






Metabolic and physiological responses to graded exercise testing in individuals with type 1 diabetes using insulin pump therapy

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Abstract

Aims: To profile acute glycaemic dynamics during graded exercise testing (GXT) and explore the influence of glycaemic indicators on the physiological responses to GXT in adults with type 1 diabetes using insulin pump therapy.

Methods: This was a retrospective analysis of pooled data from four clinical trials with identical GXT protocols. Data were obtained from 45 adults with type 1 diabetes using insulin pumps [(30 females); haemoglobin A1c 59.5 ± 0.5 mmol/mol ($7.6 \pm 1.0\%$); age 49.7 ± 13.0 years; diabetes duration 31.2 ± 13.5 years; $\dot{V}O_{2\text{peak}}$ 29.5 ± 8.0 ml/min/kg]. Integrated cardiopulmonary variables were collected continuously via spiroergometry. Plasma glucose was obtained every 3 min during GXT as well as the point of volitional exhaustion. Data were assessed via general linear modelling techniques with age and gender adjustment. Significance was accepted at $p \leq .05$.

Results: Despite increasing duration and intensity, plasma glucose concentrations remained similar to rest values (8.8 ± 2.3 mmol/L) throughout exercise ($p = .419$) with an overall change of $+0.3 \pm 1.1$ mmol/L. Starting glycaemia bore no influence on subsequent GXT responses. Per 1% increment in haemoglobin A1c there was an associated decrease in $\dot{V}O_{2\text{peak}}$ of 3.8 ml/min/kg ($p < .001$) and power_{peak} of 0.33 W/kg ($p < .001$) concomitant with attenuations in indices of peripheral oxygen extraction [(O_2 pulse) -1.2 ml/beat, $p = .023$].

Conclusion: In adults with long-standing type 1 diabetes using insulin pump therapy, circulating glucose remains stable during a graded incremental cycle test to volitional exhaustion. Glycaemic indicators are inversely associated with aerobic rate, oxygen economy and mechanical output across the exercise intensity spectrum. An

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appreciation of these nexuses may help guide appropriate decision making for optimal exercise management strategies.

KEYWORDS

type 1 diabetes, exercise, cardiopulmonary exercise testing, insulin pump therapy, graded exercise testing, plasma glucose

1 | INTRODUCTION

Cardiopulmonary exercise testing provides a comprehensive assessment of multiple physiological systems on a continuum from rest to volitional exhaustion.¹ In clinical research and rehabilitation settings, graded exercise testing (GXT) is recognized as a prototypical method for evaluating exercise tolerance and has been employed to help determine mortality risk, suitability for surgery and disease susceptibility.²⁻⁴

Although not ubiquitous,⁵⁻⁷ the majority of evidence points to an attenuated maximal aerobic rate in adults with type 1 diabetes (T1D)⁸⁻¹¹ concomitant with altered cardiovascular^{12,13} and pulmonary^{6,9,13,14} responses to GXT. Some,^{12,14-17} but not all studies,^{18,19} have indicated that glycaemic control plays a seminal role determining the physiological responses to GXT. However, compiled analysis on these studies shows that such conclusions have been drawn from rather homogeneous cohorts who are relatively young (age 34 ± 5 years), reasonably fit ($\dot{V}O_{2peak}$ 36 ± 7 ml/min/kg), modestly well controlled [haemoglobin A1c (HbA1c) $7.4 \pm 0.8\%$] and have a medium length of diabetes duration (13 ± 6 years). In addition, the majority of data have been sourced from individuals treated with multiple daily injections of insulin, representing $\sim 70\%$ of the studied population. Hence, the extent to which these relationships exist in a wider, heterogeneous cohort of exclusively insulin pump users is unknown.

A clear research emphasis has been placed on investigating the influence of general glycaemic control rather than ambient glucose levels during exercise on GXT outcomes. Although the trajectory of circulating glucose in those with T1D is somewhat known with low to moderate, and high intensity activities of a fixed duration,²⁰ GXT encompasses constant changes in both exercise duration and intensity. It therefore provides a unique opportunity to gain insight into the integrated functioning of several physiological systems across the entire exercise-intensity spectrum. Yet, despite its routine incorporation in clinical rehabilitation and research settings, there remains a scarcity of information on glucose dynamics throughout GXT, particularly in those treated with insulin pumps. Given the potential divergence in glycaemia with different delivery methods of insulin, as well as the increasing popularity of insulin pumps for the management of T1D, investigations of this nature are timely in providing up-to-date information that supports decision making in clinical care.

The aim of this study was two-fold: (a) to profile acute glycaemic dynamics during GXT, and (b) explore the influence of glycaemic

indicators on the physiological responses to GXT in adults with T1D using insulin pump therapy.

2 | METHODS AND MATERIALS

2.1 | Study design

This study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Committee of Denmark. All participants were provided with a full written and verbal description of the study and gave informed consent before taking part. The study was retrospective and involved a pooled data set derived from four separate randomized controlled trials (Clinical trials.gov: NCT04472962, NCT05268705, NCT05134025, NCT05133765) that included identical GXT protocols and pre-visit preparatory procedures.

2.2 | Inclusion and exclusion criteria

The main study inclusion criteria were: diagnosis of T1D for ≥ 2 years, aged 18-75 years (both inclusive), treatment with insulin pumps for ≥ 12 months, use of a continuous, or intermittently scanned, glucose monitoring system for ≥ 3 months, familiar with carbohydrate counting, use of the insulin pump bolus calculator for most snacks and meals.

The main exclusion criteria were: women who were breast-feeding, pregnant, or planning to become pregnant during the trial period, use of antidiabetic medicine (other than insulin), use of corticosteroids or other drugs affecting glucose metabolism during, or within 30 days prior to, the study period, daily use of paracetamol (acetaminophen), evidence of alcohol or drug abuse, presence of severe cardiac disease or retinopathy contraindicating a HbA1c of $< 7\%$ (53 mmol/mol), presence of any other concomitant medical or psychological condition that could interfere with study participation.

2.3 | Participant characteristics

Data from, in total, 45 adults with T1D [30 females (67%)] were included in this study. Baseline characteristics of the included cohort are displayed in Table 1. Information regarding comorbidities as well as baseline characteristics when participants were split into groups

TABLE 1 Baseline characteristics of study participants

Characteristic	Mean \pm SD	Range (min-max)
Age (years)	49.7 \pm 13.0	47 (25-72)
BMI (kg/m ²)	26.2 \pm 3.7	14.5 (19.3-33.8)
HbA1c (%)	7.6 \pm 1.0	4.5 (5.5-10.0)
Diabetes duration (years)	31.2 \pm 13.5	45 (12-57)
Age of diabetes onset (years)	18.6 \pm 13.0	43 (0-43)
Total daily insulin dose (U/kg)	0.5 \pm 0.2	0.6 (0.3-0.9)
Total daily bolus insulin dose (U)	20.0 \pm 9.0	36.1 (3.9-40.0)
Total daily basal insulin dose (U)	18.7 \pm 7.2	30.6 (8.0-38.6)
Average daily CHO intake (g)	133 \pm 58	232 (53-285)
Average 14-day BG (mmol/L)	9.8 \pm 1.7	8.4 (5.7-14.1)
Average 14-day BG measurements (no. of days)	5 \pm 3	12 (1-13)
Average 14-day SG (mmol/L)	8.7 \pm 1.3	6.1 (6.3-12.4)
Average 14-day SG TBR (%)	3 \pm 3	9 (0-9)
Average 14-day SG CoV (%)	35.3 \pm 4.8	20 (26-46)
Average 14-day SG TIR (%)	66 \pm 13	49 (39-88)
Average 14-day SG TAR (%)	31 \pm 14	50 (11-61)
Systolic blood pressure (mmHg)	132 \pm 12	49 (106-155)
Diastolic blood pressure (mmHg)	80 \pm 9	41 (55-96)
Mean arterial pressure (mmHg)	97 \pm 8	36 (79-115)
Resting heart rate (bpm)	67 \pm 11	46 (49-95)
HDL (mmol/L)	2.0 \pm 0.5	1.9 (1.2-3.1)
LDL (mmol/L)	2.2 \pm 0.5	2.4 (1.1-3.5)
VLDL (mmol/L)	0.4 \pm 0.2	0.8 (0.1-0.9)
Triglycerides (mmol/L)	0.8 \pm 0.3	1.3 (0.3-1.6)
Total cholesterol (mmol/L)	4.5 \pm 0.7	2.5 (3.3-5.8)

Note: data are presented as mean \pm SD as well as the range (minimum to maximum) in values.

Abbreviations: BG, blood glucose (quantified via glucometer-derived capillary finger-tip sampling); BMI, body mass index; CHO, carbohydrates; CoV, coefficient of variation; HbA1c, haemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SG, sensor glucose; TAR, time spent with sensor glucose values above the target range (>10.0 mmol/L); TBR, time spent with sensor glucose values below the target range (<3.9 mmol/L); TIR, time spent with sensor glucose values within the target range (3-9 to 10.0 mmol/L); VLDL, very low-density lipoprotein.

based on HbA1c, and cardiorespiratory fitness (CRF) can be found in supplementary file; Tables S1, S2 and S5, respectively.

Participants were using a range of different insulin pumps: Medtronic [(Northridge, CA, USA) $n = 28$; MiniMed 640G ($n = 14$), MiniMed 670G ($n = 1$), MiniMed 780G ($n = 10$), Paradigm Veo ($n = 3$); Insulet [(Bedford, MA, USA) $n = 9$ Omnipod DASH]; Tandem Diabetes [(San Diego, CA, USA) $n = 5$ t:slim X2]; YPSOMED [(Burgdorf, Switzerland) $n = 1$ YpsoPump]; and Roche Diabetes Care [(Mannheim, Germany) $n = 2$ Accu-Chek Insight]. Of the 45 participants, 39 (87%) were using insulin Aspart with the remaining six using Fast-acting insulin Aspart (NovoNordisk, Bagsværd, Denmark).

2.4 | Preparatory procedures before experimental trail days

Before laboratory attendance, participants were asked to avoid caffeine for 12 h as well as alcohol and physical exercise for 24 h. Participants were also encouraged to be vigilant in the avoidance of hypoglycaemia (defined as a capillary fingertip blood glucose value of ≤ 3.9 mmol/L) in the 24 h before their arrival. Participants were advised to maintain their routine insulin dose regimen and consume a meal ≥ 2 h ahead of their scheduled appointment. If they were to eat within this window, participants were instructed to take a 10%-20% reduction in their mealtime insulin dose.

2.5 | Glycaemic safety monitoring on experimental trial days

Upon arrival to the laboratory, participants were screened by a member of the research team and study physician. Following successful inclusion against the study protocol criteria, participants provided a glucose measurement 15 min before the anticipated start time for GXT. If, at this point, the glucose value was < 5 mmol/L, GXT was delayed, and participants consumed 15 g of carbohydrates in the form of dextrose tablets (Dextro Energy GmbH & Co. KG, Krefeld, Germany). A second glucose measurement was obtained 15 min later, and the process repeated until glucose was above the target threshold (≥ 5 mmol/L). Nine people were given supplementary carbohydrates ahead of GXT. The amount of carbohydrates consumed was included as a covariate in subsequent statistical modelling. If the glucose concentration was ≥ 15.0 mmol/L and blood ketones levels were low (< 0.6 mmol/L), exercise went ahead at the discretion of the participant with frequent monitoring for ketone body formation. If ketone levels were above 1.5 mmol/L, the visit was cancelled and rescheduled.

2.6 | Graded exercise testing protocol

In each study, participants performed a GXT on a workload-controlled cycle ergometer (Corival, Lode©, Groningen, The Netherlands and Monark LC4, Vansbro, Sweden). A predetermined protocol was employed that consisted of a 3-min passive resting phase, before a standardized 3-min warm up phase (20 W), followed by 1-min increases in workload until volitional exhaustion. Volitional exhaustion was defined by one or more of the following parameters: (a) an inability to maintain a pedalling cadence of > 50 rpm for > 5 s; (b) a respiratory exchange ratio of > 1.1 ; (c) an age predicted heart rate of $\geq 85\%$.^{21,22} At the point of exhaustion, the workload immediately decreased to 20 W and participants engaged in a 3-min active recovery phase before completing a final 3-min passive recovery period. To ensure a reasonably similar exercise duration between participants, the incremental increase in work rate occurred in either 15 ($n = 21$) or 20 ($n = 24$) W/min depending on participants' habitual physical

activity patterns determined via the International Physical Activity Questionnaire and a conversation with the researcher.

2.7 | Graded exercise testing measurements

Breath by breath data were measured using a pulmonary gas analyser (Vyntus™ ONE; Vyair Medical, Mettawa, IL, USA) calibrated using certified gases (Gas 1: Ambient Air; Gas 2: 15% O₂, 5% CO₂) with data displayed for standardized temperature and pressure for dry air. Integrated heart rate data were recorded continuously via chest belt telemetry (Polar Electro, Finland). Raw cardiopulmonary data were exported in 5-s intervals (SentrySuite™ software; Vyair Medical) and subsequently averaged in 30-s segments for statistical processing.

The peak rate of O₂ consumption ($\dot{V}O_{2peak}$) was defined as highest O₂ uptake (L/min) obtained in the 30 s before the test cessation. $\dot{V}O_{2peak}$ was utilized over $\dot{V}O_{2max}$ because of an inability to identify a plateau in some participants' O₂ consumption rates because of the short duration of exercise test and/or volitional termination occurring rapidly upon attainment of peak power. All other cardiopulmonary and performance parameters were indexed to the $\dot{V}O_{2peak}$ value. Using raw gas exchange data, the anaerobic threshold (AT) was computed via the Exercise Threshold App²³ with other cardiopulmonary variables timed-referenced against the indexed $\dot{V}O_2$ value.

2.8 | Blood sampling procedures

Venous-derived whole blood samples (taken from an indwelling cannula placed in the antecubital fossa) were obtained at rest, every 3 min during GXT, at the point of volitional exhaustion and during the active and passive recovery periods. Samples were centrifuged at 3000 rpm for 30 s then the resultant supernatant (plasma) was processed immediately via the YSI 2500 Biochemistry Analyzer (YSI Inc., Yellow Springs, OH, USA) to determine point concentrations of glucose (PG) and lactate (PLa).

2.9 | Data stratification and statistical analyses

Participants were grouped into CRF quartiles based on their $\dot{V}O_{2peak}$ values in 5 ml/min/kg brackets from the lowest to highest rankings. Participants were also stratified by sex to examine possible sexual dimorphisms (Table S5, supplementary file) and well as HbA1c tertiles in 1% increments (<7%, 7%-8% and ≥8%, Table's S2 and S3, supplementary file). All statistical analyses were carried out using IBM SPSS 26.0 (IBM Corp. Armonk, IL, USA) and presented as mean ± SD, unless otherwise stated. A repeated measures-ANOVA on six levels with Bonferroni-corrected pairwise comparisons was used to examine changes in acute metabolic (PG and PLa) and cardiopulmonary parameters throughout GXT. Between-group differences in exercise outcomes when participants were stratified into quartiles based on CRF and tertiles based on HbA1c were assessed via general linear

modelling (univariate and/or multivariate analyses) with age and sex accounted for as covariates and Bonferroni adjustment used in post-hoc analyses for pairwise comparisons. Sex differences were treated with age as a covariate. Linear regression was used to assess the predictive value of diabetes and anthropometric variables of GXT outcomes with regression estimates used to magnitude of effect. Multinomial logistic regression was used to assess relationships between comorbidity status and classification of aerobic fitness using the highest CRF quartile as the reference group. The chi-square test of independence (χ^2) was used to determine differences between categorical variables. Alpha was set at .05 and statistical significance was accepted when $p \leq .05$.

3 | RESULTS

3.1 | Physiological responses to graded exercise testing

The physiological responses to GXT at the AT and at peak workload are detailed in Table 2.

The total test duration [including 3 min of passive sitting, 3 min of an active warm up and 6 min of active and passive recovery periods (3 min each)] was 20.1 ± 4.0 min.

3.2 | Acute plasma glucose responses to graded exercise testing

Figure 1 displays the PG responses to GXT when data are expressed as (Figure 1A) the absolute concentrations across the work domain, (Figure 1B) the change from starting values at each stage across the work domain, (Figure 1C) the relationship between immediate pre- and post-exercise concentrations, and (Figure 1D) the individualized change in PG from immediately pre- to post-exercise when participants were ranked in descending order (highest to lowest) based on their starting PG levels.

There was no change in PG concentrations across each stage of GXT, Wilks' lambda = 0.828, F(5,25) = 1.035, $p = .419$ (Figure 1A) with values remaining comparable with rested levels throughout each stage of the test (Figure 1B).

The overall change in PG from start to end was +0.3 ± 1.1 mmol/L (black bar, Figure 1D) at a rate of 0.01 ± 0.06 mmol/L/min.

Although a higher PG at the beginning of GXT was associated with a higher glucose concentration upon test cessation ($\beta = 0.887$, $p < 0.001$; 95% CI: 0.737 to 1.018) (Figure 1C), starting PG levels did not necessarily dictate the overall change ($\beta = -0.261$, $p = .084$; 95% CI: -0.265 to 0.017); 57% of people experienced a rise in PG over exercise ($\Delta +1.0 \pm 0.8$ mmol/L) while 42% experienced a decline ($\Delta -0.6 \pm 0.5$ mmol/L).

The starting PG had no influence on cardiopulmonary or subsequent metabolic responses to GXT, nor did it influence the length of time it took to reach exhaustion. Although sex differences were

TABLE 2 Physiological responses to graded exercise testing at the anaerobic threshold and at peak work rates

Intensity domain	Parameter	Mean ± SD	Range (min-max)
AT	$\dot{V}O_2$ (ml/kg/min)	24.0 ± 6.4	26.2 (12.73-38.94)
	$\dot{V}O_2$ (L/min)	1.8 ± 0.6	2.9 (0.7-3.6)
	AT relativised to $\dot{V}O_{2peak}$ (%)	81.4 ± 5.0	23.8 (75.3-99.1)
	Power (W/kg)	1.8 ± 0.6	2.2 (0.7-2.8)
	HR (bpm)	135 ± 17	71 (102-173)
	O ₂ pulse (ml/beat/min)	13.4 ± 3.6	17.2 (5.9-23.1)
	$\dot{V}E$ (L/min)	48.7 ± 16.8	78.0 (20.0-98.0)
	RER	0.9 ± 0.1	0.4 (0.7-1.1)
	$\dot{V}E/\dot{V}O_2$	26.5 ± 3.7	17.2 (18.1-35.3)
	$\dot{V}E/\dot{V}CO_2$	28.3 ± 3.5	16.7 (20.1-36.8)
	CHO oxidation (g/min)	2.1 ± 1.3	6.5 (0.5-7)
	Lipid oxidation (g/min)	0.2 ± 0.2	0.6 (0.0-0.6)
	Time to reach (min)	11.9 ± 2.3	11.8 (7.0-18.8)
Peak	$\dot{V}O_2$ (ml/kg/min)	29.5 ± 8.0	34.7 (12.1-46.8)
	$\dot{V}O_2$ (L/min)	2.3 ± 0.7	3.6 (0.9-4.5)
	Power (W/kg)	2.8 ± 0.7	2.7 (1.4-4.1)
	HR (bpm)	166 ± 15	65 (133-198)
	HR (% predicted)	97.6 ± 6.6	33.3 (84.1-117.4)
	O ₂ pulse (ml/beat/min)	13.5 ± 4.2	20.4 (5.4-25.7)
	$\dot{V}E$ (L/min)	88.8 ± 28.6	124.9 (34.6-159.4)
	RER	1.2 ± 0.1	0.5 (1.0-1.4)
	$\dot{V}E/\dot{V}O_2$	39.6 ± 6.0	31.6 (23.6-55.2)
	$\dot{V}E/\dot{V}CO_2$	32.7 ± 4.4	16.7 (24.4-41.4)
	CHO oxidation (g/min)	5.2 ± 1.7	6.8 (2.0-8.8)
	Lipid oxidation (g/min)	-	-
	Time to reach (min)	15.9 ± 2.8	12.8 (10.0-22.8)

Note: data are presented as mean ± SD as well as the range (minimum to maximum) in values. Abbreviations: AT, anaerobic threshold; CHO, carbohydrate; HR, heart rate; RER, respiratory exchange ratio; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide; $\dot{V}E/\dot{V}O_2$, ventilatory equivalents for oxygen; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, volume of oxygen consumed.

observed in cardiopulmonary responses to GXT (supplementary file, Table S4) there were no sexual dimorphisms in PG responses (Δ start to end; males $+0.4 \pm 1.6$ vs. females $+0.3 \pm 0.8$ mmol/L, $p = .866$) with equivalent glucose concentrations between sexes across each stage of the workload ($p = .652$). Similarly, there were no differences in PG responses between those with ($n = 10$) versus without ($n = 35$) pumps with automated insulin delivery features (Δ start to end; $+0.3 \pm 1.1$ vs. $+0.3 \pm 0.12$ mmol/L, respectively, $p = .954$).

3.3 | Acute plasma lactate responses to graded exercise testing

PLa concentrations were significantly elevated from rested concentrations at each stage of GXT, Wilks' lambda = 0.122, $F(5,26) = 37.306$, $p < .001$. PLa concentrations were 1.7 ± 0.8 mmol/L at the AT and rose to 6.0 ± 2.6 mmol/L at peak work rates culminating after the recovery phase (7.7 ± 2.9 mmol/L).

3.4 | Influence of glycated haemoglobin on the physiological responses to graded exercise testing

HbA1c predicted $\dot{V}O_{2peak}$ $F(3,41) = 13.99$, $p < .001$, adjusted $R^2 = 0.470$ even after adjustment for age and sex. The regression coefficient [$B = -3.795$, 95% CI (-5.845 to -1.745)] indicated that an increase in HbA1c of 1% was associated with a decrease in $\dot{V}O_{2peak}$ value of 3.8 ml/min/kg.

HbA1c was also predictive of peak power output [$F(3,44) = 9.812$, $p < .001$, adjusted $R^2 = 0.375$] (Figure S3B). The regression coefficient [$B = -0.331$, 95% CI (-0.538 to -0.124)] indicated that an increase in HbA1c of 1% corresponded, on average, to a decrease in power output by 0.33 W/kg.

When participants were stratified into tertiles based on 1% increments in HbA1c [$<7\%$ (total $n = 12$, females $n = 9$), 7% - 8% (total $n = 17$, females $n = 8$), $\geq 8\%$ (total $n = 16$, females $n = 13$)] $\chi^2 = 4.847$, $p = .089$, those with HbA1c levels $\geq 8\%$ had notably lower $\dot{V}O_{2peak}$ values than those with $<7\%$ (24.5 ± 7.9

vs. 34.5 ± 6.8 ml/min/kg, respectively, $p = .021$) while the decrement relative to those in the 7%-8% tertile was similar (-6 ml/min/kg, $p = 1.00$).

Differences in GXT parameters between HbA1c tertiles can be found in supplementary file Table S3.

3.5 | Predictors of exercise outcomes during graded exercise testing

Table 3 shows the results from a multiple regression model performed to predict GXT outcomes from various anthropometric (age, body mass index, sex), diabetes-specific (HbA1c, diabetes duration) and acute metabolic (pre-exercise PG levels) parameters.

3.6 | Influence of cardiorespiratory fitness on the physiological responses to graded exercise testing

Table 4 shows the physiological responses to GXT when participants were stratified into quartiles based on CRF. There was an equal

distribution of people and sexes between groups [very low total $n = 13$ (females $n = 10$); low total $n = 12$ (females $n = 9$); moderate total $n = 8$ (females $n = 5$); high total $n = 12$ (females $n = 6$); $\chi^2 = 2.55$, $p = .466$].

Relative to those ranked in the highest quartile of CRF, those in the lowest quartile had lower physiological responses to GXT including peak aerobic rate, oxygen economy and mechanical power output (Table 4). Baseline characteristics of participants when stratified into CRF quartiles can be found in the supplementary file, Table S5.

4 | DISCUSSION

For decades, GXT has served as an established and validated method for diagnostic and prognostic assessment of cardiovascular disease risk in the clinical setting. Yet despite its widespread integration in rehabilitation and research settings, there is scant information detailing the acute glycaemic responses that occur throughout GXT in people with T1D using insulin pumps. Furthermore, there is poor understanding of the influence of glycaemic indicators of the physiological responses to incremental,

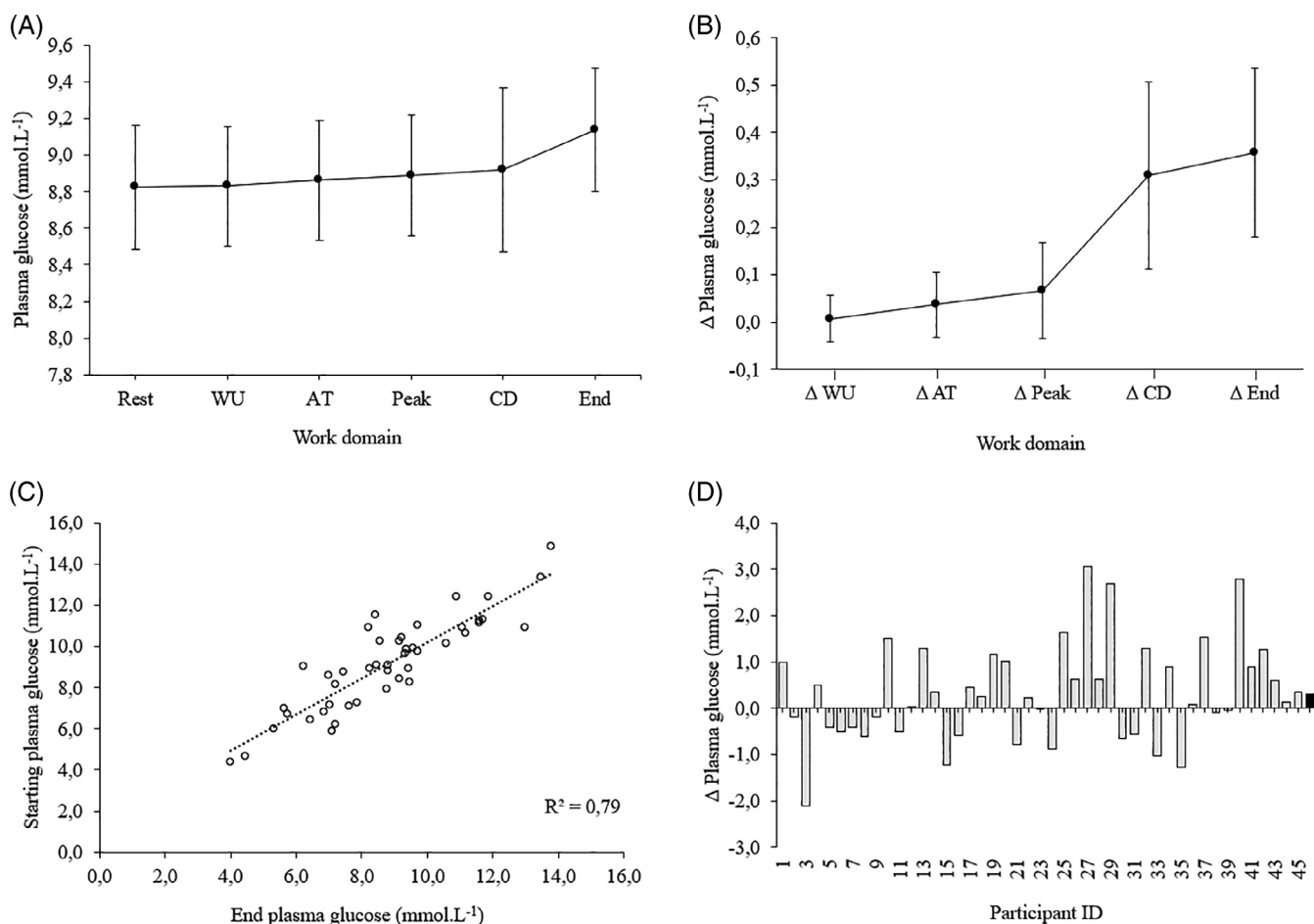


FIGURE 1 Plasma glucose responses to graded exercise testing when data are expressed as (A) the absolute concentrations across the work domain, (B) the change from starting values at each stage across the work domain (C) the relationship between immediately pre- and post-exercise concentrations, and (D) the individualized change from rest to end when participants have been ranked in descending order (highest to lowest) based on their starting plasma glucose levels. AT, anaerobic threshold; CD, cool down; WU, warm up

TABLE 3 Predictors of exercise outcomes at peak work rates and at the anaerobic threshold during graded exercise testing from various anthropometric, diabetes-specified and acute metabolic parameters

Parameter	$\dot{V}O_{2AT}$	$\dot{V}O_{2peak}$	Power _{AT}	Power _{peak}	HR _{AT}	HR _{peak}	PLa _{AT}	PLa _{peak}	O ₂ pulse _{AT}	O ₂ pulse _{peak}	Time _{toAT}	Time _{topeak}
Standardized coefficients β												
Age (years)	-0.242	-0.221	-0.402**	-0.364**	-0.499**	-0.654**	-0.465*	-0.734**	-0.103	-0.035	-0.295	-0.371
BMI (kg/m ²)	-0.334**	-0.318**	-0.333**	-0.438**	-0.284*	-0.310*	0.025	-0.113	0.206	0.164	0.091	0.071
Sex (1 = M, 2 = F)	-0.341**	-0.327**	-0.379**	-0.313**	-0.030	0.058	-0.249	-0.410**	-0.686**	-0.607**	-0.574**	-0.582**
HbA1c (%)	-0.371**	-0.394**	-0.305*	-0.304*	-0.230	-0.018	-0.043	0.181	-0.252*	-0.355**	-0.126	-0.038
Diabetes duration (years)	-0.084	-0.169	0.074	0.075	-0.100	-0.083	0.004	0.011	-0.089	-0.181	-0.045	0.055
Starting PG (mmol/L)	-0.049	-0.040	-0.052	-0.074	0.053	0.037	-0.047	-0.143	-0.006	0.028	0.057	0.017
R	0.756	0.785	0.761	0.761	0.756	0.768	0.521	0.734	0.802	0.786	0.692	0.660
R ²	0.571	0.616	0.579	0.580	0.571	0.590	0.271	0.538	0.643	0.618	0.479	0.436
Adjusted R ²	0.503	0.555	0.513	0.513	0.498	0.520	0.156	0.465	0.581	0.553	0.387	0.347
Final model p-value	<.001	<.001	<.001	<.001	<.001	<.001	.049	>.001	>.001	>.001	<.001	.001

Abbreviations: AT, anaerobic threshold; BMI, body mass index; HbA1c, glycated haemoglobin; HR, heart rate; O₂, oxygen; PG, plasma glucose; PLa, plasma lactate; $\dot{V}O_2$, volume of inhaled oxygen.

* $p \leq .05$.

** $p \leq .01$.

TABLE 4 Physiological responses to graded exercise testing when participants were stratified into cardiorespiratory fitness quartiles based on their $\dot{V}O_{2\text{peak}}$ values

Parameter	Very low (<25 ml/min/kg)	Low (≥ 25 to <30 ml/min/kg)	Moderate (≥ 30 to <35 ml/min/kg)	High (≥ 35 ml/min/kg)	p Value
Time to reach _{AT} (min)	10.0 ± 2.0	11.8 ± 1.3	12.8 ± 1.7	13.6 ± 2.4	.014 ^c
Time to reach _{peak} (min)	14.1 ± 3.1	15.9 ± 2.9	16.3 ± 1.5	17.6 ± 2.3	.313
Power _{AT} (W/kg)	1.2 ± 0.4	1.7 ± 0.3	2.0 ± 0.4	2.4 ± 0.3	<.001 ^{a,b,c,e,f}
Power _{peak} (W/kg)	2.0 ± 0.6	2.7 ± 0.4	2.9 ± 0.4	3.6 ± 0.3	<.001 ^{a,b,c,e,f}
$\dot{V}O_{2AT}$ (ml/min/kg)	16.9 ± 2.9	22.4 ± 2.3	26.1 ± 1.5	32.0 ± 3.8	<.001 ^{a,b,c,d,e,f}
$\dot{V}O_{2\text{peak}}$ (ml/min/kg)	20.4 ± 3.6	27.1 ± 1.4	32.6 ± 1.8	39.6 ± 4.0	<.001 ^{a,b,c,d,e,f}
HR _{AT} (bpm)	119 ± 14	135 ± 13	142 ± 7	149 ± 13	<.001 ^{a,b,c}
HR _{peak} (bpm)	154 ± 13	168 ± 15	170 ± 16	174 ± 11	.094
O ₂ pulse _{AT} (ml/beat/min)	11.4 ± 3.1	11.8 ± 1.8	14.1 ± 3.4	16.5 ± 3.3	.004 ^{c,e}
O ₂ pulse _{peak} (ml/beat/min)	10.7 ± 3.4	11.6 ± 1.6	14.7 ± 3.7	17.6 ± 3.5	<.001 ^{c,e}
RER _{AT}	0.88 ± 0.08	0.94 ± 0.10	0.99 ± 0.07	0.96 ± 0.05	.073
RER _{peak}	1.19 ± 0.10	1.23 ± 0.10	1.23 ± 0.07	1.19 ± 0.05	.193
Lipid oxidation _{AT} (g/min)	0.26 ± 0.18	0.23 ± 0.19	0.10 ± 0.09	0.19 ± 0.14	.397
MFO (g/min)	0.32 ± 0.13	0.38 ± 0.11	0.39 ± 0.06	0.48 ± 0.11	.009 ^c
CHO oxidation _{AT} (g/min)	1.21 ± 0.57	1.77 ± 0.82	2.65 ± 1.01	3.10 ± 1.45	.016 ^c
CHO oxidation _{peak} (g/min)	3.53 ± 1.14	4.92 ± 1.51	5.81 ± 1.20	6.70 ± 1.20	<.001 ^{b,c,e}
$\dot{V}E_{AT}$ (L/min)	35.0 ± 11.1	43.3 ± 10.0	54.0 ± 15.6	65.3 ± 13.1	<.001 ^{b,c,e}
$\dot{V}E_{\text{peak}}$ (L/min)	63.6 ± 23.1	83.0 ± 18.3	95.3 ± 18.4	117.5 ± 20.8	<.001 ^{b,c,e}
$\dot{V}E/\dot{V}O_{2AT}$	26.0 ± 4.1	26.1 ± 3.7	27.6 ± 5.1	26.6 ± 2.4	.440
$\dot{V}E/\dot{V}O_{2\text{peak}}$	29.4 ± 3.5	27.8 ± 2.9	27.9 ± 5.2	27.9 ± 3.0	.761
$\dot{V}E/\dot{V}CO_{2AT}$	39.2 ± 7.9	41.2 ± 6.8	39.2 ± 5.1	38.7 ± 3.1	.760
$\dot{V}E/\dot{V}CO_{2\text{peak}}$	32.8 ± 5.4	33.3 ± 4.6	32.0 ± 4.8	32.5 ± 2.6	.869
PLa _{AT}	1.5 ± 0.7	1.3 ± 0.5	2.1 ± 1.0	2.1 ± 0.8	.194
PLa _{peak}	4.8 ± 1.9	6.0 ± 2.2	5.9 ± 2.4	7.4 ± 3.2	.541

Note: data have been assessed via multivariate GLM with age and gender accounted for as covariates in the model.

Abbreviations: AT, anaerobic threshold; CHO, carbohydrate; HR, heart rate; MFO, maximal rate of fat oxidation; PLa, plasma lactate; RER, respiratory exchange ratio; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide; $\dot{V}E/\dot{V}O_2$, ventilatory equivalents for oxygen; VE, pulmonary ventilation; $\dot{V}O_2$, volume of inhaled oxygen.

^ap ≤ .05 between very low and low.

^bp ≤ .05 between very low and moderate.

^cp ≤ .05 between very low and high.

^dp ≤ .05 between low and moderate.

^ep ≤ .05 between low and high.

^fp ≤ .05 between moderate and high.

exhaustive exercise in people with long-standing diabetes, poor glycaemic control and low CRF levels. The purpose of this study was to investigate these questions so to address outstanding knowledge gaps.

4.1 | Acute glycaemic findings

In agreement with our previous work in those using multiple daily insulin injections,²⁴ these results confirm stable PG responses to GXT when a set of prudent preparatory procedures are put in place in people with type 1 diabetes treated with insulin pumps. Indeed, we observed a non-significant change in PG of $\Delta +0.3$ mmol/L, the

magnitude of which is in keeping with our findings in those with multiple daily injections (MDI) ($\Delta -0.3$ mmol/L), albeit directional diametric. The minimal change in PG over GXT in our present and previously published studies is markedly lower than the +1.6 mmol/L increase observed by Matejko et al.,¹⁹ during their investigation of predictors of $\dot{V}O_{2\text{peak}}$ in adult patients with T1D using the insulin pump. A possible explanation for the pronouncement of this gap is their incorporation of reductions in both basal (50% 30 min before to 60 min after) and bolus (25%) insulin dosing alongside the provision of a fixed carbohydrate-based meal (50 g total from high glycaemic index foods) 2 h before GXT. This led to starting glucose levels in both sexes that were hyperglycaemic (males: 11.3 mmol/L and females: 10.6 mmol/L). One could therefore question as to whether such heavy dose

reductions are needed in advance of GXT of short duration. Hyperglycaemia at GXT onset (10.7 mmol/L) was also apparent in a study by Turinese et al.¹⁰ with only one other group¹⁶ showing normoglycaemic concentrations in their T1D participants ahead of GXT (7.1 ± 0.2 mmol/L). Unfortunately, missing data on PG post-exercise prevents equitable comparison against our data and an exploration as to whether acute glycaemia influenced GXT responses was unexplored in these studies.

Although we found no influence of starting PG on subsequent GXT performance outcomes in the present study, only a fraction (24%) of our participants breached the hyperglycaemic (>10 mmol/L) threshold at exercise onset. Even in those who commenced above the physiological range, mean PG concentrations (11.9 ± 1.1 mmol/L ranging from 10.6 to 13.8 mmol/L) were considered mildly, rather than severely (i.e. >13.9 mmol/L) hyperglycaemic, with no one surpassing the latter. Even so, these data contrast our recent MDI study, during which we observed relationships between starting glucose levels and some cardiorespiratory (heart rate and O₂ pulse) and metabolic (blood lactate) responses to GXT. In that study, 31% of the participants started with hyperglycaemic concentrations, of whom the mean pre-exercise values were 12.2 ± 1.4 mmol/L (ranging from 10.4 to 14.3 mmol/L). Hence, assessing the magnitude of effect in the present study is difficult and, in any case, the inherent limitations of inter-individual comparisons in the context of physiology should always be considered.

Worth mentioning is the similarity in starting PG concentrations between our previous insulin pen and present insulin pump studies (pen: 8.9 ± 2.9 vs. pump: 8.8 ± 2.3 mmol/L), with the vast majority of participants commencing (pen: 73%, pump: 76%), and indeed completing (pen: 69%, pump: 62%), the test in a euglycaemic state. We employed identical protocols and similar preparatory procedures in these trials (please see Section 2 for further information). Thus, replication of these steps may serve to benefit others when performing GXT in those with T1D. Nevertheless, although minimal, the directional change in glycaemia in our study was not 'fixed' with a proportional amount of people experiencing a rise as a decline (57% vs. 42%). Furthermore, similar to others,^{16,19,24} we observed no hypoglycaemic events during the test despite pronounced swings in glucose between participants [range (min to max): 5.2 mmol/L (−2.1 to +3.2 mmol/L)].

Taken collectively, it seems as though when prudent preparatory procedures are followed, GXT can be performed with little acute glycaemic disturbance and minimal risk of hypoglycaemia, irrespective of whether a person is using insulin pen or pump therapy.

4.2 | Cardiorespiratory fitness findings

The mean level of aerobic fitness of participants ($\dot{V}O_{2peak}$ 29.5 ± 8.0 ml/min/kg) was similar to that typically seen in sedentary subjects without diabetes (<30 ml/min/kg)²⁵ with over half (56%) failing to exceed that threshold. Interestingly, 27 of 45 (60%) of our participants had at least one diabetes-related complication (i.e. neuropathy, retinopathy,

albuminuria and ischaemic heart disease; please see supplementary file, Table S1). Further stratification of our study participants into two groups of 'fitness' applying the aforementioned cut-off point of 30 ml/min/kg ('below' n = 25 vs. 'above' n = 20) revealed that there were nearly double the amount of people with a diabetes-related complication in the 'below' versus 'above' [n = 18 (72% of group n) vs. n = 9 (45% of group n), respectively] χ^2 , (1, n = 45), 3.375, *p* = .06. Indeed, 97% of men and 80% of women in our study were notably below consensus sex-specific thresholds associated with an increased risk of cardiovascular disease in healthy individuals (i.e. 44.2 ml/min/kg in men and 35.1 ml/min/kg in women) with just over a 10 ml/min/kg relative deficit in the mean levels of each sex in our cohort (33.4 ml/min/kg in men and 24.5 ml/min/kg in women). Previous reports have indicated that for every 5 ml/min/kg decrement in $\dot{V}O_{2peak}$ there is a concomitant ~56% higher odds for cardiovascular disease risk factor clustering.²⁶ This inverse relationship is supported by several other groups, with consistent associations found between $\dot{V}O_{2peak}$ levels and the risk of all-cause mortality, cardiovascular disease and metabolic syndrome.^{27–30} These data re-enforce the prognostic value of GXT in not only providing quantification of the magnitude of exercise intolerance but also the potential impacts of underlying pathophysiological complications in already 'at-risk' cohorts.

It is interesting to note how high the identified AT was when relativized as a percentage of $\dot{V}O_{2peak}$ (~80%). Although seemingly paradoxical on first pass (as one would intuitively expect a rightward shift in the point of AT plotted against $\dot{V}O_{2peak}$ in fitter individuals), the explanation for this finding could be that our participants reached their self-determined 'peak' within a 20% margin of surpassing a moderate and supposedly 'sustainable' exercise intensity. Hence, in older populations with poor glycaemic control, low CRF levels and who have a high prevalence of diabetes-related complications, the sensation of performing difficult exercise may be unfamiliar, thus motivational reinforcement to encourage the attainment of true exhaustion may be warranted.

4.3 | Long-term glycaemic control findings

We found that poor glycaemic control was associated with attenuation in peak aerobic rate and mechanical power at both submaximal and peak workloads, even after adjustment for both age and sex. Indeed, for every 1% increment in HbA1c there was an associated decrease in $\dot{V}O_{2peak}$ by ~4 ml/min/kg and power_{peak} by 0.3 W/kg. Considering the CVD-related risks associated with 5 ml/min/kg decrements in $\dot{V}O_{2peak}$,²⁶ the importance of optimizing glycaemic control is underscored. Further subanalysis on our data set revealed that those with HbA1c levels ≥8% had notably lower $\dot{V}O_{2peak}$ values than those with <7% (24.5 ± 7.9 vs. 34.5 ± 6.8 ml/min/kg, respectively, *p* = .021) while the decrement relative to those categorized within the 7%–8% bracket fell short of significance (Δ approximately −6 ml/min/kg *p* = 1.00). These findings somewhat contrast those of Tagougui et al.,¹⁶ who in comparing those with 'inadequate' [HbA1c ≥8% ranging from 8% to 10.3%, n = 12 (8 pen, 4 pump)] versus 'adequate' [HbA1c <7% ranging from 5.5% to 7.5%, n = 11 (9 pen, 2 pump)] glycaemic control to matched healthy controls, found no difference between the two T1D groups per se, but noted a

deficit between those with T1D and inadequate glycaemic control to their healthy peers. Rather importantly, in those considered 'adequately controlled', four of the 11 (36%) participants actually breached the 7% threshold in the time from their initial screening to conducting the GXT. In our study, the larger population size allowed us to group participants into tertiles [HbA1c; <7% ranging from 5.5 to 6.9% (n = 12); 7%-8% ranging from 7.1 to 7.9% (n = 17) and ≥8% ranging from 8.1 to 10.0% (n = 16), $p < .001$] thereby providing scope to disentangle threshold effects with greater certainty.

Worth nothing is the lack of upward shift in $O_{2\text{pulse}}$ from the AT to peak work rate in those with a HbA1c >7%, with a decreasing trajectory noted in those ≥8%. This may imply impaired exercise stroke volume (driven by chronotropic incompetence) and perhaps cardiocirculatory dysfunction.³¹ Previous work has shown that inadequate glycaemic control (i.e. HbA1c ≥8%) is associated with abnormal heart rate dynamics,¹² blunted deoxyhaemoglobin responses¹⁶ and reduced muscle blood volume during GXT.¹⁶ Incorporating GXT as a prognostic tool may therefore serve as a cautionary signal for possible vascular dysfunction and enable early intervention before clinical manifestation. Taken collectively, 7% seems to be the threshold at which maximal aerobic rate deteriorates and altered cardiopulmonary responses may manifest. Thus, given the association of higher CRF with better health outcomes, optimizing long-term glycaemic control in accordance with recommended guidelines³² remains a focal goal for T1D management.

4.4 | Strengths, limitations, and future directions

To our knowledge, this is the first study to detail plasma glucose dynamics throughout GXT as well as profile the influence of glycaemic indicators the physiological responses to incremental, exhaustive exercise in a heterogeneous cohort of individuals with T1D using exclusively insulin pump therapy. The considerable range in several diabetes-specific, demographic and fitness-related characteristics in our cohort provided a unique opportunity to identify potential population-based divergences in GXT outcomes and assess the true magnitude of effect. This information may help provide a basis from which others can formulate prudent therapy management strategies ahead of GXT performance to maximize safety and minimize glycaemic disturbance. Longitudinal monitoring of GXT outcomes mapped against changes in diabetes-specific characteristics and clinical biomarkers in the absence and presence of regular exercise training programmes should be considered for further research.

5 | CONCLUSION

In adults with long-standing T1D using insulin pump therapy, circulating glucose remains stable during a graded incremental cycle test to volitional exhaustion. Glycaemic indicators are inversely associated with aerobic rate, oxygen economy and mechanical output across the exercise intensity spectrum. With this in mind, attaining good

glycaemic control remains a focal point for the optimal management of T1D and encouraging regular physical activity to improve CRF stands high among the hierarchy of lifestyle interventions aimed at improving health outcomes in high-risk cohorts.

AUTHOR CONTRIBUTIONS

OMM, KBK, SS, RMB, SCB and KN contributed to the conception and design of the study. OMM, KBK, MBC, SS, KN, AGR and SCB contributed to the acquisition of data. OMM and CN were responsible for data analyses. All authors were responsible for data interpretation. OMM wrote the original draft of the manuscript. All authors contributed to revising the article. All authors provided final approval of the version to be published.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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