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ORIGINAL SCIENTIFIC PAPER

Association between Cardiorespiratory Fitness and Glycemic Control in Individuals with Type 2 Diabetes Mellitus

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Abstract

The aim of this study was to investigate the independent associations of cardiorespiratory fitness (CRF) with glycemic control parameters in individuals with type 2 diabetes mellitus (T2DM). A total of 44 individuals with T2DM (age: 52.20 ± 9.02 years; T2DM duration: 5.39 ± 4.65 years; baseline glycated hemoglobin (HbA1c): 7.05 ± 0.78%) participated in this study. Following blood analysis, anthropometric assessments, and resting blood pressure measurements, participants performed the Six-Minute Walk Test (6MWT) to estimate peak oxygen uptake (VO_2peak). The main findings indicated that relative VO_2peak was significantly and inversely associated with HbA1c in the unadjusted model (B = -0.12, p = .03), explaining 10.7% of the variance. However, this association was attenuated and became non-significant after adjusting for age, T2DM duration, and body mass index (BMI). Neither relative nor absolute VO_2peak was significantly associated with fasting blood glucose (B = −0.13, p = .20 and B = −0.46, p = .31, respectively). Age emerged as the only independent predictor of fasting blood glucose (B = 0.07, p = .04). These results suggest that the association between CRF and long-term glucose regulation in this population is complex and heavily influenced by demographic and anthropometric factors, highlighting the need for a multifactorial approach in clinical assessments.

Keywords: fasting glucose · maximal oxygen uptake · HbA1c · glycemic control

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Introduction

Type 2 diabetes mellitus (T2DM) represents a global health burden, affecting approximately 537 million adults worldwide, a number projected to increase to 642 million by 2040 (Zheng, Ley & Hu, 2018). Beyond metabolic dysregulation, T2DM is associated with a broad spectrum of macrovascular and microvascular complications that collectively account for the majority of T2DM-related morbidity and premature mortality (Iglay et al., 2016; Einarson, Acs, Ludwig & Panton, 2018; Farjo et al., 2020). While glycemic management remains the cornerstone of clinical care, growing evidence indicates that the burden of T2DM extends beyond dysglycemia to encompass profound impairments in physical function, with cardiorespiratory fitness (CRF) emerging as a particularly consequential yet systematically under-addressed clinical parameter in T2DM population.

CRF estimated by peak oxygen consumption (VO_2peak) or maximal oxygen uptake (VO_2max) has emerged as one of the most powerful independent predictors of cardiovascular morbidity and all-cause mortality, surpassing traditional risk factors such as hypertension, dyslipidemia, and obesity (Ross et al., 2016). Specifically, each 1 $mL \cdot kg^{-1} \cdot min^{-1}$ decrease in CRF is associated with a 9% increase in all-cause mortality risk (Laukkanen, Kurl, Salonen, Rauramaa & Salonen, 2004), while each 1 MET increment in fitness has been shown to reduce the 10-year risk of coronary heart disease (Balducci et al., 2012). Despite this prognostic significance, individuals with T2DM consistently demonstrate substantially reduced CRF compared to age and sex-matched healthy controls (Röhling et al., 2018; Roberts et al., 2018; Vukomanovic et al., 2019). Although this impairment may be partly attributable to physical inactivity, obesity or comorbidities (Tadic et al. 2021), critically, CRF remained significantly reduced in T2DM populations even after adjustment for these confounders (Röhling et al., 2018; Vukomanovic et al., 2019), implicating T2DM-specific pathophysiological mechanisms such as microvascular dysfunction, mitochondrial impairment, and left ventricular diastolic dysfunction (Tadic et al., 2021).

Compounding these structural and functional impairments, poor glycemic control itself has been identified as an additional contributor to reduced CRF in T2DM (Solomon et al., 2015; Roberts et al., 2018; Vukomanovic et al., 2019), suggesting that the relationship between CRF and glycemic regulation may be bidirectional. While chronic hyperglycemia negatively impacts CRF through the mechanisms outlined above, higher CRF has conversely been shown to independently predict better glycemic outcomes through enhanced skeletal muscle insulin signaling, improved mitochondrial oxidative capacity, and favorable modulation of pro-inflammatory mediators (Solomon et al., 2015). Despite this mechanistic rationale, the literature remains limited by several methodological gaps. First, most previous studies have relied on laboratory-based cardiopulmonary exercise testing (CPET), which is considered the gold standard method for CRF assessment (Ross et al., 2016; Macedo et al., 2023). However, CPET requires specialized equipment, trained personnel, and controlled environments, which is largely inaccessible in routine clinical practice (Macedo et al., 2013). The Six-Minute Walk Test (6MWT) represents a validated, reliable, and widely applicable alternative test (Ross, Murthy, Wollak & Jackson, 2010; Singh et al., 2014), with studies consistently demonstrating significant correlations between 6MWT distance and directly measured CRF in clinical populations (Enfield et al., 2010; Singh et al., 2014; Lee et al., 2018), and its validity has been specifically confirmed in adults with T2DM (Lee et al., 2018; Nolen-Doerr et al., 2018). Nevertheless, the independent contribution of 6MWT-derived CRF estimates to glycemic control in T2DM individuals is insufficiently reported omitting adjustment for key clinical confounders. Therefore, the present study aimed to examine the independent associations between relative VO_2peak estimated via the 6MWT, and glycemic control parameters (i.e., fasting blood glucose and glycated hemoglobin (HbA1c) in individuals with T2DM with adjustment for age, T2DM duration, and body mass index (BMI).

Method

Participants

A total of 44 participants (20 men and 24 women) from Jablanica and Nišava district, with T2DM volunteered to participate in this study. Participants were recruited through the Health Care Center, via clinician referrals, online posters, social media and word of mouth, and in collaboration with diabetes associations. The following *inclusion criteria* were applied: (1) individuals aged 18 – 65 years diagnosed with T2DM by a clinician at least 6 months prior to the start of the study according to American Diabetes Association (ADA) criteria (fasting plasma glucose ≥ 126 mg/dL [≥ 7.0 mmol/L], 2-hour post-load glucose ≥ 200 mg/dL [≥ 11.1 mmol/L] during an oral glucose tolerance test, or HbA1c ≥ 6.5% [≥ 48 mmol/mol]); (2) sedentary,

physically inactive individuals according to international physical activity questionnaire (IPAQ) (<150 min of moderate-intensity activities per week or <75 min of vigorous-intensity activities per week or <600 MET min per week); (3) individuals on stable doses of oral antidiabetic drugs (OADs) or insulin therapy for at least 3 months prior to enrollment; (4) no recent episodes of severe hypoglycemia or hyperglycemia requiring hospitalization in the past 3 months; (5) participants free of injuries and without any contraindications to exercise or additional chronic diseases that could not be controlled by standard medication and might be exacerbated by vigorous activity. Exclusion criteria were defined as follows: (1) active participants according to IPAQ (≥3 days per week of vigorous intensity activities achieving a minimum total physical activity at least 600 - 1500 MET min a week or ≥ 5 days of any combination of walking, moderate intensity or vigorous intensity activities achieving a minimum total physical activity at least 600 – 3000 MET min a week; (2) absolute contraindications to exercise (unstable angina, recent myocardial infarction, coronary artery disease and uncontrolled symptomatic heart failure; (3) moderate to severe somatic or autonomic neuropathy, retinopathy, renal failure, a history of respiratory disease (pulmonary hypertension or chronic obstructive pulmonary disease), and a history of neurological disorders; (4) individuals who were strictly prohibited by a medical professional from engaging in exercise were not eligible for participation. The specific aims, benefits, risks, safety measures, and procedures were explained both verbally and in writing to all participants and all participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Sport and Physical Education, University of Niš (approval ref: 04-2363/2; approval date: 17 December 2025 and Health Care Center, Leskovac (approval ref: 116; approval date: 19 January 2026).

Study design and procedures

This study employed a cross-sectional design. Due to the large sample size, blood sampling was conducted over a one-week period and 5 to 7 days prior to the laboratory testing session. All laboratory testing sessions were conducted in the morning hours (between 8:00 and 11:00 AM), and participants were scheduled according to their individual availability, attending the laboratory on a single visit. Upon arrival, anthropometric characteristics and body composition parameters were assessed under fasting conditions. Body height was determined to the nearest 0.1 cm using a standardized anthropometric set with a portable stadiometer (SECA model 284; SECA, Hamburg, Germany), while body composition parameters were assessed via tetrapolar bioelectrical impedance analysis (BIA) using a calibrated device (Omron BF511; Omron Healthcare, Kyoto, Japan). The measurements obtained included body mass, BMI, body fat percentage, and skeletal muscle mass percentage. Subsequently, resting blood pressure was measured following a 5-minute seated rest period. Participants then proceeded to an outdoor testing area to perform the Six-Minute Walk Test (6MWT).

Outcomes

Glycemic parameters

Glycemic control was evaluated through the assessment of fasting blood glucose (mmol/L), and HbA1c, %. Blood samples were collected via venipuncture from the cubital vein, previously disinfected with alcohol, in the morning hours between 7.00 and 10.00 AM, following an 8 – 12 h fasting period, and all procedures were performed by qualified clinical personnel. For the determination of fasting blood glucose, blood was collected into vacutainer tubes without anticoagulant additives and subsequently centrifuged for 15 minutes at 3.000 revolutions per minute. The isolated serum was then pipetted into sterile cuvettes for biochemical analysis using the Beckman Coulter DxC 700 AU Chemistry Analyzer. HbA1c was determined from whole blood collected into vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant to prevent coagulation and preserve sample integrity.

Six-Minute Walk Test (6MWT)

The Six-Minute Walk Test (6MWT) was performed in accordance with the guidelines of the American Thoracic Society (Singh et al., 2017). The test was conducted outdoors along a 30 m course, marked at every 3 m to ensure precise distance measurement, with a cone placed at the 30 m endpoint. Participants began from the starting line, walked to the cone, turned around, and repeated this activity continuously for 6 minutes, with the instruction to cover the greatest possible distance within the allotted time. Participants were informed that they could stop and rest if they experienced fatigue or any discomfort, while the timer continued to run; they resumed walking as soon as they were able.

Heart rate was continuously monitored throughout the duration of the test. The total distance walked in 6 minutes was recorded to the nearest meter. Peak oxygen uptake (VO_2peak) was subsequently estimated from the 6MWT using the following validated equation (Ross et al., 2010):

$VO_2peak\ (mL \cdot kg^{-1} \cdot min^{-1}) = (0.025 \times 6MWD\ [m]) + 4.682$

The 6MWT has previously been applied in individuals with T2DM as valid and reliable test (Nolen-Doerr et al., 2018; Lee, 2018).

Statistical analysis

All continuous variables are presented as mean ± standard deviation (SD) with 95% confidence intervals (95% CI). The normality of data distribution was assessed using the Kolmogorov-Smirnov test, and since normality was confirmed for all key variables, parametric statistical methods were applied. To examine the independent contribution of cardiorespiratory fitness to glycemic control, linear regression analysis was performed separately for each glycemic parameter (HbA1c and fasting blood glucose) as the dependent variable. For each outcome, two models were constructed: Model 1 (unadjusted) included relative and absolute VO_2peak as the sole predictor, while Model 2 (adjusted) additionally included age, T2DM duration, and BMI as clinically relevant covariates. Model fit was assessed using the F-test, and the proportion of explained variance was reported as R^2 and adjusted R^2. Unstandardized (B) and standardized (β) regression coefficients are reported alongside 95% CI and p-values. Statistical significance was set at $p < .05$. All analyses were performed using IBM SPSS Statistics (version 26.0; SPSS Inc., Chicago, IL, United States).

Results

Baseline characteristics of the 44 participants are presented in Table 1. The mean age was 52.20 ± 9.02 years, with a mean T2DM duration of 5.39 ± 4.65 years and BMI of 27.35 ± 2.54 kg/m². Mean fasting blood glucose was 7.93 ± 1.44 mmol/L and HbA1c was 7.05 ± 0.78 %. Cardiorespiratory fitness parameters included a mean relative VO_2peak of 16.97 ± 2.12 $mL \cdot kg^{-1} \cdot min^{-1}$ and absolute VO_2peak of 1.37 ± 0.26 $L \cdot min^{-1}$. On the 6MWT, participants covered a mean distance of 522.89 ± 92.22 m.

Table 1. Descriptive statistics of the participants

Variable	Mean ± SD
Demographics	
n (m/f)	44 (20/24)
Age (y)	52.20 ± 9.02
T2DM duration (y)	5.39 ± 4.65
Anthropometrics and body composition parameters	
Body height (cm)	172.30 ± 7.41
Body mass (kg)	81.06 ± 11.22
Skeletal muscle mass (%)	29.26 ± 3.69
Body fat (%)	33.44 ± 5.83
BMI (kg/m²)	27.35 ± 2.54
Glycemic parameters	
Fasting glucose (mmol/L)	7.93 ± 1.44
HbA1c (%)	7.05 ± 0.78
Hemodynamic parameters	
SBP (mmHg)	133.30 ± 11.15
DBP (mmHg)	84.45 ± 8.07
HR rest (bpm)	71.86 ± 10.45
Cardiorespiratory fitness parameters	
Distance covered on 6MWT (m)	522.89 ± 92.22
Absolute VO_2peak ($L \cdot min^{-1}$)	1.37 ± 0.26
Relative VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	16.97 ± 2.12
HRmax (bpm)	132.66 ± 8.88

BMI – body mass index; **HbA1c** – glycated hemoglobin; **SBP** – systolic blood pressure; **DBP** – diastolic blood pressure; **HR rest** – resting heart rate**; 6MWT** – six-minute walk test; **VO_2peak** – peak oxygen uptake; **HRmax** – maximal heart rate

Regression analysis showed that for HbA1c, the unadjusted model (Model 1) revealed a significant negative association with relative VO_2peak (B = -0.12, 95% CI: -0.23 to -0.01, β = -0.33, p = .03), with relative VO_2peak explaining 10.7% of the variance in HbA1c (R^2 = 0.11, F (1, 42) = 5.03, p = .03). Following adjustment for participants' age, T2DM duration, and BMI (Model 2), this association was insignificant (B = -0.09, p = .13), and the overall model did not reach significance F (4, 39) = 1.51, p = .22; R^2 = 0.13). Absolute VO_2peak was not significantly associated with HbA1c in either the unadjusted (p = .31) or adjusted model (p = .22) (Table 2).

For fasting blood glucose, neither relative nor absolute VO_2peak demonstrated a significant association in unadjusted or adjusted models. Although the adjusted model with relative VO_2peak yielded the highest R^2 value for fasting blood glucose (R^2 = 0.14), the overall model did not reach statistical significance F (4, 39) = 1.64, p = .19). In the adjusted fasting blood glucose models, age was the only significant predictor (B = 0.07, 95% CI: 0.01 to 0.13, p = .04), indicating that each additional year of age was associated with a 0.069 mmol/L increase in fasting blood glucose, after controlling for VO_2peak, T2DM duration, and BMI. Neither T2DM duration nor BMI reached statistical significance in any of the models (Table 2).

Table 2. Regression models for the association between cardiorespiratory fitness and glycemic parameters

Variable	Model 1 (unadjusted)				Model 2 (adjusted)			
	B	95% CI	β	p	B	95% CI	β	p
HbA1c (%)								
Relative VO_2peak (mL·kg⁻¹·min⁻¹)	-0.12	-0.23 to -0.01	-0.33	.03*	-0.09	-0.22 to 0.03	-0.25	.13
Absolute VO_2peak (L·min⁻¹)	-0.46	-1.37 to 0.44	-0.16	.31	-0.37	-1.66 to 0.39	-0.22	.22
Age (y)					-0.01	-0.03 to 0.03	-0.02	.91
T2DM duration (y)					0.03	-0.04 to 0.09	0.15	.47
BMI (kg/m²)					0.04	-0.06 to 0.14	0.14	.40
R^2 (relative VO_2peak)	0.11				0.13			
F (p)	F (1, 42) = 5.03, p = .03				F (4, 39) = 1.51, p = .22			
R^2 (absolute VO_2peak)	0.025				0.117			
F (p)	F (1, 42) = 1.01, p = .31				F (4, 39) = 1.29, p = .29			
Fasting blood glucose (mmol/L)								
Relative VO_2peak (mL·kg⁻¹·min⁻¹)	-0.13	-0.34 to 0.07	-0.11	.20	-0.13	-0.35 to 0.09	-0.19	.25
Absolute VO_2peak (L·min⁻¹)	-0.41	-2.10 to 1.27	-0.08	.62	-0.62	-2.50 to 1.27	-0.14	.51
Age (y)					0.07	0.01 to 0.13	0.44	.04*
T2DM duration (y)					-0.08	-0.21 to 0.04	-0.27	.20
BMI (kg/m²)					-0.02	-0.16 to 0.20	0.03	.83
R^2 (relative VO_2peak)	0.04				0.14			
F (p)	F (1, 42) = 1.72, p = .20				F (4, 39) = 1.64, p = .19			
R^2 (absolute VO_2peak)	0.01				0.12			
F (p)	F (1, 42) = 0.24, p = .62				F (4, 39) = 1.37, p = .26			

BMI – body mass index; **B** – unstandardized regression coefficient; **β** – standardized regression coefficient; **HbA1c** – glycated hemoglobin; **VO_2peak** – peak oxygen uptake; **R^2** – coefficient of determination**; 95% CI** – 95% confidence interval; ***** - significance

Discussion

The main findings of this study are the following: 1) relative VO_2peak was significantly and inversely associated with HbA1c in individuals with T2DM in the unadjusted model, explaining 10.7% of the variance in HbA1c. However, this association was attenuated and became non-significant after adjustment for age, T2DM duration, and BMI; 2) neither relative nor absolute VO_2peak was significantly associated with fasting blood glucose; 3) age emerged as the only independent predictor of fasting blood glucose, with each additional year associated with a 0.07 mmol/L increase in fasting blood glucose.

The existing literature on the relationship between CRF and HbA1c reports inconsistent findings. While some authors (Fang et al., 2005; Brassard et al., 2006; Bacchi et al., 2014; Gürdal, Kasikcioglu, Yakal & Bugra, 2015; Tayade, Chitta, Rode & Phatak, 2017), have found non-significant associations, the present study aligns with those that have demonstrated inverse relationships between CRF and HbA1c (Fang et al., 2005; Gürdal et al., 2015; Tayade et al., 2017). Specifically, Fang et al. (2005) showed that VO_2peak is a significant determinant of HbA1c in individuals with T2DM, with an inverse association with HbA1c that persisted even after adjustment for age and BMI. Similarly, Gürdal et al. (2015) reported a significant negative correlation between VO_2peak and HbA1c in normotensive T2DM individuals without coronary artery disease. More recently, Alvares et al. (2024) confirmed that the magnitude of CRF impairment is significantly associated with HbA1c levels across individual studies. However, Alvares et al. (2024) included both T1DM and T2DM individuals and found that BMI and sedentary behavior were more associated with impaired CRF than HbA1c itself. In our study, the magnitude of the unadjusted association between relative VO_2peak and HbA1c was small to moderate. Consequently, this underscores that HbA1c is a multifactorial outcome shaped by medication treatment, dietary habits, and individual metabolic heterogeneity. This further justifies the adjustment for age, T2DM duration, and BMI in our regression model after which the association between VO_2peak and HbA1c was no longer significant. This is further supported by Roberts et al. (2018) who observed that the association between VO_2peak and HbA1c weakened when age, sex, and T2DM duration were simultaneously entered into the model, meaning that the relationship between CRF and HbA1c may be partially mediated by shared confounders in T2DM. Nevertheless, the findings should be interpreted with caution due to the limited sample size. Furthermore, participants in our study had well-controlled glycemia (HbA1c: 7.05 ± 0.78%), which likely restricted the range of glycemic variation available to detect significant associations after adjustment.

Another interesting finding is that only relative VO_2peak demonstrated a significant association with HbA1c whereas absolute VO_2peak did not. This differential pattern is biologically coherent. Relative VO_2peak inherently incorporates body mass, making it a more sensitive indicator of CRF that is directly relevant to whole-body metabolic regulation particularly in populations characterized by excess adiposity and insulin resistance, as is typical in T2DM (Chandrasekaran & Weiskirchen, 2024; Zhou, 2021). In contrast, absolute VO_2peak reflects total oxygen consumption capacity without adjustment for body mass (Ross et al., 2016), and may therefore be less sensitive to the weight-mediated metabolic pathways linking CRF to glycemic control (Goran et al., 2000).

On the other hand, neither relative nor absolute VO_2peak was significantly associated with fasting blood glucose in any model. This finding is consistent with the claim that CRF is more mechanistically aligned with chronic rather than acute glycemic regulation. More precisely, HbA1c integrates average plasma glucose over three months (Nathan et al., 2008), reflecting the cumulative metabolic environment including sustained insulin resistance, endothelial dysfunction (Montero, 2015), and chronic low-grade inflammation (Church et al., 2002), all of which determine CRF. In contrast, fasting blood glucose represents a single time-point measurement subject to considerable day-to-day variability driven by hepatic glucose output, pharmacological effects of antidiabetic medications, dietary intake, and counter-regulatory hormones (Muggeo et al., 2000; Spyer, Hattersley, MacDonald, Amiel & MacLeod, 2000; Bock et al., 2007), which are independent of CRF. Solomon et al. (2015) reported similar findings across the glucose tolerance continuum, demonstrating that VO_2max showed stronger inverse associations with HbA1c than with fasting blood glucose. Finally, an interesting finding was that age was the only independent predictor of fasting blood glucose in both adjusted models, indicating that each additional year of age was associated with a 0.069 mmol/L increase in fasting blood glucose, independent of CRF, T2DM duration, and BMI. This finding is consistent with established evidence that aging independently impairs fasting glucose regulation through reduced hepatic insulin sensitivity, diminished first-phase insulin secretion capacity, and increased basal

gluconeogenesis driven by age-related declines in mitochondrial function and muscle mass (Chang & Halter, 2003; Huang et al., 2023).

The strength of this study is that by accounting for confounding variables such as age, T2DM duration, and BMI in our regression models, we were able to demonstrate that the initial association between CRF and HbA1c is largely mediated by anthropometric and demographic factors rather than being an independent physiological link. Several limitations warrant acknowledgment. The sample size of 44 participants limits statistical power, precluding the inclusion of additional clinically relevant covariates such as medication type and sex. CRF was estimated via the 6MWT rather than directly measured by CPET; while the 6MWT demonstrates adequate validity in T2DM individuals, some measurement imprecision inherent to field-based estimation is acknowledged. Finally, the cross-sectional design precludes causal inference regarding the direction of the CRF – glycemic control relationship.

Conclusion

The study demonstrated that relative VO_2peak is significantly and inversely associated with HbA1c in adults with T2DM, independently explaining 10.7 % of the variance. This association was attenuated following adjustment for age, T2DM duration, and BMI. Neither relative nor absolute VO_2peak demonstrated significant associations with fasting blood glucose in any model, suggesting that CRF is more closely linked to chronic than acute glycemic regulation in this population. Age emerged as the only independent predictor of fasting blood glucose in the adjusted models, underscoring its role as a primary determinant of fasting glycemia independent of fitness level. Collectively, these findings support the clinical relevance of CRF assessment in T2DM management and highlight the 6MWT as a practical, accessible tool for evaluating CRF in individuals with T2DM.

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