Differences in physiological responses to cardio-pulmonary exercise testing in adults with type 1 diabetes and healthy individuals – a pooled analysis

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OBJECTIVE

To investigate physiological responses to cardio-pulmonary exercise testing in adults with recent-onset type 1 diabetes compared to age, sex and BMI-matched healthy controls.

RESEARCH DESIGN AND METHODS

In this pooled analysis we compared cardio-pulmonary exercise (CPX) tests on a cycle ergometer in individuals with type 1 diabetes and healthy controls matched for age, body mass index (BMI) and sex. Main outcome parameters were peak and threshold variables of oxygen uptake, heart rate and power output. Differences between groups were investigated via restricted maximum likelihood modelling and post-hoc tests. Main differences between groups were explained by stepwise linear regression modelling ($p<0.05$).

RESULTS

Among 303 individuals with type 1 diabetes, peak oxygen uptake (32.55 [26.49; 38.72] vs. 42.67 ± 10.44) (mL/kg/min), peak heart rate (179 [170; 187] vs. 184 [175; 191]) (bpm) and peak power (216 [171; 253] vs. 245 [200; 300]) (Watt) were lower in comparison to 308 healthy individuals (all $p<0.0001$). Furthermore, power output at the anaerobic threshold was decreased in individuals with type 1 diabetes compared to healthy individuals ($p<0.0001$). Stepwise linear regression modelling showed that none of exercise physiological responses to CPX testing were associated with HbA_{1c} in individuals with type 1 diabetes.

CONCLUSIONS

Individuals with recent-onset type 1 diabetes have altered physiological response to CPX testing when compared to healthy individuals, which cannot be explained by HbA_{1c}.

INTRODUCTION

Type 1 Diabetes (T1D) is an autoimmune disease characterized by a destruction of pancreatic beta cells, resulting in hypoinsulinemia with subsequent hyperglycemia and diabetic ketoacidosis (1). People with T1D can feature cardiac autonomic neuropathy (2) and cardiomyopathy (3), already soon after diagnosis. However, neither the etiology nor the mechanisms behind the occurrence of these cardiac diseases are yet fully understood in individuals with T1D.

Although the *Diabetes Control and Complications Trial* (DCCT) and the *Epidemiology of Diabetes Interventions and Complications* (EDIC) trial provided compelling evidence that a glycated hemoglobin (HbA_{1c}) of ≤7% (53 mmol/mol) reduces the risk of cardiovascular diseases (4,5), it is unclear if T1D *per se*, independent of specific diabetes– and anthropometric characteristics alters cardiovascular function in such way that functional capacity during progressive exercise to exhaustion is impaired.

Cardio-pulmonary exercise (CPX) testing may offer insights into the origin and complexity of acute cardio-vascular and respiratory impairments, since it provides information about the course of cardio-pulmonary and circulatory responses to physical stress (6). This functional assessment has often been advocated as initial non-invasive choice in testing for cardiovascular disease due to its high sensitivity, cost-effectiveness and widespread availability (7). Additionally, CPX testing provides information about general health status of individuals, as peak oxygen consumption expressed relative to body mass (VO_{2peak}, [$mL.kg.min^{-1}$]) is associated with morbidity status and mortality risk in healthy and individuals with chronic conditions (8–10). Furthermore, submaximal aerobic and anaerobic markers of performance derived from CPX testing serve as a tool to accurately prescribe exercise intensity in both healthy individuals and those with T1D (11–13).

As studies have shown that regular physical activity and exercise are associated with reduced risk of mortality (14), retinopathy, hypertension and dyslipidemia (15), the question arises if subclinical alterations of cardiac-pulmonary function can already be detected during CPX testing. Individuals with T1D showed decreased peak oxygen uptake (16) and lower oxygen economy at submaximal metabolic thresholds when compared to healthy individuals (17). Also, previous research investigating cardiac responses to CPX testing showed that individuals with T1D had linear heart rate dynamics with increasing exercise intensity, which is contrary to healthy individuals (17). This may propose that independent of T1D *per se*, specific diabetes characteristics such as elevated HbA_{1c} levels, diabetes duration, low c-peptide levels and high doses of total daily insulin might be detrimental for functional capacity. Yet, most of the aforementioned studies were limited by their sample size and/or a missing or not accurately matched healthy control group.

Consequently, a comprehensive assessment of the impact of T1D and its associated specific diabetes characteristics on functional capacity is missing. In particular in recent-onset T1D, it is hypothesized that the impact of T1D on alterations to functional and physiological capacity might be low, due to lower incidences of micro- and macrovascular complications in this cohort (18). Therefore, the aim of this study was to investigate acute physiological responses to CPX testing in individuals with T1D when compared to matched healthy controls. Furthermore, we sought to investigate if submaximal and peak responses to CPX testing are associated with HbA_{1c} and other diabetes characteristics.

RESEARCH DESIGN AND METHODS

This study was performed as a prospective pooled analysis, in which data from CPX testing until maximal exhaustion were assessed in individuals with T1D and matched healthy controls. After contacting other researchers, data from research institutions across Europe, North America and South America were included (Supplemental Material Fig. S1). The study protocol was approved by the ethics committee of the Medical University of Graz (32-381 ex 19/20) and registered at the German Clinical Trials Register (drks.de; DRKS00022106). Furthermore, the study was conducted in full conformity with the 1964 declaration of Helsinki and all subsequent revisions, as well as in accordance with the guidelines provided by the International Conference on Harmonization for Good Clinical Practice (ICH GCP E6 guidelines).

Study Population

All participants received a medical examination prior to each CPX assessment. Eligibility criteria were defined as follows: clinical diagnosis of T1D according to country specific guidelines, age 18 to 65 years (both inclusive) at the time of CPX testing and availability of age and body mass index (BMI). Additionally, HbA_{1c}, diabetes duration and total daily insulin dose were included. C-peptide levels were included if available. Individuals with T1D and healthy controls were matched 1:1 for age, body mass index (BMI) and sex. No specific health parameters were obtained from the healthy controls except body weight and BMI.

Assessment of CPX data

Prior to the start of the analysis, CPX testing data were screened for eligibility. All CPX tests were conducted on cycle ergometers. Main eligibility criteria were the provision of the CPX testing protocol (wattage increase/time), heart rate (HR; bpm), absolute oxygen consumption (VO_2; L/min), absolute carbon dioxide production (VCO_2; L/min), ventilation (VE; L/min) and power output (W) throughout the entire CPX measurement. Pulmonary gas-exchange variables were provided in the form of breath-by-breath measurement, averaged over 5- or 10 seconds. Heart rate variables were measured via chest belt telemetry or electrocardiography (ECG) and were provided in 5 or 10 seconds averages. Data were excluded if submaximal ventilatory thresholds or peak values were not reached or not detectable due to low data quality, as assessed by a certified exercise physiologist.

Following the assessment of eligibility and quality, data were randomized by a statistician. The pre-exercise resting period, submaximal aerobic ventilatory threshold 1 (VT_1), anaerobic ventilatory threshold 2 (VT_2) and peak performance were determined by one researcher. Pre-CPX testing resting values were considered as the last 30 seconds on the cycle ergometer prior to the start of CPX testing. The VT_1 was defined as the first increase in VE accompanied by an increase in VE/VO_2 without an increase in VE/VCO_2. The VT_2 was defined as the second abrupt increase in VE accompanied by an increase in both VE/VO_2 and VE/VCO_2 (13).

All research groups terminated CPX testing if participants reached volitional maximal exhaustion. Contrary to guidelines by the *American College of Sports Medicine (ACSM)* for the general population, reaching a plateau in VO_2 was not a criterion for peak performance in our analysis, since patients as well as exercise inexperienced healthy individuals often do not achieve a plateau in oxygen uptake during maximum CPX testing, particularly with cycling exercise (19). Therefore, volitional exhaustion

was defined as the point when the HR failed to rise with increasing exercise intensity ≥85% age-predicted HR_{peak} and reaching a respiratory exchange ratio (RER) of ≥ 1.10. Peak values were calculated as the mean value over the last 30 seconds prior to termination of the CPX test (19). If these criteria were not met, data was excluded from the analysis.

Additionally, the degree and direction of the deflection (k_{HR}) of the HR to performance curve was calculated by a second-degree polynomial function between VT_1 and the maximum power output (20,21). With this function two slopes of two tangents were calculated between VT_1 and maximum power output by applying the formula of factor *k* ($k= (k_1-k_2)/(1+k_1*k_2)$). *k*-values were classified as linear deflection ($-0.1 \leq k \leq 0.1$), downward deflection ($k > 0.1$) (regular) and upward deflection ($k < -0.1$) (atypical) (Fig.1) (22). The CPX data were analyzed via Vienna CPX-Tool (Vienna University, Vienna, Austria) and results were reviewed independently by two investigators for consistency (23). Inclusion and exclusion of data is shown in Supplemental Material Fig. S1.

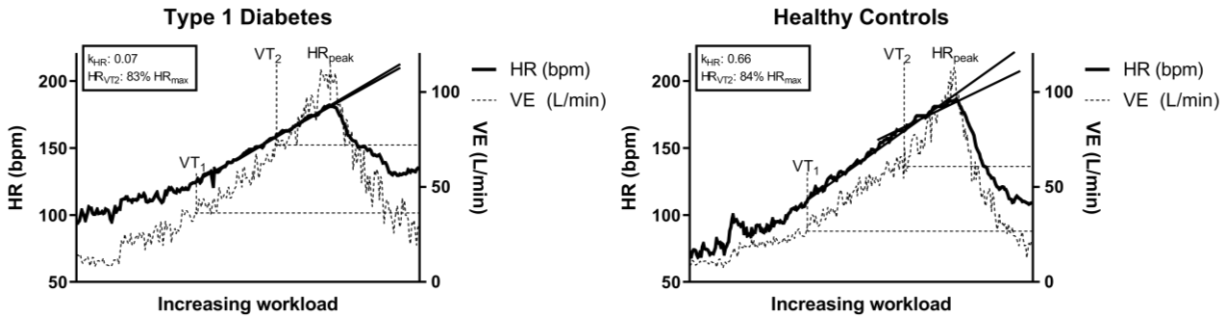

Figure 1: Schematic presentation of the calculation of the degree and the direction of the HR to performance curve (k_{HR}) for individuals with type 1 diabetes and healthy controls.

Statistical analyses

Data were tested for normal distribution by Kolmogorov-Smirnov test. Data are presented according to their distribution as mean ± standard deviation (SD) or median [interquartile range] for participant's anthropometric data, specific diabetes characteristics and performance data (Table 1). Performance data for pre-CPX testing, VT_1, VT_2 and peak values were compared for differences over time and between groups via restricted maximum likelihood model (REML) with post-hoc testing (Sidak's multiple comparisons test). Sex-specific differences were calculated via Fisher's exact test for each group.

A stepwise linear regression approach was used to explore relationships when significant differences were found between groups for k_{HR}, VT_1, VT_2 and peak parameters of relative VO_2, HR and Power (P) (dependent variables) against anthropometric (sex, BMI, age) and specific diabetes characteristics (diabetes duration, total daily insulin dose, HbA_{1c}, c-peptide) as independent variables. Stepwise linear regressions were adjusted for anthropometric variables if not included in the regression model.

If data were non-normally distributed, logarithmic transformations were performed. Statistics was performed via SPSS 26 (IBM Corporation, USA) and a standard software package Prism 8.0 (GraphPad, USA). Statistical significance was accepted at $p<0.05$.

RESULTS

A total of 303 individuals with T1D and 308 healthy individuals were included in the final analysis. Baseline characteristics prior to the CPX testing are shown in Table 1.

Table 1–Baseline characteristics of the study cohort

Characteristics	Healthy Control (n=308)	Type 1 Diabetes (n=303)	P-Value
Age (years)	32 [26; 41]	33 [22; 43]	0.88
BMI (kg/m^2)	24.1 [22; 26]	23.6 [22; 26]	0.21
Males/Females (n)	220/88	210/93	0.59
Diabetes duration (years)		0.8 [0.4; 12.3]	
Total daily insulin dose (IU)		30 [14; 50]	
HbA_{1c} (%)		6.9 [6.2; 7.7]	
HbA_{1c} (mmol/mol)		52 [44; 61]	
C-peptide (nmol/L)		0.27 [0.14; 0.43]	

Data are shown as median (quartiles, n or (%) unless otherwise indicated.

CPX testing

Sixty-two participants performed stepwise test protocols with 180 seconds increments with either 30 W (female) or 40 W (male). A ramp protocol was performed by 242 participants, in which the workload increased linearly every minute between 8 W and 60 W dependent on the expected performance as determined by experienced exercise physiologists. A quasi-ramp protocol was performed by 307 participants, in which the workload increased by 15 W (female) or 20 W (male) per minute.

In total, 50 quasi-ramp protocols, 191 ramp protocols and 62 step protocols were conducted in the T1D group while 257 quasi-ramp protocols and 51 ramp tests were conducted in the healthy control group. Test protocols increased the workload by 7% [6; 8] of the individual peak power (P_{peak}) per minute in healthy individuals while by 8% [7; 10] in individuals with T1D.

Physiological Response

Oxygen consumption

Relative VO_2 was lower in individuals with T1D compared to healthy controls at the aerobic (VT_1) (13.41 [11.18; 15.95] vs 16.49 [14.00; 19.47]) and anaerobic (VT_2) threshold (23.33 [19.34; 28.73] vs. 31.20 ± 7.82) and also at VO_{2peak} (32.55 [26.49; 38.72] vs. 42.67 ± 10.44) (mL/kg/min) (all $p<0.0001$). Absolute VO_2 was lower in individuals with T1D compared to healthy controls at VT_1 (1.00 [0.79; 1.29] vs.1.23 [0.99; 1.52]), VT_2 (1.69 [1.39; 2.16] vs. 2.32 [1.81; 2.81]) and VO_{2peak} (2.41 [1.87; 3.01] vs. 3.22 [2.43; 3.83]) (L/min) (all $p<0.0001$). Measured VO_2 Reserve (VO_2R) was lower in individuals with T1D compared to healthy controls at VT_1 (7.80 [5.73; 9.99] vs 11.61 [8.91; 14.41]), VT_2 (17.82 [13.68; 22.37] vs. 26.17 ± 7.60) and peak (27.10 [21.01; 32.94] vs. 37.65 ± 10.33) (mL/kg/min) (all $p<0.0001$). Oxygen pulse was lower in individuals with T1D compared to healthy controls at VT_1 (9.60 [7.25; 11.40] vs. 12.49 [9.84; 15.41]), VT_2 (12.30 [9.50; 15.30] vs. 17.61 ± 5.58) and peak (14.14 [11.19; 17.27] vs. 20.36 ± 6.07) (mL O_2/beat) (all $p<0.0001$) compared to healthy controls (Fig. 2).

Heart Rate

The HR to performance curve increased linearly in individuals with T1D detailing a median k_{HR} of 0.07 [-0.75; 1.09] while in healthy individuals a k_{HR} of 0.66 [-0.28; 1.45] was present ($p<0.0001$) (Fig. 2).

In individuals with T1D HR was significantly lower when compared to healthy controls at VT_1 (109 [101; 118] vs. 115 ± 15) ($p<0.01$), VT_2 (149 ± 15 vs. 156 [144; 167]) ($p<0.001$) and HR_{peak} (179 [170; 187] vs. 184 [175; 191]) (bpm) ($p<0.01$). Measured heart rate reserve (HRR) was also lower in individuals with T1D at VT_1 (25 [19; 30] vs.

29 ± 10) ($p<0.001$), VT_2 (64 ± 14 vs. 69 ± 14) ($p<0.0001$) and peak (93 ± 14 vs. 98 [88; 108]) ($p<0.01$) (Fig. 1 and 2).

Power output

Relative power output was lower in individuals with T1D compared to healthy individuals at VT_2 (1.95 [1.64; 2.33]) vs. 2.31 ± 0.60) and peak (2.78 [2.35; 3.32] vs. 3.33 ± 0.83) (W/kg) ($p<0.0001$) but not at VT_1 (0.93 [0.79; 1.07] vs. 1.03 ± 0.30) ($p=0.14$). Absolute power output was also lower in individuals with T1D at VT_2 (155 [120; 180] vs. 170 [140; 200]) and peak (216 [171; 253] vs. 245 [200; 300]) (W) ($p<0.0001$) with no significant difference at VT_1 (72 [56; 89] vs. 80 [65; 100]) (W) ($p=0.22$) (Fig. 2). Additional parameters of performance for both groups are presented in Supplemental Material Tables 1-3.

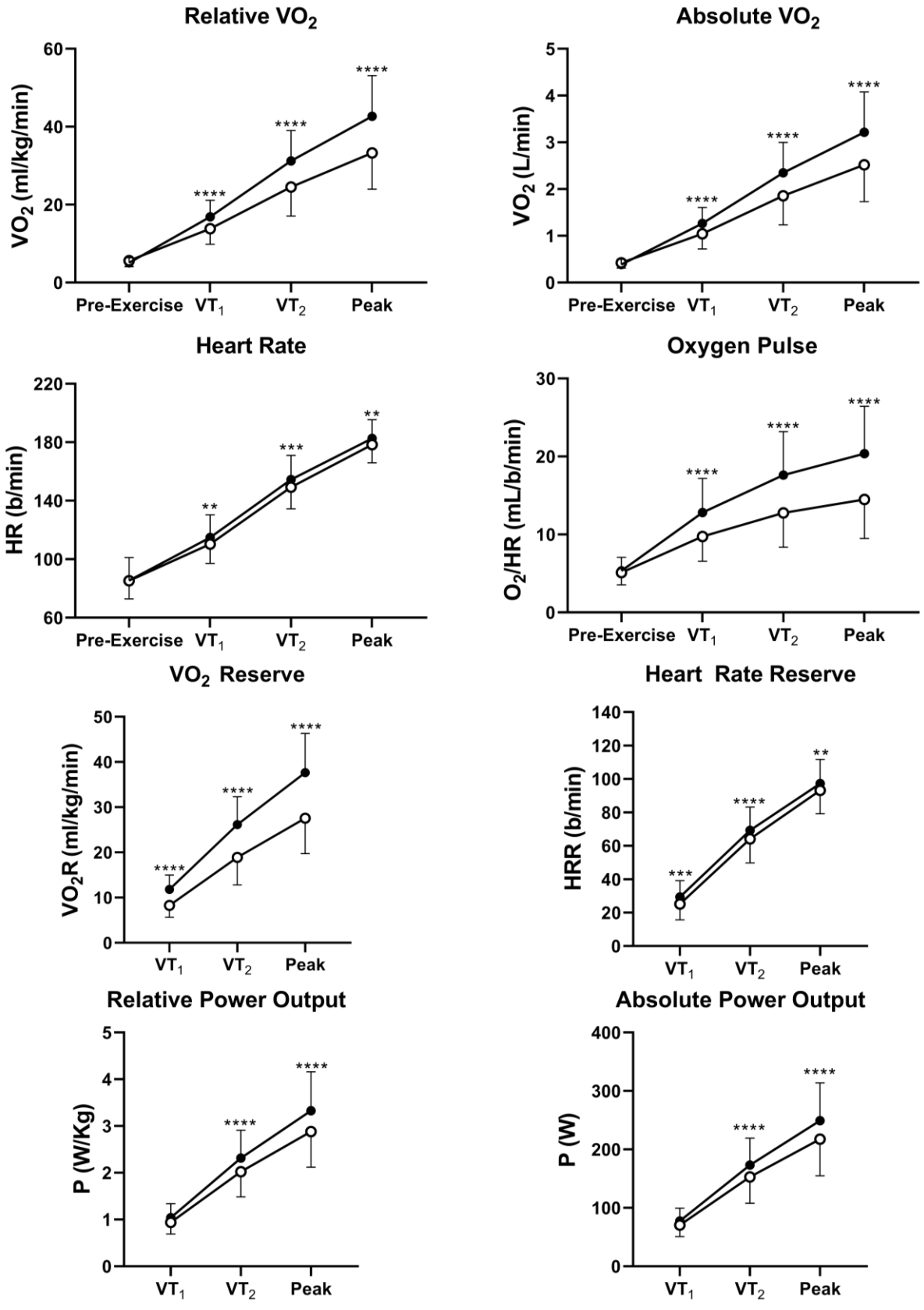

Figure 2: Physiological responses to cardio-pulmonary exercise testing. Black circles represent healthy individuals. Open circles represent individuals with T1D. Stars indicate significant differences between groups. * indicates p<0.05. ** indicates p<0.01. *** indicates p<0.001. **** indicates p<0.0001.

Association between diabetes characteristics and functional capacity

We found statistically significant associations between anthropometric and specific diabetes characteristics with physiological parameters of submaximal and peak performance in individuals with T1D (Table 2). Furthermore, significant relationships between physiological parameters of exercise performance and anthropometric variables for healthy controls are shown in Table 3.

Table 2–Associations for submaximal and peak parameters in individuals with type 1 diabetes

	VO_{2VT1}	VO_{2VT2}	VO_{2peak}	HR_{VT1}	HR_{VT2}	HR_{peak}	P_{VT1}	P_{VT2}	P_{peak}	k_{HR}
						β				
Age		-0.17**		-0.48****	-0.57****	-0.63****		-0.14***		0.24***
BMI	-0.37****	-0.28****	-0.19**				0.22**	0.24***		
Male sex	-0.16*	-0.46****	-0.52****				-0.57****	-0.64****	-0.60****	
Female sex				0.18**						
HbA_{1c}										
TDD		-0.27****	-0.23***					-0.18**		0.20*
DD						0.15**				
C-peptide		-0.29****	-0.32****				-0.21***	-0.26****		
R	0.38	0.65	0.64	0.51	0.57	0.67	0.62	0.68	0.59	0.28
R^2	0.15	0.42	0.41	0.26	0.33	0.45	0.39	0.46	0.36	0.08
Adjusted R	0.32	0.65	0.64	0.44	0.46	0.59	0.64	0.68	0.63	0.29
Adjusted R^2	0.10	0.42	0.41	0.19	0.21	0.34	0.41	0.46	0.40	0.09
p-value (both)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

TDD: Total daily dose. DD: Diabetes duration. Stars indicate level of significance. *p<0.05. **p<0.01. ***p<0.001. ****p<0.0001.

Table 3–Associations for submaximal and peak parameters in healthy controls

	VO_{2VT1}	VO_{2VT2}	VO_{2peak}	HR_{VT1}	HR_{VT2}	HR_{peak}	P_{VT1}	P_{VT2}	P_{peak}	k_{HR}
						β				
Age	-0.28****	-0.36****	-0.42****	-0.36****	-0.42****	-0.53****	-0.44****	-0.39****	-0.39****	-0.18****
BMI	-0.33****	-0.31****	-0.33****		-0.17					-0.33****
Male sex	-0.35****	-0.45****	-0.56****				-0.62****	-0.72****	-0.73****	
Female sex				0.16***						
R	0.53	0.61	0.72	0.43	0.53	0.53	0.68	0.74	0.75	0.45
R^2	0.28	0.38	0.53	0.18	0.28	0.28	0.46	0.55	0.56	0.20
Adjusted R				0.43	0.53	0.54	0.68	0.74	0.75	0.45
Adjusted R^2				0.18	0.28	0.29	0.46	0.55	0.56	0.20
p-value (both)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Stars indicate level of significance. *p<0.05. **p<0.01. ***p<0.001. ****p<0.0001.

Discussion

Our study showed that individuals with recent-onset T1D have impaired submaximal- and peak responses for VO_2, HR and power output to CPX testing when compared to matched healthy controls. These alterations in functional capacity coincide with data by Turinese et al. showing lower relative VO_{2peak} in individuals with T1D (16). However, they disagree partly with results by Moser et al. that did not find any differences in HR_{peak} but in k_{HR} between groups (17) and are contrary to what was shown by Nascimento et al. where no difference in functional capacity between individuals with T1D and healthy controls during exercise testing was evident (24).

There are several potential explanations for these equivocal findings in comparison to other researchers: firstly, in contrast to our study, where diabetes duration was <1 year diabetes duration was usually longer in previous studies (16,17). Secondly, age is a major influencing factor when assessing exercise capacity, due to its inverse relationship to P_{peak}, HR_{peak} and VO_{2peak}, and this may complicate findings and prevent comparisons if not accommodated by statistical evaluation in some studies (22). Furthermore, cohorts that are being investigated in different studies tend to be much smaller in sample size and the cohort examined often varies in glycemic control, which may further have a deteriorating impact on the physiological exercise response as shown by Moser et al. (17).

In our study, it was shown that relative VO_2 was up to 30% lower in individuals with T1D at submaximal thresholds and about 20% lower at peak performance compared to healthy individuals although body mass was not significantly different between individuals with T1D and healthy controls. Values of VO_{2peak} in our healthy control group are similar to data from the Fitness Registry and the Importance of Exercise: A national database (FRIEND) (26), which implies that our included cohort is

representative which rejects the idea of an increased level of physical activity/training status.

Previously, it has been shown that poor glycemic control is detrimental for oxygen economy during CPX testing (27). However, this might not apply to our study cohort as the HbA_{1c} averaged 6.9% (52 mmol/mol), which is in line with recommendations by the *American Diabetes Association* (ADA) to help prevent micro- and macro-vascular disease (28). Since there was no relationship in glycemic control and oxygen uptake and economy in our study, it may be speculated that endothelial dysfunction might already be present early after the diagnosis with T1D, even in the absence of visible changes (29). Additionally it may also be speculated that levels of physical activity are reduced in our cohort, since early after diagnosis of T1D the attitude towards regular physical activity changes due to several barriers to physical exercise (30). In our study a higher VO_{2peak} was associated with a lower total daily insulin dose, which is not surprising, since regular physical activity reflected by a higher VO_{2peak} necessitates reduction in insulin due to improved insulin sensitivity by elevated glucose transporter type 4 activity (31).

Interestingly, VO_{2peak} was associated with lower c-peptide levels. This is a rather contradictory finding (32,33), which however, might be ascribed to the short diabetes duration of <1 year in our cohort. A detectable c-peptide level and hence endogenous insulin production is advantageous for individuals with T1D to maintain the inverse relationship between insulin and glucagon secretion (34). It has been shown that individuals with T1D and higher c-peptide levels are less prone to exercise-induced hypoglycemia (35). Nonetheless, the clinical importance of our finding in regard to endogenous insulin production is still unclear and suggests that this finding does not play a causal role.

The HR response to CPX testing was lower at submaximal and also peak parameters in individuals with T1D compared to healthy controls. An often overlooked complication in diabetes is cardiovascular autonomic neuropathy, known to impair exercise intolerance blunting heart rate responses, which may also be present at diagnosis of T1D (36). Another contributing factor is hyperglycemia leading to chronically elevated adrenaline and noradrenaline levels that potentially induce β_1-adrenoreceptor insensitivity as shown in adolescent girls with T1D (37), subsequently leading to chronotropic incompetence (38). In line with the impaired HR responses to increasing physiological demands, k_{HR} detailed an atypical HR to performance curve in the T1D group. As shown in healthy individuals (39) and those with a chronic disease (20), only a small proportion of individuals shows a linear (6%) or inverted (8%) HR response during incremental exercise testing, which might be a first indication of myocardial function alterations. Interestingly, also in adults with long standing T1D and poorer glycemic control (HbA_{1c} ~7.8% [62 mmol/mol]), the HR to performance curve shifts towards a linear or inverted curve and inadequate response of the HR to exercise demands (20). Moser et al. postulated that this chronotropic incompetence reflects dysregulated cardiac muscle contractions during CPX testing (17). From our point of view, this assumption is questionable and contrary to our findings, since a linear curve may not lead to a reduction of cardiac performance. Previous studies have shown that newly diagnosed individuals with T1D showed a higher proinflammatory cytokine response compared to age-matched healthy controls at rest (40), similar to what was shown in sedentary individuals when reaching VO_{2max} during exercise testing (41).

While in healthy individuals the proinflammatory cytokine response fades after several hours, the proinflammatory state in individuals with T1D, independent of exercise, remains elevated due to increased glucose levels (40). Chronic hyperglycemia has been shown to be responsible for the formation of advanced glycation end (AGE)

products, which have a crucial role in the development of cardiovascular and renal complications (42). It may be able to activate the mitogen-activated protein kinase (MAPK) pathway, which interacts with the cell surface receptors inducing reactive oxygen species production. This plays a pivotal role in the development of cardiovascular complications and is also suspected to be present during higher-intensity exercise (31,43). The AGE-induced pathway, responsible for micro- and macrovascular complications detrimental to organs of the human body, is a physiological response to prolonged hyperglycemia, which is not reflected by our cohort with an HbA_{1c} of 6.9% (52 mmol/mol). However, in comparison to healthy controls this still may be considered as a hyperglycemic and proinflammatory status, potentially detrimental and responsible for the overall reduced physiological performance in individuals with T1D during CPX testing. The responsible pathways require additional research to elucidate the underlying mechanisms in recent-onset T1D. However, it is challenging to draw overall conclusions, since the alterations in the HR to performance curve were neither in previous research nor in our study investigated by means of stress echocardiography.

Relative and absolute P_{VT2} and P_{peak} was lower in individuals with T1D compared to healthy controls. These findings coincide with a reduced cardio-pulmonary response throughout the CPX test. We did not find a significant difference at P_{VT1} between groups, which indicates a regular aerobic energy supply at low intensity exercise in individuals with T1D. It appears that with increasing exercise intensity the metabolic demand needed for corresponding muscular performance cannot be covered sufficiently by the cardio-pulmonary system as shown by our previous results (17).

No specific diabetes characteristic was associated with P_{peak}, while submaximal P_{VT1} and P_{VT2} both were negatively associated with c-peptide, which we consider as a

random result. A lower P_{VT2} was associated with a higher total daily insulin dose. It is of interest that submaximal parameters of power output are associated with specific diabetes characteristics, whereas P_{peak} is not. Anaerobic P_{VT2} is reached earlier during CPX testing in individuals with T1D, which is potentially due to higher mismatch in metabolic demand leading to an overall decreased P_{peak}.

A major, and yet surprising finding of our study is that HbA_{1c} was not associated with any of the main physiological outcomes measured during CPX testing. The development of cardiovascular comorbidities has often been attributed to long periods of poor glycemic control, which deteriorates functional capacity independent of acute glycemia (44). In addition, we suspect that the short duration of diabetes in our study cohort is the reason why the influence of HbA_{1c} has not come into effect yet.

Our study is not without any limitation, as data on HbA_{1c} levels and c-peptide status are missing in the healthy control group, hence a comparison between groups is not applicable even though we tried to match them as tightly as possible via sex, age and BMI. An additional limitation is the lack of data on the habitual physical activity behavior, which could be different between healthy individuals and those with T1D potentially influencing our results.

The findings of our study may have implications for the future use of CPX testing in individuals with T1D. The necessity of testing cardio-pulmonary performance shortly after the diagnosis of T1D is important, since independent of glycemic control, human physiology seems to change early in individuals with T1D. However, living with T1D is not detrimental to functional capacity, since small specific cohorts including recreationally active adults and athletes with T1D, showed up to a 2-fold higher VO_{2peak} than that in our cohort (17,25).

Physical activity and exercise have become an integral component in the therapy of T1D within the recent decades of fighting this condition. CPX testing is a very helpful method to accurately prescribe exercise as a therapy and gives further insight into early physiological alterations. Nevertheless, our study has shown that the responses to CPX testing are impaired in individuals with recent-onset diabetes independent of HbA_{1c} compared to matched healthy controls. Health care professionals should therefore be vigilant when recommending exercise at specific intensities in T1D and regularly conduct CPX tests to monitor cardio-pulmonary changes and respond accordingly if deemed necessary.

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