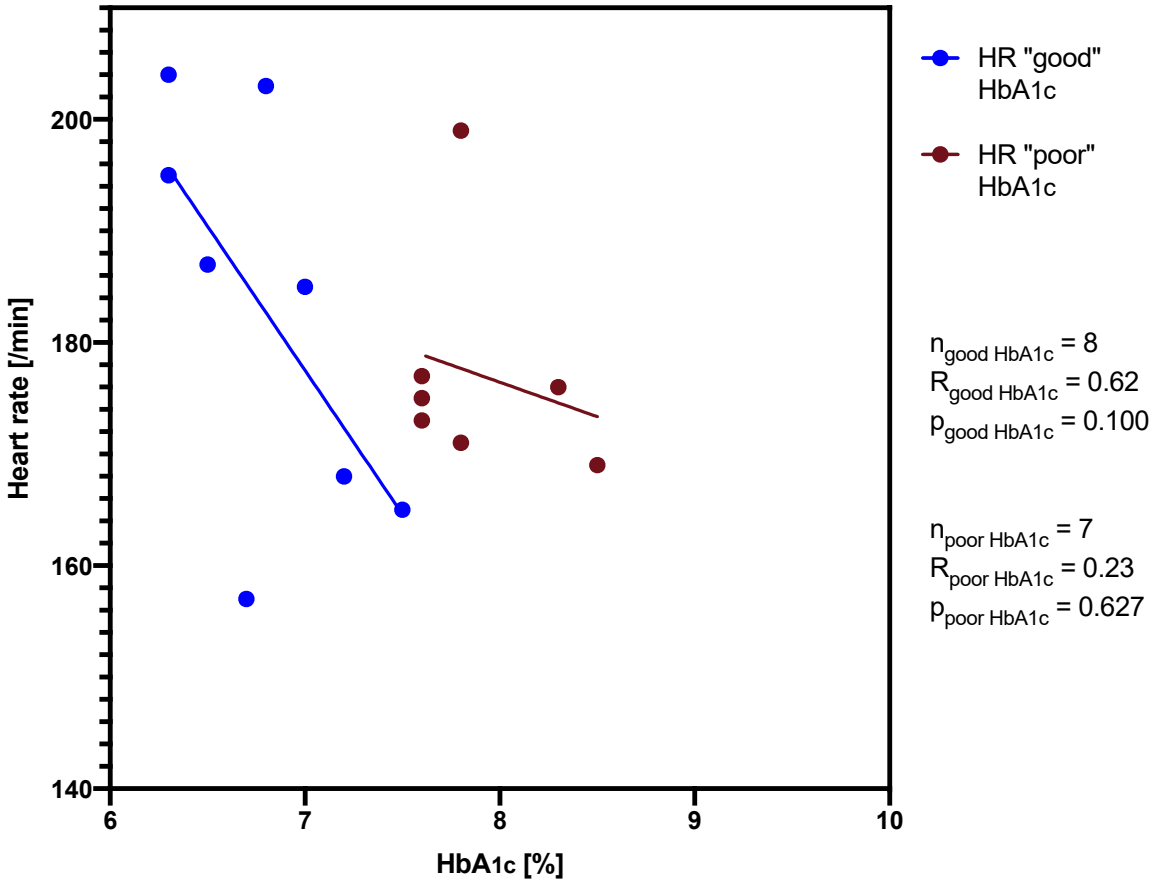

Figure 9. "Good" vs. "poor" HbA_{1c}: HR_{max}.

Furthermore, mean HR was higher in “good” HbA_{1c} compared to “poor” HbA_{1c} throughout all stages of CPX testing, though not statistically significant, as shown in table 6.

No significant correlations were found for HbA_{1c} versus age, VO_2/HR, P, VE/VO_2, VE/VCO_2, RER, VE, VT, RR, $P_{ET}O_2$ and $P_{ET}CO_2$.

3.2.2 Diabetes duration

In the following table a comparison of performance data and physiological data during CPX testing between both groups is shown:

Table 7. Values are given as mean ± SD. * represents significant difference.

	"short" diabetes duration (n = 7)	**"long" diabetes duration (n = 7)**	**p-value**
HbA_{1c} [%]	7.1 ± 0.8	7.5 ± 0.5	0.291
Absolute $VO_{2\ LTP1}$ [L/min]	1.06 ± 0.23	0.9 ± 0.18	0.409
Absolute $VO_{2\ LTP2}$ [L/min]	1.87 ± 0.65	0.97 ± 0.18	0.427
Absolute VO_{2max} [L/min]	2.94 ± 1.10	2.68 ± 0.64	0.608
Relative $VO_{2\ LTP1}$ [ml/min/kg]	14 ± 2	12 ± 3	0.209
Relative $VO_{2\ LTP2}$ [ml/min/kg]	25 ± 7	21 ± 4	0.267
Relative VO_{2max} [ml/min/kg]	39 ± 12	33 ± 5	0.287
VO_2/HR_{LTP1} [ml/b/min]	9 ± 2	10 ± 3	0.308
VO_2/HR_{LTP2} [ml/b/min]	12 ± 3	13 ± 3	0.374
VO_2/HR_{max} [ml/b/min]	15 ± 5	16 ± 4	0.759
HR_{LTP1} [/min]	118 ± 17	97 ± 15	0.036*
HR_{LTP2} [/min]	160 ± 16	131 ± 12	0.003**
HR_{max} [/min]	191 ± 13	169 ± 7	0.002**
P_{LTP1} [W]	58 ± 20	47 ± 17	0.306
P_{LTP2} [W]	141 ± 59	122 ± 25	0.429
P_{max} [W]	222 ± 96	196 ± 45	0.541
$VE/VO_{2\ LTP1}$	20.9 ± 2.3	24.1 ± 3.5	0.068
$VE/VO_{2\ LTP2}$	22.6 ± 3.4	27.4 ± 2.3	0.009**
VE/VO_{2max}	31.8 ± 5.9	40.3 ± 4.0	0.008**
$VE/VCO_{2\ LTP1}$	26.9 ± 1.9	29.1 ± 2.7	0.101
$VE/VCO_{2\ LTP2}$	24.5 ± 3.2	27.7 ± 1.7	0.035*
VE/VCO_{2max}	28.2 ± 4.7	34.9 ± 3.0	0.008**
RER_{LTP1}	0.78 ± 0.04	0.83 ± 0.04	0.048*
RER_{LTP2}	0.92 ± 0.04	0.99 ± 0.03	0.009**
RER_{max}	1.13 ± 0.08	1.15 ± 0.04	0.450
VE_{LTP1} [L/min]	24.7 ± 3.5	25.8 ± 2.7	0.736
VE_{LTP2} [L/min]	44.8 ± 12.1	50.2 ± 7.9	0.383
VE_{max} [L/min]	97.0 ± 33.0	114.7 ± 27.0	0.294
VT_{LTP1} [L]	1.5 ± 0.6	1.4 ± 0.3	0.778
VT_{LTP2} [L]	2.0 ± 0.7	2.3 ± 0.8	0.738
VT_{max} [L]	2.5 ± 0.7	2.8 ± 1.1	0.596
RR_{LTP1} [/min]	19 ± 5	20 ± 4	>0.999
RR_{LTP2} [/min]	23 ± 5	24 ± 6	0.308
RR_{max} [/min]	39 ± 7	44 ± 8	0.847
$P_{ET}O_{2\ LTP1}$ [mmHg]	93 ± 93	97 ± 6	0.193
$P_{ET}O_{2\ LTP2}$ [mmHg]	96 ± 5	102 ± 3	0.006**
$P_{ET}O_{2max}$ [mmHg]	109 ± 5	115 ± 3	0.010*

$P_{ET}CO_{2\ LTP1}$ [mmHg]	38 ± 2	37± 3	0.523
$P_{ET}CO_{2\ LTP2}$ [mmHg]	43 ± 5	38 ± 2	0.055
$P_{ET}CO_{2max}$ [mmHg]	37 ± 7	30 ± 2	0.006**

Regarding the relationship between diabetes duration and absolute VO_2 no significant correlations or differences between groups could be found.

When analyzing the relationship between diabetes duration and relative VO_2 a correlation could be found within the “short” diabetes duration group at LTP_1, though without statistical significance (n = 7, R = 0.56, p = 0.193), as displayed in figure 10. For LTP_2 and VO_{2max} no significant correlation was found in either group. Also, between-group analysis showed no significant differences (see table 7).

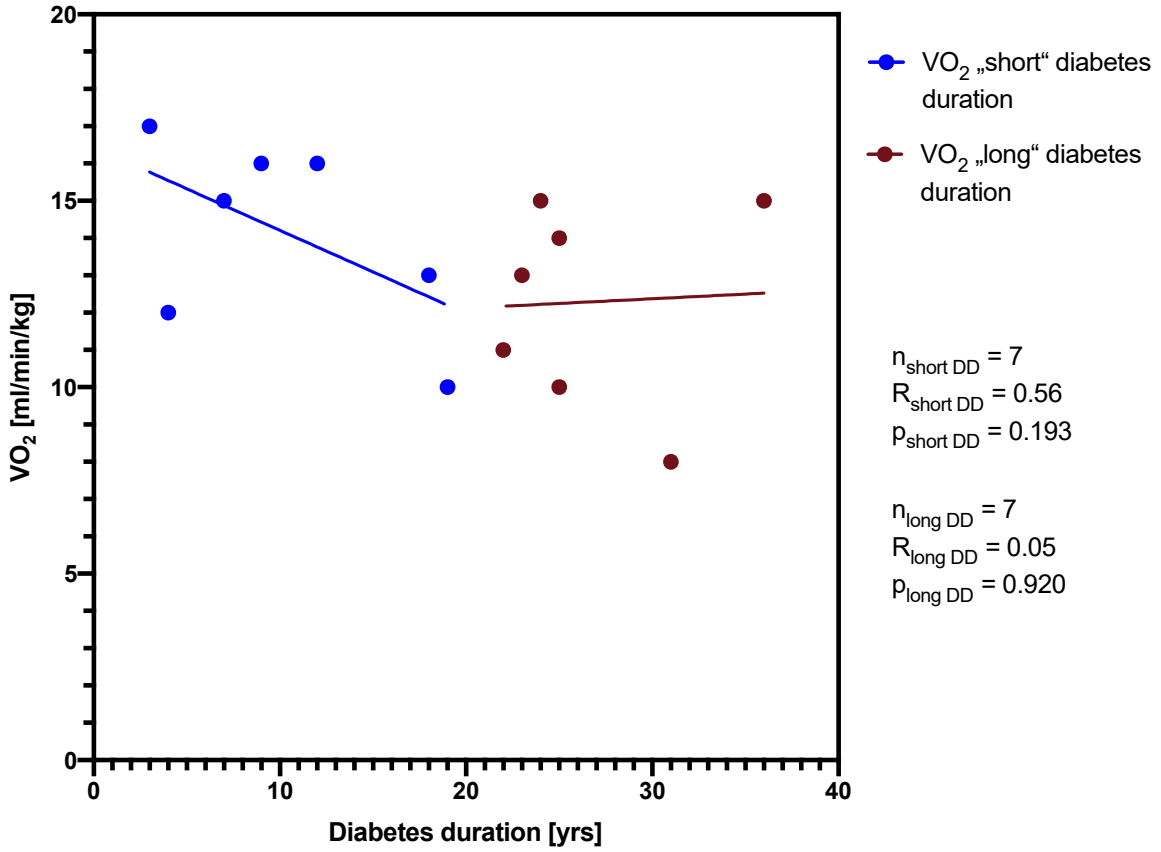

Figure 10. "Short" vs. "long" diabetes duration: relative VO_2 at LTP_1.

Correlations were also detected between “long” diabetes duration and HR at LTP_1 (n = 7, R = 0.57, p = 0.184) (see figure 11). However, no significant correlations were found for LTP_1 and maximum load.

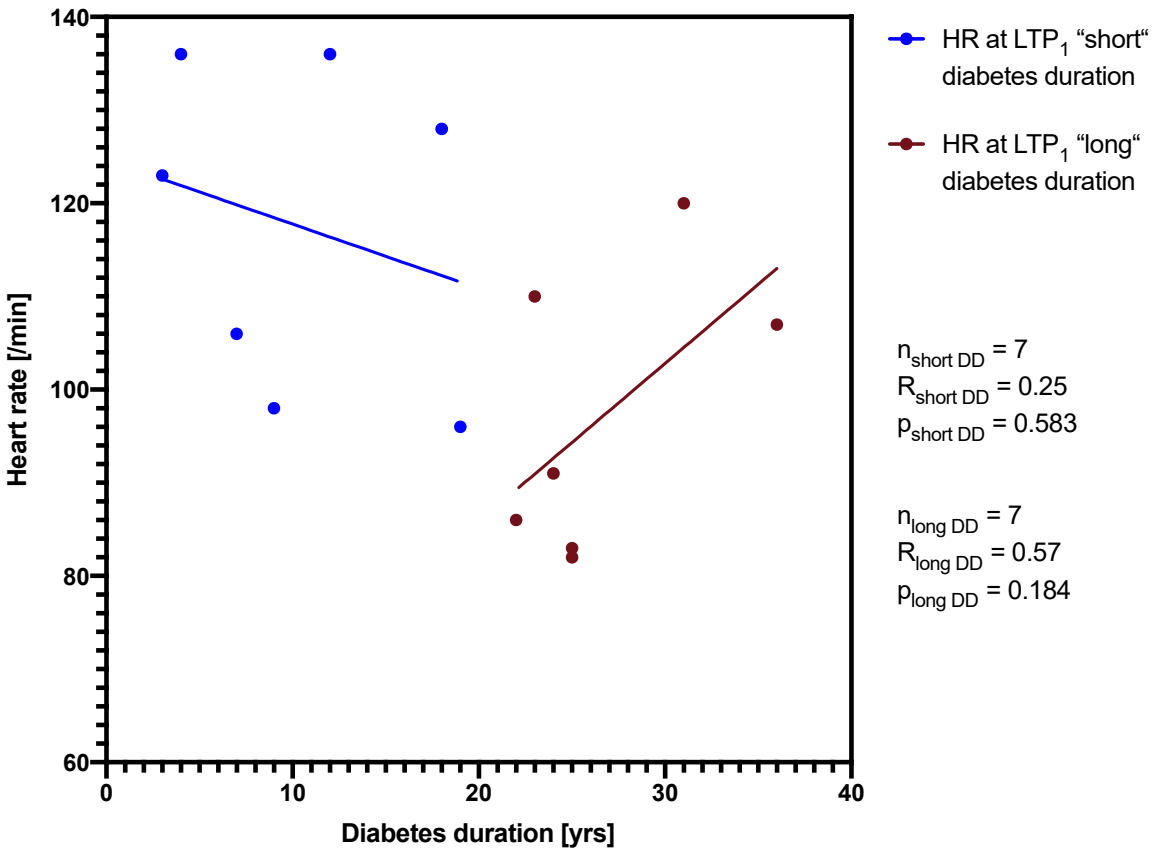

Figure 11. "Short" vs. "long" diabetes duration: HR at LTP_1.

Mean HR was higher in “short” diabetes duration compared to “long” diabetes duration throughout all stages of CPX testing with significant differences for LTP_1 ($p = 0.036^*$), LTP_2 ($p = 0.003^{**}$) and maximum exertion ($p = 0.002^{**}$), as displayed in figure 12.

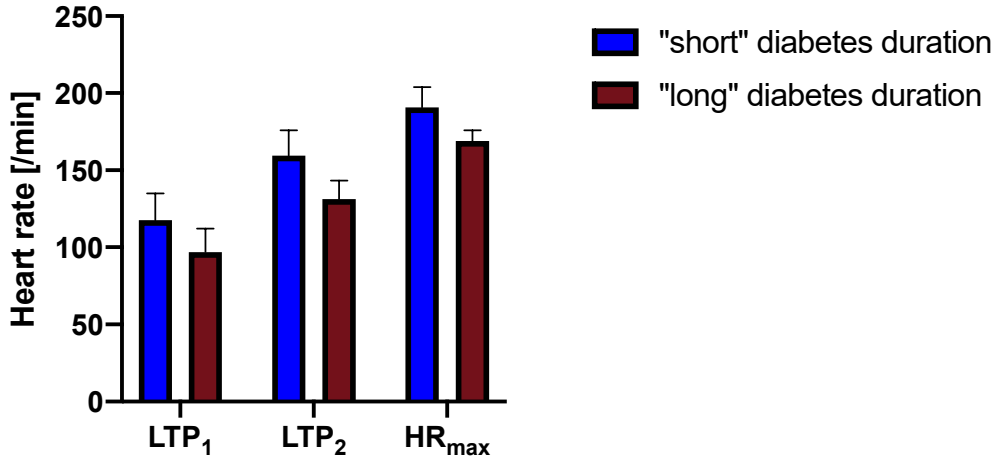

Figure 12. Comparison of mean HR between “short“ and ”long“ diabetes duration group.

Correlations were found between diabetes duration and VE/VO_2 in “short” diabetes duration at VE/VO_{2max} (n = 7, R = 0.57, p = 0.185) and in “long” diabetes duration for LTP_1 (n = 7, R = 0.70, p = 0.078), LTP_2 (n = 7, R = 0.64, p = 0.123) and maximum load (n = 7, R = 0.85, p = 0.0145*), with significance being given for the latter, as shown in figure 13.

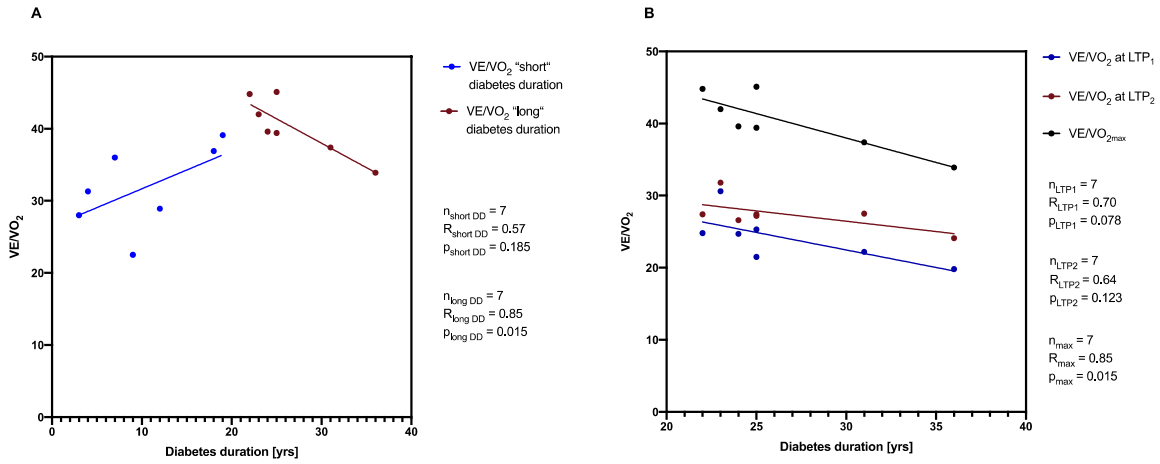

Figure 13. (A) “Short“ vs. “long“ diabetes duration: VE/VO_{2max}, **(B)** “long“ diabetes duration vs. VE/VO_2 at LTP_1, LTP_2 and maximum.

VE/VO_2 differed also significantly for LTP_2 (p = 0.009**) and maximum exertion (p = 0.008**) between the two groups, with lower mean values in “short” diabetes duration (see table 7).

“Long” diabetes duration and VE/VCO_2 correlated at LTP_1 (n = 7, R = 0.67, p = 0.010*) and maximum load (n = 7, R = 0.72 p = 0.064), with significantly higher mean values in “long” diabetes duration for LTP_2 (p = 0.035*) and maximum workload (p = 0.008**) (see figure 14).

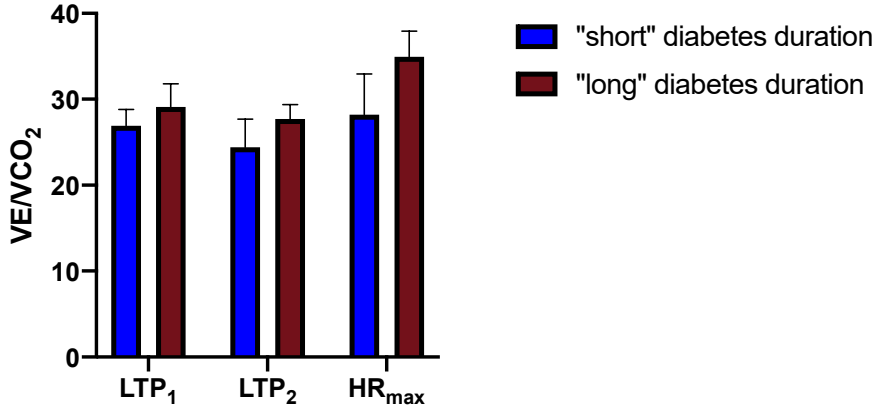

Figure 14. Comparison of mean VE/VO_2 between “short“ and “long“ diabetes duration group.

Significant correlations were found between “long” diabetes duration and RER at LTP_1 (n = 7, R = 0.79, p = 0.036*), LTP_2 (n = 7, R = 0.88, p = 0.009**) and RER_{max} (n = 7, R = 0.76, p = 0.048*). RER was also significantly lower in the “short” diabetes duration group at LTP_1 (p = 0.048*) and LTP_2 (0.009**), not at RER_{max}.

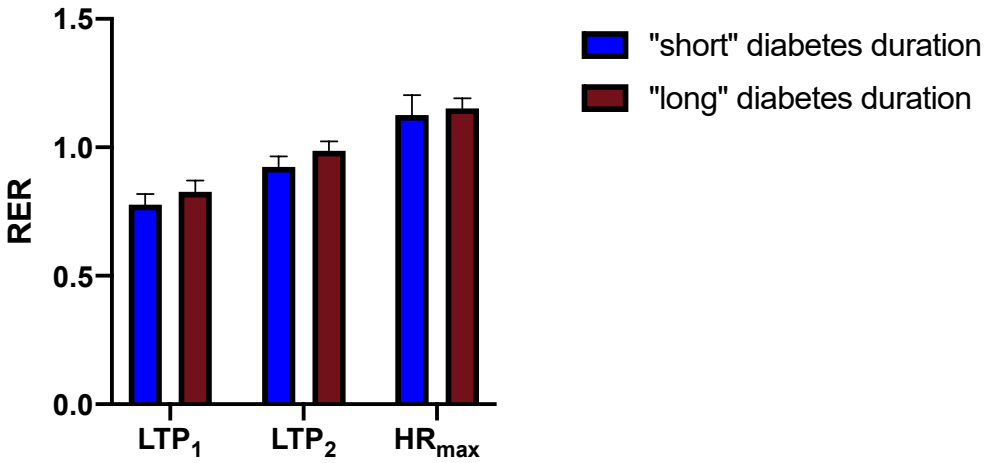

Figure 15. Comparison of mean RER between “short” and “long” diabetes duration group.

A correlation was seen between “long” diabetes duration and VE at LTP_1 (n = 7, R = 0.61 p = 0.147), with no significant differences between groups.

Correlations were also found for the following: “long” diabetes duration and $P_{ET}O_2$ at LTP_1 (n = 7, R = 0.58, p = 0.171) and $P_{ET}O_{2max}$ (n = 7, R = 0.77, p = 0.041*) with significant differences between groups at LTP_2 (p = 0.006**) and $P_{ET}O_{2max}$ (p = 0.010**) as well as “long” diabetes duration and $P_{ET}CO_2$ at maximum exertion (n = 7, R = 0.92, p = 0.003**) with significant differences between both groups at $P_{ET}CO_{2max}$ (p = 0.006**).

No significant correlations were found for diabetes duration versus VO_2/HR, P, VT and RR.

3.2.3 C-peptide

In the following table a comparison of performance data and physiological data during CPX testing between both groups is shown:

Table 8. Values are given as mean ± SD. * represents significant difference.

	C-peptide positive (n = 7)	C-peptide negative (n = 8)	p-value
C-peptide	0.23 ± 0.28	0.00 ± 0.00	0.0002***
HbA_{1c} [%]	7.2 ± 0.6	7.4 ± 0.8	0.616
Absolute $VO_{2\ LTP1}$ [L/min]	1.10 ± 0.25	0.90 ± 0.13	0.067
Absolute $VO_{2\ LTP2}$ [L/min]	1.99 ± 0.65	1.56 ± 0.19	0.095
Absolute VO_{2max} [L/min]	3.11 ± 1.09	2.46 ± 0.49	0.149
Relative $VO_{2\ LTP1}$ [ml/min/kg]	15 ± 2	12 ± 2	0.022*
Relative $VO_{2\ LTP2}$ [ml/min/kg]	26 ± 6	20 ± 3	0.018*
Relative VO_{2max} [ml/min/kg]	41 ± 10	31 ± 5	0.032*
VO_2/HR_{LTP1} [ml/b/min]	11 ± 3	8 ± 2	0.133
VO_2/HR_{LTP2} [ml/b/min]	13 ± 3	11 ± 2	0.262
VO_2/HR_{max} [ml/b/min]	16 ± 5	14 ± 3	0.295
HR_{LTP1} [/min]	105 ± 19	108 ± 19	0.706
HR_{LTP2} [/min]	151 ± 21	141 ± 141	0.359
HR_{max} [/min]	187 ± 15	174 ± 12	0.072
P_{LTP1} [W]	61 ± 21	41 ± 13	0.041*
P_{LTP2} [W]	150 ± 56	110 ± 18	0.080
P_{max} [W]	238 ± 91	177 ± 35	0.100
$VE/VO_{2\ LTP1}$	21.1 ± 2.5	24.2 ± 3.2	0.058
$VE/VO_{2\ LTP2}$	23.2 ± 3.8	27.1 ± 2.7	0.034*
$VE/VO_{2\ max}$	33.4 ± 6.9	38.8 ± 5.0	0.098
$VE/VCO_{2\ LTP1}$	27.0 ± 2.0	29.6 ± 2.9	0.069
$VE/VCO_{2\ LTP2}$	24.4 ± 24.4	27.9 ± 1.8	0.017*
VE/VCO_{2max}	28.8 ± 28.8	34.5 ± 3.3	0.020*
RER_{LTP1}	0.78 ± 0.04	0.82 ± 0.05	0.150
RER_{LTP2}	0.95 ± 0.05	0.97 ± 0.05	0.336
RER_{max}	1.16 ± 0.07	1.12 ± 0.05	0.256
VE_{LTP1} [L/min]	25.5 ± 4.2	24.5 ± 2.1	0.580
VE_{LTP2} [L/min]	48.6 ± 14.1	45.8 ± 5.0	0.608
VE_{max} [L/min]	107.4 ± 36.2	102.2 ± 24.9	0.753
VT_{LTP1} [L]	1.53 ± 0.63	1.25 ± 0.21	0.482
VT_{LTP2} [L]	2.19 ± 0.76	2.05 ± 0.74	0.719
VT_{max} [L]	2.73 ± 0.73	2.57 ± 1.00	0.645
RR_{LTP1} [/min]	18.9 ± 6	20 ± 3	0.660
RR_{LTP2} [/min]	22.8 ± 4	24 ± 6	0.566
RR_{max} [/min]	39.4 ± 8	42 ± 7	0.534
$P_{ET}O_{2\ LTP1}$ [mmHg]	92 ± 5	98 ± 5	0.026*
$P_{ET}O_{2\ LTP2}$ [mmHg]	96 ± 5	102 ± 3	0.015*
$P_{ET}O_{2max}$ [mmHg]	110 ± 6	115 ± 3	0.046*
$P_{ET}CO_{2\ LTP1}$ [mmHg]	38 ± 2	36 ± 2	0.040*
$P_{ET}CO_{2\ LTP2}$ [mmHg]	43 ± 4	38 ± 2	0.022*
$P_{ET}CO_{2max}$ [mmHg]	36 ± 7	30 ± 3	0.055

Concerning the relationship between C-peptide and absolute VO_2 no significant correlations or differences between groups could be found.

When analyzing the relationship between C-peptide and relative VO_2 no significant correlations were observed within either group, however, there were significantly higher mean relative VO_2 values at LTP_1 ($p = 0.022^*$), LTP_2 ($p = 0.018^*$) and relative VO_{2max} ($p = 0.032^*$) in the C-peptide positive group, as shown in table 8 and figure 16.

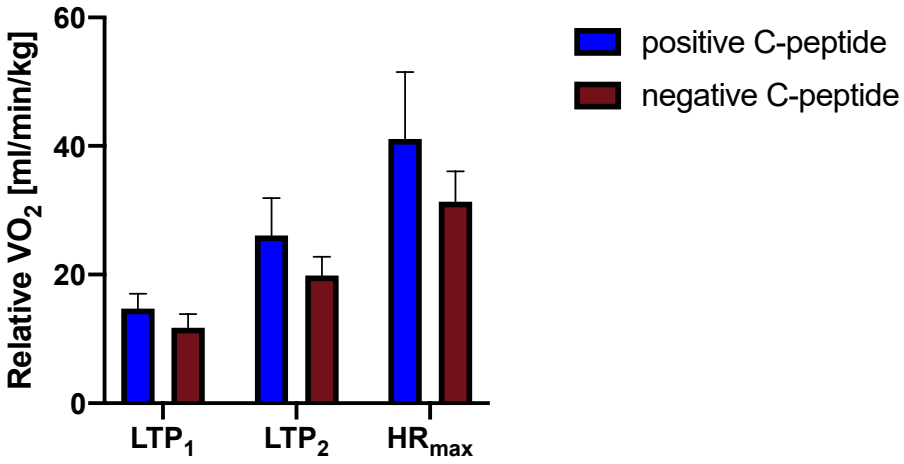

Figure 16. Comparison of mean relative VO_2 between C-peptide positive and negative group.

Correlations could be detected in positive C-peptide and HR at LTP_2 ($n = 7$, $R = 0.61$, $p = 0.147$) and HR_{max} ($n = 7$, $R = 0.57$, $p = 0.178$), though without any statistical relevance. Mean HR was slightly higher in the C-peptide positive group, also without significant differences however (see table 8).

A correlation was also found between positive C-peptide and RER at LTP_1 ($n = 7$, $R = 0.64$, $p = 0.125$), though without statistical significance.

There were also significant between-group differences for P at LTP_1, VE/VO_2 at LTP_2, VE/VCO_2 at LTP_2 and maximum exertion and $P_{ET}O_2$ at LTP_1, LTP_2 and $P_{ET}O_{2max}$, as summarized in table 8.

No significant correlations were found for C-peptide versus VO_2/HR, P, VE/VO_2, VE/VCO_2, RR, VE, VT, RR, $P_{ET}O_2$, $P_{ET}CO_2$ at LTP_1, LTP_2 and maximum exertion.

3.2.4 Age

In the following table a comparison of performance data and physiological data during CPX testing between both groups is shown:

Table 9. Values are given as mean ± SD. * represents significant difference.

	"young" (n = 8)	**"old" (n = 7)**	**p-value**
Absolute $VO_{2\ LTP1}$ [L/min]	1.05 ± 0.20	0.92 ± 0.21	0.241
Absolute $VO_{2\ LTP2}$ [L/min]	1.91 ± 0.56	1.59 ± 0.40	0.229
Absolute VO_{2max} [L/min]	3.03 ± 0.94	2.45 ± 0.72	0.410
Relative $VO_{2\ LTP1}$ [ml/min/kg]	14 ± 2	12 ± 2	0.044*
Relative $VO_{2\ LTP2}$ [ml/min/kg]	26 ± 5	20 ± 4	0.043*
Relative VO_{2max} [ml/min/kg]	41 ± 9	31 ± 6	0.030*
VO_2/HR_{LTP1} [ml/b/min]	10 ± 3	9 ± 3	0.372
VO_2/HR_{LTP2} [ml/b/min]	13 ± 3	12 ± 3	0.547
VO_2/HR_{max} [ml/b/min]	16 ± 5	14 ± 4	0.525
HR_{LTP1} [/min]	105 ± 20	105 ± 20	0.726
HR_{LTP2} [/min]	148 ± 20	137 ± 13	0.112
HR_{max} [/min]	186 ± 13	170 ± 7	0.004**
P_{LTP1} [W]	56 ± 21	45 ± 19	0.317
P_{LTP2} [W]	142 ± 44	110 ± 32	0.117
P_{max} [W]	223 ± 68	176 ± 55	0.149
$VE/VO_{2\ LTP1}$	22.1 ± 2.9	23.7 ± 3.5	0.296
$VE/VO_{2\ LTP2}$	24.5 ± 4.3	26.7 ± 2.9	0.185
VE/VO_{2max}	34.9 ± 7.6	38.3 ± 4.7	0.257
$VE/VCO_{2\ LTP1}$	28.1 ± 3.0	28.7 ± 2.7	0.680
$VE/VCO_{2\ LTP2}$	25.6 ± 3.6	27.6 ± 1.8	0.124
VE/VCO_{2max}	30.7 ± 6.1	33.6 ± 3.2	0.216
RER_{LTP1}	0.79 ± 0.04	0.82 ± 0.04	0.055
RER_{LTP2}	0.95 ± 0.05	0.96 ± 0.05	0.613
RER_{max}	1.13 ± 0.06	1.14 ± 0.06	0.978
VE_{LTP1} [L/min]	26.1 ± 2.9	24.3 ± 4.0	0.454
VE_{LTP2} [L/min]	49.0 ± 10.7	45.9 ± 11.3	0.672
VE_{max} [L/min]	108.7 ± 31.5	100.2 ± 29.6	0.609
VT_{LTP1} [L]	1.47 ± 0.61	1.33 ± 0.26	0.802
VT_{LTP2} [L]	2.20 ± 0.78	2.08 ± 0.78	0.865
VT_{max} [L]	2.75 ± 0.70	2.58 ± 1.11	0.811
RR_{LTP1} [/min]	20 ± 5	19 ± 3	0.577
RR_{LTP2} [/min]	24 ± 5	23 ± 5	0.867
RR_{max} [/min]	40 ± 7	41 ± 8	0.882
$P_{ET}O_{2\ LTP1}$ [mmHg]	94 ± 4	97 ± 6	0.205
$P_{ET}O_{2\ LTP2}$ [mmHg]	98 ± 6	101 ± 4	0.182
$P_{ET}O_{2max}$ [mmHg]	111 ± 7	114 ± 3	0.291
$P_{ET}CO_{2\ LTP1}$ [mmHg]	37 ± 2	37 ± 3	0.525
$P_{ET}CO_{2\ LTP2}$ [mmHg]	41 ± 5	38 ± 2	0.102

$P_{ET}CO_{2max}$ [mmHg]	34 ± 8	31 ± 3	0.313

Correlations could be shown between age and absolute VO_2 for the "young" group at LTP_1 (n = 8, R = 0.55, p = 0.161), LTP_2 (n = 8, R = 0.70, p = 0.051) and maximum exertion (n = 8, R = 0.66, p = 0.074), though without significance, as displayed in figure 17. No significant differences could be found between both groups for mean absolute VO_2 (see table 9).

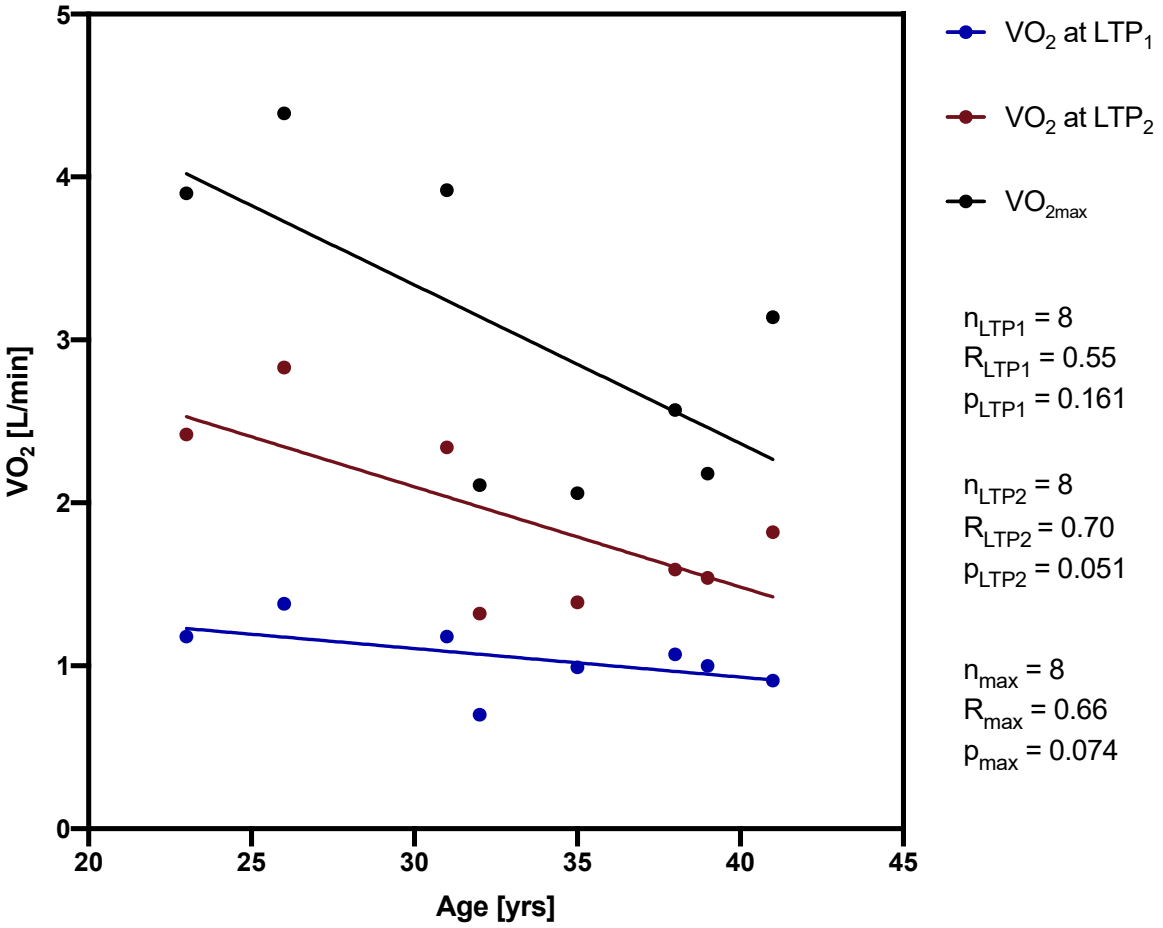

Figure 17. "Young" vs. absolute VO_2 at LTP_1, LTP_2 and maximum.

When exploring the relationship between age and relative VO_2 correlations could be found within "young" at LTP_1 (n = 8, R = 0.54, p = 0.166), LTP_2 (n = 8, R = 0.88, p = 0.004**) and relative VO_{2max} (n = 8, R = 0.84, p = 0.008**), with statistical significance for the two latter ones, as shown in figure 18. Also, when comparing the two groups, mean relative VO_2 was significantly higher in "young" than in "old" (p_{LTP1} = 0.044*, p_{LTP2} = 0.043*, p_{max} = 0.030*).

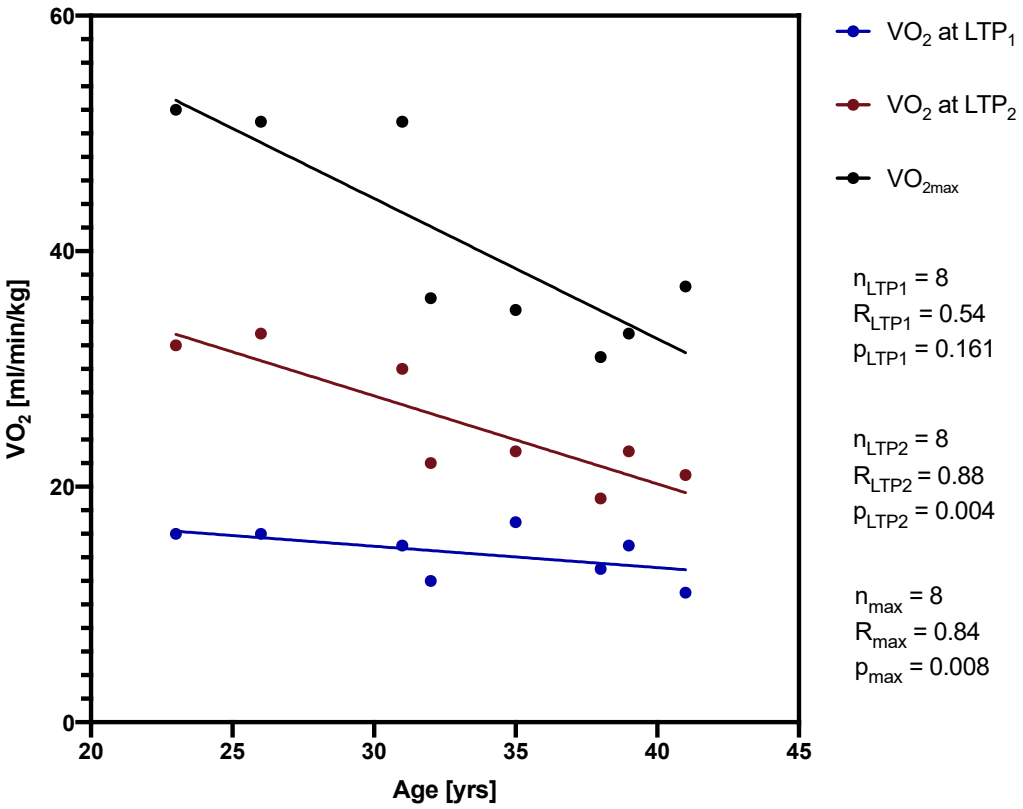

Figure 18. "Young" vs. relative VO_2 at LTP_1, LTP_2 and maximum.

Correlations could be found for "young" versus HR at LTP_2 (n = 8, R = 0.59, p = 0.122) and HR_{max} (n = 8, R = 0.70, p = 0.054) as well "old" versus HR at LTP_1 (n = 8, R = 0.72, p = 0.067) and LTP_2 (n = 8, R = 0.58, p = 0.174), as displayed in figure 19. Mean HR_{max} was also significantly higher in the "young" group (p = 0.004**).

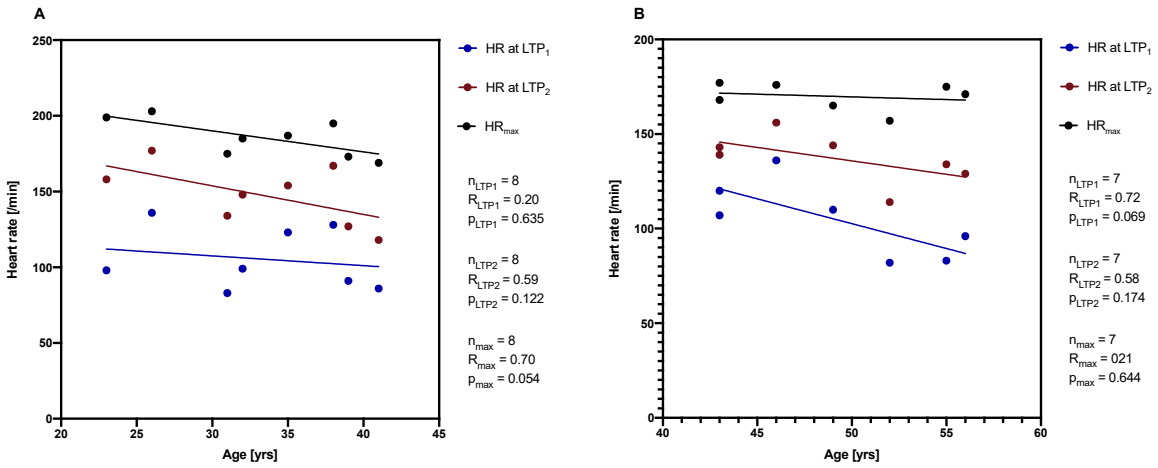

Figure 19. (A) "Young" vs. HR at LTP_1, LTP_2 and maximum, **(B)** "old" vs. HR at LTP_1, LTP_2 and maximum.

Correlations were found also for the parameters displayed in table 10.

Table 10. Linear regression results age vs. P, VE/VO_2, VE/VCO_2, RER, RR and $P_{ET}O_2$. *represents significance.

	$R_{"young"}$	$p_{"young"}$	$R_{"old"}$	$p_{"old"}$
P_{LTP2}	0.68	0.063	-	-
P_{max}	0.64	0.085		
$VE/VO_{2\ LTP1}$	-	-	0.69	0.085
$VE/VCO_{2\ LTP1}$	0.60	0.115	-	-
$VE/VCO_{2\ LTP2}$	0.70	0.051	-	-
VE/VCO_{2max}	0.78	0.022*	-	-
RER_{LTP1}	0.83	0.011*	-	-
RER_{LTP2}	0.56	0.152	-	-
RER_{max}	-	-	0.82	0.023*
RR_{max}	0.64	0.088	-	-
$P_{ET}O_{2\ LTP1}$	0.81	0.014*	-	-
$P_{ET}O_{2\ LTP2}$	0.79	0.020*	-	-
$P_{ET}O_{2max}$	0.77	0.024*	-	-

No significant correlations were found for age versus VO_2/HR, VE, VT and $P_{ET}CO_2$ at LTP_1, LTP_2 and maximum exertion.

3.2.5 BMI

In the following table a comparison of performance data and physiological data during CPX testing between both groups is shown, with no significant differences being detected:

Table 11. Values are given as mean ± SD.

	"good" BMI (n = 8)	**"poor" BMI (n = 7)**	**p-value**
Absolute $VO_{2\ LTP1}$ [L/min]	0.94 ± 0.25	1.05 ± 0.14	0.306
Absolute $VO_{2\ LTP2}$ [L/min]	1.68 ± 0.61	1.85 ± 0.35	0.189
Absolute VO_{2max} [L/min]	2.56 ± 1.00	2.99 ± 0.68	0.232
VO_2/HR_{LTP1} [ml/b/min]	9 ± 2	10 ± 3	0.525

VO_2/HR_{LTP2} [ml/b/min]	11 ± 3	13 ± 3	0.444
VO_2/HR_{max} [ml/b/min]	14 ± 4	17 ± 4	0.240
HR_{LTP1} [/min]	104 ± 18	109 ± 20	0.613
HR_{LTP2} [/min]	144 ± 20	148 ± 20	0.727
HR_{max} [/min]	180 ± 16	181 ± 14	0.943
P_{LTP1} [W]	47 ± 21	55 ± 19	0.465
P_{LTP2} [W]	121 ± 51	138 ± 36	0.242
P_{max} [W]	190 ± 76	224 ± 68	0.198
$VE/VO_{2\ LTP1}$	23.4 ± 4.2	21.9 ± 1.7	0.397
$VE/VO_{2\ LTP2}$	24.9 ± 4.9	25.7 ± 2.0	0.803
VE/VO_{2max}	35.6 ± 8.0	37.1 ± 4.3	0.652
$VE/VCO_{2\ LTP1}$	29.0 ± 3.7	27.7 ± 1.2	0.359
$VE/VCO_{2\ LTP2}$	25.9 ± 3.9	26.8 ± 1.6	0.574
VE/VCO_{2max}	31.0 ± 6.4	32.8 ± 3.0	0.514
RER_{LTP1}	0.80 ± 0.06	0.79 ± 0.04	0.454
RER_{LTP2}	0.96 ± 0.06	0.96 ± 0.04	0.778
RER_{max}	1.14 ± 0.06	1.13 ± 0.06	0.649
VE_{LTP1} [L/min]	24.2 ± 3.6	25.9 ± 2.7	0.333
VE_{LTP2} [L/min]	43.3 ± 9.2	51.5 ± 9.5	0.116
VE_{max} [L/min]	92.3 ± 22.4	118.8 ± 32.1	0.083
VT_{LTP1} [L]	1.37 ± 0.61	1.39 ± 0.25	0.346
VT_{LTP2} [L]	1.93 ± 0.61	2.32 ± 0.84	0.717
VT_{max} [L]	2.42 ± 0.59	2.89 ± 1.09	0.301
RR_{LTP1} [/min]	20 ± 5	19 ± 3	0.748
RR_{LTP2} [/min]	23 ± 4	24 ± 6	0.737
RR_{max} [/min]	39 ± 8	43 ± 8	0.265
$P_{ET}O_{2\ LTP1}$ [mmHg]	97 ± 6	94 ± 5	0.354
$P_{ET}O_{2\ LTP2}$ [mmHg]	99 ± 7	100 ± 2	0.933
$P_{ET}O_{2max}$ [mmHg]	112 ± 7	113 ± 3	0.927
$P_{ET}CO_{2\ LTP1}$ [mmHg]	36 ± 3	38 ± 2	0.394
$P_{ET}CO_{2\ LTP2}$ [mmHg]	41 ± 5	40 ± 2	0.555
$P_{ET}CO_{2max}$ [mmHg]	34 ± 8	31 ± 2	0.716

When analyzing the correlations between BMI and absolute VO_2, no significant results were found within both groups. Also mean absolute VO_2 showed no significant between-group differences (see table 11).

A correlation could be observed between “poor” BMI and HR at LTP_1 (n = 7, R = 0.68, p = 0.090). However, no significant differences were found for HR between the two groups.

Correlations were also found for the following parameters, though without significance:

Table 12. Linear regression results: BMI vs. P, VT, RR and $P_{ET}CO_2$.

	$R_{"good" BMI}$	$p_{"good" BMI}$	$R_{"poor" BMI}$	$p_{"poor" BMI}$
P_{LTP1}	-	-	0.63	0.130
P_{LTP2}	-	-	0.59	0.163
VT_{max}	0.59	0.122	-	-
RR_{max}	-	-	0.70	0.081
$P_{ET}CO2_{LTP1}$	0.62	0.104	0.56	0.912

No significant correlations were found for BMI versus VO_2/HR, VE/VO_2, VE/VCO_2, RER, VE and $P_{ET}CO_2$ at LTP_1, LTP_2 and maximum exertion.

3.2.6 Sex

In the following table a comparison of performance data and physiological data during CPX testing stratified by sex is shown:

Table 13. Values are given as mean ± SD. * represents significant difference.

	female (n = 7)	male (n = 8)	p-value
Age [years]	43.7 ± 7.3	37.9 ± 11.8	0.278
Absolute $VO_{2\,LTP1}$ [L/min]	0.91 ± 0.16	1.06 ± 0.24	0.447
Absolute $VO_{2\,LTP2}$ [L/min]	1.43 ± 0.20	2.04 ± 0.51	0.011*
Absolute VO_{2max} [L/min]	2.12 ± 0.31	3.32 ± 0.80	0.003**
Relative $VO_{2\,LTP1}$ [ml/min/kg]	13 ± 2	13 ± 3	0.564
Relative $VO_{2\,LTP2}$ [ml/min/kg]	21 ± 3	25 ± 7	0.202
Relative VO_{2max} [ml/min/kg]	31 ± 4	40 ± 10	0.052
VO_2/HR_{LTP1} [ml/b/min]	8 ± 1	11 ± 3	0.041*
VO_2/HR_{LTP2} [ml/b/min]	10 ± 2	14 ± 3	0.004**
VO_2/HR_{max} [ml/b/min]	12 ± 2	18 ± 3	0.001**
HR_{LTP1} [/min]	113 ± 17	101 ± 19	0.229
HR_{LTP2} [/min]	145 ± 15	146 ± 24	0.936
HR_{max} [/min]	176 ± 11	184 ± 17	0.358
P_{LTP1} [W]	45 ± 12	56 ± 24	0.305
P_{LTP2} [W]	101 ± 19	153 ± 46	0.016*
P_{max} [W]	156 ± 29	249 ± 70	0.006**
$VE/VO_{2\,LTP1}$	23.6 ± 3.5	22.0 ± 3.1	0.350
$VE/VO_{2\,LTP2}$	25.7 ± 3.4	24.9 ± 4.2	0.671
VE/VO_{2max}	35.8 ± 5.0	36.7 ± 7.7	0.813
$VE/VCO_{2\,LTP1}$	28.8 ± 2.6	28.0 ± 3.1	0.629
$VE/VCO_{2\,LTP2}$	26.9 ± 2.1	25.8 ± 3.7	0.477

VE/VCO_{2max}	31.7 ± 3.1	32.0 ± 6.5	0.920
RER_{LTP1}	0.82 ± 0.05	0.78 ± 0.04	0.376
RER_{LTP2}	0.95 ± 0.06	0.96 ± 0.04	0.343
RER_{max}	1.13 ± 0.07	1.15 ± 0.05	0.435
VE_{LTP1} [L/min]	24.3 ± 3.6	25.6 ± 2.9	0.454
VE_{LTP2} [L/min]	40.5 ± 6.9	52.9 ± 8.7	0.010*
VE_{max} [L/min]	81.9 ± 14.3	124.5 ± 24.8	0.002**
VT_{LTP1} [L]	1.15 ± 0.04	1.58 ± 0.57	0.017*
VT_{LTP2} [L]	1.51 ± 0.10	2.64 ± 0.61	0.0003***
VT_{max} [L]	1.95 ± 0.29	3.25 ± 0.71	0.0005***
RR_{LTP1} [/min]	21 ± 3	18 ± 5	0.170
RR_{LTP2} [/min]	27 ± 5	21 ± 3	0.007**
RR_{max} [/min]	43 ± 8	39 ± 7	0.387
$P_{ET}O_{2\ LTP1}$ [mmHg]	98 ± 5	93 ± 5	0.171
$P_{ET}O_{2\ LTP2}$ [mmHg]	100 ± 4	98 ± 6	0.453
$P_{ET}O_{2max}$ [mmHg]	113 ± 3	112 ± 7	0.916
$P_{ET}CO_{2\ LTP1}$ [mmHg]	36 ± 2	38 ± 2	0.394
$P_{ET}CO_{2\ LTP2}$ [mmHg]	39 ± 3	41 ± 5	0.334
$P_{ET}CO_{2max}$ [mmHg]	33 ± 3	33 ± 8	0.479

When analyzing sex and absolute VO_2, significantly higher mean absolute VO_2 values were found in males at LTP_2 ($p = 0.011^*$) and maximum exertion ($p = 0.003^{**}$), as displayed in figure 20. There were no significant differences for relative VO_2 between both groups.

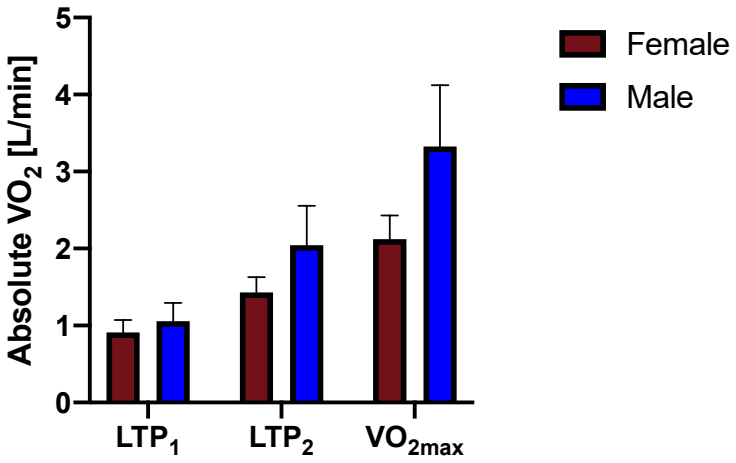

Figure 20. Comparison of mean absolute VO_2 between females and males.

Significantly higher mean values were found for oxygen pulse in males at LTP_1 ($p = 0.041^*$), LTP_2 ($p = 0.004^{**}$) and maximum oxygen pulse ($p = 0.001^{**}$) (see figure 21).

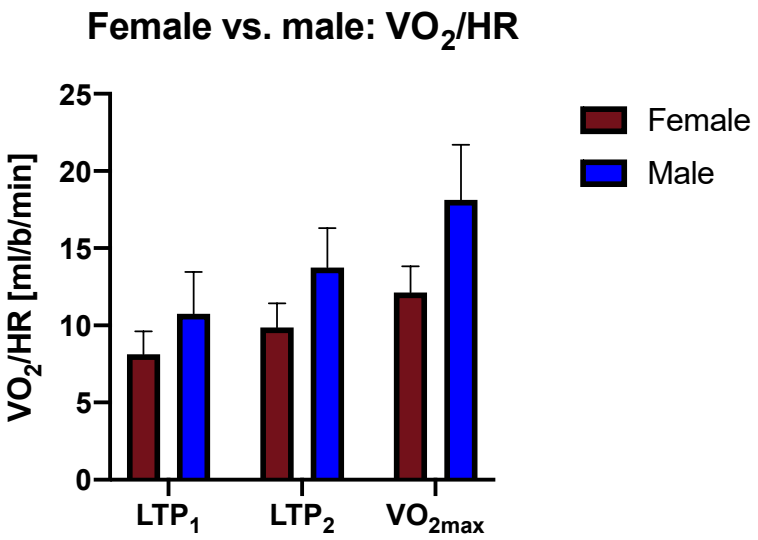

Figure 21. Comparison of VO_2/HR between females and males.

There were also significantly higher values in males for P_{LTP2} and P_{max}, VE_{LTP2} and VE_{max} as well as VT at all stages and RR at LTP_2, as summarized in table 13.

4 Discussion

The aim of this thesis was to assess the influence of diabetes-specific markers, anthropometric and demographic data on functional capacity and other cardiorespiratory parameters in people with T1D.

Regarding the primary outcome of this thesis – the relationship between HbA_{1c} and VO_{2max} – no significant correlations could be found, neither for absolute nor relative VO_2. Also, between-group comparisons for mean absolute and relative VO_2 values showed no significant differences.

These findings are in concordance with previous work by Turinese et al. (1), Stubbe et al. (4), Peltonen et al. (9) and Nadeau et al. (15), in which no significant correlations could be found between HbA_{1C} and aerobic capacity. However, they disagree with a study by Baldi et al., in which peak exercise performance was the same in highly endurance-trained ironman triathletes with and without diabetes with the same training volume in both groups – however, when subdivided into a low-HbA_{1C} and a high-HbA_{1C} group, VO_{2peak} was lower in the poorly controlled group (7). They are also partially contrary to findings by Tagougiu et al., in which lower VO_{2max} in individuals with poorly controlled T1D compared to their healthy counterparts was demonstrated, while there was no difference observed between subjects with good glycemic control and their counterparts without diabetes (20). Similarly, Gusso et al. inversely associated HbA_{1C} with VO_{2peak} (10). Also Moser et al. correlated higher HbA_{1C} levels with higher rates of O_2 use at sub-maximal work rates, indicating reduced exercise economy (3).

Possible explanations for the results observed in this thesis might be that both “good” as well as “poor” HbA_{1c} group showed rather low HbA_{1c} levels in terms of their primary disease. Furthermore, physically active people with T1D might show higher HbA_{1c} levels because of insulin dose reduction and greater carbohydrate ingestion prior to, during and after physical activity due to fear of hypoglycemia and nonetheless reach higher VO_2. Kennedy et al. for example could not find evidence for exercise-induced lower HbA_{1c} levels in a systemic review and meta-analysis (74). Also, some studies have shown that intense aerobic training had no effect on HbA_{1C} but instead significant rises in VO_{2max} (13,75). Niranjan et al. (13)

found that VO_{2max} was higher in untrained individuals with T1D with chronic normoglycemia than in their hyperglycemic counterparts, suggesting that inadequate glycemic control reduces aerobic capacity but that training has little or no effect on HbA_{1C} in individuals with T1D (6), while others have demonstrated that more than 150 minutes of intense physical activity per week does significantly lower HbA_{1c} (76).
However, contrary to most studies conducted on this topic, this thesis assessed functional capacity only within diabetic people and did not compare them to healthy individuals.

Diabetes duration did not seem to have a significant influence on absolute and relative VO_2, which might be explainable by a greater importance of long-term glycemic control rather than diabetes duration itself.
In terms of the observed significantly higher mean relative VO_2 values at LTP_1, LTP_2 and maximum exertion in the C-peptide positive group, one might suggest that higher rest C-peptide levels could lead to somewhat better glycemic control than in people with no pancreatic rest function and might therefore benefit HbA_{1c} and possibly functional capacity. However, no significant differences were seen in HbA_{1c} levels between and C-peptide positive and negative groups. Furthermore, beta cell responsiveness to hyperglycemia with benefits for glycemic control might occur only at high levels of residual C-peptide above 0.4 pmol/ml, as indicated in one study found in adults with T1D (26).
The weak correlations found between age and absolute VO_2 at LTP_1, LTP_2 and maximum exertion for „young“ participants as well as the weak to strong correlations between “young” and relative VO_2 at LTP_1, LTP_2 and maximum exertion plus the respective significant differences between the two groups for relative VO_2 with higher values in “young” people were to be expected since it is well established that VO_2 decreases with age (30,33–35).
BMI did not seem to play a major role in absolute VO_2. However, BMI might not be a representative determinant in physically active people with a high lean body mass, as people with higher and supposedly worse BMI might actually have more muscle strength und therefore better functional capacity.

Surprisingly, no significant differences were found between sex and relative VO_2, even though aerobic capacity is usually 10-20% greater in men than in women regardless of age (30).

Regarding potential influencing factors on HR in people with T1D, a weak correlation could be found between "good" HbA_{1c} and HR_{max}. Also mean HR was higher in "good" HbA_{1c} compared to "poor" HbA_{1c} throughout all stages of CPX testing, though none of these showed statistical significance. T1D has been linked to β_1-adrenoceptor insensitivity due to chronically elevated HbA_{1C} and associated elevated catecholamine levels as well as inflammatory processes and therefore lower maximum heart rates, as thoroughly explained in the introduction part (41,46,48–52). However, as mentioned earlier, HbA_{1c} was not exceedingly high in either group, which might explain the non-significance.
Mean HR was significantly higher in the "short" diabetes duration group compared to the "long" diabetes duration group throughout all stages of CPX testing, which might be attributable to the same reasons mentioned above, with longer diabetes duration potentially leading to more β_1-adrenoceptor insensitivity and therefore chronotropic incompetence.
C-peptide, BMI and sex did not seem to have a significant influence on HR, while age did show correlations between "young" and HR at LTP_2 and HR_{max} as well as "old" and HR at LTP_1. Also mean HR_{max} was significantly higher in the "young" group. These findings were to be expected since it is well established that maximum HR decreases with age (77,78).

Concerning the influence of T1D on VE/VO_2, weak correlations were found for diabetes duration in the "short" diabetes duration group at VE/VO_{2max} and weak to strong correlations were detected in the "long" diabetes duration group for LTP_1, with significance for LTP_2 and maximum load. There were also significantly lower mean VE/VO_2 values for LTP_2 and maximum exertion in the "short" diabetes duration group. All of the data might indicate more efficient ventilation in subjects with shorter lasting diabetes.
Concordantly with the results regarding VE/VO_2, there were rather strong correlations between the "long" diabetes duration group and VE/VCO_2 for LTP_1 and maximum exertion, with significantly higher mean VE/VCO_2 values for „long"

diabetes duration at LTP_2 and maximum. Maximum VE/VCO_2 also exceeded the threshold of 30, which is considered normal in the general population, suggesting less efficient ventilation in subjects with long lasting diabetes (54).
Furthermore, C-peptide might play a role in ventilatory efficiency since VE/VO_2 at LTP_2 and VE/VCO_2 at LTP_2 and maximum exertion were significantly higher in the C-peptide positive group.
However, it is not clear whether the above-mentioned factors actually and independently influence ventilatory parameters.

The strong and significant correlations found between “long” diabetes duration and RER at LTP_1, LTP_2 and RER_{max} in combination with the significantly lower mean RER values in the “short” diabetes duration versus the “long” diabetes duration group at LTP_1 and LTP_2 might suggest that individuals with shorter diabetes duration utilize fats to a greater extent as an energy source under physical activity than individuals with longer diabetes duration. This might be due to better physical shape in subjects with shorter diabetes duration or higher blood insulin levels, which may impair the glycolytic response in patients with T1D, as explained in the introduction part (1,12,62,63). However, this potential causality is questionable since the observed results may not be due to diabetes duration per se but determined by individual training status.

A strong and significant correlation could be found between “long” diabetes duration and $P_{ET}CO_2$ at maximum exertion with surprisingly significantly lower $P_{ET}CO_{2max}$ values in the “short” diabetes duration group, possibly indicating lower ventilatory capacity in the “short” than in the “long” diabetes duration group.
Mean $P_{ET}CO_2$ was significantly higher in the C-peptide positive group than in the C-peptide negative group at LTP_1 and LTP_2, which might suggest better ventilatory capacity in subjects with higher C-peptide levels.
However, as before, causality between these parameters is questionable since these findings might not be associated with diabetes duration or C-peptide per se but with other factors.

Lastly, significant between-group differences were found for sex with higher values in males regarding stroke volume (VO_2/HR) at all stages, for P at LTP_2 and P_{max} as

well as ventilatory measurements (VE at LTP_2 and maximum exertion, VT at all stages of CPX testing). This is not surprising since sex-related differences in cardiovascular and cardiorespiratory parameters and thus cardiorespiratory fitness have been well investigated (30,33–35).

Other minor, statistically significant or insignificant results of the between-group analyses as well as correlations of the linear regressions are displayed in the results section of this thesis; however, they are not further discussed within this part since they seemed to play an inconsequential role in the interpretation of the results.

Possible limitations to the observed results are that the 15 participants included represented a rather small and homogenous population of physically active individuals with an overall healthy lifestyle, without major concomitant illnesses or medication apart from insulin treatment, so that some findings in this thesis might show statistical insignificance despite potential underlying causality. Furthermore, due to the participants' homogenous characteristics, the observed results might not be representative for the majority of people with T1D, since physical inactivity remains high within the T1D population, as explained in the introduction part (3,71,72).

5 Conclusions

According to the existing literature and the results of this very thesis it is still not entirely clear whether HbA_{1c} per se is an independent determinant of functional capacity in terms of VO_2 in people with T1D and if physical activity itself lowers HbA_{1c}, therefore further research with potentially greater sample sizes needs to be conducted.

Further analysis should also be carried out regarding the other diabetes-specific markers investigated, as none of them provided very clear directions as to their possible influence on functional capacity.

There was stronger indication that maximum heart rate is higher in individuals with lower HbA_{1c} and shorter diabetes duration, though not all of them showed statistical significance. These results are in line with other studies that confirmed altered heart rate dynamics in people with T1D (41,46,48–52), as explained in the introduction.

Within the framework of this thesis it has also been suggested that diabetes-specific markers might play a role in ventilatory sufficiency. However, it is not evident if these factors independently influence ventilatory parameters, which is why further investigation should be encouraged.

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