


Predictors of the maximal oxygen consumption in adult patients with type 1 diabetes treated with personal insulin pumps

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ABSTRACT

Aims/Introduction: Regular physical activity for adults with type 1 diabetes mellitus improves cardiorespiratory fitness (CF) and quality of life. The aim of our study was to evaluate clinical and biochemical features that might be associated with CF in a homogenous group of adults with type 1 diabetes mellitus who are all treated with a personal insulin pump (continuous subcutaneous insulin infusion).

Materials and Methods: We assessed CF in 62 patients (74.2% of whom were men) who fulfilled the eligibility criteria. To determine maximal oxygen consumption, the march-running test on the treadmill was carried out. Two hours before the test, the patients consumed a defined meal covered by a dose of rapid acting insulin analog that was reduced by 25% from their regular dose. Basal insulin infusion was reduced by 50% for an hour. Additionally, the Perceived Stress Scale-10 questionnaire was used to measure the perception of stress.

Results: There was no episode of severe hypoglycemia during or after the test. In the final model, independent predictors of maximal oxygen consumption were sex, body fat percentage, lactate at 20 min after CF test and Perceived Stress Scale-10 score. Of interest, neither short-term (continuous glucose monitoring) nor long-term (glycosylated hemoglobin) metabolic control parameters were predictors of CF.

Conclusions: In our selected homogenous group of patients with type 1 diabetes mellitus treated with personal insulin pumps, higher CF was associated with a lower percentage of body fat, male sex, higher lactate level after the CF test and the Perceived Stress Scale-10 score. The proposed protocol in our cohort proved to be safe with regard to glycemic control.

INTRODUCTION

Regular exercise decreases the risk of long-term diabetes-related complications and improves quality of life^{1,2}. A high level of cardiorespiratory fitness (CF) in healthy individuals is associated with a reduced risk of cardiovascular diseases and death, as well as with longevity with no upper limit of observed benefits^{3–5}. The best quantitative measure of CF is maximal oxygen consumption (VO₂max), which is defined as the amount of

oxygen the body uses when a person reaches maximum ability to supply oxygen during exercise. Those who are fit have higher VO₂max values and can exercise more intensely than those who are not as well-conditioned.

It is widely accepted that individuals with type 1 diabetes mellitus using intensive insulin therapy can practice almost all types of physical activity, even extreme types, such as very high mountain climbing, ultramarathons and combat sports^{6–9}. Practicing sports by individuals with type 1 diabetes mellitus, however, might be challenging because of possible difficulties in

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maintaining glucose control, including the risk of hypoglycemic events. At the same time, with adequate experience, a high level of physical activity might be beneficial for glycemic control, as results from a meta-analysis show that long-term aerobic exercise improves glycemic control in type 1 diabetes mellitus patients¹⁰. Also, high-intensity interval training and/or strength training in type 1 diabetes mellitus was associated with enhanced anti-oxidant system measures and an improvement in glucose-related parameters¹¹.

An interesting angle is also the ability of individuals type 1 diabetes mellitus carrying out intense sport activities to achieve high CF. There is some evidence showing that CF might be reduced in patients with type 1 diabetes mellitus when compared with healthy controls^{10,12,13}. Identifying factors influencing CF in individuals with type 1 diabetes mellitus might have practical implications in this group of patients.

Some previous studies showed that CF is associated with glycosylated hemoglobin (HbA1c), whereas some others did not^{12–14}. Additionally, there are only a limited number of small studies analyzing continuous glucose monitoring parameters showing that glycemic variability is inversely associated with CF¹⁵. Finally, although there are some guidelines regarding aerobic and anaerobic exercise^{16,17}, there are no recommended algorithms recommending how a VO₂max test should be carried out in type 1 diabetes mellitus patients.

Hence, we endeavored to evaluate clinical and biochemical features that might be associated with CF in a homogenous group of adults with type 1 diabetes mellitus who are all treated with a personal insulin pump (continuous subcutaneous insulin infusion). We also proposed new CF measurement procedures.

MATERIALS AND METHODS

Out of the 78 patients consecutively invited to the study, 70 met inclusion criteria, eight were excluded due to electrocardiogram abnormalities (tachycardia, extra supraventricular or ventricular contraction, first-degree atrioventricular block or cardiac murmurs) and eight resigned from the performance test after obtaining medical qualification (1 cold, 1 abdominal pain, 1 sprained ankle, 5 personal reasons). In the end, we enrolled 62 patients (46 men, 74.2%) with type 1 diabetes mellitus who were receiving medical care at the Department of Metabolic Diseases, University Hospital, Krakow (an academic referral center for diabetes in southeastern Poland).

The inclusion criteria for the study included the presence of type 1 diabetes mellitus, treatment with a personal insulin pump for at least a year, a last HbA1c level <75 mmol/mol (9%), a lack of advanced chronic complications and signed written informed consent.

Diagnosis of type 1 diabetes mellitus was made based on World Health Organization criteria, the presence of typical clinical symptoms and insulin therapy requirement from the beginning of the disease. Ethical approval for the study was granted by the Jagiellonian University Bioethics Committee (1072.6120.113.2017).

Exclusion criteria included the presence of pre-proliferative or proliferative retinopathy, autonomic neuropathy, polyneuropathy, stage 3 or higher chronic kidney disease, severe hypoglycemia, diabetic ketoacidosis within the last 7 days before the test, significant locomotor disorders, body mass index (BMI) ≥ 35 kg/m², abnormalities in resting electrocardiogram or not being qualified for examination by an internal medicine doctor. The chronic diabetes complications were assessed based on medical records, previously carried out tests and consultations in different time frames. No additional examinations were carried out solely for the purpose of this study, except for the eligibility visit.

The chronic diabetes complications were assessed based on medical records, previously carried out tests and consultations in different time frames. No additional examinations were carried out solely for the purpose of the present study, except for the eligibility visit.

There were eight patients disqualified from participating in the study due to electrocardiogram abnormalities. Patients were also excluded from the study if during the day of the test, their pre-standardized meal glycemia was >250 mg/dL (11.1 mmol/L), <50 mg/dL (3.3 mmol/L), <70 mg/dL (3.8 mmol/L) with accompanying symptoms of hypoglycemia or the presence of ketone bodies in urine, or if their postprandial glucose (measured after 90 min) was >300 mg/dL (13.8 mmol/L) with the presence of ketone bodies in urine.

Procedures

All the patients' glucose patterns were monitored continuously with blinded Dexcom G4 for 10 days before the CF test; mean glycemia and coefficient of variation were assessed for correlation with CF test results. The most recent data downloaded from the personal insulin pump and blood glucose meter covering the last 10 days before the test were collected. We used these data to analyze the following variables: mean blood glucose concentration from the glucose meter; mean number of blood glucose measurements per day; mean percentage of total insulin dose provided by basal insulin; mean number of boluses per day; and mean bodyweight-adjusted daily insulin dose.

All participants were given a sport watch (Garmin Fenix G5, Garmin, Ltd., Olathe, KS, USA) to estimate their level of CF and mean number of daily steps carried out.

The weight and body structure (percentage of body fat) was determined by bioelectrical impedance analysis (Jawon Medical, Daejeon, Korea). To determine the maximal oxygen consumption (VO₂peak) and its indicators at the level of the second ventilation threshold (VT2), the march-running test on a treadmill was carried out. Two hours before the test, patients consumed a defined meal (50 g of carbohydrate: 30 g of cereal yogurt [255 kcal] and 20 g of banana [116 kcal]) covered by a dose of rapid-acting insulin analog reduced by 25% versus the regular dose assessed by the patients for a meal of this volume and structure. Basal insulin infusion was reduced by 50% 30 min before the CF test for an hour. The final meal insulin

dose was dependent on the patient's current insulin requirements when a short aerobic or anaerobic exercise was planned; of note, none of the clinical guidelines recommend a specific insulin dosing. The schematic summary of the study protocol is shown in Figure 1.

The test assessing the level of patients' CF was carried out at the Laboratory of Physiology of Basis of Adaptation, University of Physical Education (Krakow, Poland). The test was carried out on a treadmill (Saturn 250/100R; h/p/Cosmos, Nussdorf-Traunstein, Germany). The test started with a 4-min warm-up during which the participant marched at a constant speed of 6 km/h; the angle of inclination of the treadmill was 1°. Then the running speed was increased by 1.0 km/h every 2 min, and the participant smoothly moved to a run. The test was carried out as described until the patient refused to continue due to utmost fatigue. Lactate (La⁻) concentration was analyzed in arterial blood collected before the test, and then 3 and 20 min after the run. Lactate concentration was determined by plasma enzymatic method using the Lactate PAP kit from BioMérieux (Lyon, France) on a Spekol 11 spectrophotometer (Carl Zeiss, Jena, Germany).

During the test, the following parameters were recorded with the use of an ergospirometer (Cortex MetaLyzer R3): minute lung ventilation, percentage of carbon dioxide in exhaled air, minute oxygen uptake, minute carbon dioxide excretion, respiratory quotient and respiratory equivalent for carbon dioxide. The heart rate during the test was measured using a sport tester (Polar Vantage V, Kempele, Finland).

To determine the second ventilatory threshold (VT₂), changes in respiratory parameters were analyzed as work intensity increased. The criteria for determining VT₂ was as follows: the percentage of CO₂ in exhaled air reached its maximum value and then decreased, the respiratory equivalent for carbon dioxide obtained the minimum value and then increased, and when after exceeding VT₂ a large non-linear increase in lung

ventilation was noted. The maximal oxygen consumption (VO₂peak in mL/kg/min) occurring at peak exercise was used to define the participant's aerobic capacity, and was expressed as the mean value during the last 1 min of the test^{18,19}. Blood glucose level was measured before the meal, before the CF test, immediately after the CF test, and also at 30, 60 and 120 min after the test (Contour Plus meter; Ascensia Diabetes Care, Basel, Switzerland). The tests were carried out for all patients between 15.00 and 18.00 hours. To minimize the risk of nocturnal hypoglycemia after the test, patients were advised to measure their blood glucose at home at midnight, 03.00, and 06.00 hours.

Before the CF test, patients were asked to fill out the Perceived Stress Scale-10 (PSS10) questionnaire. PSS10 is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Respondents gave answers to 10 questions (e.g., 'In the last month, how often have you felt nervous or stressed?') by typing the correct digit: 0 – never, 1 – almost never, 2 – sometimes, 3 – quite often or 4 – very often. The overall score of the scale was the sum of all points and ranged from 0 to 40 points (five patients refused to complete this test). PSS10 has been found to correlate well with stressful life events, depressive symptoms and predicted health outcomes (physical symptomatology and visits to a healthcare center) better than life event measures²⁰.

Statistical analysis

Differences between the groups were analyzed with Student's *t*-test or non-parametric test, such as the Wilcoxon test as appropriate (Shapiro–Wilk test was used to assess normality of the distribution). To compare two categorical variables, the χ^2 -test was used.

Predictors of physical fitness were established by using multi-variable regression analysis (backward and forward). First, we

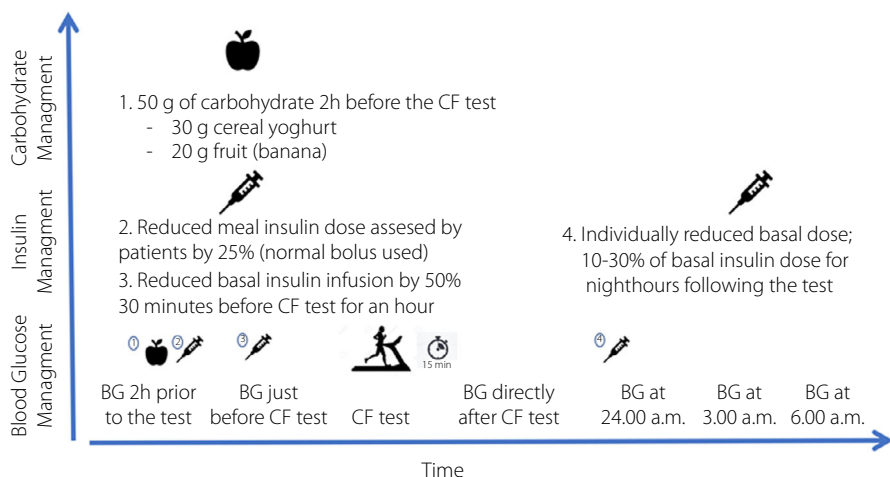


Figure 1 | Proposed protocol for diabetes management before cardiorespiratory fitness (CF) test. BG, blood glucose.

created a bivariable model with all variables from Table 1, with sex as a confounding variable. All variables with $P < 0.05$ from bivariable models were entered into a final multivariable regression model. We used a stepwise regression method in which the best model from both forward and backward selection was chosen. Results of bivariable and multivariable regression analysis are presented in Table 2. All statistical analyses were carried out in R software 3.6.3 (The R Project for Statistical Computing, Vienna, Austria)²¹.

RESULTS

The final population consisted of 62 patients with type 1 diabetes mellitus, 46 (74.2%) of whom were men and 16 (25.8%) were women. The mean (\pm standard deviation) age at study entry was 25.1 ± 6.0 years (range 19–45 years), mean type 1 diabetes mellitus duration was 12.4 ± 6.4 years (range 1–28 years) and mean BMI was 23.8 ± 3.0 kg/m² (range 16.9–31.5 kg/m²). Detailed group characteristics are presented in Table 1.

Men were found to be younger, less frequently measured their glucose level, had higher glucose levels on their glucometer and had a lower percentage of body fat as compared with the women (Table 1).

The mean CF test duration (t) was 15.2 ± 4.0 min, maximum heart rate was 194.9 ± 11.7 b.p.m. and maximum lung ventilation was 113.3 ± 29.4 L/min. The global oxygen intake (VO_2peak) was 3.1 ± 0.7 L/min, and relative to bodyweight was 42.0 ± 7.5 mL/kg/min. At the VT2 level, the individual physiological indicators were t 8.4 ± 2.5 min, heart rate 169.1 ± 9.4 spasm/min, VO_2 2.3 ± 0.5 L/min and 31.9 ± 5.5 mL/kg/min, and maximum lung ventilation 67.4 ± 11.1 L/min. The lactate level before the test was 1.7 ± 1.6 mmol/L, and at 3 and 20 min after the end of exercise had a maximal concentration of 12.7 ± 3.6 and 7.3 ± 2.8 mmol/L. Detailed CF test statistics are presented separately for women and men in Table 1. According to Astrand, two of the men's VO_2peak were classified as very good (0 women), four as good (0 women), 25 as average (9 women),

Table 1 | Clinical characteristics of the study group

Variable	Whole study group			Men			Women			P-value
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
HbA1c (%)	6.9	0.9	6.9	7.0	1.0	6.9	6.7	0.7	6.7	0.496
Age at the examination (years)	25.1	6.0	23.0	24.1	5.4	22	27.9	7.0	26	0.022
Type 1 diabetes mellitus duration (years)	12.4	6.4	14	11.8	5.8	12	14.3	7.8	14.5	0.181
Time on CSII (years)	7.7	4.6	8	7.8	4.2	7.0	8.2	5.8	8.0	0.615
Average glycemia from glucose meter (mg/dL)	148	27	143	153.1	27.8	147	133.5	20	129.5	0.005
Average daily insulin dose per kg of body mass (IU/kg)	0.70	0.17	0.70	0.70	0.18	0.70	0.71	0.15	0.70	0.937
Average percentage of basal insulin (%)	40.8	10.6	41.0	40.2	9.7	41.0	42.8	13.0	42.0	0.403
Average no. blood glucose measurements per day (n)	7.1	3.0	7.0	6.6	2.7	6.5	8.7	3.5	8.1	0.016
Average no. boluses per day (n)	6.5	1.9	6.4	6.7	2.0	6.4	6.1	1.3	6.3	0.223
BMI (kg/m ²)	23.9	3.0	23.8	24.3	3.1	24.1	22.5	2.2	22.8	0.018
Body fat percentage (%)	21.4	6.7	21.0	19.7	6.6	19.7	26.1	4.4	27.4	0.000
VO_2max estimate from sport tester	45.1	3.5	45.0	46.1	3.3	46.0	42.6	2.7	43.0	0.000
Mean no. steps per day (n)	8,858	2,667	8,499	8,684	2,585	8,499	9,357	2,921	8,574	0.389
Mean glycemia from CGM (mg/dL)	148.9	30.8	142.2	152.1	33.2	143.9	139.4	21.0	139.7	0.375
CV glycemia from CGM (mg/dL)	44.7	6.8	44.2	44.5	7.2	44.2	45.1	5.7	44.2	0.784
PSS10 score (n)	15.6	5.8	15.0	15.4	6.5	14.0	16.0	3.8	15.5	0.428
Maximum heart rate (b.p.m.)	194.9	11.7	198	197.7	10.2	200	186.9	12.2	188	0.000
Maximum lung ventilation (L/min)	113.33	29.3	119.65	125.6	23.0	127.5	78	11.6	75.1	0.000
Oxygen intake relative to bodyweight (mL/kg)	42.0	7.5	43.3	44.6	6.4	45.5	34.4	5.1	35.7	0.000
Heart rate at the VT2 level (b.p.m.)	169.1	9.4	169	169.6	9.4	168.5	167.6	9.6	169.5	0.466
Lung ventilation at the VT2 level (L/min)	64.8	14.4	61.3	69.2	13.8	67.4	52.4	7.1	51.8	0.000
Oxygen intake relative to bodyweight at the VT2 level (mL/kg)	31.9	5.5	31.4	33.2	5.4	33.0	28.0	4.1	27.9	0.000
Lactate level just after the test	1.7	0.2	1.5	1.6	0.3	1.6	1.4	0.2	1.4	0.082
Lactate level 3 min after the test	12.7	3.6	12.4	13.7	3.4	13.4	9.6	2.5	8.8	0.000
Lactate level 20 min after the test	7.3	2.8	7.0	8.0	2.8	7.4	5.4	1.7	5.6	0.000
Lactate utilization (3–20 min)	5.3	1.9	5.4	5.8	1.8	5.7	4.2	1.8	3.7	0.005

All variables are presented as the mean for entire group. CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; HbA1c, glycosylated hemoglobin; PSS10, Perceived Stress Scale-10; SD, standard deviation; VO_2max , maximal oxygen consumption; VT2, second ventilation threshold.

10 as poor (6 women) and five as very poor (1 woman; no difference between sexes, $P = 0.478$)²².

There were no episodes of severe hypoglycemia during or after the test. Fluctuations of mean blood glucose during and 2 h after CF testing are presented in Figure 2. According to the protocol, patients started to manage their blood glucose by themselves, and were recommended to reduce the basal dose during night-time by 10–30% from their usual dose. According to the patient records, 19 (9 during night-time) of the patients (of which 10 were men, $P = 0.009$) experienced mild hypoglycemia (50–70 mg/dL) before the morning after the test.

Linear regression was used to assess predictors of VO_2 peak with sex as a supposed cofounder. According to our analysis, in addition to sex, the following variables were predictors of a higher VO_2 peak: lower BMI, lower body fat percentage (%F), lower PSS10 score, higher lactate at 3 and 20 min after CF test, and a higher VO_2 max estimate from the sport tester.

In our final model of multivariable regression analysis, independent significant predictors of higher VO_2 peak remained male sex, lower body fat percentage (%F), higher lactate at 20 min after CF test and a lower PSS10 score (Table 2). The proposed model was statistically significant ($P < 0.05$) and explained 63.2% of CF variation.

DISCUSSION

We evaluated CF and assessed the safety of the CF procedure ('until refusal') in a homogenous group of adults with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion. Independent predictors of higher VO_2 peak were male sex, lower body fat percentage (%F), higher lactate at 20 min after CF test and a lower PSS10 score. Additionally, the proposed protocol appeared to be safe in the present adult type 1 diabetes mellitus patients – there were no cases of significant hyperglycemia, and more importantly, no episodes of hypoglycemia during or after the test. In a brief summary, we proposed that the VO_2 peak test was carried out in conditions including a consumption of moderate size carbohydrate-based snacks before the test, subtle bolus insulin reduction for this snack, and approximately 50% of basal insulin dose reduction 30 min before and during the test.

The mean VO_2 peak results of our total cohort were similar or higher to previously published adult type 1 diabetes mellitus patients studies^{23–26}. This could be explained by the fact that there were some male individuals in our study group who participated in very high daily physical activity. Our cohort was older compared with previously cited studies, which might

Table 2 | Results of univariate (sex), bivariate and multivariate linear regression analysis

Variable + sex	Bivariate analysis			Multivariate analysis	
	Estimate	95% CI	P-value	Estimate	P-value
Sex (female) [†]	−10.4	−13.6; −7.27	0.000	−3.82	0.028
HbA1c (%)	0.30	−1.26; 1.87	0.696		
Age at the examination (years)	−0.07	−0.32; 0.16	0.515		
Diabetes duration (years)	−0.13	−0.35; 0.09	0.238		
Time on CSII (years)	−0.22	−0.53; 0.08	0.140		
Average glycemia from glucose meter (mg/dL)	−0.04	−0.1; 0.0	0.067		
Average daily insulin dose per kg of body mass (IU/kg)	−7.08	−15.1; 0.85	0.079		
Average percentage of basal insulin (%)	0.03	−0.10; 0.17	0.610		
Average no. blood glucose measurement per day (n)	−0.21	−0.69; 0.27	0.387		
Average no. of boluses per day (n)	0.02	−0.74; 0.78	0.780		
BMI (kg/m ²)	−0.75	−1.20; −0.31	0.001		
Body fat percentage (%)	−0.50	−0.72; −0.27	0.000	−0.43	0.000
VO_2 max estimate from sport tester	0.63	0.19; 1.08	0.006	0.35	0.083
Mean no. steps per day (n)	0.000	0.00; 0.00	0.054		
Mean glycemia from CGM (mg/dL)	−0.02	−0.07; 0.02	0.293		
CV glycemia from CGM (mg/dL)	0.09	−0.11; 0.30	0.380		
TIR 70–180 mg/dL (%)	0.04	−0.07; 0.15	0.483		
PSS10 score (n)	−0.33	−0.58; −0.09	0.008	−0.29	0.015
Maximum heart rate (b.p.m.)	0.10	−0.03; 0.23	0.125		
Lactate level 3 min after the test	0.61	0.19; 1.02	0.005		
Lactate level 20 min after the test	0.70	0.31; 1.32	0.002	0.55	0.013
Lactate utilization (lactate in 3–20 min)	0.18	−0.59; 0.95	0.639		

CGM, continuous glucose monitoring; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; HbA1c, glycosylated hemoglobin; PSS10, Perceived Stress Scale-10; VO_2 max, maximal oxygen consumption. [†]For sex, variable univariate analysis was carried out; best multivariate model is significant; $P < 0.000$, adjusted $R^2 = 0.632$, intercept (estimate: 35.8; $P = 0.000$).

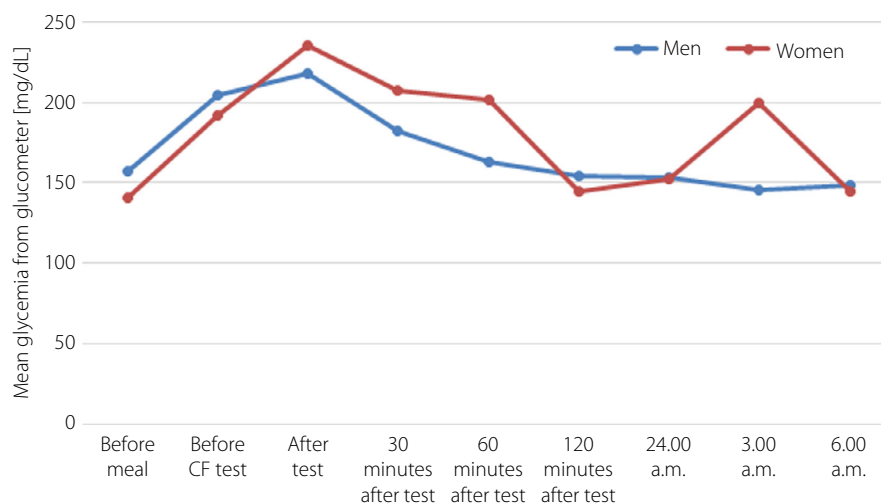


Figure 2 | Fluctuation of mean blood glucose from glucometer before and after cardiorespiratory fitness (CF) test.

impact the results; however, we did not find any correlation between VO_2 peak and age. A possible explanation is the fact that this group was characterized by a narrow range of ages (19–45 years). Similarly, in another study of adult type 1 diabetes mellitus patients, there was no correlation between mean glucose data taken from continuous glucose monitoring or age with CF²⁴. We did not confirm any association between glycaemic variability and CF in our cohort. Such an association was reported previously by Singhvi *et al.*,¹⁵ however, their cohort had a limited number of patients ($n = 19$), and the patients varied in their treatment methods (multiple daily injections and continuous subcutaneous insulin infusion).

Our final multivariable model for prediction of VO_2 peak explained 63.2% of the CF variation, which is similar to previously published models (56%)²⁴, 65.1%¹² and 67% in individuals with type 1 diabetes mellitus²⁷. According to the recently published results, independent predictors of higher CF were male sex^{12,13} and a lower percentage of body fat^{2,24,28,29}. These findings are applicable for both healthy individuals and diabetes patients^{12,13,24,27,28}. It was shown that VO_2 peak values were higher in the group with BMI values <25 kg/m²³⁰, which is also in line with the present study.

In our final model, CF was associated positively with lactate levels 20 min after the test. This is in agreement with the fact that the blood lactate concentration increases through lactate accumulation when the anaerobic glycolysis-induced lactate production rate exceeds the aerobic glycolysis-induced lactate removal rate during high-intensity exercise³¹. In healthy individuals, the lactate clearance measured at 15 and 30 min after CF test is higher in people with higher VO_2 peak³¹. In the present patients, the univariate correlation between lactate utilization and VO_2 peak was on the borderline of statistical significance ($P = 0.050$).

Finally, the variable ' VO_2 max estimate from a Garmin sport tester' stayed in the model, but it was not an independent predictor of CF ($P = 0.08$). Recent studies showed that some current sport watches are most likely not accurate enough to estimate VO_2 max¹⁹.

Other factors previously shown to be associated with higher CF were higher insulin sensitivity, better lipid profile, elevated leptin, serum 2-hydroxyvitamin D ≥ 75 nmol/L, lower levels of general anxiety and higher health-related quality of life, among other factors^{4,29,32–34}. American Diabetes Association/International Society for Pediatric and Adolescent Diabetes goal achievement (target: HbA1c $<7.5\%$, blood pressure <90 th percentile, low-density lipoprotein cholesterol <100 mg/dL, high-density lipoprotein cholesterol >35 mg/dL, triglycerides <150 mg/dL and BMI <85 th percentile) has also been shown to be associated with CF³⁵. We also should take into account that physical fitness is determined by constitutional factors, and it has been suggested that up to approximately 40% of variation in fitness might be attributable to genetic factors^{5,14,27}.

Of particular interest in the present study, VO_2 peak was not associated with HbA1c levels among adult type 1 diabetes mellitus patients. This is in contrast to previous studies^{12,13,36,37} that reported an inverse association between aerobic capacity and HbA1c in young type 1 diabetes mellitus patients. At the same time, two other studies showed that exercise capacity in type 1 diabetes mellitus patients was not influenced by the degree of hyperglycemia^{14,23}. In contrast, Tagougui *et al.*³⁸ showed that the achieved VO_2 max was lower in patients with type 1 diabetes mellitus when their HbA1c was >64 mmol/mol (8%); but if HbA1c was <53 mmol/mol (7%), then VO_2 max did not differ between people with diabetes and healthy controls. One could speculate that the lack of correlation between CF and HbA1c in the present study, as well as some other studies, was

due to the fact that these cohorts did not include patients with very high HbA1c levels, in whom the negative effects of metabolic decompensation on CF could be seen in some other reports.

Interestingly, we observed that higher cardiorespiratory fitness was independently associated with a lower PSS10 score. Some studies showed statistically significant associations between the level of fitness and the reduction of symptoms of stress-related exhaustion over time³². In healthy people, there was a correlation between occupational stress and CF³³. Another recent study showed that CF might be protective against the deleterious effects of stress³⁴. Interestingly, higher CF was associated with lower stress in men with a normal weight, but in overweight men, these relationships might differ³⁵. Scores around 13 are considered average, and scores of ≥ 20 are considered high stress (L. Harris Poll norm); for our group, the average score was 15.6, which is in the normal range.

For most patients, the recommended blood glucose level before aerobic exercise lasting up to an hour is 7–10 mmol/L (~ 126 – 180 mg/dL)¹⁶. In the present study, the mean glycemia before test meal was 157 versus 141 mg/dL before exercise, it then increased to 204 and 192 mg/dL in men and women, respectively, reaching its maximal values just after the test at 218 versus 235 mg/dL. At 2 h after exercise, it decreased to values similar to the values before the test meal (there was no additional meal or change in insulin dosing after exercise). This means that the blood sugar values before, during and after the exercise test were still acceptable according to guidelines by Riddell *et al.*^{16,17} and were found to be safe based on the fact that no hypoglycemic episodes occurred during the test.

Previous studies showed that the majority of type 1 diabetes mellitus patients experienced hypoglycemia during a CF test¹⁵. When no preventive strategies are in place to limit the drop in glycemia during prolonged exercise, the incidence of hypoglycemia is approximately 44%¹⁷. Having a high pre-exercise blood glucose concentration is only marginally protective in this situation¹⁷. Our proposed protocol with additional carbohydrates (50 g) accompanied by 25% insulin analog reduction before short (15 min) and intense exercise accompanied by 50% reduction of basal insulin infusion implemented 30 min before the performance test (for 1 h) prevented significant hypoglycemia (as well as mild hypoglycemia (<70 mg/dL) during CF test and after 1 h)¹⁶. In contrast, our protocol suggested only a moderate reduction in basal insulin rate infusion during the night after the test, which was not fully effective, as some patients developed non-severe hypoglycemic episodes. One could conclude that post-exercise overnight insulin management modification should be more individualized, with perhaps a more significant insulin dose reduction.

Despite the fact that our protocol was found to be safe, one has to emphasize that no alternative protocols were tested and compared by us during the study.

In the present cohort, we observed more hypoglycemia after the CF test in women ($P < 0.05$). This might be due to the fact

that they carried out more measurements per day than men, and simply caught all episodes of mild hypoglycemia, or perhaps they were less experienced in managing blood sugar levels during the post-exercise period.

Some study limitations should be acknowledged. Our intervention study was carried out in a homogenous group of patients with relatively good metabolic control, which might explain our difficulty in showing an association between CF and diabetes-related parameters. Thus, the results of the present study could not be automatically extrapolated on the other type 1 diabetes mellitus cohorts.

In the present selected homogenous group of patients with type 1 diabetes mellitus who were all treated with personal insulin pump, higher CF was associated with lower percentage of body fat, male sex, higher lactate level after the CF test and a PSS10 score. Neither short-term (continuous glucose monitoring) nor long-term (HbA1c) metabolic control parameters were predictors of CF. We also presented a simple protocol for carrying out CF tests, which proved to be safe with regard to glycemic control in our cohort. We postulate that the same protocol as we suggest for the VO_{2peak} test can be applied to other forms of mixed aerobic/anaerobic exercise and utilized by patients with type 1 diabetes. This will require further studies, however.

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DISCLOSURE

The authors declare no conflict of interest.

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