PHYSICAL ACTIVITY AND TYPE 1 DIABETES

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PHYSICAL ACTIVITY AND TYPE 1 DIABETES

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EDITORIAL
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Editorial: Physical Activity and Type 1 Diabetes

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Editorial on the Research Topic

Physical Activity and Type 1 Diabetes

Exercise therapy is a cornerstone for the management of both type 2 (T2D) and type 1 (T1D) diabetes at all ages. Regular physical activity (PA) is associated with many well-established health benefits in individuals with diabetes as well as in individuals without diabetes. PA has been shown to improve cardiovascular fitness, metabolic and bone-health and enhance psychological well-being (1–3) in T2D. Furthermore, regular PA, in combination with other lifestyle changes such as caloric restriction, may prevent or delay T2D development more effectively than pharmacological interventions (4–6).

In T1D, regular PA associates with several positive physical health effects such as improved cardiovascular fitness and blood lipid profile and also enhances psychological well-being (7, 8). However, the beneficial effects on health-related outcomes induced by PA has not been convincingly paralleled with improvements in glycaemic control (7, 9, 10). In addition to ambiguities in the effects that PA has on glucose control, challenges remain as different forms of PA require different approaches regarding management of nutrition and insulin prior to, during and after PA. Adverse reactions to PA such as increased glucose variability, hypo and hyperglycemia are burdens for many patients.

Most adults with diabetes, both T1D and T2D, are recommended to perform at least 150 min of moderate-to-vigorous intensity activity weekly, and the activity should be spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous intensity or interval training may be sufficient for complication free and more physically fit individuals (11–13).

What is the best type of exercise? Most likely the exercise that is being performed regularly but there are differences in how the body responds metabolically. It is still unclear as to what form, duration and intensity should be recommended for health, fitness and glycemic control and whether there is a clinically significant benefit for the various clinical outcomes examined. A combination of both aerobic, resistance training and bone strengthening activities is likely to be most effective, but the evidence is not yet convincing for any or all of these types.

New diabetes technologies, including the use of continuous and intermittent flash glucose monitoring, is helpful when it comes to reducing some of the burden around glucose management for sport and exercise. Hybrid closed loop insulin pumps (HCL) and sensor-augmented insulin pumps with automatic basal rate suspension might further facilitate the situation and reduce some of the challenges during and after exercise in T1D (14, 15).

The pharmacological treatments options are now abundant for treatment of T2D and a patient-centered approach should be used to guide the individual choice of glucose lowering agents. If the patient is engaged in sporting activities or has problems with hypoglycemia, for instance

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during PA, a glucose lowering agent with little risk of inducing hypoglycemia is recommended (16).

This special issue of *physical activity and diabetes* covers a broad field of clinical- and pre-clinical studies to better understand the effects of PA in individuals with diabetes and to better overcome the problems associated with PA in order to increase physical activity adoption.

Moser et al. demonstrate in "Different Heart Rate Patterns During Cardio-Pulmonary Exercise (CPX) Testing in Individuals with Type 1 Diabetes" that there are clear differences in the heart rate response during cardio-pulmonary exercise (CPX) testing in individuals with T1D compared to controls and suggest using other submaximal markers than rated perceived exertion and submaximal heart rate to prescribe exercise intensity in people with T1D.

Yardley et al. provide a review on possible variables for glucose control entitled "Could Age, Sex and Physical Fitness Affect Blood Glucose Responses to Exercise in Type 1 Diabetes?" and conclude that there is currently insufficient information to model a closed-loop system (HCL) that can predict the potential influence of variables accurately and consistently prevent hypoglycaemia.

Matson et al. in "Objective Measurement of Physical Activity in Adults with Newly Diagnosed Type 1 Diabetes and Healthy Individuals" conclude that adults recently diagnosed with T1D do less moderate-to-vigorous-physical-activity (MVPA) than age-matched controls. Health care workers should therefore encourage these people to engage in more PA.

Tagougui et al. discuss in their review "The Benefits and Limits of Technological Advances in Glucose Management Around Physical Activity in Patients Type 1 Diabetes" how new technological advances in insulin delivery devices and glucose monitoring could be used to help glucose management as it relates to physical activity in T1D.

Klaprat et al. describe in "Gaps in Knowledge and the Need for Patient-Partners in Research Related to Physical Activity and Type 1 Diabetes: A Narrative Review" epidemiological evidence on the benefits of PA and T1D and also identify gaps in research aiming to add information to form future guidelines. The authors also provide an overview of patient-oriented research projects co-developed with persons living with T1D.

Litchfield et al. point out, in their paper entitled "Patient and Healthcare Professionals Perspectives on the Delivery of Exercise Education for Patients with Type 1 Diabetes," that any education package developed to support exercise in patients with T1D should be offered at a time following diagnosis in accordance with patients' preferences and priorities, and also provide information on how to manage regular and irregular bouts of exercise.

Chetty et al. provide, in their review "Exercise Management for Young People with Type 1 Diabetes: A Structured Approach to the Exercise Consultation," a structured approach on how to preform exercise consultations for children/adolescents based on a framework of questions that assist the health care professionals in formulating person-specific exercise management plans for young people with T1D.

McCarthy et al. discuss in their review "Resistance Isn't Futile: The Physiological Basis of the Health Effects of Resistance Exercise in Individuals With Type 1 Diabetes" the health benefits and challenges of resistance exercise in individuals with T1D.

Finally, Mattsson et al. present an original study entitled "Carbohydrate Loading Followed by High Carbohydrate Intake During Prolonged Physical Exercise and its Impact on Glucose Control in Individuals with Diabetes Type 1—an Exploratory Study" that shows that high volume intermittent CHO feeding during prolonged PA, combined with proactive use of continuous glucose monitoring (rtCGM), is associated low glucose variability and excellent glycemic control during extreme prolonged exercise in athletes with T1D.

AUTHOR CONTRIBUTIONS

The editorial article has been written by JJ. MR has reviewed and approved the manuscript and co-edited the special issue on PA and diabetes.

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Different Heart Rate Patterns During Cardio-Pulmonary Exercise (CPX) Testing in Individuals With Type 1 Diabetes

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To investigate the heart rate during cardio-pulmonary exercise (CPX) testing in individuals with type 1 diabetes (T1D) compared to healthy (CON) individuals. Fourteen people (seven individuals with T1D and seven CON individuals) performed a CPX test until volitional exhaustion to determine the first and second lactate turn points (LTP_1 and LTP_2), ventilatory thresholds (VT_1 and VT_2), and the heart rate turn point. For these thresholds cardio-respiratory variables and percentages of maximum heart rate, heart rate reserve, maximum oxygen uptake and oxygen uptake reserve, and maximum power output were compared between groups. Additionally, the degree and direction of the deflection of the heart rate to performance curve (k_{HR}) were compared between groups. Individuals with T1D had similar heart rate at LTP_1 (mean difference) −11, [(95% confidence interval) −27 to 4 b.min^{-1}], at VT_1 (−12, −8 to 33 b.min^{-1}) and at LTP_2 (−7, −13 to 26 b.min^{-1}), at VT_2 (−7, −13 to 28 b.min^{-1}), and at the heart rate turn point (−5, −14 to 24 b.min^{-1}) ($p = 0.22$). Heart rate expressed as percentage of maximum heart rate at LTP_1, VT_1, LTP_2, VT_2 and the heart rate turn point as well as expressed as percentages of heart rate reserve at LTP_2, VT_2 and the heart rate turn point was lower in individuals with T1D ($p < 0.05$). k_{HR} was lower in T1D compared to CON individuals (0.11 ± 0.25 vs. 0.51 ± 0.32, $p = 0.02$). Our findings demonstrate that there are clear differences in the heart rate response during CPX testing in individuals with T1D compared to CON individuals. We suggest using submaximal markers to prescribe exercise intensity in people with T1D, as the heart rate at thresholds is influenced by k_{HR}.

Clinical Trial Identifier: NCT02075567 (https://clinicaltrials.gov/ct2/show/NCT02075567).

Keywords: exercise prescription, heart rate to performance curve, thresholds, type 1 diabetes, heart rate reserve

INTRODUCTION

Low amounts of structured exercise such as 3 × 30 min per week are associated with consistent improvements in health status in already healthy and physically active individuals (1). In people with both type 1 (T1D) and type 2 diabetes high doses of physical activity were found to be associated with a 40% and 29% lower risk of all-cause mortality and cardiovascular disease in comparison with inactivity (2).

Currently, standard exercise recommendations for individuals with T1D are similar to those for healthy individuals, namely 150 min or more of moderate to intense exercise and physical activity spread over at least three days per week, or a minimum of 75 min per week of vigorous-intensity exercise/physical activity (3, 4).

Intriguingly, the American Diabetes Association (ADA) recommends prescribing exercise intensity as percentages of maximum heart rate (5) even though there is an ongoing debate on how to prescribe exercise intensity (6, 7). It was shown that the variable time course of the heart rate to performance curve influences exercise prescription, translating to uncertainty to overestimate target training loads especially in the vigorous-intensity domain (8–11). Using percentages of maximum heart rate might be problematic as degree and direction of the deflection of the heart rate to performance curve (k_{HR}) during CPX testing are altered in some healthy individuals (12) and might be further impaired by autonomic cardiac neuropathy in T1D individuals (13).

Furthermore, in T1D individuals with autonomic cardiac neuropathy, left ventricular function was found to be decreased in both systole and diastole, non-dipping was more prevalent, and pulse pressure was higher compared to patients without autonomic cardiac neuropathy (14). The heart rate to performance curve was shown to be related to myocardial function (15, 16). An increase in heart rate during CPX testing reflects the ability of the autonomic nervous system to respond to an increase in metabolic demands. In healthy individuals the increase in heart rate during CPX testing is mainly originated by a withdrawal of tonic vagal activity (17). As shown recently, individuals with T1D reveal a higher risk of impaired tonic vagal activity in comparison to their healthy counterparts (18). This impaired response of the autonomic nervous system might alter heart rate to performance curve, as found in our cohort.

As shown previously, different threshold concepts are suitable for healthy (6, 19) and T1D individuals (20, 21). The first threshold occurring during cardio-pulmonary exercise (CPX) testing [e.g., first lactate turn point (LTP_1) or the first ventilatory threshold (VT_1)] translates to the inability of the muscle to entirely oxidize produced lactate and therefore it is partly shifted into the blood stream and can be metabolized by other organs. At this first threshold there is still a metabolically balanced condition but on a systemic level (22). At the second threshold [e.g., second lactate turn point (LTP_2) or the second ventilatory threshold (VT_2)] produced lactate in the working muscles cannot be muscularly or systemically eliminated, resulting in a blood lactate accumulation (metabolically unbalanced condition, no lactate steady state) (6).

The aim of the study was to investigate the time course of the heart rate to performance curve during CPX testing in T1D individuals compared to matched healthy individuals (CON), and to prove its influence on percentages of maximum heart rate, percentages heart rate reserve, percentages maximum oxygen uptake, percentages oxygen uptake reserve and percentages maximum power output compared to standard markers of submaximal performance between groups. We determined as a primary outcome the heart rate to performance curve during CPX testing and its impact on target training heart rate determination in comparison of T1D individuals and matched healthy individuals (CON) and as secondary outcomes the functional capacity, cardiorespiratory and metabolic markers in comparison of groups during CPX testing. We hypothesized that people with T1D show an altered heart rate to performance curve during CPX testing and this impacts target training heart rate determination.

METHODS

Consent Procedures

This study was carried out in accordance with the recommendations of Good Clinical Practice (GCP), "Bundesamt fuer Sicherheit im Gesundheitswesen" (BASG Austria). The protocol was approved by the ethics committee of the Medical University of Graz, AT (26-069 ex 13/14). All subjects gave written informed consent in accordance with the Declaration of Helsinki. CON individuals were matched from routine diagnostics (approved by the Ministry of Science).

Eligibility Criteria and Assessment

To be eligible for the study, T1D individuals had to be male, diagnosed with T1D for at least 12 months, aged between 18 and 35 years (both inclusive), glycated hemoglobin (HbA_{1c}) ≤ 8% (64 $mmol.mol^{-1}$), fasting c-peptide negative, treated with multiple daily insulin injections, no long-term complications and no other physical and/or mental diseases, which might influence the study results. In this primary investigation we recruited male individuals as the female menstrual cycle may influence the energy supply during CPX testing (23). Participants were excluded if they had a history of any disease that might confound the results of the trial, use of drugs, which may interfere with the interpretation of the trial's results or known to be clinically

Abbreviations: T1D, Type 1 diabetes/individuals with Type 1 diabetes; HbA_{1c}, Glycated hemoglobin; BMI, Body mass index; ADA, American Diabetes Association; $\%HR_{max}$, Percentages of maximum heart rate; HR, Heart rate; k_{HR}, Degree and direction of the deflection of the heart rate to performance curve; CPX, Cardio-pulmonary exercise testing; CON, Healthy individuals; %HRR, Percentages of heart rate reserve; $\%VO_{2max}$, Percentages of maximum oxygen uptake; $\%VO_2R$, Percentages of oxygen uptake reserve; $\%P_{max}$, Percentages of maximum power output; GCP, Good clinical practice; DoH, Declaration of Helsinki; MDII, Multiple daily insulin injections; CRF, Case Report Form; P_{max}, Maximum power output; LTP_1, First lactate turn point; LTP_2, Second lactate turn point; VT_1, First ventilatory threshold; VT_2, Second ventilatory threshold; VE, Ventilation; VE/VO_2, Ventilation of oxygen; VE/VCO_2, Ventilation of carbon dioxide; HRTP, Heart rate turn point; MD, Mean difference; CI, confidence interval.

relevant in interfering with insulin action, glucose utilization or recovery from hypoglycemia, current addiction to alcohol or any controlled substance abuse. Furthermore, participants were excluded if they had known or suspected allergy to trial products or related products, mental incapacity, unwillingness, language barriers precluding adequate understanding, and any condition that the study physician feels would interfere with the trial participation. Testing day exclusion criteria were: hypoglycemia 48 h prior to testing, illness on or before the testing day, low glucose levels immediately before testing ($\leq$ 4.4 mmol.l^{-1}) or alcohol consumption 24 h before. All data were assessed and documented in a standardized Case Report Form. CON individuals were selected with respect to T1D individuals' characteristics (matched for sex, age, and maximum power output) from routine diagnostics data at the entry to the physical education studies. CON individuals were instructed to avoid intense or long-lasting exercise 24 h prior to the investigation and to avoid alcohol within 24 h pre-testing. Written informed consent was obtained from all participants.

Participants Characteristics

T1D individuals' characteristics were: age 24 $\pm$ 5 years (min–max; 19–32), BMI 23.9 $\pm$ 2.5 kg.m^{-2} (20–28), HbA_{1c} 7.4 $\pm$ 0.6% (6.5–8) (57 $\pm$ 6.3 mmol.mol^{-1}) (47–64), c-peptide 0.13 $\pm$ 0.19 nmol.l^{-1} (0–0.4) and total daily insulin dose with insulin Degludec 41 $\pm$ 16 U (27–69). Four participants used bolus insulin Aspart (Novo Rapid, Novo Nordisk, Denmark) and three participants used bolus insulin Lispro (Humalog/ Lilly, USA). Before switching to insulin Degludec, two patients used insulin Detemir (Levemir/ Novo Nordisk, Denmark) and five patients used insulin Glargine (Lantus/ Sanofi- Aventis, France) as basal therapy. T1D participants were free of comorbidities and co-medications other than insulin. CON individuals were aged 23 $\pm$ 4 years (19–30), had a BMI of 23.4 $\pm$ 1.8 kg.m^2 (21–26) and were healthy without taking any medications.

Study Procedures

In this experimental design, T1D individuals were adjusted to the same therapy with insulin Degludec (®Tresiba/Novo Nordisk, Dagsvaerd, Denmark) as part of a basal-bolus routine. After a run-in period of 4 weeks with insulin Degludec, a CPX test was performed. Insulin Degludec was used to achieve homogeneity for the basal insulin therapy. We have chosen insulin Degludec since its pharmacodynamic profile is flat and stable, demonstrated by an even distribution of glucose-lowering effects across the 24-h period (24).

Cardio-Pulmonary Exercise (CPX) Testing

Fourteen participants performed a maximum CPX test on a cycle ergometer (Monark Ergomedic 839E, Monark, Sweden) at the Sports Science Institute, University of Graz, Austria (25). Participants were permitted to cycle at a cadence of 70–90 rpm. At the beginning of the CPX testing, participants sat on the cycle ergometer for 3 min without pedaling (0 W). Then, participants started to cycle for 3 min with a workload of 40 W. Subsequently, the workload was increased by 20 W every minute until volitional exhaustion, followed by 3 min of active recovery at 40 W and 3 min of passive recovery (0 W). LTP_1 and LTP_2 (12) as well as VT_1 and VT_2 were determined from the CPX test by means of a computer-based linear regression break point analysis (6). LTP_1 was defined as the first increase in capillary blood lactate concentration above baseline values and LTP_2 was defined as the second abrupt increase between LTP_1 and the maximum power output. VT_1 was defined as the first increase in ventilation (VE) accompanied by an increase in VE/VO_2 without an increase in VE/VCO_2. VT_2 was defined as the second abrupt increase in VE accompanied by an increase in both VE/VO_2 and VE/VCO_2. Additionally, the heart rate turn point was defined as the point of intersection of two regression lines in the heart rate to performance curve between LTP_1 and the maximum power output with minimal standard deviation of the two straight lines. The degree and direction of the deflection of the heart rate to performance curve (k_{HR}) was calculated by a second-degree polynomial function between LTP_1 and the maximum power output (12, 21).

MEASUREMENTS

Pulmonary gas-exchange variables were measured continuously during CPX testing via breath-by-breath measurement and 5 s average (ZAN 600, ZAN, Germany). Heart rate was measured continuously via chest belt telemetry and 5 s average (PE 4000, Polar Electro, Finland). A 12-lead electrocardiogram and blood pressure measurements (every 2 min) were obtained during CPX testing for cardiac monitoring. Blood lactate and blood glucose (for safety in T1D group) concentrations were determined by taking capillary blood samples from the earlobe at the end of the rest and warm-up periods, at the end of each workload step (every minute), and at the end of active and passive recovery. Blood lactate and blood glucose were analyzed by means of an enzymatic-amperometric method (®Biosen S-line, EKF Diagnostics, Germany).

Bolus Insulin Dose Reduction

After overnight fasting, T1D individuals received a standardized meal on the day of the CPX test (®Fortimel Extra, Nutricia GmbH, Germany), which was calculated from the average pre-investigational amount of consumed carbohydrates during the last 4 weeks prior to the start of the study. The standardized meal and the reduced bolus insulin dose were administered exactly 4 h before the cycle ergometer exercise tests. The bolus insulin dose was reduced by 40% of the regular dose for the CPX testing. Both groups were informed to ingest carbohydrate enriched meals at least the day prior CPX testing to ensure adequate tissue glycogen stores.

Statistical Analyses

All data were tested with Shapiro-Wilk normality test and were found to be normally distributed. Descriptive statistics included mean and standard deviation for participant's anthropometric data, performance characteristics, and diabetes specific data. Anthropometric data and k_{HR} were compared between groups by paired students' *t*-test. Differences in comparison of groups for thresholds LTP_1, VT_1, LTP_2, VT_2, and heart rate turn

point for relative and absolute power output, heart rate, oxygen consumption and lactate concentration were analyzed by a two-way ANOVA (group and threshold), with Bonferroni *post-hoc* testing. All statistics were performed with a standard software package ® Prism Software version 5.0 (GraphPad, USA) and SPSS 22.0 software (SPSS Inc., USA).

RESULTS

Post-hoc power analysis was performed for the primary outcome percentages of heart rate comparing markers of lowest significant difference between groups (VT_1) and revealed a *post hoc* power 1-β = 0.99. There were no episodes of hypoglycemia noted during the CPX testing in the T1D group. T1D individuals maintained a blood glucose steady state during CPX testing showing no significant difference between the start (10.58 ± 3.42 mmol.l^{-1}) and the end concentrations (10.24 ± 3.48 mmol.l^{-1}) ($p = 0.86$).

Cardio-respiratory and metabolic markers at LTP_1 and VT_1 [T1D: $p = 0.98$ (heart rate), $p = 0.99$ (oxygen uptake), $p = 0.92$ (lactate concentration); CON: $p = 0.96$ (heart rate), $p = 0.60$ (oxygen uptake), $p = 0.96$ (lactate concentration)] as well as LTP_2, VT_2 and heart rate turn point [T1D: $p = 0.93$ (heart rate), $p = 0.99$ (oxygen uptake), $p = 0.58$ (lactate concentration); CON: $p = 0.37$ (heart rate), $p = 0.97$ (oxygen uptake), $p = 0.76$ (lactate concentration)] were not significantly different within both groups.

No significant differences were found for power output, heart rate, oxygen uptake and lactate concentration at LTP_1, LTP_2, heart rate turn point, and maximum power output between T1D and CON individuals, except for lactate concentration at LTP_1 (**Table 1**).

Significantly lower values were found for heart rate at percentages of maximum heart rate at LTP_1, VT_1, LTP_2, VT_2, and heart rate turn point as well as for heart rate at percentages of heart rate reserve at LTP_2, VT_2, and heart rate turn point in T1D individuals ($p < 0.05$). No significant differences were found for the oxygen uptake at percentages of maximum oxygen uptake ($p = 0.88$), oxygen uptake at percentages of oxygen uptake reserve ($p = 0.71$) and heart rate at percentages of heart rate reserve (only for LTP_1 and VT_1, $p = 0.11$) as well as percentages of maximum power output %P ($p = 0.64$) at LTP_1, VT_1, LTP_2, VT_2, and heart rate turn point when comparing T1D and CON individuals (**Figure 1**).

k_{HR} was significantly lower in T1D individuals compared to CON individuals (0.11 ± 0.25 vs. 0.51 ± 0.32, $p = 0.02$). **Figure 2** shows the time course of the heart rate to performance curve for both groups indicating the differences especially important for the upper limit for vigorous intensity exercise. Usually, maximum heart rate derived calculations of the target training heart rate overestimate the true limits, as this can be seen via lactate turn points (**Figure 2**). The usual upper limit of 85% of the maximum heart rate was clearly above the exercise intensity of LTP_2 for T1D individuals and clearly below LTP_2 for CON individuals. Eighty-five percent of the maximum heart rate resulted in significant differences comparing T1D vs. CON for oxygen uptake at percentages of maximum oxygen uptake [mean difference (MD) 11.57, confidence interval (CI) 0.15 to 22.99 %, $p = 0.04$], oxygen uptake at percentages of oxygen uptake reserve (12.86, 1.43 to 24.28, $p = 0.02$), and power output at percentages of maximum power output (12.57, 1.15 to 23.99 %, $p = 0.02$), but not for heart rate at percentages of heart rate reserve (3.71, −7.70 to 15.13 %, $p = 0.87$).

TABLE 1 | Comparison of anthropometric data, performance data and physiological data during CPX testing.

	T1D ($n = 7$)	CON ($n = 7$)	p-value
Age (years)	24.5 ± 5.3	23.4 ± 4.1	0.47
BMI (kg/m^2)	23.9 ± 2.5	23.4 ± 1.8	0.70
HbA_{1c} (%)	7.4 ± 0.6	–	–
HbA_{1c} (mmol.mol^{-1})	57 ± 6.3	–	–
Diabetes duration (years)	16.9 ± 8.1	–	–
P_{LTP1} (Watt)	83 ± 18	92 ± 22	0.41
P_{VT1} (Watt)	82 ± 8	103 ± 12	0.17
P_{LTP2} (Watt)	192 ± 33	197 ± 30	0.74
P_{VT2} (Watt)	193 ± 14	198 ± 15	0.80
P_{HRTP} (Watt)	198 ± 40	197 ± 30	0.93
P_{max} (Watt)	284 ± 43	296 ± 37	0.58
HR_{LTP1} (b.min^{-1})	116 ± 14	127 ± 12	0.13
HR_{VT1} (b.min^{-1})	116 ± 5	128 ± 5	0.14
HR_{LTP2} (b.min^{-1})	159 ± 11	165 ± 10	0.28
HR_{VT2} (b.min^{-1})	159 ± 4	166 ± 5	0.17
HR_{HRTP} (b.min^{-1})	160 ± 10	165 ± 10	0.38
HR_{max} (b.min^{-1})	192 ± 4	187 ± 11	0.30
VO_{2LTP1} (ml.kg^{-1}.min^{-1})	19.88 ± 14	20.53 ± 2.73	0.80
VO_{2VT1} (ml.kg^{-1}.min^{-1})	19.89 ± 2.75	19.73 ± 1.11	0.95
VO_{2LTP2} (ml.kg^{-1}.min^{-1})	38.20 ± 9.05	38.26 ± 4.21	0.98
VO_{2VT2} (ml.kg^{-1}.min^{-1})	38.67 ± 3.50	38.07 ± 2.02	0.88
VO_{2HRTP} (ml.kg^{-1}.min^{-1})	39.82 ± 10.93	38.61 ± 4.58	0.79
VO_{2max} (ml.kg^{-1}.min^{-1})	52.49 ± 6.56	52.39 ± 8.57	0.98
LA_{LTP1} (mmol.l^{-1})	0.91 ± 0.24	1.50 ± 0.58	0.03*
LA_{VT1} (mmol.l^{-1})	0.90 ± 0.11	1.48 ± 0.24	0.05
LA_{LTP2} (mmol.l^{-1})	3.68 ± 0.53	4.10 ± 0.50	0.16
LA_{VT2} (mmol.l^{-1})	3.75 ± 0.23	4.18 ± 0.21	0.20
LA_{HRTP} (mmol.l^{-1})	3.98 ± 0.49	3.88 ± 1.12	0.83
LA_{max} (mmol.l^{-1})	12.37 ± 1.25	13.10 ± 0.79	0.21

*T1D: individuals with type 1 diabetes, CON: healthy individuals, LTP1 , first lactate turn point; LTP2, second lactate turn point; HRTP, heart rate turn point; max, maximum output; P, power output; HR, heart rate; VO2, oxygen uptake; LA, lactate concentration; Values are given as mean ± SD. * represents significant difference.*

DISCUSSION

The aim of this study was to investigate the alterations in the heart rate during CPX testing in T1D individuals compared to matched CON individuals. k_{HR} was significantly different between T1D individuals and CON individuals. T1D individuals showed a lower heart rate of percentages of the maximum

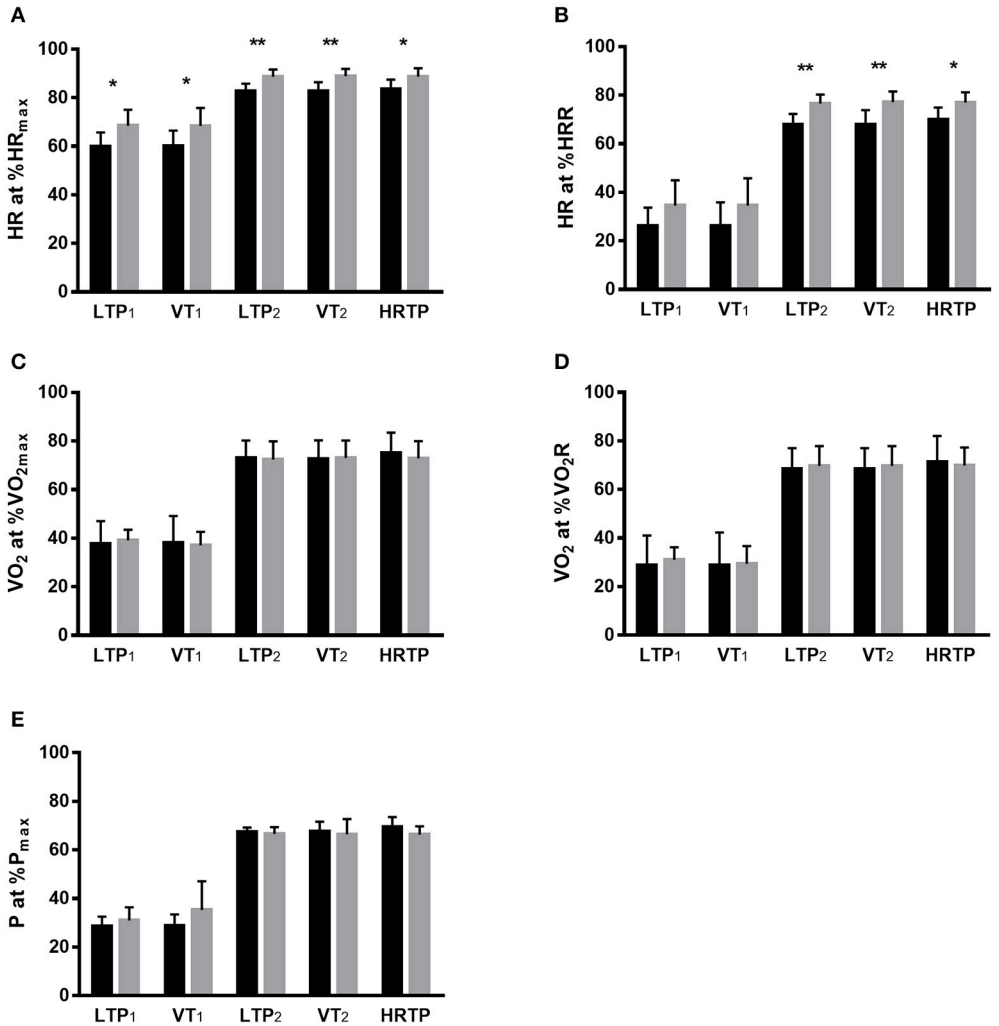

FIGURE 1 | Comparison of CPX-testing derived markers between both groups for HR at $\%HR_{max}$ **(A)**, HR at %HRR **(B)**, VO_2 at $\%VO_{2max}$ **(C)**, VO_2 at $\%VO_2R$ **(D)** and P at $\%P_{max}$ **(E)**. $\%HR_{max}$, percentage of maximum heart rate; %HRR, percentage of heart rate reserve; $\%VO_{2max}$, percentage of maximum oxygen uptake; $\%VO_2R$, percentage of oxygen uptake reserve; $\%P_{max}$, percentage of maximum power output; LTP_1, first lactate turn point; LTP_2, second lactate turn point; HRTP, heart rate turn point; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold. Values are given as mean ± SD. Stars represent significant difference, $^*p < 0.05$, $^{**}p < 0.01$. Black bar, individuals with type 1 diabetes; grey bar, healthy individuals.

heart rate at the second turn points (LTP_2, VT_2, heart rate turn point) and a significantly lower k_{HR} (**Figure 2**), which significantly influenced prescription of the target heart rate. Applying percentages of maximum heart rate derived markers overestimated T1D individuals' target training heart rate which is important especially for the upper limits for vigorous intensity exercise. All threshold values within groups were not significantly different (LTP_1 vs. VT_1; LTP_2 vs. VT_2 vs. heart rate turn point) indicating the objectivity and the validity of these markers which may be used interchangeably.

Different methods to prescribe exercise intensity for physical training show different advantages and disadvantages. As shown by our data, using percentages of maximum values [e.g., maximum heart rate or oxygen uptake (6)] is not sufficient to prescribe exercise intensity individually and might be impaired in patients with cardio-respiratory diseases. Submaximal threshold concepts (e.g., lactate-, ventilatory- and heart rate-derived) are a valid approach due to their theoretical foundation and its internal consistency. However, it must be stated that especially rater-depending software programs might be influenced by subjectivity that can alter exercise intensity prescription. Although oxygen uptake at percentages of maximum oxygen uptake, oxygen uptake at percentages of oxygen uptake reserve and heart rate at percentages of heart rate reserve (only for LTP_1 and VT_1) were not significantly different at all submaximal markers, heart rate at percentages of maximum heart rate at LTP_1, VT_1 and LTP_2, VT_2 and heart rate turn point as well as percentages of heart rate reserve at LTP_2, VT_2 and heart rate turn point were significantly lower in T1D individuals compared to CON individuals. It was previously shown that these differences were

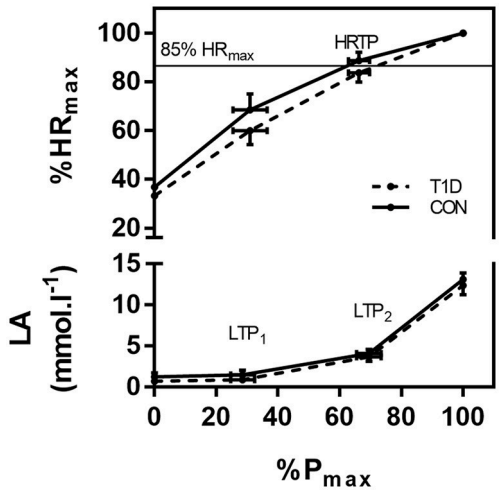

FIGURE 2 | Comparison of the relative heart rate performance curves and lactate curves between both groups. The same relative intensity of 85% HR_{max}, which is a usual upper limit for moderate intensity, resulted in different workloads related to the LTP_2. $\%HR_{max}$, percentage of maximum heart rate; LA, lactate concentration; $\%P_{max}$, percentage of maximum power output; LTP_1, first lactate turn point; LTP_2, second lactate turn point; HRTP, heart rate turn point. Values are given as mean ± SD.

also found in young healthy and trained subjects (26) with about 15% of non-regular heart rate curves. However, in our study 62.5% of T1D individuals showed an atypical heart rate response.

In several studies, it was shown that k_{HR} was associated with left ventricular ejection fraction (12, 16, 27) and β_1-adrenoceptor sensitivity (28). In particular chronically elevated HbA_{1c} levels and concomitantly elevated catecholamine levels (29) or inflammation (30) may impair β_1-adrenoreceptor sensitivity. This might change the degree and direction of the deflection of the heart rate to performance curve as shown earlier by Wonisch et al. (10). Apart from the effects of chronic hyperglycemia, hypoglycemic episodes might further promote impaired cardiovascular function (31). T1D individuals experience on average two episodes of symptomatic hypoglycemia per week and at least one severe episode per year (32). Additionally, the incidence of severe hypoglycemia increases drastically with length of diabetes. Both hyperglycemia and recurrent hypoglycemia might be perpetrators for an impaired cardiac response during CPX testing in individuals with T1D. Overall, our data show a systematic overestimation of target heart rate in T1D individuals when applying percentages of maximum heart rate compared to objective individual markers of submaximal performance such as LTP_1, VT_1, LTP_2, VT_2, and heart rate turn point.

With respect to the findings in our study we consequently recommend using percentages of submaximal markers [e.g., the first and the second turn points for lactate (LTP_1 and LTP_2) or ventilatory variables (VT_1, VT_2)] for the exercise intensity prescription in T1D which were shown to be representative for constant and intermittent type exercise of various intensities (6, 20, 25). As shown in **Figure 2**, individuals with T1D might be exercising at a too high exercise intensity if exercise is prescribed by percentages of maximum heart rate. From a clinical point of view exercise intensity should be prescribed exactly to avoid both, unexpected hypoglycemia and to induce training effects. Since insulin needs to be reduced with light to moderate exercise intensity to avoid peri-exercise hypoglycemia, glucose levels remain relatively stable during exercise with vigorous intensity (33) and rise immediately after intense exercise is performed (34). If exercise intensity and the insulin dose reduction do not match accordingly, the risk of glycemic impairments rises (35) which could lead to severe health complications, including death (36). On the other hand, if the exercise intensity is close or below the LTP_1, sub-optimal training effects on cardio-respiratory fitness may be expected, which reduces the possibility of attaining the accompanied health benefits.

To the best of our knowledge, this is the first study investigating the differences in cardio-pulmonary responses of the heart rate, heart rate reserve, oxygen uptake, and oxygen uptake reserve as well as maximum power output in relation to objective submaximal markers LTP_1, VT_1, LTP_2, VT_2, and heart rate turn point during CPX testing in T1D individuals and age, gender- and maximum power output- matched CON individuals. This study is limited by the small number of participants and that only males were included, which makes a direct transfer of the results to the general population of individuals with T1D difficult. Additionally, CON individuals were not provided with the same meal prior to the CPX testing as the T1D individuals. Further large-scale studies are needed investigating the heart rate to performance curve, which is obviously altered in this population. However, *post-hoc* power analysis confirmed the relevance of this study (power $1\text{-}\beta = 0.99$).

In conclusion, our findings demonstrate that there are clear differences in heart rate responses during CPX testing in individuals with T1D compared to CON individuals. We postulate that T1D individuals displayed an altered k_{HR} and lowered percentages of maximum heart rate / percentages of heart rate reserve at submaximal markers. We recommend additional studies to analyze e.g., HbA_{1c} levels in relation to the heart rate to performance curve in a larger group of individuals with T1D.

CONSENT OF PUBLICATION

Both groups gave written signed informed consent for publication.

AVAILABILITY OF DATA AND MATERIAL

Data will be made available on demand by the corresponding authors via email contact.

AUTHOR CONTRIBUTIONS

All authors confirm that they meet the International Committee of Medical Journal Editors (ICMJE) uniform requirements for authorship. OM participated in the

conceiving and designing the study, analyzing the data, and writing the manuscript. GT, AM, WG, and GK conceived the study and conducted the measurements. ME and RB conceived the study, analyzed data, drafted and revised the manuscript. TP and PH designed the study, supervised the measurements, and writing process. All authors have approved the final version of the manuscript to be published.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Could Age, Sex and Physical Fitness Affect Blood Glucose Responses to Exercise in Type 1 Diabetes?

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Closed-loop systems for patients with type 1 diabetes are progressing rapidly. Despite these advances, current systems may struggle in dealing with the acute stress of exercise. Algorithms to predict exercise-induced blood glucose changes in current systems are mostly derived from data involving relatively young, fit males. Little is known about the magnitude of confounding variables such as sex, age, and fitness level—underlying, uncontrollable factors that might influence blood glucose control during exercise. Sex-related differences in hormonal responses to physical exercise exist in studies involving individuals without diabetes, and result in altered fuel metabolism during exercise. Increasing age is associated with attenuated catecholamine responses and lower carbohydrate oxidation during activity. Furthermore, higher fitness levels can alter hormonal and fuel selection responses to exercise. Compounding the limited research on these factors in the metabolic response to exercise in type 1 diabetes is a limited understanding of how these variables affect blood glucose levels during different types, timing and intensities of activity in individuals with type 1 diabetes (T1D). Thus, there is currently insufficient information to model a closed-loop system that can predict them accurately and consistently prevent hypoglycemia. Further, studies involving both sexes, along with a range of ages and fitness levels, are needed to create a closed-loop system that will be more precise in regulating blood glucose during exercise in a wide variety of individuals with T1D.

Keywords: type 1 diabetes, physical activity, closed loop, sex, age, fitness

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INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disorder that destroys an individual's insulin-producing pancreatic β-cells (1). Despite many advances over the years, T1D remains a difficult disorder to manage. Exercise is very beneficial for individuals with T1D, with known improvements in cardiovascular health, insulin sensitivity, and body composition (2). However, fear of low blood glucose, or hypoglycemia, is often a barrier to partaking in exercise in this population (3). Much research has gone into investigating ways to keep blood glucose levels in the target range during and after exercise in individuals with T1D (4), most of which has noted a great deal of variability in responses.

In the past 5 years, there has been impressive progress in the development of a closed-loop system for patients with T1D to better control blood glucose. Improvements in the accuracy of hand-held glucose monitors to meet ISO criteria (5) and continuous glucose monitoring systems (CGM) (6, 7) have made this progress possible. Device development has advanced to a degree such that both single hormone (insulin) and dual hormone (insulin and glucagon) systems show improvements in time spent in target blood glucose ranges compared to continuous subcutaneous insulin infusion (insulin pump) systems when tested in small sample groups under free-living conditions (8).

In spite of these advances, perfecting the system to deal with situations other than rest, namely physical activity/exercise is still recognized as a major challenge (9–11). The need for a smart sensor that is able to detect the onset of exercise, as well as its intensity (which can have substantially different impacts on blood glucose responses) (12), has been identified. Indeed variables such as heart rate, skin temperature, heat flux, accelerometry and galvanic skin response, have been shown to correlate with changes in blood glucose during various types of exercise (13). Simply turning off insulin delivery upon sensing the start of activity, however, may be insufficient to completely prevent declines in blood glucose, and subsequently hypoglycemia (11), unless exercise is performed shortly after a meal (14). It has also been noted that a closed loop system, or artificial pancreas, will have difficulty replicating the multitude of feed-forward and feedback responses related to blood glucose equilibrium (10), in part due to the relatively long half-life of even the shortest acting synthetic insulin.

The variability in exercise responses will also be a major challenge to creating a system that will be able to adapt to all types and durations of activity for a wide variety of individuals, with a broad range of blood glucose levels at the start of exercise. The need for a sensor that not only recognizes changes in blood glucose, but also the onset, type and intensity, of physical activity/exercise has been discussed in detail elsewhere (8, 10). Current algorithms attempting to manage changes in blood glucose during exercise are also lacking information. Acute studies of the effect of different exercise modalities on blood glucose in individuals with T1D are limited in terms of their type, timing (e.g., morning vs. evening), intensity and duration of activity. For the most part, they have small sample sizes of relatively young, fit, male participants, which may obscure some potentially important differences among blood glucose responses to exercise in physiologically different groups. While we know that insulin dosage, carbohydrate intake, time of day, and prior hypoglycemia can impact blood glucose responses to exercise in T1D (**Figure 1**), little is known about the relative impact of underlying physiological factors such as sex, age, and physical fitness, which are beyond the control of the individual.

What we do know about these physiological factors (age, sex, fitness) has, for the most part, only been measured in individuals without diabetes. For example, females (without diabetes) are known to have different hormonal responses to exercise than males (15–28), resulting in differences in fuel selection (15–18, 23, 29–35) that might impact changes in blood glucose during different types of exercise. The same can be said of older individuals compared to younger individuals (36–43), and those of high physical fitness compared to those of low physical fitness (37, 38, 44–50). Where tightly controlled insulin and glucagon responses will help maintain blood glucose levels in a tight range in individuals without diabetes, differences in counter-regulatory responses to exercise depending on age, sex, or physical fitness have the potential to make a greater impact where pancreatic islet function is impaired or absent. Overall, this questions the adequacy of using existing data from acute exercise studies in T1D for modeling these activities in the context of the artificial pancreas, as much of the current research with T1D participants fails to take into account underlying physiological factors that will probably interact to affect blood glucose control. This review aims to summarize the state of knowledge on these factors, and to infer their potential impact on blood glucose responses to exercise in individuals with T1D.

EFFECT OF SEX ON EXERCISE RESPONSES IN INDIVIDUALS WITHOUT DIABETES

A large proportion of studies examining exercise metabolism have been performed uniquely in males. While limited, studies comparing the neuroendocrine and metabolic responses to exercise in healthy men and women have shown clear sex-related differences in the patterns of fuel selection (15–18, 23, 29–35), catecholamine response (15–22) and other hormonal responses such as estrogen (23–25) and growth hormone (16, 26–28). All of these factors have the potential to influence blood glucose concentrations both acutely, and in the hours following exercise (**Table 1**).

Fuel Selection

There is a clear difference between males and females in fuel selection during exercise. While there appears to be no difference between the sexes at rest (51, 52), females exhibit a lower respiratory exchange ratio (RER) during exercise in the fasted state, indicating a greater reliance on lipolysis than males for energy production (15–18, 23, 30–35, 53). This trend has been observed in healthy males and females during endurance exercise (15, 29–32, 34), submaximal exercise (16, 17, 23, 53), high intensity exercise (23) and resistance exercise (34).

The RER measurements are consistent with what has been noted at the cellular level: females use more myocellular triacylglycerol than males, whereas males deplete a greater portion of their glycogen stores during various types of exercise (18, 29, 54). Additionally, it has been observed that men shift to using carbohydrates as the dominant fuel source earlier [at 45 $\pm$ 1% of the participant's maximal aerobic capacity (VO_{2max})] than women (at 52 $\pm$ 1% VO_{2max}, $p < 0.01$) in a graded treadmill exercise test to exhaustion (55). While women still shift to oxidizing carbohydrates with higher intensity exercise, this shift is later and less extreme than in men. Less reliance on carbohydrate oxidation during exercise [53.1 $\pm$ 2.1% in men vs. 45.7 $\pm$ 1.8% ($p < 0.01$) in women during 2 h of cycling at

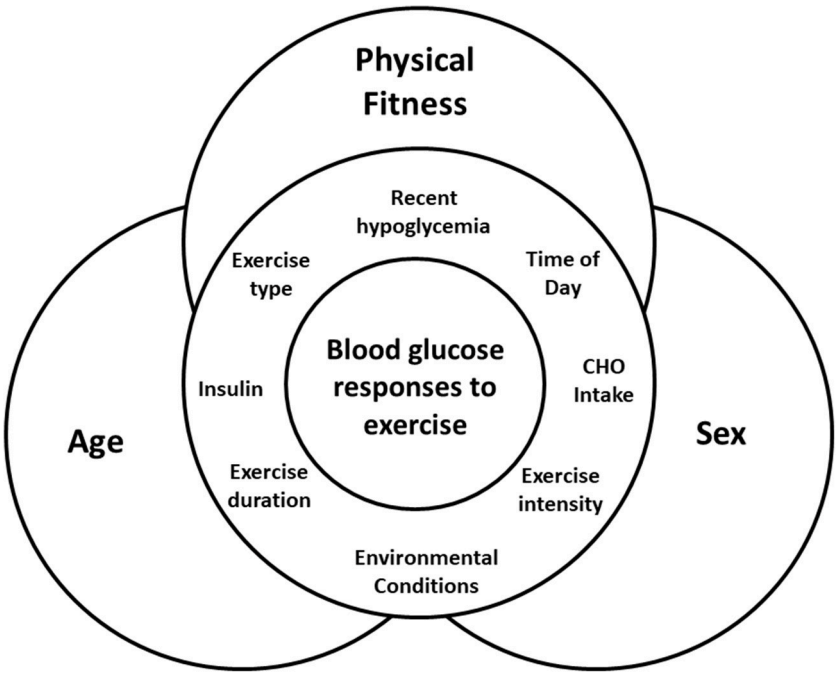

FIGURE 1 | Interaction of factors that can impact blood glucose during exercise, with the physiological factors of age, sex, and physical fitness underlying and interacting with all of them.

40%VO_{2max}] has been related to less depletion of glycogen stores in women (15).

Women also seem to be better able to conserve glycogen stores after extended exercise (90 min at 65% of VO_{2max}) (24), sparing the need for a large uptake of plasma glucose in the recovery period. One study found that women had a more precise defense of homeostasis in the recovery period post-exercise, including the control of blood glucose concentration and fuel selection (56). Due to their greater inherent capacity for lipid oxidation during exercise, women are able to regain control over glycemia and glucose flux in recovery more quickly than men (56). Therefore, men often show an increased rate of lipid mobilization post-exercise compared to women, in order to preserve glucose concentrations when restoring depleted glycogen stores from exercise (15, 33).

Important Hormones Mediating Fuel Selection

Several hormones, in addition to insulin and glucagon, are known to affect blood glucose homeostasis around exercise. Epinephrine and norepinephrine stimulate a substantial increase in hepatic glucose production. Growth hormone is known to promote lipolysis, which may in turn decrease reliance on blood glucose. Levels of estrogen, have also been shown to impact rates of lipolysis. All of these hormones respond differently between the sexes to an acute bout of exercise.

Catecholamines

There is a noticeable sex-related difference in catecholamine response to various forms and intensities of exercise. While a few exceptions exist (57, 58), the majority of studies report a significantly higher catecholamine response to various types of exercise in males compared to females (15–22). This trend has been found during moderate exercise, whether performed in the fasted state (16), or the postprandial state (18). It has also been found to hold during moderate intensity exercise of longer (2 h) duration (15), high intensity resistance exercise (59), and maximal sprints in trained individuals (19). This finding is important in blood glucose regulation, as high catecholamine levels will stimulate hepatic glycogenolysis and gluconeogenesis, increasing blood glucose levels during activity (15, 60–62), but potentially decreasing blood glucose levels post-exercise when glycogen stores are being replenished.

While men have shown an increased catecholamine response to exercise compared to women, there is also an apparent sex-related difference in the adrenergic receptor sensitivity during exercise. Horton et al. (15) found that men had significantly elevated levels of epinephrine, which stimulates lipolysis, at the end of moderate endurance exercise (post-exercise epinephrine: men $= 208 \pm 36$ vs. women $= 121 \pm 15$ pg/ml, $p < 0.007$), but had similar levels of circulating glycerol to women. This finding would suggest a greater sensitivity to the lipolytic action of the catecholamines in women. It is postulated that women may have a higher ß-adrenergic sensitivity, and decreased α-adrenergic sensitivity compared to men (17, 18, 23, 63). ß-adrenoreceptors are known to stimulate, whereas α-adrenoreceptors inhibit lipolysis, and thus a higher sensitivity of ß receptors in women during exercise results in greater net lipolysis (17). Indeed, when epinephrine was kept constant by infusion (63), women showed

TABLE 1 | Summary of hormonal responses to exercise by sex, age, and fitness level and their potential effect on blood glucose responses in type 1 diabetes.

Key factors	Fuel selection	Catecholamine	Growth hormone	Other hormones	Potential blood glucose response in type 1 diabetes
Sex	• Males favor CHO oxidation; Females rely to a greater extent on lipid oxidation.	• Greater E and NE response in males. • Females exhibit greater sensitivity to lipolytic action of E and NE.	• Similar magnitude of response during and after exercise. • Peaks are larger and sooner in females; more prolonged response in males.	• Estrogen: females exhibit greater increase during exercise than males. • Glucagon: no sex differences.	• Potential greater risk of hypoglycemia during and post-exercise in males. Better blood glucose control in post-exercise period in females.
Age	• MOD elicits similar responses. • HI: CHO oxidation decreases with age.	• Lower E response with age. • Blunted lipolytic response to E and NE with age.	• Attenuated GH response in older individuals compared to younger in MOD, HI and RE.	• Glucagon, cortisol and lactate responses decrease with age.	• Suggests higher blood glucose levels with age.
Fitness level	• Greater reliance on lipids during LO-MOD, and increased CHO oxidation during HI with higher fitness levels.	• Increased E response to MOD and HI with higher fitness levels.	• Higher GH responses to HI and RE with higher fitness levels.	• Glucagon: No change in fasting or peak levels with training.	• Improved glucose homeostasis with training. • Potential greater risk of nocturnal hypoglycemia with higher fitness levels.

CHO, carbohydrate; E, epinephrine; NE, norepinephrine; GH, growth hormone; T1D, type 1 diabetes; MOD, moderate intensity exercise; HI, high intensity exercise; RE, resistance exercise; LO, low intensity exercise.

greater lipolytic responses than men, suggesting less activation of the α-adrenergic receptors in women. Overall, this would support the trends seen in fuel selection, where women have relatively greater levels of lipolysis and fat oxidation than men during exercise.

Estrogen

Another factor influencing fuel selection during exercise is the difference in estrogen, between men and women. Estrogen, specifically 17ß-estradiol, has been shown to promote lipid oxidation and glycogen sparing during exercise (15, 23–25). Two separate blinded placebo control studies have shown that intake of 17ß-estradiol in males shifted fuel selection in the direction of lipid oxidation in recreationally-active men so that it was similar to that of women during moderate (65% VO_{2max}) aerobic exercise (25, 64).

While sex has a prominent effect on fuel selection, different phases of the menstrual cycle can also influence metabolism during exercise, and should thus be controlled for in studies involving women. Most studies test women in the early follicular phase, where estrogen concentrations do not differ markedly between men and women (34). This limits the proportion that estrogen contributes to determining fuel selection during exercise. During the luteal phase of the menstrual cycle, there is a higher concentration of estrogen and, consequently, a higher relative rate of fat utilization in females (31). While RER values (and therefore glucose utilization) are uniformly lower in women performing endurance exercise when compared to men, the luteal phase has been shown to produce lower glucose appearance and disappearance rates and less glycogen depletion than when exercise is performed in the follicular phase (24). There is also a greater increase in estradiol during exercise (both aerobic and resistance), which may contribute to greater fat oxidation for energy production in females during the luteal phase (35, 65, 66).

Growth Hormone

There is a lack of consensus regarding differences in growth hormone response to exercise between men and women. While some studies report a significantly increased growth hormone response in men compared to women after sprint (19) or submaximal exercise (67), others report an increased growth hormone response in women following resistance exercise (26, 68) or sprints (28). The majority of studies, however, report a similar response between the sexes in which both men and women experience an increase in growth hormone levels during and following exercise that is >10 min in length (16, 65, 69–71).

Although the majority of studies report similar relative increases in growth hormone during exercise compared to resting controls, there is a sexually dimorphic pattern in the way this occurs. Growth hormone peaks in women are reported to be larger and appear sooner than men, whereas men sustain a more prolonged response (16, 26–28). Sex-related differences in growth hormone levels can be attributed to a lack of testosterone response in women (65). Because women experience little or no increase in testosterone levels in response to exercise, growth hormone appears to compensate for the anabolic requirements stimulated by acute exercise (34, 72). Additionally, women have a higher resting basal level of growth hormone (65, 68, 70), particularly in the early follicular phase of the menstrual cycle (73). Because most exercise studies are performed on women during the early follicular phase of the menstrual cycle due to low levels of estrogen in this phase, there are marked sex differences in basal growth hormone levels (34), and subsequently higher levels of growth hormone during and after exercise. Additionally, increased levels of circulating estradiol are associated with higher

growth hormone concentrations (26), as estradiol releases a growth hormone stimulating factor (65).

Increases in growth hormone stimulate lipolysis and lipid oxidation, suppressing glucose oxidation and consequently sparing plasma glucose (74). Higher resting levels of estradiol in women stimulates growth hormone release, which inhibits glucose uptake, thereby enhancing lipolysis, and again, preserving plasma glucose levels in women. The difference in growth hormone response to exercise between the sexes, thus, has the potential to affect blood glucose control directly.

EFFECT OF AGE ON EXERCISE RESPONSES IN INDIVIDUALS WITHOUT DIABETES

While there are clear differences in exercise responses between the sexes, it would seem that declines in functional fitness with age occur evenly in both sexes, and are due mostly to the reduction in upper and lower limb muscle strength, increases in body-fat percentage, and decreases in flexibility, agility and endurance (36). There are also changes in the hormonal response to exercise, which may alter fuel selection patterns during different types of activity, resulting in differences in fuel usage during exercise between younger and older individuals. Aging is also associated with a decrease in cardio-respiratory fitness (reflected by lower maximum oxygen consumption values) (75), which in itself may impact exercise responses (discussed in the section on physical fitness below). There are minimal published data to date examining how these age-related alterations in exercise response affect changes in blood glucose during activity of any type.

Body Composition

Aging is characterized by a decrease in muscle mass and strength (76), and an increase in adiposity (77), which generally translates into declines in physical capacity (78). Older adults also have a decreased resting metabolic rate, which may only be partly due to the changes in body composition (79). A higher level of abdominal adiposity in particular is a significant predictor of insulin sensitivity in older adults (80). With decreases in muscle mass, metabolic rate and aerobic fitness, older individuals will be burning less fuel overall for the same relative intensity of exercise.

Fuel Selection

When exercise is of moderate intensity relative to the individual's peak aerobic rate, the proportion of fuel supplied by carbohydrates is similar among older and younger individuals (37, 76). However, where more intense/anaerobic exercise is concerned, carbohydrate oxidation decreases up to 20% from roughly 20–50 years of age in sedentary (but not trained) men (37). Sedentary men also have a decrease in the lactate threshold during sub-maximal exercise with age (38), however, in spite of this, younger men are able to produce more lactate during activities such as resistance exercise (39), thereby indicating a greater reliance on carbohydrates as a fuel source. This may be part of the reason why one study showed that blood glucose was ∼1.0 mmol/L higher before, during and for 30 min after heavy resistance training in older (mean age ∼62 years) men without diabetes compared to a younger cohort (mean age ∼30 years) (39). Several of these differences between older and younger individuals can be attenuated, however, if a higher level of physical fitness is maintained through the life course. The impact of physical fitness will be discussed in greater detail in the following section.

Important Hormones Mediating Fuel Selection

Catecholamines

A lower reliance on carbohydrate with increasing age may, in part, be due to a lower epinephrine response to exercise of both moderate and high intensity with age. One study showed that men aged 60–70 years old experienced a lower epinephrine response to sub-maximal exercise (∼70% VO_{2max}) than 20–32 year old men regardless of fitness level (40). Similarly, ∼15 min of exercise at ∼78% VO_{2max} resulted in a lower epinephrine response (109 ± 10 vs. 228 ± 29 pg/ml; $p < 0.01$) in a group of older men and women (mean 64 years) compared to younger adults (mean 24 years) (41). Very high intensity exercise (a maximal sprint cycle—Wingate test) also produced lower epinephrine responses in a group of male athletes with a mean age of 34 years (1.86 ± 0.26 mmol/l), compared to a group of athletes with a mean age of 21 years (3.24 ± 0.28 mmol/l; $p < 0.05$) (42). It should also be noted that in older men, there is a blunted lipolytic response to catecholamines compared to younger men, possibly due to decreased sensitivity of the hormone-sensitive lipase complex (43).

Growth Hormone

Older individuals show altered growth hormone responses to several different types and intensities of exercise. Where moderate intensity exercise is concerned, one study found that older men, whether they were trained (10.1 ± 5.5 ng/ml) or untrained (7.7 ± 6.5 ng/ml), had attenuated growth hormone response to 60 min of running at 70% VO_{2max} compared to younger men (trained = 18.1 ± 6.7 vs. untrained = 20.4 ± 11.2 ng/ml) (40). Another study, however, found that responses were similar when exercise was sub-maximal, but that high intensity exercise produced a lower growth hormone response (11.3 ± 3.5 ng/ml vs. 21.9 ± 4.0 ng/ml; $p < 0.05$) in older men (mean ∼64 years) compared to younger ones (mean ∼23 years) (38). Differences were also found with resistance exercise, where growth hormone levels continued to increase post-exercise in young men (mean ∼30 years) while decreasing in older (∼62 years) men (39). Attenuated growth hormone responses to heavy resistance exercise have also been observed in older women (∼62 years) in comparison to younger women (∼24 years) (81), which may impact the fuels that are selected for use both during and after exercise.

Other Hormones

Glucagon and cortisol levels may also be influenced by increasing age. One study showed that glucagon levels were lower at

rest in older men (60–70 years) compared to younger men (20–32 years), regardless of training status (older sedentary = 89 ± 28 pg/ml, older trained = 114 ± 34 pg/ml, younger sedentary = 141 ± 73 pg/ml, younger trained = 136 ± 35 pg/ml; $p < 0.05$ for both younger groups compared to both older groups) (40). Changes during exercise, however, were more dependent on physical fitness (discussed below) than age *per se* (40). Finally, lactate and cortisol responses to maximal exercise are also attenuated with age in both men and women (80), which would be consistent with what is known about reliance on carbohydrates as a fuel source being decreased within the same context.

EFFECT OF PHYSICAL FITNESS ON EXERCISE RESPONSES IN INDIVIDUALS WITHOUT DIABETES

While age-related declines in physical activity/exercise and hormonal responses lead to differences in fuel selection between older and younger individuals, some of these changes can be delayed or attenuated by maintaining higher levels of physical fitness (37, 38). In both younger and older men and women, higher levels of physical fitness lead to increases in hormonal responses to exercise fitness (37, 38, 44, 46), and a greater ability to mobilize and use fuels during exercise fitness (37, 38, 45–49) when compared to sedentary counterparts (**Table 1**). Individuals with higher fitness levels are also known to have greater insulin sensitivity than those who are sedentary (44, 50).

Fuel Selection

Improvements in physical fitness are known to change the proportion of fuels oxidized during exercise, with a greater reliance on lipids during low to moderate aerobic activities (37, 38), and an increase in carbohydrate dependence during high intensity exercise (37, 45, 59). At the same relative intensities, trained individuals will burn more calories, with the difference being made up for with fat oxidation (82), while at the same absolute intensities, trained individuals will have a greater reliance on lipid oxidation than untrained individuals (82). Male athletes are also more efficient at using lactate as a gluconeogenic precursor compared to sedentary males when exercising in the fasting state, which may spare endogenous glucose during extended and/or intense exercise (83).

The effects of physical fitness on fuel selection during exercise remain apparent as individuals age. In a study of older (∼74 years) individuals, 16 weeks of endurance training caused an increase in whole body fat oxidation (from 166 ± 17 to 221 ± 28 μmol/min; $p = 0.002$) and a decrease in carbohydrate oxidation (from 3937 ± 483 to 3180 ± 461 μmol/min; $p = 0.003$) when exercise was performed at the same absolute intensity post-training (49). Another study of older (∼64 years) males noted that carbohydrate oxidation increased with greater exercise intensity, and that trained men experienced a greater increase than untrained men (47). Similar to the case with sex- and age-related differences in metabolism, it is likely that fitness-related differences in hormonal responses to exercise drive these changes in fuel selection.

Important Hormones Mediating Fuel Selection

Catecholamines

As previously discussed, higher levels of epinephrine are associated with a greater amount of hepatic glycogenolysis, and consequently higher levels of blood glucose. Overall, higher levels of physical fitness in men are associated with increased epinephrine responses to both sub-maximal (38, 40) and high intensity exercise (46). In addition, the type of training performed will have an impact on the magnitude of epinephrine responses: male sprinters have a higher sympatho-adrenal output than endurance trained and untrained individuals when faced with supra-maximal exercise. These responses will have a direct impact on glucose metabolism.

Growth Hormone

Growth hormone responses to high intensity exercise can also be affected by the fitness levels of the participant. One study of lean and obese men found that age and physical fitness (and not adiposity) were the strongest predictors of growth hormone responses to a maximal exercise test (84). In spite of the lower response with increasing age, it has also been found that individuals with higher levels of physical fitness maintain higher growth hormone responses to maximal exercise (38, 44). In addition, trained men have demonstrated higher growth hormone responses to heavy resistance exercise, compared to untrained men (from 0.65 ± 0.47 to 5.32 ± 6.67 ng/ml in trained, from 0.50 ± 0.001 to 1.87 ± 3.47 ng/ml in untrained; $p < 0.05$) (85). Where moderate intensity exercise is concerned, one study observed similar growth hormone responses in trained and untrained men, when exercise was performed at the same relative intensity (38), but others have found a significantly higher response in trained men across all age groups (38, 40). There is a paucity of studies to elucidate if these trends hold true for women, or how these differences may impact glucoregulation during exercise.

TYPE 1 DIABETES: EFFECT OF SEX ON EXERCISE RESPONSES

There is currently little exercise research examining differences between men and women with T1D. Many exercise studies involving individuals with T1D have only male participants, or very few female participants. Where studies include both men and women, they generally fail to recognize potential differences between the sexes that may affect the counter-regulatory response to exercise, and affect blood glucose homeostasis. Current studies that do look at sex-related differences are also limited to aerobic exercise, leaving a complete absence of information related to high intensity activities and resistance exercise. In addition, there is currently no information about how fluctuating levels

of estrogen throughout the menstrual cycle could affect blood glucose responses to exercise in women with T1D. What we do know about sex-related differences in hormonal responses to exercise in T1D, however, tends to mirror the outcomes of previous studies in individuals without diabetes.

Fuel Selection

Very few studies have examined sex-related differences in fuel selection during exercise in individuals with T1D, and those that do involve small sample sizes (e.g., <10 individuals of each sex). One study that measured RER during 90 min of aerobic exercise (50% VO_{2max} on a cycle ergometer) noted a tendency toward higher carbohydrate oxidation among men during the last 30 min of exercise, although differences were not statistically significant (86). As the study in question used constant dextrose and insulin infusion to maintain blood glucose, it was not possible to examine the impact of sex on changes in blood glucose during this type of activity. From what we know of studies in non-diabetic individuals, however, the greater reliance on glycogen stores in men during exercise compared to women poses a greater risk, in theory, for post-exercise hypoglycemia in men with T1D, as greater uptake of plasma glucose will be needed to replenish depleted glycogen stores during recovery.

Important Hormones Mediating Fuel Selection

While there is a current lack of information regarding sex-related differences in blood glucose responses to exercise in T1D, there is evidence that hormonal responses differ between the sexes. Similar to studies involving individuals without diabetes, Galassetti et al. (86) found that epinephrine (men = 938 ± 104; women = 628 ± 142 pmol/l; post-exercise; $p < 0.05$) and norepinephrine (men = 5.9 ± 0.8; women = 4.0 ± 0.7 nmol/l; post-exercise $p < 0.05$) responses to exercise were greater in men compared to women with T1D after 90 min of exercise on a cycle ergometer at 50% VO_{2max}. The growth hormone response was also significantly lower in women (from 4 ± 2 to 14 ± 3 μg/l) compared to men (from 1 ± 0.4 to 24 ± 9μg/l; $p < 0.05$) (87). However, women still elicited a greater lipolytic response to exercise (glycerol increased from 46 ± 7 to 188 ± 40 μM compared to 31 ± 5 to 131 ± 10 μM in men; $p < 0.05$ area under the curve), with a suggestion of greater tissue sensitivity in women to growth hormone than men (86).

Where glucagon is concerned, sex-related differences seem to exist only where individuals have experienced hypoglycemia prior to exercise. The pancreatic β-cell death that characterizes T1D is accompanied by a progressive loss of α-cell function over time (87), resulting in an impaired glucagon response to falling blood glucose levels (88). The decline in function appears to happen evenly across the sexes, resulting in similar glucagon responses to exercise and to hypoglycemia at rest. Davis et al. (89) found that glucagon responses to hypoglycemia were similar among men and women with T1D (63 ± 18 and 58 ± 12 ng/l respectively). Similarly Galassetti et al. (86) found no sex-related differences in glucagon responses (51 ± 3 ng/l for men vs. 47 ± 7 ng/l for women) to 90 min of cycling at 50% VO_{2max} in participants with T1D who were matched for age, glycemic control, duration of diabetes and exercise fitness.

With the presence of antecedent hypoglycemia, however, Galassetti et al. (90) discovered a greater blunting of counter-regulatory hormonal responses to exercise in men with T1D, compared to women matched for age, fitness, diabetes duration, and glycemic control. The exercise involved 90 min of euglycemic exercise (cycling at 50%VO_{2max}) performed 24 h after a 2 h hypoglycemic period. While both groups had a noticeably blunted response, the differences in counter-regulatory hormones, particularly glucagon (11 ± 2 ng/l lower in men, but only 5 ± 2 ng/l lower in women, $p < 0.05$) led to a higher level of suppression of endogenous glucose production during exercise in the men (90). In the absence of a constant insulin and glucose infusion to maintain blood glucose concentration, this would most likely result in greater declines in blood glucose in males compared to females. Overall, more research in the area of sex and its effects on blood glucose responses to different types, timing, and intensity of exercise in T1D are required.

TYPE 1 DIABETES: EFFECT OF AGE ON EXERCISE RESPONSES

Within the context of T1D, aging is associated with increasing insulin dosage, as resistance to insulin increases with both age (mostly due to decreasing physical activity levels) (91) and disease duration (92). To date, it has yet to be examined whether older adults with T1D have different responses to exercise across various intensities compared to young adults. The differences in fuel selection and hormonal response seen between age groups in individuals without diabetes would indicate that age should be considered as an important factor. As improvements in diabetes care have led to a greater number of individuals with T1D living longer, healthier lives, determining the impact of age on blood glucose responses to different types and durations of exercise will become increasingly important.

TYPE 1 DIABETES: EFFECT OF PHYSICAL FITNESS ON EXERCISE RESPONSES

Where fuel selection is concerned, it would seem that improvements in physical fitness have a similar impact in individuals with T1D as they do in individuals without diabetes. One small study with T1D participants showed that improvements in physical fitness after 7 weeks of sprint training increased the participants' reliance on lipids as a fuel source (as measured by lower RER) during moderate intensity activity (93). This decreased reliance on carbohydrate as a fuel source during exercise, however, does not seem to protect against hypoglycemia: a recent study of 44 participants with T1D found that those who were more fit seemed to be more prone to hypoglycemia during moderate (60% VO_{2max}) aerobic exercise (94).

In individuals with T1D, elevated epinephrine responses can lead to elevations of blood glucose during high intensity exercise that can persist for up to 2 h post-exercise (60). The extent to which fitness levels offer this glucose raising effect in individuals

with T1D requires further examination, as current studies of high intensity exercise (either on its own or in the form of high intensity interval exercise) tend to have small sample sizes, of heterogeneous composition. It is also uncertain as to whether higher fitness levels will lead to a greater risk of nocturnal hypoglycemia in trained individuals vs. untrained individuals due to the need to replenish a greater amount of glycogen post-exercise.

CLOSED LOOP/ARTIFICIAL PANCREAS EXERCISE STUDIES TO DATE

A small handful of studies have been completed to assess the performance of existing closed loop systems when faced with the challenge of controlling blood glucose during exercise (95–100). The task of managing blood glucose for different intensities of exercise in individuals with T1D is highlighted in a study by Jayawardene et al. (97) where a high intensity interval exercise protocol of similar energy expenditure to a moderate aerobic exercise protocol resulted in significantly different blood glucose levels 60 min post-exercise (high intensity intermittent exercise: 11.3 ± 0.5 mmol/L vs. aerobic exercise 8.9 ± mmol/L; $p < 0.001$) while using a hybrid closed loop system. This occurred in spite of standardization of exercise timing and food intake. One out of the 12 participants also experienced hypoglycemia (plasma glucose <4.0 mmol/L for more than 15 min) after the moderate exercise session (97).

For hypoglycemia prevention during and after exercise, it has been suggested that closed loop systems should include both insulin and glucagon so that they can more closely replicate the hormonal changes that usually take place. Unfortunately, stable liquid glucagon formulations are currently lacking (101), making the widespread use of bi-hormonal devices impossible at this point. While dual hormone systems have generally been more successful at hypoglycemia prevention during exercise when compared to systems using insulin alone, they still cannot fully prevent hypoglycemia. Taleb et al. (96), for example, examined the performance of dual and single hormone systems in relation to a bout of aerobic exercise (60 min at 60% VO_{2max}) and high intensity intermittent exercise (alternating between 50 and 85% VO_{2max} every 2 min). While the dual hormone system resulted in a trend toward fewer participants experiencing hypoglycemia during the aerobic exercise trial (17.6 vs. 52.9%, $p = 0.07$), it still did not prevent it. Findings were similar for the high intensity intermittent protocol with respect to the number of participants experiencing hypoglycemia during exercise (6.25 for dual vs. 40% for single hormone, $p = 0.07$). Castle et al. (100) also had similar findings for a 45 min exercise session at 60% VO_{2max} where a dual hormone system decreased time spent in hypoglycemia (3.4 ± 4.5% for dual hormone, 8.3 ± 12.6% for single hormone, $p = 0.009$). Hypoglycemia still occurred, albeit in lesser amounts. It is likely that there simply is not enough information available on exercise in T1D for these systems to predict exercise responses accurately.

SUMMARY

Changes in blood glucose during the 24 h after physical activity/exercise (i.e., the recovery period) are likely to be slow enough that a closed loop system will be able to manage them appropriately. The variability in responses to exercise and the magnitude of blood glucose changes over short periods, however, may prove to be a challenging obstacle due to the diversity of responses in a very heterogeneous population. A highly fit, young, female, may have very different responses to various types and intensities of exercise than an older, sedentary male. In the context of how little is currently known about all of the possible variables that might affect blood glucose responses to exercise in individuals with T1D, there may be insufficient information to produce a model that fully predicts it. Additional studies in this area involving participants with a greater range of ages, sexes, and fitness levels are required in order to provide the necessary information to successfully model physical activity/exercise in the context of the artificial pancreas.

AUTHOR CONTRIBUTIONS

All authors JY, NB and RB made equal contributions in the research, drafting and editing of this manuscript.

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Objective Measurement of Physical Activity in Adults With Newly Diagnosed Type 1 Diabetes and Healthy Individuals

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Matson RIB, Leary SD, Cooper AR, Thompson C, Narendran P and Andrews RC (2018) Objective Measurement of Physical Activity in Adults With Newly Diagnosed Type 1 Diabetes and Healthy Individuals. Front. Public Health 6:360. doi: 10.3389/fpubh.2018.00360

Aims: Physical activity (PA) has many benefits in type 1 diabetes mellitus (type 1 DM). However, PA levels in people with type 1 DM have not previously been measured accurately. We aimed to compare objectively measured PA in adults recently diagnosed with type 1 DM and healthy adults.

Methods: Accelerometer data from 65 healthy adults [mean (SD) age 31 (13), 29% men] were compared with data from 50 people with type 1 DM [mean (SD) age 33 (10), 64% men], time since diagnosis <3months, HbA1c 76 ± 25 mmol/mol) in the EXTOD (Exercise for Type 1 Diabetes) pilot study. Briefly, EXTOD investigated the feasibility of recruiting recently diagnosed adults with type 1 DM into a yearlong exercise intervention. Multiple-regression models were used to investigate the association between diabetes status and activity outcomes.

Results: Adults recently diagnosed with type 1 DM spent on average a quarter less time in moderate-to-vigorous-physical-activity (MVPA) per day than healthy adults [after adjusting for confounders, predicted values: type 1 DM adults: [mean (SD)] 37.4 mins/day (9.1) Healthy adults: 52.9 mins/day (11.0)]. No difference in MVPA between the groups was seen at the weekend, but adults with type 1 DM spent more time in light physical activity (LPA), and less time in sedentary behavior. Time spent in sedentary or LPA during weekdays did not differ between groups.

Summary: Adults recently diagnosed with type 1 DM do less MVPA. Health care workers should encourage these people to engage in more PA. Further studies are needed to assess PA in people with type 1 DM of longer duration.

Keywords: type 1 diabetes, physical activity, sedentary behaviors, newly diagnosed, moderate-to-vigorous-physical-activity

KEY MESSAGES

- This is the first study to compare objectively measured physical activity in adults newly diagnosed with Type 1 diabetes mellitus (type 1 DM) with people without type 1 DM.
- Adults with newly diagnosed type 1 DM spent over a quarter less time in moderate-to-vigorous-physical-activity (MVPA) than adults without type 1 DM.
- Clinicians should assess activity levels of adults with newly diagnosed type 1 DM and encourage those who are not reaching guideline targets to do more.

INTRODUCTION

Regular physical activity (PA) plays a key role in the management of type 1 diabetes mellitus (type 1 DM) (1). It improves insulin sensitivity and well-being, reduces cardiovascular risk factors such as blood pressure and lipids and may help to preserve beta cell function (2). As a result, guidelines recommend that adults with type 1 DM undertake at least 150 min per week of moderate to vigorous aerobic exercise, spread out over at least 3 days, with no more than two consecutive days between bouts of aerobic activity (3, 4).

Most studies investigating physical activity (PA) levels in adults with type 1 DM have been based on self-reported data rather than objective data. A retrospective analysis of the Diabetes and Complications Trial found 19% of participants (271/1,441) were not achieving recommended PA levels (5). In the EURODIAB prospective cohort study of 2,185 people with type 1 DM from 16 European countries, 786 (36%) people were doing no or only mild PA (6). Similarly, 23% of people with type 1 DM were classed as sedentary and a further 21% were doing less than one session of exercise per week in the Finnish Diabetic Nephropathy Study (7). Only one study has objectively measured PA in adults with type 1 DM. This Canadian study found that only 43% of women and 55% of men with type 1 DM were active (8). No difference was found in activity levels between adults with or without type 1 DM.

In people with established type 1 DM many of the barriers, motivators and facilitators to PA are similar to the general public, such as lack of time, work pressures and bad weather (9–11). They do however require education about the effect of PA on diabetes control to help prevent low and high blood glucose around PA something they struggle to manage and worry about. A qualitative study from our group suggests that newly diagnosed adults with type 1 DM reduce their levels of PA around the time of diagnosis (12). They also face additional barriers to PA such as feeling overwhelmed by their diagnosis and receiving conflicting advice by healthcare professionals to stop exercising.

No studies have objectively measured the PA levels or patterns of people recently diagnosed with type 1 DM, a time when exercise habits may be greatly influenced. This study aimed to compare objectively measured PA levels in recently diagnosed adults with type 1 DM to healthy adults.

Abbreviations: Type 1 DM, type 1 diabetes mellitus; PA, Physical activity; LPA, Light physical activity; MVPA, moderate-to-vigorous-physical-activity.

METHODS

This is an observational cross-sectional study comparing objectively measured PA data of adults newly diagnosed with type 1 DM with that of healthy adults. The EXTOD study was approved by the Birmingham East, North and Solihull Research Ethics Committee (0/H1206/4), UK, and the study to measure activity in healthy adults was approved by the Centre for Exercise, Nutrition and Health Science Ethics Committee, University of Bristol (EAN 001-15) and was part of RIBM MRes project. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Recruitment and Procedures

Objectively measured PA in adults with type 1 DM came from participants in the Exercise in type 1 diabetes (EXTOD) study (2). This was a pilot RCT that aimed to assess uptake, intervention adherence, dropout rates and rate of uptake in a usual care group and exercise intervention group over 12-months. This study has been described in detail elsewhere (2, 13). In brief, people aged between 16 and 60 years, clinically diagnosed with type 1 DM in the previous 3-months and self-administering their insulin as part of a multiple dose injection regime, and from 19 UK hospital sites were invited to participate. A member of the clinical team (doctor/diabetes nurse/dietician) at each site approached people newly diagnosed with type 1 DM and obtained written informed consent. Objectively measured PA of participants in this study was measured at baseline, 3, 6, 9 and 12 months. For the present study, the data from the baseline visit were used. Five hundred and eight adults with type 1 DM were invited to take part. Of these 15 took part in the qualitative study and 58 were randomized into the main EXTOD Study (13).

Healthy adults were recruited from the University of Bristol and Taunton and Somerset NHS trust during March-June 2016. A global e-mail was sent out to all members of these two institutions explaining briefly about the study. In addition, flyers were put out in public areas. Participants had to be between 18 and 65 years old and on no medication. Upon request from potential participants, they were sent the participant information sheet, and if interested they were invited to attend an appointment at either the Centre for Exercise, Nutrition and Health Sciences at the University of Bristol or the Diabetes research unit at Taunton and Somerset NHS trust.

Procedures

Following informed consent, participants completed a questionnaire to confirm their health status, smoking status, and alcohol consumption. Weight and height were measured using standard procedures. BMI was calculated as weight (kg) divided by height (m) squared. Participants were provided with an accelerometer and instructions were given on how to wear the accelerometer for the next 7 days. Participants returned the accelerometer 1 week later either by appointment or by post. Brief feedback was given to the participants on their levels of activity over the 7 days they wore the accelerometer; a graphical interpretation of their physical activity over the 7 days was

delivered via email after they had returned the accelerometer and the data had been downloaded.

Accelerometry

Participants wore the accelerometer (Actigraph Model GT1M or GT3X+; Actigraph LLC, Pensacola, FL, USA) on a belt around the waist during waking hours, apart from swimming or bathing, for 7 days. The accelerometers were set to record data at 30 Hz and data were summarized for every minute. Accelerometer data were downloaded using Actilife software (version 6.11.9, Actigraph LLC) and processed to generate outcome variables using KineSoft (version 3.3.62; KineSoft, Saskatoon, SK, Canada). Non-wear time was defined as a period of 60 min or longer with continuous zero values, with a spike tolerance of 2 min. Thresholds of $\geq$1,952 counts per minute (cpm) and $<$100 cpm were used to derive MVPA and sedentary time respectively (14), with light activity defined as 100–1,951 cpm. For a day to be considered valid, a minimum of 480 min (8 h) of wear time was required. For a participant's data to be included in the analysis a minimum of 3 valid days were required.

Outcome measures were time spent in sedentary behavior (minutes per day), time spent in LPA (minutes per day), and time spent in MVPA (minutes per day). Each of these variables were then summarized by weekday, weekend and all week to investigate the pattern of PA throughout the week. The number of bouts of MVPA $\geq$10 min was also used as a comparison between groups. We used bouts of over 10 min as guidelines suggest that the bouts of exercise that count toward the 150 min a week of moderate or intense activity should be of 10 or more minutes [3.4].

Analyses

Means/standard deviations and percentages were used to describe the characteristics of the participants. Differences between means of the two groups were tested by two-sample *t*-tests (normal data), Mann-Whitney *U*-tests (non-normal data), and Chi-squared tests (categorical data).

Multiple linear regression was used to assess the association between diabetes status and activity intensity (minutes of sedentary activity, light activity and MVPA). Model A was adjusted for sex, age, wear time, and model B was further adjusted lifestyle factors (BMI, smoking status, and alcohol consumption).

To investigate the difference in the total number of bouts accumulated by both groups, logistic regression was used. Adjustment for confounders (model A and B) was made by creating a binary outcome (equal to or more than the median number of bouts vs. less than the median number of bouts) and fitting multiple logistic regression models. Due to not every participant wearing their accelerometer for 7 days, a sensitivity analysis was performed, which restricted the analysis to only those with 7 valid days of accelerometry.

It had not been appropriate to perform a power calculation for the original study (EXTOD), as it was a pilot. However, a *post-hoc* power calculation showed that with an alpha level of 0.05, a minimum sample size of $n = 50$ in each arm, means of 52 and 37 min/standard deviations of 21 and 28 min of MVPA/day for healthy adults and adults with type 1 DM respectively, this study had 85% power to detect differences between the groups.

All analyses were performed using Stata v15 (*Stata Statistical Software: Release 15*. StataCorp LLC, College Station, TX).

RESULTS

Fifty-nine participants with type 1 DM had their activity measured at baseline in the EXTOD study and 79 healthy adults were recruited to the study. After excluding participants with invalid accelerometry, there were 50 participants with type 1 DM (85%) and 65 healthy adults (82%) left for analysis. Demographic information for those included in analysis is shown in **Table 1**. The participants with type 1 DM had a higher percentage of males, higher BMI and a slightly higher amount of accelerometer wear time than the healthy adults but were otherwise similar. Those excluded from analysis were similar to those included in terms of ethnicity, sex, age, smoking status, HbA1c, and duration of diagnosis of type 1 DM, but had lower alcohol consumption and BMI (**Supplementary Table 1**).

Associations Between Diabetes Status and Activity Intensity

Table 2 shows the multiple linear regression models for time spent in sedentary behaviors, LPA, and MVPA in minutes per day.

For time spent in sedentary behaviors and LPA, there was no evidence of a difference on weekdays and over the whole week, but there was evidence for the adults with type 1 DM spending more time in LPA and less time in sedentary behaviors at the weekend.

For MVPA, statistical evidence was found for a difference on weekdays and across the whole week, but not on weekends. On average the type 1 DM group spent 10.9 min less in MVPA per day than the healthy adults after adjustment for confounders [(95% CI-22.2, 0.4) $p = 0.06$], over a quarter less time in MVPA [Predicted values [Mean (SD)] type 1 DM adults: 37.4 mins/day (9.1) Healthy adults: 52.9 mins/day (11.0)].

Associations Between Diabetes Status and Bouts of MVPA

We investigated the difference in number of bouts of MVPA $\geq$10 min further by logistic regression, using the binary variable based on the median number of bouts as the outcome. No statistical evidence was found for a difference in numbers of bouts between the groups for either models (**Supplementary Table 2**).

DISCUSSION

We have shown for the first time that adults recently diagnosed with type 1 DM spent over a quarter less time doing MVPA over the week than healthy adults. This difference seemed to be driven by the weekdays rather than weekend. There was also evidence that people with type 1 DM spent more time in LPA and less

TABLE 1 | Characteristics of adults with Type 1 diabetes and healthy adults.

	Type 1 diabetes ($n = 50$)	Healthy adults ($n = 65$)	p-value
Sex (men) (%)	64%	29%	<0.001
Age (years)	33 (10)	31 (13)	0.6
Ethnicity (% white-british)	85%	85%	0.7
Ex-smoker	20%[a]	20%[b]	0.3
Current smoker	18%[a]	18%[b]	
Never smoked	62%[a]	62%[b]	
Alcohol consumption (units) [Median (IQR)]	3 (10)[a]	6 (7)[b]	0.09
BMI (Kg/m^2)	24.9 (3.9)	23.4 (3.7)	0.006
HbA1c (mmol/mol) [DCCT (%)]	76.3 (24.6) (9.1%)	–	–
Duration of diagnosis of T1D (days)	62 (23)	–	–
DAYS OF ACCELEROMETER WEAR (DAYS)			
Weekday	4.4 (0.8)	4.1 (1.1)	0.07
Weekend	1.6 (0.7)	1.7 (0.5)	0.01
All week	6.0 (1.0)	5.8 (1.5)	0.01

Mean (SD) unless otherwise stated. [a]n = 49 for Diabetes. [b]n = 51 for the healthy adults.

TABLE 2 | Multiple linear regression investigating the associations between diabetes status and activity intensity.

	Model A		Model B	
Diabetes vs. no diabetes	**Regression coefficient (95%CI)**	**p-value**	**Regression coefficient (95%CI)**	**p-value**
SEDENTARY				
Weekday	20.2 (−17.6, 58.0)	0.3	18.0 (−24.6, 60.5)	0.4
Weekend	−19.3 (−56.7, 18.1)	0.3	−40.6 (−82.1, 0.9)	0.06
All week	9.9 (−23.4, 43.2)	0.6	3.5 (−34.3, 41.4)	0.9
LIGHT				
Weekday	−3.8 (−39.1, 31.5)	0.8	−3.7 (−44.7, 37.3)	0.9
Weekend	35.2 (3.3, 67.0)	0.03	48.3 (12.5, 84.0)	0.009
All week	5.1 (−25.4, 35.6)	0.7	7.2 (−27.8, 42.2)	0.7
MVPA				
Weekday	−16.7 (−27.5, −6.0)	0.003	−13.5 (−25.5, −1.5)	0.03
Weekend	−15.8 (−31.6, 0.07)	0.05	−7.5 (−25.4, 10.4)	0.4
All week	−15.2 (−25.2, −5.1)	0.003	−10.9 (−22.2, 0.4)	0.06

All week and weekday sedentary time, light physical activity (LPA) and moderate-to-vigorous-physical-activity (MVPA): Model A n = 115 Model B n = 99. Weekend sedentary, light and MVPA: Model A n = 107 and Model B n = 91. Model A adjusts for sex, age, and wear time. Model B adjusts for sex, age, wear time, BMI, smoking status, alcohol consumption.

time being sedentary than healthy adults at the weekend, but no differences in these behaviors was seen on weekdays.

We could only find two studies that have compared objectivity measured physical activity of people with type 1 DM with healthy adults. In the first study Brazeau and colleagues using a motion sensor (SenseWear Pro 3 Armband) measured the activity of 75 Canadian adults with established type 1 DM and 75 Canadian adults without type 1 DM (8). They found that although the PA levels of the adults with type 1 DM were low, only 43% of women and 55% of men being classed as being active, they were not different from those seen in adults without type 1 DM. The difference between our finding and the findings of this study could be due to the fact that our participants were adults with newly diagnosed diabetes whereas in the Brazeau et al. study the participants had had type 1 DM on average for 23 years. In a qualitative study that our group conducted of newly diagnosed people with type 1 DM around half reported a reduction in activity levels around diagnosis (12). In addition, some participants reported being advised by healthcare practitioners not to exercise. Finally, adults newly diagnosed with type 1 DM placed greater emphasis on fear of hypoglycaemia than previous studies of people with longstanding type 1 DM (11).

In the second study, by Finn and colleagues, PA was measured objectivity using an accelerometer (Actigraph) in 72 (34 males) Irish adults with type 1 DM (15). Subjectively reported PA levels were also captured using the International Physical Activity Questionnaire (IPAQ). The mean age (± SD) was 41 (± 13) years and mean diabetes duration of 18 (± 12) years. This study found 23 (32%) participants exercised to PA recommendations as measured by accelerometry,

compared with 69 (97%) participants reporting meeting the recommendations as per the IPAQ. This study as well as confirming that people with type 1 DM are not very active also underlined the inaccuracy of physical activity questionnaires and the need to use objective measures of activity.

It is interesting that the lower MVPA in adults with type 1 DM appears to be driven by changes in weekday activity rather than weekend activity. During the week activity is influenced by work patterns and the type of job a person does whereas at the weekend people tend to have more control over their activity patterns. It might well be that the difference we are seeing in this study are due to a difference in the way that people travel to work (walking vs. driving car) (16). We were unable to look at this, as occupation was not recorded. Alternatively, people newly diagnosed with type 1 DM may have had restrictions placed on them by their work due to their diagnosis that may have reduced their levels of activity. This is not something that came up in our interviews with newly diagnosed people with type 1 DM (12) but is something that people on occasions have mentioned to us in clinic. Studies are needed to confirm whether this does happen and if so how often. People with type 1 DM often have to plan their exercise as they may have to make a change to their insulin dose at the meal prior to exercise or eat before exercise. This may mean that they tend to focus on exercise at the weekend rather than during the week when they have more time to plan for exercise. People with type 1 DM can have problems with low or high blood glucose for 24 h after exercise. Because they do not want to have these problems on a working day, they might decide to do their exercise at the end of the week and at the weekend.

More time spent being sedentary is associated with poorer metabolic health. In a systematic review of 29 observational studies, accelerometer-measured total sedentary time was detrimentally associated with both glycaemic control and lipid profile (17). People with newly diagnosed type 2 diabetes mellitus as well as doing less MVPA than healthy controls spend more time being sedentary (18). Conversely, in the present study adults newly diagnosed with type 1 DM were not found to be more sedentary than healthy controls. If this finding is replicated in other studies, then exploring why this is the case might give us better insight in how to promote higher levels of MVPA and reduce sedentary time.

The lack of difference in sedentary time could be due to the fact that although their worries about hypoglycaemia, and lack of knowledge and/or confidence in managing their glucose around exercise prevents them from doing moderate and high intensity activities it does not stop them doing low intensity activities. Alternatively, it could be that a reduction in sedentary time is only seen after people have had type 1 DM for a number of years. Brazeau and colleagues did not report sedentary time in their study (8). In the study by Finn and colleagues time spent in sedentary time was high, with the mean time spent being sedentary 8.4 $\pm$ 1.6 h per day (15), but as they did not have healthy controls it is difficult to know if this is more than that seen in people without type 1 DM of similar age and weight. Further studies will be needed to clarify how sedentary people with type 1 DM are and whether this changes with time.

In our data set, women were less active than men (data not shown). This is in keeping with an American study that objectively measured PA in 6,329 participants and found men to be more active than women (19) but at odds with objectively measured activity data from 93,015 participants in the UK Biobank study where no difference in activity was seen between men and women (20). In our analysis we have tried to adjust for the fact that there were more men in the Type 1 group but we might have found a greater difference in MVPA if our two groups had been equally matched for men and women.

Strengths and Limitations

A major strength of this study is the use of an objective and reliable method to assesses the physical activity levels (21). In addition, people with type 1 DM came from the EXTOD study (2) which recruited from multiple UK sites covering both large teaching and district general hospitals, and participants spanned a wide age range. However, there are limitations to this study. Due to the fact that we only measured activity at one time point, we are unable to comment on any causal associations between recent diabetes diagnosis and changes in PA. Healthy controls were recruited from only two sites both in the South West of the UK, which may limit generalizability. It is also likely that study participants were more interested in exercise than those who declined, and PA may be lower in the general population of both type 1 DM and healthy people. The small sample size of the two groups in this study is a further limitation of this study. Nonetheless, this study adds to the literature suggesting that longitudinal observational studies of PA of people with newly diagnosed type 1 DM are warranted.

CONCLUSION

In conclusion, our results indicate that adults newly diagnosed with type 1 DM spend more than a quarter less time doing MVPA over the week compared to healthy adults. This suggests that steps need to be taken to try and improve the activity levels of adults newly diagnosed with type 1 DM. To do this clinicians will need to be trained in how to assess and encourage activity and also be furnished with knowledge about how to advise patients to manage their glucose around exercise. In addition, people with type 1 DM will need to be provided with knowledge and skills to safely manage their glucose around exercise. We and others are working on programmes to help support these changes.

AUTHOR CONTRIBUTIONS

RM, SL, AC, and RA had full access to the primary data. All authors contributed to data analysis and interpretation, and the writing and editing of the report. All authors approved the final version of the report. The corresponding author had full access

to all the data in the study and had final responsibility for the decision to submit for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2018.00360/full#supplementary-material

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REVIEW
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The Benefits and Limits of Technological Advances in Glucose Management Around Physical Activity in Patients Type 1 Diabetes

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Physical activity is highly recommended for patients living with type 1 diabetes (T1D) due to its varied health benefits. Nevertheless, glucose management, during and in the hours following exercise, represents a great challenge for these patients who most often end up leading a sedentary life style. Important technological advances in insulin delivery devices and glucose monitoring are now available and continue to progress. These technologies could be used to alleviate glucose management related to physical activity in T1D. Continuous glucose monitoring (CGM) helps patients observe the trends of glycemic fluctuations when exercising and in the following night to deal pre-emptively with hypoglycemic risks and treat hypoglycemic episodes in a timely manner. Insulin pumps offer the flexibility of adjusting insulin basal rates and boluses according to patient's specific needs around exercise. The artificial pancreas links CGM to pump through an intelligent hormone dosing algorithm to close the loop of glucose control and has thus the potential to ease the burden of exercise in T1D. This review will examine and discuss the literature related to physical activity practice using each of these technologies. The aim is to discuss their benefits as well as their limitations and finally the additional research needed in the future to optimize their use in T1D.

Keywords: type 1 diabetes, exercise, continuous subcutaneous insulin infusion, continuous subcutaneous glucose monitoring, artificial pancreas, single-hormone, dual-hormone, closed-loop

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INTRODUCTION

Regular physical activity (PA) offers many potential health benefits for individuals with type 1 diabetes (T1D) including improvements in insulin sensitivity and requirements, reduced risk of cardiovascular diseases and increased overall life expectancy (1). Despite these benefits, physical activity is practiced at a much lower frequency than recommended by patients with T1D (2) who may adopt unhealthy lifestyles worsening their cardiometabolic risk profile (3). The principal barrier for PA is the fear of hypoglycemia that is mainly driven by the inability to identify and/or implement effective strategies for hypoglycemia avoidance (2).

As compared to people without T1D, the inability to reduce circulating insulin during and after exercise restricts hepatic glucose production concurrently to an enhanced glucose disposal rate

into skeletal muscle. Skeletal muscle plays a considerable role in maintaining homeostasis of blood glucose. It uses glucose as a source of energy during dynamic exercise, and represents the major site for insulin-stimulated glucose uptake. Glucose is transported from blood into muscle fibers by the glucose transporter-4. This process is regulated by the translocation of glucose transporters-4 to the plasma membrane and transverse tubules under insulin and exercise-stimulated conditions (4) (**Figure 1**). Because of the disparity between glucose production and utilization (e.g., combined exercise and relative hyperinsulinemic conditions), hypoglycemia can occur during and in the hours following exercise (5). The type, intensity, duration, and distance to meals of exercise as well as the aerobic fitness are all important factors influencing glucose homeostasis (6, 7) (**Figure 2**). Therefore, aerobic, sprint, and resistance training can be responsible for wide variations in blood glucose responses (8, 9). While low to moderate aerobic exercise usually induces progressive glucose lowering, high intensity activities can trigger significant release of counter regulatory hormones (e.g., epinephrine and glucagon) causing rapid elevations in blood glucose levels (**Figure 2**). Exercise duration also affects glucose control for example, extended periods of exercise results in a higher rate of glucose disposal and thus increased risk of hypoglycemia. Hormonal counter-regulatory response (e.g., catecholamines, glucagon, etc.) to different types of prolonged exercise could be highly variable inter- and intra- individuals as shown in well-controlled T1D (10, 11). For very intense exercise it can trigger a short but large hepatic glucose output exceeding glucose utilization ability by other tissues resulting in transient but significant hyperglycemia (5) (**Figure 2**). Even with low intensity and realtively short duration exercise practiced during the day, an increase in insulin sensitivity can last up to 11–16 h post-exercise which combined with glycogen store replacement can increase the risk of late-onset or nocturnal hypoglycemia (**Figure 2**).

Guidelines for minimizing exercise-related hypo- and hyperglycemic risks exist but remain general (12). In practice, 3 main adjustments may be considered (13, 14): **1/** carbohydrate (CHO) supplementation (15, 16), particularly for unanticipated exercise and for prolonged exercise; **2/** premeal insulin-dose reduction (17, 18) provided exercise can be anticipated and undertaken within meal bolus insulin action and for patients using continuous subcutaneous insulin infusion (CSII: pump) for both post-prandial and post-absorptive periods using temporary basal insulin reduction; **3/** adding high intensity sprints in intervals, or resistance training at beginning or end of exercise sessions (9). However, even when one or combinations of these strategies are used, the right combination for a specific exercise is complex to establish and most patients still have wide exercise-related glucose fluctuations.

Remarkable progress has been achieved in technologies to improve and facilitate diabetes management including insulin pumps, continuous glucose monitoring (CGM), and external artificial pancreas systems. This review aims to discuss how technological advances could be used to alleviate the burden of glucose management during exercise in patients with T1D. Each of these technologies is reviewed to examine its benefits as well as limitations around exercise.

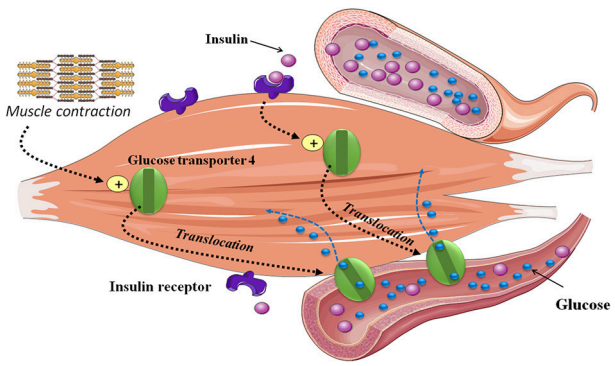

FIGURE 1 | Skeletal muscle glucose uptake during exercise. Exercise increases insulin-stimulated glucose uptake in skeletal muscle. This process is regulated by the translocation of glucose transporter-4 glucose to the plasma membrane and transverse tubules. Both exercise and insulin utilize different signaling pathways, both of which lead to the activation of glucose transport.

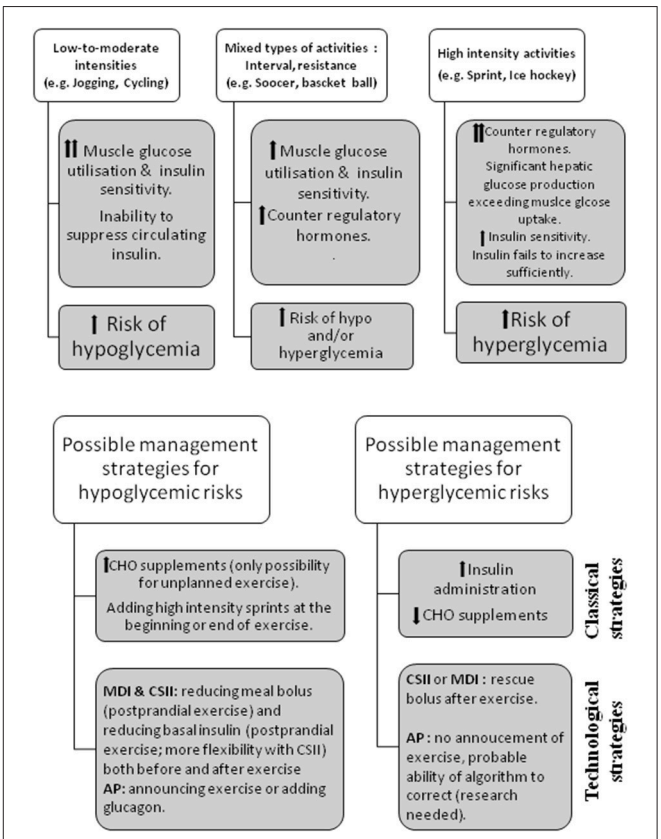

FIGURE 2 | Physiological mechanisms related to hypo and hyperglycemia & strategies to limit exercise-induced hypo and hyperglycaemia in patients with type 1 diabete. CHO, carbohydrate; CSII, continuous subcutaneous insulin infusion; MDI, Multiple dose injection; AP, artificial pancreas.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII: INSULIN PUMPS)

In this section we aim to present an update of practical management strategies during exercise in patients using insulin pump therapy. The introduction in the 1980's of CSII therapy in the form of pump systems was an important landmark in technological advances in insulin delivery (19). Insulin pumps provides a flexibility in an attempt to mimic physiologic insulin delivery, infusing rapid acting insulin subcutaneously at preselected basal rates to cover a 24 h period in addition to insulin boluses at mealtimes or to correct hyperglycemia that are activated on demand by the patient (20).

New insulin pumps are small in size and endowed with many programming options that facilitate their use. Insulin pumps exist in various designs the main difference being patch or tubeless pump vs. using an external catheter. In patch pumps, a container housing the insulin ampoule attaches directly to the skin with a catheter directly under the patch and a controller communicates wirelessly with the patch pump. In contrast, with the conventional design, the pump holds the insulin reservoir and connects to the body through a tubule up to a subcutaneous insulin catheter (21). While for aquatic physical activity patch pump since it is waterproof and does not require disconnection, the ability to transiently disconnect the pump with offered by conventional pumps can be useful for some other activities with contact (judo, hockey, etc.).

CSII therapy is proven to improve glucose control in many patients with diabetes resulting in lower HbA_{1c} levels and frequency of hypoglycemia, it is however associated with higher treatment cost and require to be continuously worn (22–24). Furthermore, a change in basal insulin delivery rate around the time of exercise is only possible with insulin pumps; an approach that cannot be used in multiple dose insulin injections (MDI) regimens where basal insulin is injected once or twice daily at preset timings. Indeed, for physically active patients with T1D, CSII can be a preferred option to facilitate glucose regulation.

Mild to moderate intensity aerobic exercise is probably the most chosen type of physical activity by patients and entails a high risk of hypoglycemia as discussed above. Therefore, this type of exercise was included in most of the conducted studies that have looked up ways to reduce hypoglycemia in patients with T1D (5). When exercise is planned within 90–120 min post meal, a pre-meal insulin bolus reduction that is proportional to exercise duration and intensity has been backed-up by a couple of studies and thus endorsed consensus statements (5, 17, 18, 25). When an exercise session is practiced in close proximity to a meal without anticipation, which is very frequent in adolescents and children, or when a longer than expected activity occurs then the consumption of carbohydrates (CHO) is usually required (15, 16). The CHO rescue could be an effective strategy to improve performance for certain patients who wish to improve their performance but could be counter-productive for those who wish to lose weight.

A third approach that can be applied in insulin pumps users consists of reducing temporarily basal insulin rate. Franc et al. (26) have tested the efficacy of reducing hypoglycemia by decreasing or stopping basal insulin rate at exercise onset. Adult patients with T1D performed 30 min of either moderate or high intensity aerobic in a post-absorptive state (>3 h post-meal). No hypoglycemia events (glucose <3.3 mmol/l) were recorded: when basal insulin was reduced: **1/** by 50% or 80% during moderate exercise (50% VO_{2peak}) or **2/** by 80% or pump stopped for the intense exercise sessions (75%VO_{2peak}). Another relevant observation from this study is that late post-exercise hypoglycemia risk was similar to rest interventions with the implementation of an 80% basal insulin reduction for moderate exercise and with pump suspension for the intense exercise (26). Another study conducted in an adult population with T1D looked at the effects of basal insulin suspension at exercise onset on blood glucose levels during 40-min continuous (40–50% VO_{2peak}) vs. circuit-based exercise. The authors reported that basal insulin suspension at the onset of exercise leads to a greater drop in glycemia during Continuous vs. Circuit-Based Exercise (27). Currently, studies comparing the effects of basal rate reduction during continuous exercise vs. interval exercise remain uncommon. Considering that these type of exercise have a different impact the blood glucose level in T1D patients, it will be important to test strategies to determine the optimal approach to reduce hypoglycemia during these 2 types of exercise.

The studies cited above (26, 27) showed that as compared to no action, significant reduction in insulin infusion at exercise onset is generally helpful in improving time spent with blood glucose levels in target ranges during exercise, but the risk of hypoglycemia remains largely present. Thus, other studies have thereafter focused on completely suspending insulin infusion. In a pediatric study ($n = 10$), hypoglycemia episodes and the drop in glycemia during a 40–45-min exercise sessions were similar between a pump-on vs. pump-off strategies (28). In 49 children and adolescents (8–17 years old) with T1D, the DirecNet Study Group were able to bring down the risk of hypoglycemia from 43 to 16% by a pump-off design at exercise onset; 60-min aerobic exercise performed 4 h after lunch (29). The drawback in this study was an increased risk of post-exercise hyperglycemia.

Although reducing insulin basal rate at exercise onset seems could help in attenuating the hypoglycemia risk, earlier timings might be needed for a better effect. This is mostly supported by the pharmacokinetics of available rapid acting insulin analogs; suggesting that decreasing insulin rates up to 90 min prior to exercise onset might be needed to sufficiently reduce circulating insulin levels during a post-absorptive activity (26, 30). Practically speaking, though, such early anticipation is not practical for a large fraction of patients. A recent study compared 3 more practical timings of 80% basal insulin reduction: 40 min, 20 min prior and at exercise onset (31). This study reiterated the fact that exercise-induced hypoglycemia is frequent (close to 50% of exercise sessions). Moreover, although some favorable trends were observed with the reduction at 40 min prior to exercise, hypoglycemia remained a frequent event with that timing. Similarly, McAuley et al. (32) reported that reducing insulin infusion by 50% 1 h prior to a 30-min exercise at moderate intensity did not reduce plasma insulin levels at exercise onset and did not fully prevent exercise-induced hypoglycemia. An

earlier basal rate reduction is thus probably needed to have a more significant impact on hypoglycemic risk.

It should be noted that practicing physical activity does not increase the risk of hypoglycemia only during exercise but also in the following hours frequently including overnight a time at which hypoglycemia prevention, detection and treatment is harder. To mitigate post-exercise hypoglycemia, very few evidence-based data is available. We have reviewed the impact of bedtime snack on nocturnal hypoglycemic risk and highlighted the very low level of evidence of this widely recommended practice (33). Taplin et al. (34) showed that children on CSII could significantly reduce their nocturnal hypoglycemia risk by stopping insulin infusion during exercise and reducing its rate by 20% over the following night (between 21 h:00 and 03 h:00).

The available studies are generally of a small scale (summarized in **Table 1**) and mostly conducted in laboratory settings, but could still help shaping some guidelines for glucose management around exercise for patients using insulin pumps. For anticipated exercise, if exercise occur during meal bolus action a reduction of this bolus proportional to exercise intensity and duration is a reasonably well-validated strategy; for exercise undertaken in the post-absorptive period in patients using CSII, the best timing and amount of insulin reduction prior to exercise onset is still a pending question. In all situations (post-meal vs. post absorptive as well as CSII vs. MDI) different timings and percentages need to be tested in different types of exercise (e.g., aerobic vs. resistance vs. interval; duration; intensity; etc.). In the case of unanticipated exercise, although insulin suspension at exercise onset seems the best solution for the time being, related studies have tackled mainly continuous moderate intensity exercise sessions. An increased risk of hyperglycemia could be speculated for intense continuous or interval exercise with pump suspension and evidence-based data is lacking. In that situation, to correct post exercise hyperglycemia, a recent study validated the efficacy and safety of a correction bolus based on usual correction factor (35). Finally to prevent late post-exercise hypoglycemic risk a nighttime basal rate reduction could be useful strategy.

Further studies are clearly warranted to guide insulin dose adjustments with CSII use. Because of the large inter- and intra-individual variability in glycemic responses to exercise, recommendations can only serve as general starting points that will need to be individualized.

CONTINUOUS GLUCOSE MONITORING

With the difficulty of glucose management during and post exercise in patients with T1D due to rapidly changing levels and hypoglycemia risks, individuals must increase the frequency of glucose monitoring during exercise and the following recovery period. This can be very cumbersome and undesired by many patients, especially when based on capillary glucose measurements. However, the introduction of continuous glucose monitoring in the early 2,000 has had a great impact on facilitating glucose profiling and helping with diabetes management. With CGM, interstitial glucose is measured repeatedly (e.g., each 10 min) via a subcutaneous sensor linked to a skin applied transmitter that relays these readings wirelessly either to a matched insulin pump or to a separate receiver which can be a cell-phone. CGM provides detailed glucose profiling in contrast to the readings that are possible with capillary measurements and has proved its efficacy in improving diabetes management and reducing hypoglycemia rates (36–38).

For physical activity, CGM has helped in gaining better understanding of changing glucose levels during and particularly in the hours following different types and conditions of exercise [an aspect reviewed recently by Houlder et al. (39).

One of the first reports to demonstrate the utility of CGM during exercise was an observational study conducted in 25 adolescents (8–17 years old) during a 2-week sports camp (40). An algorithm of CHO consumption (8–20 g) was followed according to CGM alerts, tendencies and rates of glucose change. Out of 22 uses of the CHO intake algorithm after CGM trend arrows indicated rapidly dropping glucose levels, only 2 hypoglycemia (3–3.9 mmol/l) events occurred (9%). The rate of hypoglycemia was higher (38%) though when glucose was lower than 5 mmol/l at the time of the alert despite consuming 16 g CHO (40). A recent study has also shed the light on the efficacy of combining CGM with a decision support system (DSS) in managing diabetes (41). The CGM+DSS helped patients adjust their insulin and CHO intake through insulin bolus, exercise and automated insulin titration advice. In a cross-over design with a wash-out period, 24 adults (on CSII or insulin injections) spent 48 h at a research clinic using CGM+DSS vs. usual care (41). The protocol included 2 sessions of 45 min (three 15 min exercise with 5 min rest in between) of mild to moderate aerobic exercise. Less time was spent in hypoglycemia (<3.9 mmol/l) with CGM+DSS during exercise (1.8 $\pm$ 2 vs. 3.8 $\pm$ 4.6%, $p = 0.018$). This improvement with CGM+DSS was observed despite significantly lower consumption of CHO before initiating and during exercise and reduced glucose variability in comparison to usual care (41).

Interestingly, patients with T1D and health professionals who attended a boot camp that included real time CGM, in-class teaching and supervised exercise sessions have identified real time CGM as the best learning tool about glucose changes during exercise (42). Patients reported that CGM helped improve glucose control by keeping it in target ranges during sports without needing extra capillary measurements (e.g., less fear of hypoglycemia as well as decreased intake of unnecessary CHO with CGM use) (42).

One possible limitation to CGM usage is a lower accuracy during exercise. This has been recognized in the literature and needs to be understood by patients and healthcare professionals. Among factors involved to explain this lower accuracy rapid blood glucose changes that accompany physical activity is probably a dominant factor. Such situations increase the lag time between blood and interstitial glucose values due to delay to reach equilibration between compartments (5). This CGM delay has been estimated to reach up to 15 min during exercise and could result in either over- or most frequently underestimation of blood glucose. For example, mean difference between CGM

TABLE 1 | Main continuous subcutaneous insulin infusion studies with reported exercise related conclusions.

References	Participants, *n*	Design, insulin adjustments	Exercise description	Study conclusion
Franc et al. (26)	Adults, 20	Randomized, single-blind, single-center, crossover study: 1/Moderate-intensity exercise: 50% BRR at start of exercise (+2 h in recovery) vs. 80% BRR at start of exercise (+2 h during recovery) 2/ Intense exercise: Pump suspended during exercise vs. 80% BRR	1/30 min aerobic cycling (50% of VO_{2peak}) 2/30 min intense cycling (75% of VO_{2peak})	To limit the hypoglycaemic risk associated with 30 min of exercise 3 h after lunch, without CHO supplements, the best strategy seem to be to reduce BR by 80% or to stop the pump for moderate or intense exercise, or for moderate exercise 90 min after lunch, to reduce the prandial bolus (∼50%) rather than the basal rate
McAuley et al. (32)	Adults, 14	Prospective, open-label, two-stage randomized crossover study: 50% BRR 1 h prior exercise after single insulin BRR overnight vs. Rest condition (T1D maintained a constant BR)	30 min aerobic cycling (65–70% of maximum heart rate)	Halving the BR 1 h prior to exercise did not significantly reduce circulating free insulin when BG is in low-normal range When BG<7.0 mmol/L before exercise, consider carbohydrate snack and BR >50%
Zaharieva et al. (27)	Adults, 12	Randomized and counterbalanced study: Suspended BR during aerobic exercise vs. Suspended BR during circuit exercise	40 min aerobic exercise of treadmill walking (∼50% of VO_{2max}) 40 min circuit exercise (mean intensity ∼55% of VO_{2max})	With BR suspension, aerobic exercise is associated with a greater drop in BG compared with circuit-based exercise
Roy-Fleming et al. (31)	Adults, 22	Randomized, 3-way crossover study: 80% BBR 40 min before exercise vs. 80% BBR, 20 min before exercise vs. BRR at the start of exercise	45 min submaximal cycling (∼60% of VO_{2max})	Decreasing BR by 80% up to 40 min before exercise onset is insufficient to reduce exercise-induced hypoglycaemia.
Admon et al. (28)	Children and adolescents, 10	Randomized, single-blind, crossover study: Pump on (50% BRR) during exercise. vs. Pump off (Suspended BR) during exercise.	40–45 min submaximal cycling (∼60% of VO_{2max})	No difference in hypoglycemia episodes between pump on vs. pump off and no significant difference in the drop in glycemia.
DirecNet Trial group. (29)	Children and adolescents, 49	Randomized crossover study: Pump on (normal BR) during exercise vs. Pump off (suspended BR) during exercise.	Four 15-min intervals on the treadmill at a target heart rate of 140 bpm (interspersed with three 5-min rest breaks over 75 min), followed by a 45-min observation period	Discontinuing BR during exercise is an effective strategy for reducing hypoglycemia in children with T1D, but the risk of hyperglycemia is increased.
Taplin et al. (34)	Children and adolescents, 16	Randomized crossover study: Suspended BR during exercise flowed by 50% BRR for 45 min during the 3 conditions: 20% basal rate reduction for 6 h vs. 2.5 mg oral terbutaline vs. No treatment	Four 15-min intervals on the treadmill a target heart rate of 140 bpm (interspersed with three 5-min rest)	The authors speculate that suspending BR during exercise and reducing BR for 45 min post-exercise, reduce the frequency of afternoon hypoglycemia was well as delayed hypoglycemia during the night. BRR was safe and effective in raising post-exercise nocturnal BG nadir and in reducing hypoglycemia

BR, basal rate; BRR, basal rate reduction; BG, blood glucose.

(Medtronic Guardian Real-Time system) and plasma glucose was 1.4 ± 0.8 mmol/L during continuous aerobic exercise implicating an overestimation of plasma glucose (43). On the other hand, an underestimation of blood glucose by CGM has been reported with resistance type of exercise (44).

Most manufacturers and studies report CGM accuracy with median absolute relative difference (MARD) of CGM relative to blood glucose (capillary or venous); reflecting an average deviation from the reference in either direction. MARD of two CGM devices Dexcom G4 Platinum and Enlite in reference to

plasma glucose was evaluated at rest vs. exercise (continuous and interval) (45). MARD was increased from 13.3 (6.1–12.2)% at rest to 15.1 (9.4–26.8 %; $p = 0{,}02$) during exercise for Dexcom and from 11.9 (7.8–14.2)% to 14.1 (8.5–22.7%, $p = 0.02$) for Enlite (45). In this cross-over trial design, no significant differences in MARD were observed between continuous vs. interval exercise that were notably matched in total energy expenditure per patient (45), this is in congruence with another study comparing continuous moderate intensity and high intensity interval exercise sessions (46). On the other hand, significant differences in accuracy by MARD during continuous vs. interval exercise was reported by another group despite comparing the two types of exercise at similar intensities (47). Contrasting conclusions from these reports about CGM accuracy per distinct exercise types could be related to the respective studies design and small sample size. For example, including a pre-exercise snack (slower decline in blood glucose) or hypoglycemia correction with CHO are all factors that could affect the interpretation and comparison of MARD across different studies.

The overall accuracy of CGM devices during exercise is lower but still remains acceptable under exercising conditions. Patients are encouraged to follow the arrow trends in their GCM devices and set their hypoglycemia alarms to higher values to anticipate events (5). Future research efforts should thus consider more comprehensive analysis of CGM biases over the course of different types of exercise and not only reporting average over the whole exercise session. Studies should also report clear analysis of CGM accuracy during hypoglycemic episodes (onset to reduce occurrence and following correction to reduce possible overcorrection) preferably in comparison to capillary or venous reference values. The results of such analyses could then be translated into clinical messages to help patients choose thresholds when setting their alarms to optimize the use of this option while concurrently following CGM arrow trends.

In summary, CGM technology eases the challenge of glucose management during and after physical activity in patients with T1D but patients need to be educated about the lower accuracy of these devices during exercise.

ARTIFICIAL PANCREAS SYSTEMS:

Further technological progress has been achieved by linking CGM to insulin pumps (48, 49) including sensor-augmented pumps (SAP), low suspend and predictive-suspend pump systems. In order to reduce hypoglycemia frequency, importance and length these technologies helps patients adjust their insulin treatment based on real-time feedback from the CGM function (50). These systems are technological steps along the way to closing the loop of glucose control with the artificial pancreas systems targeting both hypo and hyperglycemia.

The artificial pancreas (AP), equally referred to as closed-loop system, constitute to date the most advanced, and promising technology for insulin delivery in T1D (51). Readings from CGM are communicated every few minutes to hormonal dosing algorithm which dynamically commands changes in hormonal basal rates or boluses administered by subcutaneous infusion pumps. Clinical studies investigating artificial pancreas systems are increasing exponentially. These clinical trials mainly cover research on two AP versions; single-hormone AP (SH-AP) which delivers only insulin and dual-hormone AP (DH-AP) which delivers besides insulin mini-boluses of glucagon. Two approaches govern the addition of glucagon to AP, either to allow more aggressive insulin delivery while avoiding hypoglycemia and generally aiming for lower glucoses targets or a more conservative approach which uses glucagon only after suspending insulin for low blood glucose in attempt to prevent pre-emptive hypoglycemia (51). Around two-thirds to one-third is the proportion of SH-AP to DH-AP in the published literature with a lot of heterogeneity in terms of design, reported parameters, types of algorithms used and patient populations tested.

Two recent meta-analyses have clearly shown the clinical efficacy of AP systems in comparison to conventional or sensor-augmented insulin pumps (52, 53). Time spent with glucose levels in-target-range (most used definition is 3.9–10 mmol/l) was increased in both analysis by means of 10–15% which are equivalent to 2.5 and 3 additional hours in target per 24 h (52, 53). The percentage of time spent in hypoglycemia (<3.09 mmol/l) was decreased by means of 1.5–2.5 %, equivalent to a decrease by 20 and 35 min over 24 h (52, 53). *Post-hoc* analyses showed an added benefit of DH-AP with an increase by +8.4 and +8.6% in time-in-target and a further decrease by 1.9 and 1.6% over 24 h in hypoglycemia (52, 53). Some of these studies included exercise in their protocol but their designs and outcomes were not primarily centered around exercise and/or did not specifically present data during exercise limiting the conclusions that can be drawn in relation to physical activity practice. For this reason, we will limit the discussions in the following sections to the clinical trials that specifically reported exercise related outcomes.

Clinical research in AP examining exercise span a spectrum from SH-AP studies adopting fully closed loop systems to those testing hybrid systems with required input from patients/research team to guide the algorithm. Ideally, fully closed loop AP would be the easiest especially in the case of unplanned exercise. The algorithm would then be expected to adjust insulin delivery solely based on changing glucose readings. On the other end of the spectrum, hybrid systems involve exercise announcement by the patient to the algorithm to adjust glucose target ranges (higher targets) and adopt a more cautious insulin delivery. In between the two ends, trials include addition of glucagon in DH-AP, use of exercise detectors (such as heart rate or movement) to guide the algorithm to self-adjust or combinations of these approaches.

The aim behind investigating these different strategies is to account for exercise-induced: 1-increases in insulin sensitivity and absorption from subcutaneous depot due to skin heat and movement, 2- delays in CGM due to rapid changes in blood glucose levels (5, 6). As discussed in the previous sections, the effect on glucose of different types, duration, intensity and timing of exercise need to be taken into consideration when examining AP studies around physical activity (6).

Good overall results were observed in a study conducted with unannounced 40 min exercise performed in a postprandial state as moderate and interval sessions in children and adolescents with T1D (54). Median time of glucose-in-target (3.9–10 mmol/l) was improved during exercise with SH-AP vs. standard insulin

TABLE 2 | Main artificial pancreas studies with reported exercise related outcomes.

References	Participants, *n*	Design, comparators	Exercise description	Main outcomes
Dovc et al. (54)	Chidren and adolescents, 20	Cross-over randomized SH-AP vs. CSII CSII: pump stopped during exercise and basal rate reduced by 20% for 4 h post exercise AP: exercise unannounced	Two exercise types of 40 min, postabsorptive Cycle ergometer Moderate 55% VO_2 max Interval 55%/85% VO_2 max	No difference in time spent in hypoglycemia range during exercise Better median time-in-target (3.9–10 mmol/l) with AP for interval: 75.3 (IQR: 66.6–92.9) % vs. 68.4 (52.1–77.2) %, $p = 0.02$ and for moderate 80.9 (64.3–92.2)% vs. 68.1(59.1–83.6)%, $p = 0.09$ No difference in hypoglycemia events requiring CHO correction over the whole study period 22 h (7 AP vs. 8 CSII)
Breton et al. (55)	Adolescents, 32 (16 per group)	Controlled randomized SH-AP vs. SAP AP: exercise unannounced	5 days skiing camp Two skiing sessions/day 9 h:30 to 12h:00 13 h:00 to 16h:00	No difference in mean time-in-target (3.9–10 mmol/l) between AP and SAP during skiing sessions: 63.2 ± 31.1% vs. 62.8 ± 31.4%, $p = 0.60$ less time spent below 3.9 mmol/l in AP: 1.4 ± 1.6% vs. 2.3 ± 6.4%, $p = 0.04$ No difference in hypoglycemia events or CHO requiring incidences
Patel et al. (56)	Adolescents and adults, 12	Cross-over randomized SH-AP vs. SH-AP + snack Snack: 15–30 g CHO before and midway during exercise for PG <8.3 and > 8.3 mmol/l respectively AP: exercise unannounced	Four 15 min 60–75% of maximal heart rate, with three 5 min in between rest and 30 min recovery Treadmill ergometer	15 g CHO were given to 75% of participants prior to exercise and to all of them midway through exercise Hypoglycemia events requiring CHO were 3 in AP vs. 0 in AP+snack Mean PG at end of session was 10 ± 0.5 vs. 6.1 ± 0.9 mmol/l in AP+snack vs. AP, $p = 0.004$
Jacobs et al. (57)	Adults, 21	Cross-over randomized DH-AP with adjustments vs. DH-AP without adjustments vs. SAP(with allowed adjustment per patient) Adjustment description at start of exercise: Insulin suspended for 30 min then reduced by 50% for 1 hr Glucagon doubled for 90 min AP: exercise announced at start	45 min exercise at 60% of maximal heart rate 2 h post breakfast Treadmill ergometer	Mean time in hypoglycemia (<3.9 mmol/L) was 0.3 (95%CI: −0.1%,0.7)% with adjustment, 3.1 (0.8–5.3)% with no adjustment and 0.8 (0.1–1.4)% with SAP, adjustment vs. no adjustment $p = 0.001$, adjustment vs. AP $p = 0.16$ No difference for time spent in target among the three trial arms
Taleb et al. (58)	Adults, 17	Cross-over, randomized, 4 arms SH-AP vs. DH-AP during continuous and interval exercise AP: exercise announced 20 min prior to start	60 min exercise, postabsorptive continuous session: 60% VO_2 max Interval session: 2 min interval alternating 50%/85% Cycle ergometer	Benefit of DH-AP vs. SH-AP seen with both types of exercise, more glucagon used during continuous than interval For pooled exercise sessions, DH-AP vs. SH-AP: median time PG in target was 100 (IQR: 100–100)% vs. 71.4 (53.2–100)%, $p = 0.003$ and in hypoglycemia (< 3.9 mmol/l) was 0% vs. 11 (0–46.7)%, $p = 0.0001$ 3 vs. 15 hypoglycemia events corrected with CHO in DH-ap vs. SH-AP
Breton at al. (59)	Adults, 12	Cross-over, randomized, 2 arms SH-AP+heart rate vs. SH-AP AP: exercise detected	mild intensity exercise reaching 9–10 on exhaustion borg scale Postprandial Cycle ergometer	less glucose decline in SH-AP with heart rate at −0.3 vs. −1.6 mmol/l, $p = 0.02$ less hypoglycemia events with heart monitoring but not significant (0 vs. 2)

(Continued)

TABLE 2 | Continued

References	Participants, *n*	Design, comparators	Exercise description	Main outcomes
Jacobs et al. (60)	Adolescents, 18	Cross-over, randomized, 2 arms SH-AP+heart rate vs. SH-AP AP: exercise detected	45 min exercise, postabsorptive Three 15 min episodes of exercise with HR reaching 140 beats/min separated with 5 min rest Cycle ergometer	Mean time spent in hypoglycemia (< 3.9 mmol/l) was 0.5 ± 2.1 % in SH-AP+HR. vs. SH-AP 7.4 ± 12% (p = 0.03) No difference in hypoglycemia events which were overall low in both arms
Castle et al. (61)	Adults, 20	Cross-over, randomized, 4 arms DH-AP, SH-AP, Predictive low glucose suspend and Current care (pre-exercise insulin adjustments were allowed) Both DH-AP and DH-AP had exercise detection algorithms with inputs from heart rate and accelerometer (ZephyrLife BioPatch) AP: exercise detected then confirmed to algorithm	45 min exercise 2 h post lunch at 60% of VO_2 max performed on days 1 and 4 in research lab while the rest was free living at home	Time in hypoglycemia (< 3.9 mmol/l) during exercise was lowest with DH-AP 3.4 ± 4.5 % vs. 8.3 ± 12.6% with SH-AP (P = 0.009) vs.7.6% ± 8.0% with predictive low glucose suspend (P < 0.001) vs. 4.3 ± 6.8% with current care (P = 0.49), (p-values are DH-AP against the other arms) lower hypoglycemia events requiring CHO correction was seen with DH-AP over the 4 day period

DH-AP, dual-hormone artificial pancreas; SH-AP, single-hormone artificial pancreas; CSII, continuous subcutaneous insulin infusion; SAP, sensor-augmented pump, CHO, carbohydrates.

pump therapy; however, there were no differences in percentage of time in hypoglycemia ranges or in events requiring CHO replacement (54). In another study, unannounced exercise to SH-AP algorithm was examined during prolonged skiing activity (two sessions per day, 5 day camp) in a group of adolescents and compared to another matched group under sensor augmented pump (SAP) control (55). Although an overall benefit was seen with SH-AP vs. SAP per 24 h and overnight for time spent with glucose-in-target, this was not maintained during the pooled skiing sessions and the hypoglycemia events requiring CHO correction (**Table 2**) (55).

With unannounced exercise to SH-AP, adding a snack (15 or 30 g CHO for PG <8.3 mmol/l and > 8.3 mmol/l, respectively) prior and midway through moderate intensity aerobic exercise could prevent drops in plasma glucose and hypoglycemia requiring correction (0 in AP with snack vs. 3 in AP without snack) (56). Authors in this study did not report percentages of time-in-target, hypo- or hyperglycemia, but around half of the participants ended up with plasma glucose between 10 and 13 mmol/l in SH-AP+snack. These results support the use of a simple snacking strategy to avoid exercise-induced lowering of PG while on AP (56). However, snack consumption may be undesired given the increased prevalence of the metabolic syndrome in patients with T1D who frequently practice exercise with in weight loss or maintenance objectives (3).

Other strategies to improve AP performance around physical activity consisted of examining the effect of glucagon addition through DH-AP systems and exercise announcement to the algorithm. Jacobs et al. tested if announcing physical activity to their DH-AP algorithm by adjusting its insulin and glucagon dosing at the start of a 45 min aerobic moderate intensity exercise could improve glucose management in the following hours (57). Insulin was suspended for 30 min and reduced by 50% for the following 60 min while glucagon was doubled for 90 min from start of exercise (57). Less time was spent in hypoglycemia with adjustment to DH-AP by 2.8% vs. no adjustment ($p = 0.001$) and no difference vs. sensor augmented pump ($p = 0.16$). The authors observed a similar time spent with glucose-in-target between the three arms (57).

Another head-to-head SH-AP to DH-AP comparison in which insulin dosing algorithm is similar in order to specifically investigate the additional benefit of glucagon incorporation in AP during exercise (58). Two types of exercise sessions consisting of 60 min of continuous and interval exercise were performed in the postprandial state under both SH-AP and DH-AP on 4 separate visits (58). Exercise was announced 20 min prior to its start which resulted in changing the target glucose level from 5.3 to 8.3 mmol/l till the end of the 60 min session. Overall, with DH-AP, median time spent with glucose-in-target was increased by 28.6% ($p = 0.003$) and time in hypoglycemia (PG < 3.9 mmol/l) was decreased by 11% ($p = 0.0001$) in comparison to SH-AP. The number of hypoglycemia events requiring CHO treatment were also reduced (3 in DH-AP vs. 15 in SH-AP), all showing an added benefit of glucagon in AP during exercise (58).

An alternative to directly announcing exercise sessions to an AP algorithm was sought by some groups using exercise detectors such as heart rate monitors or accelerometers. The idea

behind exercise detection and indirect announcement is to relieve patients from active inputs especially during unplanned and unknown activity intensities. Such systems would be particularly interesting to investigate in youngsters whose activity level is often unpredictable making them at high risk for both hypo- and hyperglycemia. Breton et al. were among the first to study the feasibility of adding heart rate monitoring to a SH-AP in 12 adults performing mild 30 min exercise sessions (exhaustion at 9–10 on Borg scale) (59). Whenever the heart rate exceeded 125% of its resting value, the algorithm was informed manually which would result in less aggressive insulin delivery and modification of hypoglycemia risk (59). A significant decrease in glucose decline during exercise was noticed when adding HR monitoring (−0.3 vs. −1.6 mmol/l, $p = 0.02$), but only a mild non-significant effect was observed in terms of hypoglycemia events (59). Similar results were observed by Jacobs et al. with their SH-AP with a heart rate monitor connected via blue tooth which informed the algorithm of exercise of physical activity when heart rate exceeded 125% of resting levels (60). This triggered a change in glucose target from 6.2 to 7.8 mmol/l and subsequent insulin delivery by the algorithm. A decrease in time spent in hypoglycemia (<3.9 mmol/l) was significantly reduced with heart rate signal integration to SH-AP 0.5 ± 2.1% vs. 7.4 ± 12.5% ($p = 0.028$) without an effect on the incidence of hypoglycemic events which was however low in both arms (60).

A combination of different strategies was also tested. Recently, an interesting study was performed in adults comparing DH-AP and SH-AP that adapt to exercise using wearable sensors with predictive low glucose suspend and current care during and after exercise (61). Both AP systems had an integrated algorithm for exercise detection that receives input from heart rate monitor and accelerometer (the ZephyrLife BioPatch). Once exercise was detected, the participant was asked by the algorithm to confirm it and the changes to insulin and glucagon were similar to what is described above for the study by Jacobs et al. (57). Additionally the DH-AP was adaptive with adjustments to glucagon delivery at earlier timings and higher glucose levels on subsequent days 2–4 in comparison to day 1. Day 1 and 4 were partly spent at research clinic and the rest at home, formal 45 min exercise sessions 2 h post lunch were performed at 60% VO_{2max} during clinic stay (day 1 and day 4) (61). The lowest time spent in hypoglycemia (< 3.9 mmol/l) during exercise till next meal was with DH-AP 3.4 ± 4.5 vs. 8.3 ± 12.6% with SH-AP ($p = 0.009$) vs. 7.6 ± 8.0% with predictive low glucose suspend pump ($p < 0.001$) vs. 4.3 ± 6.8% during usual care ($p = 0.49$) (61). Number of hypoglycemia events requiring CHO consumption was also lowest with DH-AP over the whole study period with a mean of 0.8 ± 0.7 treatments per day vs. 1.7 ± 1.4 with SH-AP ($p = 0.004$), 1.3 ± 1.3 with the predictive low glucose suspend pump ($p = 0.065$), and 1.5 ± 1.2 with usual care ($p = 0.10$) (61).

The AP studies that specifically tackled glucose control in relation to exercise are still heterogeneous, small in size and do not cover all exercise scenarios (**Table 2** summarizes the discussed trials). Most to date cover moderate intensity exercise performed in the post-absorptive state (**Table 2**). Nevertheless, they highlight the positive impact of artificial pancreas systems around exercise. AP is still an emerging technology and many future trials at large scale and in outpatient settings are needed in general and around exercise in particular.

Directly announcing exercise seems to still be needed for optimized results but the timing of the announcement from the start of exercise maybe an area to explore in future studies particularly for postprandial exercise when meal insulin boluses are active. Exercise detection by sensors is an interesting avenue particularly for children and adolescents living with T1D but adds the burden of wearing additional devices necessitating active research efforts in the future to develop small sensors integrated to the artificial pancreas itself.

Glucagon clearly shows an added benefit but the complexity of adding an additional chamber and material needs to be weighed against the additional hypoglycemia benefit. Therefore, future research trails should be designed to carefully identify patients who are most in need of glucagon and show high rates of exercise-induced hypoglycemia. While SH-AP currently reach the market in various countries, DH-AP are not expected to be commercialized in the near future since stable glucagon formulations are not yet available for use but promising research is underway. Clinical trials with DH-AP may still be conducted with the commercially available glucagon used for severe hypoglycemia treatment but needs to be reconstituted every 24 h (62). Meanwhile, another pressing aspect is proving the safety profile of chronic glucagon use in its different formulations or analogs given its multisystemic effects in humans (63).

CONCLUSIONS

Technological advances have endowed individuals with T1D with important tools to help them better manage their blood glucose during exercise mainly allowing more secure conditions with reduced hypoglycemia risks. Some limitations to the different technologies have been detailed in this review and future research areas that need to be explored have been highlighted as well. The hope is that optimizing the use of these different technologies during exercise will encourage the majority of patients with T1D to regularly engage in physical activity.

AUTHOR CONTRIBUTIONS

ST, NT, and RR-L conceived the study design and content. ST and NT drafted the manuscript which was critically reviewed by RR-L.

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REVIEW
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Gaps in Knowledge and the Need for Patient-Partners in Research Related to Physical Activity and Type 1 Diabetes: A Narrative Review

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Regular physical activity (PA) is a cornerstone in the management of complications associated with type 1 diabetes (T1D). Most national guidelines advocate for regular PA for persons living with T1D, however the evidence to support these recommendations has not be reviewed recently. Additionally, in an era of patient-centered care and patient oriented research, the role of patient partners in the area of PA and T1D interventions has never been explored. The purpose of this narrative review is to overcome these two gaps in the literature. Here we review selected epidemiological evidence and identify gaps in research that would add important information to guide practitioners and future guidelines. We also provide an overview of patient-oriented research projects co-developed with persons living with T1D. Significant gaps in the field include: (1) a lack of adequately powered prospective cohort studies using serial measures of PA and hard chronic disease end-points; (2) no multi-centered, highly powered, randomized controlled trials of PA, and long-term health outcomes; (3) little data on the role of new technologies to support PA-related behavior change, and (4) no trials that involved patients in the design and execution of PA-based clinical trials. This review provides a template for scientists and patient partners to develop future research priorities and agendas in the field.

Keywords: exercise, outcomes, epidemiology, clinical trials, cardiovascular disease, patient oriented research, priority setting, continuous glucose monitoring

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INTRODUCTION

The Rationale for Additional Research in the Area of Physical Activity and Health Outcomes in Persons Living With Type 1 Diabetes

Rates of type 1 diabetes (T1D) have increased globally over the past 2 decades (1–4) and it currently is the most common endocrine condition in children and young adults (5). A diagnosis of T1D increases the risk of micro- and macro-vascular complications that reduce life expectancy by as much as 15 years (6–10). The increased morbidity associated with T1D is significantly reduced with improved blood glucose control (11, 12). In conjunction with carefully

titrated insulin and dietary modifications, most national health guidelines strongly recommend participation in regular physical activity (PA) for achieving optimal health for people with T1D. Unfortunately, there is little experimental evidence available to guide recommendations and/or behavior modification for persons living with T1D, particularly children and adolescents (13). This review is distinct from recently published comprehensive reviews (14–19) that have addressed areas of weight management, glucose monitoring, managing glucose during exercise and the physiological responses to exercise. We suggest readers also read the comprehensive review by Riddell et al. (14) that emerged from a consensus conference hosted by the JRDF PEAK programme and the Exercise for Type One Diabetes (EXTOD) group as it provides an excellent overview on the strategies for safely adopting an active lifestyle for persons living with T1D. We also recommend a review by Codella et al. (19) as it provides a thorough overview of the physiological benefits of exercise for persons with T1D and the potential for new technologies in supporting a more active lifestyle. The purpose of this narrative review is to provide an updated overview of the highest quality evidence for what we know about PA for persons living with T1D, gaps in the literature that could guide future research programs and finally, explore the benefits of patient engagement and co-development of a research agenda for the next wave of research in the field. This narrative review will complement other recent reviews as it will include a larger scope of research designs to summarize and describe the current state of evidence and identify literature gaps. While the studies included were not selected using a systematic process, we attempted to restrict the discussion to those with the most representative samples, robust designs and clinically relevant end-points. Additionally, we will explore the role of patient partners and models for patient-centered priority setting in determining the next generation of clinical trials/studies for persons living with T1D, which has not been an included goal in previously published reviews in this area.

The Benefits of Physical Activity on Health Outcomes in Persons Living With T1D

Evidence for most PA guidelines are derived largely from prospective observational cohort studies (20, 21). Recent studies exemplify the advantages of a prospective cohort design for studying the association between PA and health outcomes (22–24). With adequately powered, representative samples, PA can be quantified across various domains (intensity, duration, frequency, type, timing) and with sufficient follow-up, differences in major health-related outcomes, including mortality, can be compared across these domains. As is the current trend, these associations can be replicated in similar cohorts and confounders can be controlled for using state-of-the-art methods (25). As some of these landmark cohort studies include serial measures, it is also possible to assess the association between changes in behavior over time and health outcomes (26, 27); however, few studies have applied this approach to the study of PA and major chronic diseases. As changing and sustaining PA behavior is challenging, adequately powered randomized controlled trials with sufficient follow-up time to examine dose-specific effects are extremely rare. Therefore, prospective cohort studies provide the bulk of the evidence to date on the association between PA and health outcomes in the general population and persons living with T1D.

Observational studies clearly demonstrate that regular PA is associated with several health benefits for patients with T1D (28), including higher cardiorespiratory fitness, lower serum cholesterol, enhanced vascular health, more favorable body composition and higher quality of life (29–44). A large cross sectional study of 18,000 persons with T1D from clinics across Germany revealed that higher levels of PA were associated with lower HbA1c, BMI, risk of hypertension, and dyslipidemia (45). Collectively, these benefits may contribute to the lower risk of complications (46) and increased life expectancy seen in physically active persons with T1D (47, 48). The first prospective study to examine this question, the Pittsburgh Insulin Dependent Diabetes Mellitus Morbidity and Mortality Study (46, 48), relied on a cohort of 671 patients within a registry of ∼2,000 patients with T1D. Activity was assessed using a standardized questionnaire during a clinical visit and patients were followed for up to 25 years for rates of macro- and micro-vascular complications. Among men, those that did not participate in sport-related activities were ∼3-fold more likely (31 vs. 11%, $p < 0.05$) to develop macro-vascular disease, compared to those that did. In a follow-up study, the authors found that participation in competitive sports as an adolescent was associated with a reduced odds of nephropathy, neuropathy and macro-vascular disease, relative to those that did not participate in competitive sports during high school. This association was not observed in women and it is unclear to what extent the analyses controlled for confounders.

More recent studies of larger cohorts (∼2,000–3,000) of persons living with T1D in Europe and Scandinavia suggest that the association between PA and long-term cardiovascular disease (CVD) risk is modest and may be modified by other lifestyle factors that cluster with activity levels, particularly smoking. The FinnDiane study has published several analyses of self-reported PA on all-cause and CVD-specific mortality (49, 50). FinnDiane enrolled ∼5,000 adults with T1D into a cohort study in 1995, with 2,300–2,600 completing questionnaires on the type, duration and intensity of weekly PA. Early work revealed that participation in more frequent (>2 days/week vs. < 1 day) and intense activity (high degree of subjective shortness of breath and sweating vs. none) were both associated with a ∼50% reduced risk of proteinuria and progression to chronic kidney disease (51). As of 2014, 270 participants in the cohort had died and ∼300 lived with chronic kidney disease. In the two most recent analyses, mortality was 70–100% higher in the most sedentary sub-groups in the cohort compared to those the highest tertiles of total leisure time PA and intensity of PA (50, 51). Importantly however, the strength of these associations are significantly reduced when adjusted for key confounders, particularly smoking (50). Therefore, the precision of these estimates remains questionable. Similarly, a preliminary analysis of the Joslin 50 years Medalist cohort in which participants self-reported PA showed that those who reported exercising regularly

experienced a 45% lower risk of mortality; however, similar to previous studies, these analyses were only adjusted for a handful of confounders (52). Incredibly, no systematic reviews with meta-analysis of prospective cohort studies of PA and health outcomes among persons with T1D has ever been published. Accordingly, the strength of these associations remains restricted to small cohorts followed for a limited number of years.

These associations provide promising evidence for a protective association of PA on CVD and mortality among persons living with T1D, however they are far from conclusive. The findings presented above could be significantly strengthened by (1) conducting a rigorous systematic review of observational studies; (2) conducting larger cohort studies or a meta-analysis of individual level data with longer follow-up using objective measures of PA; (3) creating cohort studies with serial measures of PA over time to determine the association between changes in PA and long term CVD risk and finally, (4) creating cohort studies that conduct more robust analyses using propensity score matching or instrumental variable analysis to rigorously control for measured and unmeasured confounding. Finally, as PA is a behavior that tracks from adolescence through to adulthood, there is a major gap in our understanding of PA behavior in adolescence and health outcomes in adulthood. As recently argued (53), there is a dire need for more robust epidemiological work in the area of PA and chronic disease risk among persons living with T1D.

CLINICAL TRIALS OF PHYSICAL ACTIVITY AND HEALTH OUTCOMES AMONG PERSONS LIVING WITH TYPE 1 DIABETES

A series of systematic reviews of clinical trials of PA and health outcomes in persons with T1D were published in the past few years, by our group (54) and others (55, 56). The most recent systematic review published in May 2018 (55), included 15 randomized trials of aerobic-only exercise interventions lasting 12–26 weeks that included 596 participants. Of these, 11 reported changes in HbA1c, 7 changes in body weight and 6 changes in VO2peak. Fewer studies reported changes in blood pressure or serum lipid profiles. Meta-analysis of available clinical trials revealed that structured exercise had no effect on HbA1c (MD: −0.08%, 95% CI: −0.38, 0.22; $p = 0.6$). However, structured exercise lowered daily insulin requirements (MD: −0.23 IU/kg, 95% CI −0.37, −0.09; $p = 0.002$) and body weight MD: −2.20 kg, 95% CI: −3.79, −0.61; $p = 0.007$) and increased peak oxygen uptake (4.08 mLO_2/kg/min, 95% CI 2.18, 5.98; $p < 0.0001$). The authors attempted to discern a dose effect of PA on health outcomes as others have done (57), however were significantly underpowered to compare interventions that achieved recommended weekly requirements for moderate to vigorous PA (>150 min), compared to those that did not. Similar effects were seen in a systematic review and meta-analysis of 10 randomized and 16 non-randomized trials of exercise interventions lasting 2–39 weeks among children and adolescents (56). A relatively small trial ($n = 51$) of adolescents with T1D (58), published 3 years after this review, found that 20 weeks of endurance training, delivered four times weekly for 60 min, reduced total daily insulin dose and improved body composition and cardiorespiratory fitness compared to controls. The program also elicited modest improvements in measures of left ventricular systolic function and submaximal total peripheral resistance compared to controls, without any change in glycemic control or systolic and diastolic blood pressure. Overall, there is insufficient clinical trial data available to determine if structured exercise reduces risk factors for CVD in persons with T1D. Accordingly, there is a need for highly powered randomized controlled trials with prolonged follow-up to determine the efficacy of structured exercise on CVD-related health outcomes among persons living with T1D.

BEHAVIORAL TRIALS OF PROMOTING PA AMONG PERSONS LIVING WITH TYPE 1 DIABETES

Randomized trials of structured, supervised exercise provide insight into the physiological adaptations associated with increased PA. In contrast, behavioral trials provide insight into how best to motivate individuals to adopt a more active lifestyle (59). The most recent systematic review of randomized trials of behavior modification for persons with T1D was published in 2015 (60). The authors identified 27 trials with 2,351 participants with T1D that delivered an intervention to modify self-management behaviors, some of which included PA (60). The trials that measured HbA1c ($n = 22$) observed an overall effect size of 0.16 (95% CI: 0.0–0.3), suggesting modest improvements in glycemic control with behavioral interventions. This effect was nearly twice as large if the intervention was grounded in an established theoretical model (Cohen's d: 0.22 vs. 0.12, $p < 0.001$). An updated review with recently published trials has not been conducted and therefore the efficacy of behavioral-based interventions to increase PA among persons with T1D remains unclear.

In a recent behavioral pilot trial in the UK (61), 58 young adults (32 ± 11 years) were randomized to a motivational interviewing intervention to increase daily PA with near biweekly meetings with a registered nurse, or standard clinical care. Participants in the intervention arm were targeting 150 min of moderate to vigorous PA weekly initially, with a long-term goal of achieving 240 min of moderate to vigorous PA weekly (61). An analysis restricted to participants that completed all data collection procedures found that the intervention group increased their weekly moderate to vigorous PA by ∼40 min and experienced a ∼10% increase in peak oxygen uptake. The control group decreased their weekly moderate to vigorous PA and experienced a ∼10% decline in peak oxygen uptake. Patients in the intervention arm also experienced improvements in insulin sensitivity and reductions in total daily insulin relative to those in the control arm. This pilot trial suggests that motivational interviewing may be effective for increasing weekly PA among persons with T1D and that these changes may elicit benefits in the determinants of metabolic control, however larger trials with more prolonged follow-up are needed to confirm these results.

An excellent example of a clinically relevant behavioral intervention to support increased PA was recently published by the FLEX study group (62). An 18 months intervention that relied on motivational intervention and problem solving skills significantly improved quality of life and motivation for self-care among adolescents with T1D. Flexibility in program delivery and strategies to overcome barriers were core elements for eliciting behavior change. As the authors did not quantify PA behavior, it would be interesting to determine if a similar approach, focused on barriers to being active, would elicit similar effects, particularly among adults living with T1D.

The major take-away from these systematic reviews and recently published trials is that there is a glaring lack of adequately powered clinical trials of PA on health-related outcomes in persons living with T1D (Summarized in **Table 1**). Furthermore, among those published to date, few have reported outcomes beyond glycemic control and bodyweight. Therefore, there is a major gap in our understanding of the role, dose and long-term effectiveness of PA on clinically-relevant health outcomes (cardio-renal risk, mental health, quality of life, diabetes self-management) among persons with T1D. Adequately powered randomized trials with an extended long-term follow-up, similar to the Diabetes Prevention Program (63), The Finnish Diabetes Prevention Study (64) and the Look-AHEAD trial (65) are needed to provide clear evidence for the long-term health benefits of increasing PA among persons living with T1D.

PHYSICAL ACTIVITY AND HYPOGLYCEMIA IN PERSONS WITH TYPE 1 DIABETES

Hypoglycemia is the most common and life-threatening acute complication for persons living with T1D. It is also a key barrier to achieving optimal glycaemic control (66, 67). In the seminal Diabetes Control and Complications Trial, severe hypoglycemic events were 2- to 3-fold higher in the intervention arm (11) and 65% of patients in that arm experienced at least one severe hypoglycaemic event per year during the 7 years intervention (66). The risk of hypoglycemia is intimately linked with participating in PA for persons living with T1D (68–70). The fear of hypoglycaemia is a significant barrier to adopting a physically active lifestyle for persons with T1D (71, 72). While prolonged intervention and cohort studies provide insight into the long-term health benefits accrued with increased PA, studies of a single bout of exercise provide insight to the role of exercise on acute glucose control and the risk of hypoglycemia (73–75).

Exercise-induced hypoglycemia occurs secondary to a rapid increase in glucose uptake and insulin sensitivity (76–78) that persists for up to 48 h following exercise (76). As little as 30 min of moderate intensity PA increases the risk of nocturnal hypoglycemia by as much as 30% (79), while 75 min of moderate intensity PA triples the rate of nocturnal hypoglycemia (69). Several strategies exist to prevent exercise-induced hypoglycemia in patients with T1D. They include withholding pre-exercise insulin (80, 81), increasing carbohydrate intake during or following exercise (80, 82) and reducing basal or night time insulin (68). Unfortunately, as these strategies all result in transient hyperglycaemia (73), they compromise glycaemic control (68, 83), which can be an undesired consequence of exercise for patients who desire tight glycaemic control.

TABLE 1 | Knowledge and gaps in epidemiological research of physical activity for persons living with type 1 diabetes.

Type of study	Physical activity knowledge	Gaps
Prospective Cohort Studies	Lower lipid profiles Lower BP Reduced risk of CVD	Small sample sizes Lack of triangulation of data Poor control of confounding
	Reduced mortality	Lack of objective measures of PA
Clinical Trials	No effect on HbA1c Lower daily insulin requirement Weight loss Increased VO_2peak	Efficacy for lowering BP Efficacy for improving lipid profiles
Behavioral trials	Improved self-management Reduced HbA1c Increased short-term PA	Optimal theoretical model for long term adherence to PA Optimal delivery model for increasing PA

BP, blood pressure; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; PA, physical activity; VO_2, oxygen uptake.

Vigorous Intensity Physical Activity and Glucose Control in Persons With Type 1 Diabetes

Physical activities can be stratified into light, moderate and vigorous intensity activities (84, 85). Moderate intensity PA is defined as exercise that requires 3–6 metabolic equivalents (METS) of energy expenditure (equivalent to walking 4.0–6.8 km/h). Exercising at this intensity significantly increases glucose disposal, enhances insulin sensitivity and improves metabolic health outcomes (85–88). In individuals without T1D, insulin levels decrease at the onset of moderate-intensity PA to counter the enhanced glucose uptake and protect individuals from hypoglycemia (89). In individuals with T1D, insulin is supplied exogenously and does not decrease at the onset of exercise (89). The combination of insulin- and contraction-mediated glucose uptake significantly increase their risk for hypoglycemia during and after exercise (90). As moderate intensity PA is associated with health benefits and is perceived to be easy for most sedentary patients, it is the most commonly recommended intensity of PA by health care professionals and clinical guidelines (81, 82). However, this approach may exacerbate the fear of hypoglycaemia (71), as it is the intensity with which hypoglycemia is most likely to occur.

Similar to moderate intensity PA, exercising at >85% of maximal oxygen consumption (VO_2max—i.e., vigorous intensity PA) significantly increases glucose disposal into skeletal muscle (89). In contrast to moderate-intensity PA however, vigorous intensity PA also causes a rapid and sustained increase in counter-regulatory hormones (catecholamines, glucagon, and cortisol) (14, 91, 92). This surge in hormones stimulates glucose output from the liver (89, 93) and partially reduces glucose

uptake into skeletal muscle (94). This hormonal surge and accompanying increase in hepatic glucose output (89) causes mild, transient hyperglycaemia, especially in individuals with T1D (91, 92). Several acute, cross-over laboratory-based trials suggest that adding vigorous intensity intervals to standard moderate intensity exercise sessions (the typical type of exercise prescribed by diabetes educators) stabilizes blood glucose during and following exercise, thereby preventing hypoglycemia (73).

Vigorous Intensity Exercise Can Prevent Hypoglycaemia?

Recent single-session laboratory-based studies have examined the potential role of adding high intensity intervals exercise sessions to combat the post-exercise hypoglycemic risk associated with moderate-intensity activity. A number of investigators have cleverly capitalized on this physiological response and prevention strategy over the past 10 years. Our group (73) and others (75) completed systematic reviews with a meta-analysis of studies of the acute blood glucose response to exercise (91, 92, 95–99) to determine the magnitude of this effect. We restricted analyses to studies that directly compared intermittent vigorous intensity exercise to continuous moderate intensity exercise on post-exercise glucose control during a single exercise session using a randomized cross-over trial design. Five of six studies found that adding bouts of vigorous intensity exercise lasting 4–15 s at 80–100% of VO_2max with ∼2 min of rest increased counter-regulatory hormones 2- to 4-fold above levels seen with moderate intensity exercise and reduced post-exercise hypoglycemia by 30–70%(91, 92, 96, 97, 99, 100). One study by Riddell et al. (14) found that adding vigorous intensity sprint intervals (15 s at 100% of VO_2max) effectively normalized nocturnal blood glucose levels and decreased the time spent in hypoglycemia (≤3.9 mmol/L) by >70% (97). The overall effect of adding vigorous intensity exercise to a standard moderate intensity exercise session was a 38% reduction in post-exercise hypoglycemia. These data provide evidence that adding vigorous intensity PA to a standard moderate intensity exercise may prevent hypoglycemia acutely. However, no randomized controlled trial has ever determined if this approach would prevent hypoglycemia over the course of a longer exercise intervention. Therefore, the practical implications of this strategy remain in question.

CONTROVERSY SURROUNDING VIGOROUS INTENSITY PHYSICAL ACTIVITY AND GLUCOSE CONTROL IN TYPE 1 DIABETES

In an attempt to translate these observations into a real-world context, our lab recently completed a series of studies examining the acute effects of adding vigorous intensity exercise to moderate intensity exercise sessions on hypoglycemia and glucose variability for the subsequent 24 h (101). In contrast to previous studies, we relied on running-based intervals (vs. cycling), administered the intervals in the late afternoon, when most people select to train, and did not rigorously control glucose levels, to reflect a persons daily variation in glucose. In studies of sedentary persons across multiple intensities of intervals (101) followed for a week during their training and in the lab following a session of vigorous intensity intervals (1 min at 90% of max; 2 min easy), we were unable to replicate these findings. Several other groups were unable to replicate the effects of vigorous intensity exercise on hypoglycemic risk seen in these earlier studies (98, 102, 103). These findings suggest that the practical application of adding vigorous intensity intervals to a moderate exercise session for predictable prevention of hypoglycemia remains uncertain.

In addition to these studies, recent work in Denmark suggests that the addition of high intensity exercise to a regular exercise training regimen may be hazardous among individuals who are hypoglycemia unaware (104, 105). This is a dangerous observation as reducing the physiological response to hypoglycemia is a major risk factor for severe hypoglycemic events. Taken together, there is growing evidence that vigorous intensity exercise may not be the key to improving metabolic control in persons with T1D and should be done progressively and consciously of its effects on counter-regulatory response to hypoglycemia.

The Influence of Physical Activity on Glucose Variability in Persons With T1D

One of the most robust predictors of hypoglycemia in persons with diabetes is the degree of glucose variability (106–108). Glucose variability is defined as the magnitude of changes in glucose beyond what is usually or normally expected for an individual (81, 82). Identification of glucose variability relies on frequent, systematic glucose monitoring (109, 110), which can provide a sensitive, quantifiable measure of glycemic variance over a given time period. For example, while two individuals may display similar HbA1c levels, they may differ significantly on the frequency or magnitude of glucose dispersion from fasting levels, particularly in the post-prandial period (110, 111). Data from 3,100 episodes of hypoglycemia from 655 patients in the DCCT found that the risk of hypoglycemia increased in a dose-response manner with increasing glucose variability (106). With the widespread use of continuous glucose monitors in clinical management and research (112), more sensitive and robust measures of glycemic control and variability are available as outcomes for exercise studies (113–115). With the advances made with continuous glucose monitors, there are limitless opportunities to examine the influence of exercise on glucose variability (16), the role of glucose monitors in supporting safe and predictable adoption of a more active lifestyle and the long-term impact how achieving time in target range can improve the perceived benefits of exercise by persons living with T1D. To date, no study has ever examined the chronic effects of exercise training on glucose variability in persons with T1D. With the increasing use and availability of continuous glucose monitoring (112), there is a huge opportunity to study the impact of exercise at various doses on glucose variability, particularly when performed at different times of the day. A summary of what is currently known regarding vigorous intensity PA and health

among persons with T1D and the major perceived gaps in the literature is provided in **Table 2**.

PATIENT-ORIENTED RESEARCH WITHIN THE FIELD PHYSICAL ACTIVITY AND HEALTH OUTCOMES AMONG PERSONS LIVING WITH TYPE 1 DIABETES

With a dearth of evidence within nearly every sub-field of PA and T1D research, opportunities are limitless to launch clinically meaningful studies that are aligned with the priorities of the individuals living with T1D. Patient-oriented research is founded upon four main tenets of practice: (1) inclusive research processes; (2) collaborating respectfully with stakeholder populations; (3) recognizing the value of patient experiences with conditions and; (4) conducting research informed by the needs of the patients (116). As there are major gaps across all study designs in the field of PA and T1D, research should be encouraged to engage patients when addressing the gaps identified above (117). The Canadian Institutes of Health Research (CIHR), a major funding body of research in Canada, launched the Strategy for Patient-Oriented Research in 2010 to fund and facilitate research projects involving patients (118, 119). Patient-centered medicine, the provision of personalized medical care that accounts for the needs and preferences of individual patients (120) is ideal for this field as both patients and providers (121, 122) struggle with including PA in routine self-management plans. In an effort to make PA research more relevant to patients and providers, PA-based interventions for persons with T1D should include patient-reported outcomes and explore models of shared decision making for adopting a more active lifestyle.

TABLE 2 | Vigorous intensity intervals and hypoglycemia risk in persons with type 1 diabetes.

Type of study	Physical activity knowledge	Gaps
Carefully controlled laboratory Studies—Tight glucose control; mid-morning activity	Attenuates decline in glucose during exercise Reduced post-exercise decline in blood glucose	Influence of timing (morning, afternoon, evening) unclear. Little data on glucose variability
Laboratory-based studies, less control, mid afternoon	No influence on hypoglycemia risk or glucose variability	Minimal intensity needed to alter glucose response undetermined Unclear if gender or fitness influence the effect
Epidemiological or Clinical trial Data	None	No observational studies comparing time spent in different PA intensities on health No long term trials existing comparing vigorous to moderate intensity training on health outcomes

Patient engagement in PA and T1D research programs is in its infancy, relative to other areas of endocrine research. The two main goals for engaging patients in PA-based research are to improve health outcomes during interventions and optimizing the patient experience of health care (123). In terms of research, CIHR defines patient engagement as "meaningful and active collaboration in governance, priority setting, conducting research and knowledge translation" (119). In the United Kingdom, the term "public involvement" is preferred and supported by the National Institutes of Health Research to describe this same concept [NIH (124) Public Involvement]. Engaging patients within PA and T1D research programs could facilitate the implementation and relevance of study findings, ease the recruitment process, improve validity/credibility of results and address disparities between funded research and end user needs (116, 124). All of these are major limitations to the research summarized above.

The first step in the process of patient engagement for PA-related research for persons living with T1D is to set priorities from patients, caregivers and providers. Several recent examples for persons living with type 1 and type 2 diabetes serve as models for future research programs. One example is a large multinational survey study published in 2013 collected data from 16,000 individuals with a significant connection to type 2 diabetes (i.e., patients, family members, and health care providers) (125). The survey queried these stakeholders regarding perceived gaps in diabetes health care and suggestions on improving care. The James Lind Alliance (JLA) is an initiative funded by the National Institutes of Health Research in the United Kingdom (126, 127). This group has developed an internationally recognized method of establishing patient priorities for treatment research and has worked on projects spanning over 100 different diseases (128). This process involves the distribution of an open-ended survey to the public regarding questions about treatments, and partners with stakeholders to prioritize the responses into a top ten list of research questions (129). This partnership approach has created research priorities for persons living with T1D (130) (**Table 3**), type 2 diabetes (131), hypertension, and childhood disability. The JLA model is an excellent starting point for determining the next steps for PA research with persons living with T1D as it will provide scientists with the topics more relevant and meaningful to patients.

Examples of Patient Engagement in Research for Persons Living With T1D

In 2012, data from a piloted intervention became available that tested the effectiveness of an iPhone application named "bant" to increase the frequency of blood glucose testing in youth (132). The app was designed, developed and pilot tested in consultation with patients, parents and health care providers and was found to be moderately effective in increasing the number of blood glucose tests per day. Another eHealth

TABLE 3 | Patient, caregiver and provider priorities for research related to type 1 diabetes.

James lind alliance top 10 research questions	
1	Is it possible to constantly and accurately monitor blood sugar levels, in people with type 1 diabetes, with a discrete device (non-invasive or invasive)?
2	Is insulin pump therapy effective? (immediate v deferred pump, and comparing outcomes with multiple injections)
3	Is an artificial pancreas for type 1 diabetes (closed loop system) effective?
4	What are the characteristics of the best type 1 diabetes patient education programmes (from diagnosis to long term care) and do they improve outcomes?
5	What are the cognitive and psychological effects of living with type 1 diabetes?
6	How can awareness of and prevention of hypoglycaemia in type 1 diabetes be improved?
7	How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes?
8	Does treatment of type 1 diabetics by specialists (e.g., doctors, nurses, dieticians, podiatrists, ophthalmologists, and psychologists) trained in person-centred skills provide better blood glucose control, patient satisfaction and self-confidence in management of type 1 diabetes, compared to treatment by non-specialists with standard skills?
9	What makes self-management successful for some people with type 1 diabetes, and not others?
10	Which insulins are safest and have the fewest (long term) adverse effects?

intervention engaged young patients, parents, health care providers, and teachers in designing an online education program aimed at helping youth understand appropriate insulin adjustments to account for food intake (133). The youth patients were involved in designing the host website and address potential barriers to user-friendliness, and the collective steering group worked in unison to develop the content of the program (Kids In Control OF Food—KICk-OFF). To the best of our knowledge, similar patient-developed, exercise-focused applications have yet to be developed or tested for individuals living with T1D.

Perhaps one of the largest examples of patient engagement in T1D research is the D1 Now study in Ireland (134, 135). This project recruited a young adult panel as co-investigators who were involved in writing grants, organizing a large international workshop, writing plain English summaries in journal articles and promoting the study using social media outlets. One purpose of the consensus conference organized by the panel was to obtain consensus from a wide range of stakeholders regarding a core outcome set to be measured in a new complex intervention trial for improving blood glucose monitoring in T1D youth (135). The conference was attended by 110 individuals from seven different countries, including Canada. This process resulted in consensus on eight core outcomes to be included in the trial: (1) measures of diabetes-related stress; (2) diabetes-related quality of life; (3) number of severe hypoglycemic events; (4) self-management behaviors; (5) number of diabetic ketoacidosis events; (6) HbA1c; (7) level of clinic engagement and; (8) perceived level of diabetes control (135). The conference also included a "Hackathon" that paired computer programmers with diabetes stakeholders to create technological supports for T1D youth (134), where the winning pitch involved the use of motivational and informational content on an existing popular social media platform, Snapchat. These outcomes should be included in the design of future clinical trials and cohort studies of PA and health outcomes among persons living with T1D as they reflect the priorities of young people and could be harmonized for replication of findings with the D1 Now study group.

The James Lind Alliance published the results from their T1D partnership in 2012 (130). This partnership engaged 10 stakeholders in prioritizing the 1,259 initially submitted research questions to develop a top 10 list (**Table 3**). This list included but was not limited to questions pertaining to the artificial pancreas, prevention of hypoglycemia, insulin pump therapy and long-term effects of various insulin analogs. A secondary analysis compared this list to recently funded research projects and found that several of the research topics were being pursued, but many were also not (136). Areas of disagreement between patient priorities and funded research included health care cost-effectiveness of providing additional blood test strips to patients, disparities in regular diabetes care, development of alternative methods of insulin delivery, psychosocial health and the female reproductive health cycle. Although the JLA process is highly recognized, the T1D partnership was not without its limitations. Snow and colleagues examined the research questions that were submitted by stakeholders but excluded in early phases of data analysis (137). Incredibly, they found that having lived experience (patient or caregiver) of T1D increased the likelihood of having a research question rejected relative to questions provided by health care providers. This project also thematically analyzed the excluded questions and discovered four major themes of researchable questions that were not analyzed due to the inclusion criteria: (1) questions concerned with finding a cure for T1D; (2) questions concerned with the cause or possible prevention of T1D; (3) questions to further understand the mechanisms of the disease (i.e., blood glucose fluctuations, risk factors etc.) and; (4) questions concerned with practice and policy changes.

Patient Reported Outcomes and Experiences

A starting point for working with patient partners in PA and health outcomes research for persons living with T1D, would be to ensure that future studies include patient reported outcome measures and patient reported experiences, as they pertain to PA. With regards to patient reported outcome measures, simple tools including quality of life, diabetes-related quality of life and measures related to self-management are standard in other clinical trials. As PA can be viewed as burdensome to patients, potentially increasing the challenging of achieving target glucose control, these

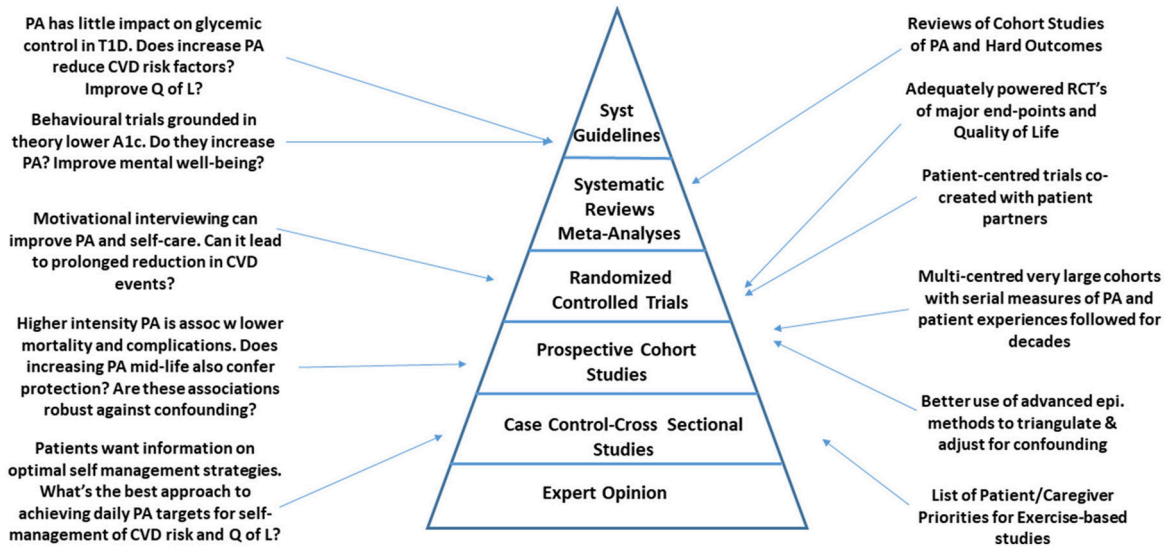

FIGURE 1 | Gaps in the field of physical activity and type 1 diabetes research.

measures become even more important for providers and caregivers.

The patient experience is a key element of quality of care and health systems improvement. The experience of a provider's confidence prescribing activity, ability to tailor management to meet the needs of individuals active lifestyle and ability to share in the decision making process around including PA in a person's self-management plan are examples of patient experiences that could limit engagement in regular daily PA. Our group intends to conduct an extensive scoping review of clinical trials published to date, to identify if any trials have been conducted that included patient-reported outcome measures, patient experiences or evidence of patient engagement in research related to PA. To the best of our knowledge, these experiences have yet to be captured within PA-based trials, therefore best practices for enhancing the experience of providing PA consultation to persons living with T1D remains unclear.

CONCLUSION AND SUMMARY

We recognize that the studies described about were not systematically selected and therefore are at risk of a selection bias. However, we attempted to focus on the most robust, representative and clinically relevant studies published to date, in an effort to identify gaps in the most rigorously designed studies to date. Despite this limitation, among the studies described, we identified that the area of PA and health among persons living with T1D is rife with gaps that limit the uptake of this work into clinical practice (**Figure 1**). Across the spectrum of study designs, there are multiple opportunities for scientists to make meaningful contributions to the field. As outlined in **Figure 1**, many of the gaps in epidemiological research that would inform guidelines, could be addressed through large scale, multi-center observational studies and clinical trials focused on hard health-related outcomes. These studies could be designed in a way that would facilitate uptake into clinical practice by including patient partners throughout the research process. Partnering with experts in patient engagement and patient reported outcome/experience measures will facilitate this process.

AUTHOR CONTRIBUTIONS

NK and JM designed the concept for the manuscript. NK, AM, and JM all contributed to writing and revising the manuscript. NK and AM reviewed abstracts and extracted data for the systematic review. All authors read and approved the final version.

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Patient and Healthcare Professionals Perspectives on the Delivery of Exercise Education for Patients With Type 1 Diabetes

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Objective: One way of improving the prognosis for the growing numbers of people with type 1 diabetes (T1D) is to increase their frequency of exercise. One known barrier to this is the lack of cohesive support and information from care providers. To better understand the issues around existing support for patients wishing to exercise and inform the design of an education package specifically to facilitate safe exercise we interviewed care providers and patients about the existing provision of support.

Research Design and Methods: The study was based within two large UK teaching hospitals where four focus groups were undertaken two consisting of patients diagnosed with T1D who undertook regular exercise, and two with health care providers (HCPs) that were part of the diabetes care team. In all 14 patients and 11 staff were involved. These were complemented by two 1:1 interviews with staff unable to attend group discussions.

Results: We found the successful provision of education and advice was influenced by factors relating to the individual patient and their service provider. Patient factors included the type of activity and complexity of the exercise regime, the level of engagement with their condition and care and health literacy. Service-related factors included inconsistent training, a lack of capacity and continuity, and limited coherence of information from across their care team.

Conclusions: Any education package developed to support exercise in patients with type 1 diabetes should be offered at a time following diagnosis in accordance with patients' preferences and priorities, contain information on how to manage regular and irregular bouts of exercise. Patients described how they related more closely to the stories of their peers than famous sports stars and one way this can be facilitated is

by group delivery. The content and relevance of any supporting materials should be closely considered. Training in the delivery of a novel education package should be made available to staff across the care team to enable them to either deliver the course or increase their confidence in offering salient advice as part of routine care.

Keywords: type 1 diabetes (T1D), exercise, service delivery and organization, structured education program, staff development

INTRODUCTION

The number of individuals affected by Type 1 Diabetes (T1D) continues to increase with some 20 million affected globally (1). In the United States the estimated 3 million with the condition is set to treble by 2050 (2, 3) with a concomitant increase in economic burden that is currently estimated at some $14.4 billion annually (4). One way in which the effects of T1D might be mitigated and the associated costs might be reduced is by meeting the recommendations for patients with T1D to undertake regular moderate-intensity exercise (5–9)[1]. The potential benefits both for patients and service utilization of their maintaining such a regime are numerous (10, 11) including a reduced risk of cardiovascular disease (12, 13), microvascular complications, hypoglycaemia (14) as well as enhanced psychological well-being (15). Existing guidelines recommend that patients with T1D should exercise regularly[1,2] however, with a reported 50% undertaking little or no physical activity either in Europe (14) or the United States (16), the need to increase the amount of sustained exercise and physical activity undertaken by patients with T1D remains[1](17). To this end research on both sides of the Atlantic (18–21) has identified a number of barriers that might inhibit patients with T1D exercising including a lack of concerted information on exercise management. In the United States, it's recommended that patients seek the advice of physiologists or fitness coaches with experience of managing patients with T1D (22) whereas in the UK its expected support will be provided by dieticians, specialist diabetic nurses, educators and consultants as part of their routine care[1].

The content of any advice is frequently generic focussing on the basics of carbohydrate counting and insulin management. However, the implementation of this advice is influenced by numerous factors such as the duration and intensity of physical activity (23), the presence of co-morbidities (24), the level of patient engagement (25), and environmental parameters such as temperature (26). All of these contribute to variable glycaemic responses that make uniform recommendations challenging (22). In the UK patients attempting to negotiate these multiple influences are often dependent upon multiple care providers, with diverse levels of training and experience (27–29) with a recent survey reporting that two thirds were unfamiliar with the evidence-based guidance[1] leaving them unable to offer basic advice on insulin action (27).

There appears to be a clear need in T1D care both in the UK and elsewhere for a structured educational package specifically addressing safe exercise. Our study "Supporting adults with Type 1 Diabetes to undertake exercise; Developing and piloting an Education programme for exercise in Type 1 Diabetes" (EXTOD) was established to co-design an education package to support the management of exercise by both patients and staff[3]. The initial phase used focus groups to better understand the existing provision of advice and education on exercise that explored both patient and provider perspectives and preferences. The findings presented here describe for the first time the existing influences on how successfully the content of the information provided and the processes by which it is delivered meets the needs of patients. In doing so we offer valuable insight into the requirements of patients with T1D and their care providers as they attempt to maintain or increase levels of exercise. Our findings can inform the actions of all providers supporting patients with exercise and have been integral in the development of the EXTOD educational package.

METHODS

Settings

The study took place in two hospitals in the UK. Taunton and Somerset NHS Foundation trust which is a medium sized hospital in the Southwest that provides care for people living in a mixture of rural and urban environments and the Queen Elizabeth Hospital Birmingham. This is a large teaching hospital in the West Midlands that provides care for people living predominantly in an urbanized Metropolitan environment.

Recruitment

Patients

To participate in the study patients must have a clinical diagnosis of T1D, be aged between 18 and 70, be on a basal bolus insulin regime, and have attended their local approved T1D Education Programme [DAFNE, BERTIE, Living with diabetes, or equivalent[4,5] (30)]. Finally they should be exercising regularly or starting to train for a specific sporting event. All eligible patients were approached directly in diabetes clinics in a consecutive manner in each hospital by healthcare professionals aware of their existing or planned exercise activities. Those that expressed an interest were provided with an information sheet

[1]https://www.nice.org.uk/guidance/ng17 (accessed October 2017)

[2]American Diabetes Association Diabetes Care (2018). 41(Supplement 1):S38–50.

[3]http://www.isrctn.com/ISRCTN61403534?q=&filters=&sort=&offset=5&totalResults=14839&page=1&pageSize=10&searchType=basic-search(accessed November 2017)

[4]https://www.bertieonline.org.uk/ (accessed November 2017)

[5]https://www.nhs.uk/conditions/type-1-diabetes/living-with/ (accessed October 2017)

and offered an appointment with the research nurse who would answer their queries, discuss eligibility, and consent participants.

Staff

Any Health Care Professional (HCP) involved in the care of patients with T1D across the Southwest and West Midlands were contacted via email by the research teams in each hospital to ask if they would be interested in taking part in this study. As with patients those that expressed an interest were provided with an information sheet and offered an appointment to see the research nurse to discuss their involvement, to check their eligibility and to be consented.

Ethics

This study was carried out in accordance with the recommendations of the National Health Service Health Research Authority, through the Coventry and Warwickshire research Ethics Committee. The protocol was approved by the same committee and given the reference code 16/WM/0034. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Data Collection

We collected data on experiences of existing exercise education provision from staff and patients using focus groups or for those unable to attend the groups by semi-structured telephone interviews. Focus groups were chosen as the primary method of data collection as they offer opportunity for participants to reflect and test ideas rather than formulate ideas on the spot (31). The uninhibited discussion can also serve to remind participants of their past experiences and produce new thoughts about the delivery of education on exercise. In this study, the ability to generate information on collective views is useful to generate consensus to inform the nascent education package (31).

Two focus groups, were convened at each hospital (32). One was comprised of people with T1D and the second multi-disciplinary HCPs involved in T1D patient care. Each group was facilitated by IL a research fellow with extensive experience of qualitative methodologies used in improving health service delivery. A topic guide was used, tailored to either patients (see **Box 1**) or providers (see **Box 2**) and designed to allow themes and issues to arise naturally from the interaction of the group during the course of the meeting (33).

Box 1 | Patient Topic guide

Your own exercise programme

1. Can you tell me about the sort of exercise you regularly take each week?
   - ***Prompts;*** When, who with, length/intensity/frequency, type of sport
2. Do you do anything special to prepare yourself – before, during or after exercising?
   - ***Prompts:*** Food, diet, drinks - including alcohol
3. Do you have any problems when you exercise?
   - ***Prompts:*** Tiredness, muscle fatigue, other
4. Is there anything that makes it easier/more difficult to exercise?
   - ***Prompts:*** T1D, other medical condition, related non-medical factors

Current provision of information around exercise and managing your condition

5. Who have you spoken with about T1D and exercise?
   - ***Prompts:*** Consultant, other hospital doctor, GP, nurse, dietician, other
6. When did you discuss this?
   - ***Prompts:*** At diagnosis, at each consultation, every so often, a specific session
7. What was the content of the discussion?
   - **Prompts:** Condition related - insulin, glucose levels, what to do about hypos Other health related - exercising when feeling unwell (colds etc.) Exercise related - different types of exercise and how much Preparation for exercise – steps to take during and recovering from exercise Diet - different foods, liquid and alcohol intake Environmental factors - the influence of hot/cold weather Personal characteristics – age, any other barriers and facilitators
8. Did you use additional sources of information?
   - **Prompts:** Webinar, peer group, online, correspondence course, booklet

Analysis

Focus groups in the South West were conducted and analyzed first. These began with the patient focus group and were followed by the HCP group. This allowed for a preliminary analysis to inform the topic guide of the second set of focus groups conducted in the West Midlands. Staggering the focus groups and their analysis helped ensure that the key points were recognized and explored. Semi-structured interviews were carried out with participants unable to attend by the researcher using the same topic guide as in the focus groups.

The patient and staff transcripts from the focus groups conducted in the South West were independently coded by IL and SG a medical sociologist. Although IL moderated the focus groups and conducted the interviews the potential for bias was checked by the close involvement of SG who was not involved in data collection. All data were analyzed using thematic analysis (33) and underwent three key phases of coding. The first involved multiple detailed codes relating to the various responses of the participants following the first two focus groups. During the second phase these were grouped into broader over-arching themes which IL discussed with SG who had independently read the same two transcripts. The final phase was again conducted with SG where the over-arching themes and sub-themes were agreed following the final two focus groups and 1:1 interviews. IL and SG then met and agreed emerging themes and sub-themes from across both patient and staff groups. This then became the coding framework for the remaining focus groups at the West Midlands site and the semi-structured interviews. Initially the patient and HCP transcripts were coded separately but when IL and SG discussed the coding it was apparent that the initial overarching themes extended across all the interviews. As a result the data from all transcripts were combined and the results presented together.

Group discussions were digitally audio-recorded with permission, and transcribed verbatim for analysis, Data were managed using N-Vivo software. The intention in this instance was not to reach data saturation but instead to use the content

Box 2 | Staff topic guide

Current provision of information around exercise and T1D

1. What aspects of exercise do you usually discuss with patients?
   Prompts: The impact of different sports, length/intensity/frequency aerobic vs. anaerobic
2. When do you introduce this topic
   Prompts: At diagnosis, at each consultation, every so often, in a separate or targeted session (e.g. DAFNE)
3. Are there any particular types of patients with whom you find it easier/more difficult to talk about exercise with?
   Prompts: Age, ethnicity, gender, preferred exercise
4. What are the barriers if any to your discussing exercise?
   Prompts: Time, lack of knowledge
5. Which healthcare professionals should talk to patients about exercise?
   Prompts: Consultant, other hospital doctor, GP, nurse, dietician, other
6. What sorts of issues do you discuss?
   Prompts: Condition related - insulin, glucose levels, what to do about hypos; Other health related - exercising when feeling unwell (colds etc.) Exercise related - different types of exercise and how much, Preparation for exercise – including steps taken during and recovering Diet - different foods, liquid and alcohol intake Environmental factors - the influence of hot/cold weather

of the various discussions to inform the content and format of a novel education package[3]. However, by the end of the four focus groups and interviews no new themes or sub-themes were emerging.

RESULTS

Patients

Two focus groups were conducted consisting of a total of 14 patients. They were aged from 22 to 71 of which eight were males and six female. The group in the South West (SW) contained four male and four female participants and the time since diagnosis varied from 3 to 50 years. Those that exercised or competed regularly were predominantly found in the SW group, where five of the eight regularly exercised a minimum of four times a week. The discussion here lasted 80 min. In the West Midlands (WM) group there were four male participants and two female with a slightly broader range in the time since diagnosis than the SW group of between two and 60 years. They tended to exercise less in this group with only one participant undertaking exercise more than three times a week. The discussion lasted 86 min. The characteristics of all patient participants are summarized in **Table 1**.

TABLE 1 | Patient participants.

Study ID	Time since diagnosis (years)	Exercise regime (Sessions per week)
SOUTH WEST (SW)		
P1	3.5	Gym x2, Karate x2
P2	20	Dance x4, Perform x1
P3	5	Hockey training x4, Play at the weekend
P4	3	Football x1, Cycle commute and run regularly
P5	50+	Gym x2, Keep fit class x1
P6	5.5	Horse riding x7 (Competes on weekends)
P7	3	Gym x3
P8	4	Cycling x2, Gym x1
WEST MIDLANDS (WM)		
P9	17.5	Gardening, Aikido x3
P10	2	Swim x1, Keep fit x1
P11	56	Gardening, Walking, Infrequent cycling
P12	36	Walking short distances x7
P13	6	Badminton x3
P14	6	Squash x1, Cycling x5

Health Care Professionals

A total of 11 staff were interviewed in the two focus groups; of the five participants in SW three were dieticians and two were specialist diabetes nurses with between 6 and 21 years experience, four of them had taught on DAFNE or equivalent courses. The discussion lasted 69 min. The group from the West Midlands consisted of three specialist nurses, two dieticians and a speciality doctor, their experience ranged from between 4 and 15 years, four had experience of teaching on DAFNE or equivalent courses and the group ran for 75 min. Two semi-structured interviews were conducted both with consultant diabetologists from the South West (HCP6 and HCP7) who were unable to attend the focus groups as originally intended. The interviews lasted between 45 and 55 min. The characteristics of staff participants are summarized in **Table 2**.

Analysis

Themes were combined across patient and staff groups and four emerged which are presented together below. The first concerns the nature of the exercise regime undertaken by each individual relating to both its complexity in terms of the types and combination of exercise and the consistency in the pattern of exercise. The second theme centers on patient engagement, specifically how their ability to manage health is affected by the knowledge, skills and confidence they possess as reflected in their preferences, the use of self-management techniques and level of health literacy. The third theme is related to organizational factors concerning staff training, limits of capacity, consistency of care, and existing education strategies. These themes and sub-themes are summarized in **Table 3** and below we present exemplar quotes for each alongside the key characteristics of the participant that provided them. Additional and extended quotes can be found in **Supplementary Table 1**.

Exercise Regime

The types of exercise individuals enjoyed, the consistency of their exercise regime and the intensity of the activity all impacted

TABLE 2 | Staff participants.

Study ID	Job title	Time in post (years)	Exercise education provided
SOUTH WEST			
HCP1	Diabetes dietician	21	Teach on carbohydrate counting course (plus 4 h a week research)
HCP2	Diabetes dietician	8	Teaches on carbohydrate counting course, specialist interest in sport
HCP3	Diabetes dietician		Pediatrician (previously adult) Teaches on carbohydrate counting course
HCP4	Diabetes specialist nurse	6	Teaches on carbohydrate counting course
HCP5	Diabetes specialist nurse	12	1 day a week "pumps adviser"
HCP 6	Consultant in diabetes endocrinology, acute and general internal medicine	13	Proactive enquiry around exercise during consultation. Advises on range of exercise and activity
HCP 7	Consultant diabetes endocrinologist, and the clinical lead for patient specialities	8	Advises patients on recreational exercise and events such as marathons
WEST MIDLANDS			
HCP8	Speciality Doctor	8	Educates patients on exercise in response to their enquiries
HCP9	Diabetes dietician	2	Deliver the exercise section of the carbohydrate counting course.
HCP10	Specialist dietician	4	Teaches exercise as part of education programmes for both Type 1 and Type 2 diabetes.
HCP11	Diabetes specialist nurse	15	Teaches on carbohydrate counting course
HCP12	Diabetes specialist nurse	15	Teaches on carbohydrate counting course
HCP13	Diabetes specialist nurse	14.5	Teaches on carbohydrate counting course

on the ability of staff to advise them how to safely conduct this exercise.

Type of Exercise

Predictable Intensity

The nature of the exercise being undertaken was a key indicator of how confident staff felt in delivering appropriate advice. Staff described feeling most comfortable presenting advice to individuals who took part in relatively consistent bouts of aerobic exercise such as long-distance running or cycling.

TABLE 3 | Influences on the successful delivery of exercise education: themes and sub-themes.

Theme	Sub theme 1	Sub theme 2
1.0 Exercise regime	1.1 Type of exercise	Predictable intensity Anaerobic exercise Specialized sport
	1.2 Patterns of exercise	Routine vs. sporadic
	1.3 Intensity	Competitive vs. non-competitive
2.0 Patient engagement	2.1 Patient preference	Priority of exercise
	2.2 Self-management	Monitoring Carbohydrate counting
	2.3 Health Literacy	Understanding advice
3.0 Organizational factors	3.1 Staff training	Limited knowledge of the effects of exercise Deskilling
	3.2 Capacity	Limited access to education packages Limited access to specialist providers Length of consultation
	3.3 Coherence of care	Consistency of message Continuity of care
4.0 Existing education strategies	4.1 Structured education package	Criteria for inclusion
	4.2 Format and content	Patient stories Generic written information

> "… the longer distance runners, triathletes, and cyclists I tend to find a bit easier to work with, …maybe because their activity is a bit more predictable? They tend to have…more structured training, and more obvious responses to their activity."
> - *HCP6 Consultant*

Patients reflected on how difficult it was to accurately predict the varying intensity of an individual bout of exercise and the difficulty this presented in managing their body's response.

> "…with the intensity, because that varies depending on just even how you're feeling on the day… you might not feel like you want to go too far…and therefore you get different readings than what you might have done a week ago doing the same distance, or length in time of exercise, or whatever."
> – *Patient 8*

Anaerobic Exercise

A notable area of uncertainty was instructing patients about anaerobic exercise such as weight-training. One diabetic specialist nurse (DSN) described how it felt counter-intuitive that blood sugar levels should rise after lifting weights and the struggle they had in coming to terms with the concept.

> "I still find it a bit hard around the anaerobic sport, when they're doing weights and things like that, and actually their blood sugars go up, so one guy I mentioned he does that first thing in the morning, so he has no breakfast and three units of insulin and

goes to the gym, and then his blood sugars are okay. I sort in my head think "Oh!" [laughter] but it does work. But that took a lot on both of us gradually edging that up, but it doesn't seem right does it?"
- HCP5 Diabetes Specialist Nurse

Patients also recognized the different effects on their physiology of aerobic as opposed to anaerobic exercise.

" …you know what to do for let's say, I don't know, spin class, you know how you need to fuel yourself for that, then if you want to change what exercise you do, if you want, I don't know… a spin class and a weight class affects me completely differently and I have to fuel differently for that,"
– Patient 7

Specialized Sport

Staff spoke about how their personal experience of a particular sport would inform the advice they provided. Where patients undertook more specialized or unusual forms of exercise they felt less able to offer advice. For example one DSN described how her lack of understanding of the physical demand of extreme triathlons made it harder for her to provide relevant advice.

"I get quite… we've got a couple that one is training to do the iron man competition, and one is doing a triathlon and I have absolutely no idea where to start, because I don't understand the sports themselves and exactly what they're actually trying to achieve. So not knowing what they're doing it's hard to give advice when you don't know, and I'm certainly not going to go and do a triathlon [laughs]."
- HCP13, Diabetes Specialist Nurse

Patterns of Exercise

Routine vs. Sporadic

Whether the individual's exercise regime was predictable impacted on how readily it might be managed and the level of sophistication of advice and education they required. For example one patient expressed their uncertainty of how to manage change in their exercise routine.

"…it's any kind change to your routine, if you can stick to your routine you're fine, but I find any kind of change is when I have problems."
-Patient 10

Staff also described the issues they had informing patients who took on a variety of sports in various combinations. For example, one dietician described their apprehension in advising those that played an aerobically intense sport like rugby in the winter then a sport of lengthier duration with bursts of aerobic and anaerobic exercise such as cricket.

"I think people that have a routine where they do things, the same exercise, are easier to advise, but those people like you were saying who do a different sport, or do cricket in the summer, rugby in the winter, and actually need to do very different things, and there's parts of the year when you're doing both."
– HCP5, Diabetes Specialist Nurse

Intensity

Competitive vs. Non-competitive

Another factor central to the level of confidence of staff in speaking to patients about managing exercise was the standard at which individuals exercised or played sport. In the view of one dietician the sporting ability of a patient would impact on their own confidence to offer appropriate advice.

"I think my difficulty comes when I've got people who are very sporty, either competitive sport or are training for something specific like for a marathon or something. Then I feel it stops my confidence not theirs, and that might rub off on them, I don't know, because then it becomes quite difficult, because you're managing quite a lot regarding their diabetes, and I suppose that's just experience of what to do with people that are very sporty or training…"
– HCP12, Diabetes Specialist Nurse

One patient described how the impact of aerobically demanding competitive sport is more difficult to manage.

"I used to event, luckily I don't event anymore, I just do dressage, so it's very controlled, so it's not a huge high impact thing. You work hard but your heart rate never [rapidly increases]… it probably does through adrenaline, but not like a run or if you're cycling hundreds of miles, it's quite controlled."
– Patient 6

Patient Engagement

Patient engagement is defined as an individual's knowledge, skills, ability, and willingness to manage their own health and care[6]. Here we describe three factors related to the level of this engagement amongst our patients and how it shaped the support they requested, received, and assimilated. These factors are, their preference for the content of consultations, the level of competence in their self-management, and related to this, their level of health literacy.

Patient Preference

Priority of Exercise

We found that the content of any advice provided around exercise was frequently led by patient enquiry and related to their preferences and priorities. If regular exercise was a central activity prior to diagnosis then patients would be more likely to ask additional questions and require greater detail in the response. In this example a DSN described how the importance of exercise to the individual would be apparent from the first consultation and shape subsequent conversations.

"It all depends very much on the patient because you might have somebody who is newly diagnosed who is a regular sportsperson and they're doing a particular activity, and they want to know whether they can keep it going, and they would introduce the fact that they need to have the advice, whereas you might have another person who is fairly newly diagnosed who actually wants to just concentrate on getting to terms with diabetes without looking

[6]https://www.kingsfund.org.uk/projects/gp-inquiry/patient-engagement-involvement (accessed October 2017)

at other things that can affect it. So it's all very much down to the individual."
– *HCP13, Diabetes Specialist Nurse*

Self-Management

Self-management describes the capability of an individual to recognize, treat, and manage their own health whether independently or in partnership with the healthcare system[7]. The basic advice offered to any patients with T1D irrespective of exercise regimen involves a number of self-management techniques, in particular how to monitor and record blood glucose levels, and count the carbohydrates they have consumed. The ability or willingness of patients to consistently fulfill these tasks would vary.

Monitoring

For clinicians to provide salient advice they must have some understanding of an individual's metabolic response to the exercise they undertake and the carbohydrates they consume. One patient who cycled for lengthy periods described how they would monitor their blood glucose sugar as often as every 30 min.

"…you've got to try and work it out like we've said before. But I think they said that every half an hour you've got to re-evaluate the situation, so when you're doing something like four and a half hours, I'm sure with cycling and things, if you do cycling you've got to look at it every half an hour and just take on fuel, it's hard work."
- *Patient 4*

However, some patients outwardly interested in undertaking regular exercise would fail to provide any information on their blood glucose levels. In its absence providers felt unable to offer relevant advice. For example a dietician described an instance where a patient wanted to increase their level of exercise without collecting or presenting the relevant information.

"…and I think the problem is we are generally presented with a person who maybe wants to increase activity or who has got problems, but presents you with no testing and no information, and then you say to them "Well you've got to go away, you've got to do some testing.…"
– *HCP5, Diabetes Specialist Nurse*

Carbohydrate Counting

A basic knowledge of carbohydrate counting is necessary to exercise safely with T1D yet patients did not always possess this capability. One dietician described how patients with a keen interest in sport would not be able to complete the basic task of carbohydrate counting.

"Some people who come to you want to specifically talk about their interest in sport and how to manage it. But I find that some of them aren't even carbohydrate counting or have any of the foundations. So where you've set out to think this is all going to be targeted around sport you then begin stripping it back and doing all the foundations of the basic principles or carbohydrate counting and dose adjustment. So I found that it's pointless giving much information until they've even got that foundation, because otherwise that's more important than then tailoring for all the sports advice."
– *HCP2, Diabetes Dietician*

Related to this a patient described how they only learnt to control their body's response to training after an extended period of trial and error.

"Mine is a little bit involved with diet as well. So I tend to reduce the amount of insulin I'm having if I'm training, but if I'm performing at the weekend? I tend to carb load the day before, and then I have less [food] but fully protein based the day off, so that [way] my liver doesn't go into overdrive with my blood sugar spikes. It took me quite a while to work out how to manage that."
– *Patient 2*

Health Literacy

Understanding Advice

The term health literacy describes the ability of a patient to understand and assimilate health-related information[8]. Health literate patients with T1DM were able to independently use the written information contained within the booklets or pamphlets provided as part of their structured education package. For example a patient described how one such booklet provided by their diabetes team remained a useful reference point and allowed them to cope with some of the less common side-effects.

"I know that when I've been quite ill and I've used sick day rules through DAFNE, I'm glad I can grab that leaflet and that booklet and I can read, because it's hard to remember it because you don't often get ketones when you get ill, but if you've got good control you know you're getting ill and you can keep your levels low enough that you don't get ketones."
– *Patient 6*

In terms of communicating to patients one HCP described how they would use the "talking test" to help a patient understand the various levels of intensity of their exercise.

Talk about the talking test, whether they can talk and how red in the face they go, that's what we talk about, to calibrate it.
- *HCP7*

Organizational Factors

Organizational factors are related to the levels of staff training (and the ensuing confidence they have in imparting advice), the limited capacity of the system to cope with large numbers of patients, and the coherence of care provided across the patient's care team.

[7]https://www.england.nhs.uk/ourwork/patient-participation/self-care/ (accessed November 2017)

[8]https://www.hee.nhs.uk/our-work/health-literacy (accessed November 2017)

Staff Training

Limited Knowledge of the Effects of Exercise

Both staff and patients recognized there was a gap in providers' knowledge beyond a certain intensity or duration of exercise. One dietician described how they would impart advice on the basic tenets of carbohydrate counting and the principles of managing exercise but if asked to provide specific information they would instead refer the patient to a consultant.

> "The DAFNE and all our in-house carbohydrate counting covers the basic aspects of sport management but we were finding that we were getting people referred for they're going to climb Mount Kilimanjaro, and they're going to… and because it's slightly out of our depth we were finding that we were then referring a lot of those patients up to [specialist consultant] and there was a gap in terms of the basic level of education to the more elite, and whilst I was trying to bridge the gap and give information I didn't really feel fully qualified to give."
> – *HCP2, Diabetes Dietician*

The apparent reluctance of some HCPs to entertain discussions around exercise was also noted by patients. One felt that dieticians were very supportive of the general management of diabetes but hesitant to discuss exercise.

> "The dieticians in the formalized setting have been brilliant with everything else, so they would say to me "keep a diary, come back, let's see what did you do here?" And "that's the result of this," and "you've got the ratios correct, they're working for me". But the nurses and the dieticians whenever it comes to exercise they step back…"
> – *Patient 13*

Some of the carbohydrate counting courses offered to patients incorporated a practical element with patients measuring blood glucose levels before and after a spell of exercise. The HCPs we spoke to raised concerns around their involvement in any such element, at least without appropriate support. For example one Specialist Diabetic Nurse felt unwilling to take patients for a supervised gym session without being accompanied by a specialist member of staff.

> "…I wouldn't feel comfortable to take a group of people to a gym for multiple reasons. If it was a trainer now that's different… people who knew what they were doing and specialists in that field then fine, but not if it was just nurse and a dietician."
> - *HCP10, Specialist dietician*

Deskilling

The UK's guidance produced by the National Institute for Health and Care Excellence (NICE) recommends that carbohydrate counting courses be delivered by a trained educator (7). One unforeseen consequence of bringing in a specialist educator was that other members of the multidisciplinary team that would otherwise be involved in delivering the programme can become deskilled. One DSN described how the diabetes team were unfamiliar with the format of a new blood glucose diary as they had not been involved in its conception or introduction to patients.

> "I think the other thing is what we find when we have got some individual educators for DAFNE or whatever courses that are in a trust, and then what happens is they go back to their regular care, and that the other specialist consultant, or the registrar or the other DSN isn't geared up enough to deal with their new blood glucose diary they're faced with."
> – *HCP12, Diabetes Specialist Nurse*

Limited Capacity

The number of patients with T1D is growing and staff described how the ability of the service to provide education to all patients was inhibited by limited places on structured education programmes, shortages of relevant staff, and constraints on lengths of consultations.

Limited Access to Education Packages

The NICE guidance recommends that all those diagnosed with T1D should be offered a place on a structured education course between 6 and 12 months after diagnosis[1]. However, a consultant in the South West described how places on the course at their hospital were limited and expressed regret that they could not offer a place to everyone eligible.

> "It's not for every patient unfortunately. It would be lovely to have it for [everyone]…is just the SWIFT course is completely chocka for the next how many months, because it's multidisciplinary teaching, quite intensive, it takes the days out of their normal work…"
> – HCP 7, *Consultant diabetologist*

Limited Access to Specialist Providers

The restricted availability of specialist diabetic nurses was reported by one consultant who described how patients were unable to follow a prescribed care plan that involved reviews by specialist nurses because of a lack of appointments within the relevant time frame.

> "I will pick up the problem probably so, for those that I don't transfer out, I'll pick up what I think should…set out a plan, and I'll ask the nursing team to pick up in a follow up. The problem we have is actually the nursing clinic appointments are full, they do get longer with patients but there's little availability and sometimes I will have seen the patient again before the nurses have seen them. So that's obviously a barrier to getting good information off."
> – HCP7 *Consultant*

Length of Consultation

Both dieticians and consultants described how limits on the time they could spend with individual patients prevented a more detailed dialogue around exercise. The time constraints meant they would prioritize other aspects of T1D management in accordance with patient preference or clinical urgency.

> "Time is a nightmare. I think if I go into activity in detail I reckon you're looking at 45 minutes minimum, if you're trying to unpick… so I have a 20 minute slot and I'll spend 45 minutes with

someone who's doing regular sport and we're trying to unpick things, because by the time you have unpicked other stuff and you've dealt with other questions . . . "
– HCP7 *Consultant*

"It's the time element as well; somebody is coming to you with [exercise] just up to a certain level - which may be their weekend football session with their pub team or something - that's okay, and I think that's fine and you can manage that within normal sessions. But if you've got somebody who is becoming a higher level, more competitive, or training for something, and quite big, then it takes a lot of your time up as well and you don't always get *that* amount of time to see the patient.."
– HCP12, Diabetes Specialist Nurse

Coherence of Care

Consistency of Message

Within the multi-disciplinary T1D care team staff possess varying levels of training, experience and interest and these differences appeared to lead to patients receiving inconsistent messages from even quite senior staff. For example, one consultant acknowledged that varied levels of awareness of the impact of exercising with T1D might mean advice differs depending on which consultant a patient speaks to.

"So we've got a number of consultants here, and I think you will… there's a couple of us who are much more interested than the others, and I am not sure you would get entirely consistent advice across the consultant group let alone a broader body."
– HCP7 Consultant

Issues emerged around inconsistent information from clinicians with expertise in other specialities whether based in secondary or primary care settings. One DSN described how colleagues in cardiology had experienced a patient with diabetes having hypoglycaemic episodes and so tried to prevent them from attending future cardio-rehabilitation classes.

"We've had people go to the cardiac rehab and we have phone calls because they've had hypos and they want to stop their exercise sessions at the cardiac rehab, and you're like "Yes but we can manage the hypos, the whole point of the cardiac rehab is after their heart attack or whatever else they've had…" and that is then a barrier but it's other healthcare professionals putting that barrier of a person doing the activity."
– HCP12, Diabetes Specialist Nurse

This variation in knowledge of TID between clinicians was also experienced by patients in primary care. One patient described how a locum general practitioner had failed to grasp the differences between Type 1 and Type 2 Diabetes.

"Like the GP thing - when I first started having conversations about the fact that I increase my exercise way back then, and then I was doing DAFNE, we had a locum GP and he said, "Well just low carb anything," and that was his response, and I went, "I'm Type 1!" he went, "It's the same thing." So I didn't listen to anything he said…"
– Patient 2

Continuity of Care

The benefits of continuity of care have been widely recognized across many healthcare settings (34, 35). The knowledge of the physical and mental characteristics of patients gained over time help to inform clinical decision making. In offering individual advice on exercising with T1D staff acknowledged the benefits of building up a relationship with a patient over time, and the increased understanding of how their body responded to exercise.

"It's just really individual. I think though when you are talking to certain people and you might get it right for their training, and then they have a race, and then their training then pushes their blood sugars up so they've got to do something different that day. So it's very hard to go 'I'll just go and get from the cupboard, because this is what you need…' because it is really individual, so you have to really know that person, how fit they are, what preparation they can and will do, and then try and tailor it that way to keep them safe and perform well."
– HCP2, Diabetes Dietician

A patient described how continuity of care was inhibited by a perceived lack of communication between primary and secondary clinicians.

"I think part of my problem with my GP surgery is they seem to think all of my care is being done by the hospital, the hospital thinks some of it is being done by the GP and I'm left in limbo with do I need to book an appointment with the GP, do I just wait for my letter to say I'm coming into the hospital?"
– Patient 8

Existing Education Strategies

Current guidance recommends that all patients are offered a place on a structured education package that teaches the basic skills of how to self-manage their condition between 6 and 12 months from diagnosis. The criteria used to determine who should be invited to attend and when was queried by patients. As well as taught courses a variety of written information is also made available to patients via their care provider and the design and content of some of these materials was also questioned.

Criteria for Invitation to Existing Packages

Criteria for Inclusion

Current guidelines recommend a period of 6 months before patients attend a course teaching them the basics of carbohydrate counting and insulin management as this would allow for their T1D to stabilize. However, some patients felt they would have benefitted from attending closer to their diagnosis, feeling the information would have been valuable to them earlier, particularly with relevance to their desire to exercise.

"…I personally feel that if I had been able to access DAFNE when I first started I would have handled it in such a different way. The National Health isn't giving individual choice of at what level you want to consume and take control. So a gentleman who had come on the DAFNE he had just been diagnosed, and it was all just too much for him and basically he had to leave. But for me it was just

the most… I wish that I didn't have the complications, if I had DAFNE five years ago I would have been able to handle it and my body would have been a lot better than what it is. So that's one thing that the National Health needs to do, it's one fits all kind of thing."
– *Patient 13*

Another criterion applied to the selection of patients for attendance on the course was the level of an individual's insulin consumption. One patient reported how they were not invited to attend because staff felt their insulin consumption was too low to justify attendance. However, the patient felt that information contained in the course would still have been useful as they had experienced difficulties in maintaining blood sugar levels from the beginning.

"I think you should be put on it quite quickly, even if you're not necessarily going to use the information they've given you. I wasn't on it until… I didn't go on DAFNE until May, and I think that was too late for me, it was just because I wasn't taking enough insulin to warrant going on it, but I don't think they should really use that, because especially - not necessarily for situations at home, because you know that you're cooking and stuff - but when you go out and things like that? It's really, it's difficult enough at home when you're just starting, it's really difficult to get it right, and I found that I was always way off my insulin when I was out, or if I was on holiday or something like that. But I think even if you're not necessarily going to use the information just have it there so that you can access it if you need to would have been helpful."
– *Patient 7*

Format and Content

Patient Stories

One educational tool frequently used as part of the structured education package but also via other platforms was the "patient story," a device that uses real-world examples to provide context for the learning point and so enable patients to more readily assimilate the information[9]. The stories used in T1D frequently involved elite sports stars whose experiences were so different to the patient's experience of living and exercising with T1D that little could be drawn from them[10].

"Look at the way they performed and they had all the back up in the world that you could ever want. Steve Redgrave is a whopper! His wife is a doctor, so she's there checking him out and pumping him full of insulin when he needs it. Danny McGrain and Mabbutt would have had the sports physios and all the doctors that professional footballers had on tap. Now the rest of us had to do it ourselves."
– *Patient 11*

[9]https://improvement.nhs.uk/documents/2140/patient-stories.pdf(accessed November 2017)
[10]https://www.diabetes.co.uk/celebrities/gary-mabbutt.html(accessed October 2017)

In contrast to the stories of famous athletes several patients spoke of the value of the support they gained from people with T1D involved in similar sports and competing at a comparable level.

"I was lucky when I started, I had one of the guys on our mat, higher grade than me, he had been Type 1 since he was six… and I said to him one day, 'What is happening? I never know if I'm going to be finishing on 3.6 or ten.' He said, 'that's the way it is; don't fret because if you fret it will make it go higher.' So that was actually my most useful bit of information I had, 'don't fret'..."
– *Patient 9*

"I think it would maybe help more to have somebody that does exercise, somebody that is in this, somebody that's on the same page that lives it and knows it would definitely help."
– *Patient 1*

Generic Written Materials

Educational materials for patients with T1D are provided in a number of formats including booklets and posters. The design and content of these elements was questioned by some of our participants. One patient expressed disappointment at the tone of a poster in a shared waiting area and felt it was uninspiring, particularly during the period they were adjusting to their diagnosis.

"I suppose if you think about the psychology right, you've got all of these hospital appointments that you never used to have to do, you go and sit in some God awful waiting room with all these posters of cartoon characters, about having a carrot or something like that, and it's all this "Here's how your plate's divided." It's quite patronizing a lot of it, it's just it's not very enticing is it?"
– *Patient 10*

DISCUSSION

Key Findings

Though exercise avoidance and physical inactivity are common in patients with T1D this is the first time that the impact of the provision of advice and education on exercising safely has been explored simultaneously with patients and providers. Subsequently we have identified a number of interrelated influences on the success of this provision, these were; the nature of an individual's exercise regime including its intensity, type, and frequency; the degree of patient engagement relating to their preference, the self-management techniques employed, and individual health literacy; Organizational factors that affected staff training, and the capacity and coherence of the system; and finally issues around existing education strategies including access to structured education packages and the content and format of written materials.

Strengths and Limitations

We have gained a number of novel insights into issues specific to educating patients with T1D on how to exercise regularly and safely. The sample was relatively small and though the intention of this qualitative work was primarily to inform the content and format of a novel education package and not necessarily to reach data saturation, the staff, and patients that took part reflect a

varied range of characteristics and by its completion saturation was reached (33). The inclusion criteria for the study meant all the patients we spoke to engaged in regular exercise and included a range of abilities, sports and exercise regimes. We recognize that patients with less ability or interest in exercise might have expressed different views and may need different support and education to encourage them to start to exercise or to exercise more regularly and safely. Similarly it is understood that staff and patients at non-participating sites may have offered alternative opinions due to differences in ethos and experience present at their facility.

Specific Findings/Existing Literature

Staff Training

Deficits in the training of health care providers (HCPs) to deliver advice on exercise were identified. The reported gaps in the knowledge of diabetes specialists reflect broader existing evidence of the repeated failure to equip clinicians with the basic knowledge, confidence and skills to promote physical activity (36, 37). There have been prior calls to train clinicians to prescribe exercise with the same regularity and level of detail as pharmaceutical options (38) and such targeted training has been shown to increase the frequency of exercise counseling for patients with chronic disease (39) including diabetes (40). In the UK and abroad recent initiatives have emerged specifically to educate care providers and patients about exercising with T1D such as JDRF's Performance in Exercise and Knowledge (PEAK) programme (41). However, it seems important that any such training initiative should be offered across the patient's entire care team. This is because we found that not only did dieticians and SDNs describe their lack of confidence in delivering advice on anything but routine and predictable exercise, but patients and staff described the conflicting advice offered to patients between staff groups, specialities, and care settings. One alternative way of ensuring advice remains consistent is to include exercise specialists as part of the existing multi-disciplinary teams (42, 43). However, staff we spoke to reported feeling deskilled as a result of using specialist educators and though effective in the short-term their presence may actually limit the ability of other providers to offer meaningful advice.

Lack of Capacity/Adherence to Guidelines

Despite current recommendations exercise did not routinely form part of current consultations among our study participants due at least in part to constraints on time and a reliance on patients to prompt any discussion on exercise. There is a lack of precision in the UK guidelines about the provision of support[1] for patients wishing to exercise. This is mirrored in the advice of the American Diabetic Association which though making a number of valuable recommendations for patients with T1D regards exercise and carbohydrate intake only suggests that patients may benefit from working with fitness experts that understand diabetes (44). There is no further stipulation of who should educate patients on the principles of managing exercise, when this should be introduced, who should provide continued and responsive support, and the explicit role of self-management (44).

Self-Management

In any chronic disease utilizing and improving the capacity of patients to self-manage is a key component of effective care leading to improved patient outcomes, adherence, and efficiency of healthcare utilization (45–48) and this includes patients with T1D (49). The need for effective education to enable patients to self-manage was apparent considering we heard how some keen on exercise failed to understand the importance of self-monitoring blood glucose levels (50). One of the current aims of the UK's National Diabetes Treatment and Care Programme is to improve the uptake of structured education packages designed to "facilitate the knowledge skills and ability for diabetes self-management" (51, 52). Currently the nationally reported take-up is <30% (53) perhaps due in part to the limitations in availability described by some providers we spoke to.

Existing Provision

The lack of capacity within the system places more importance on sources of educational material that can be independently accessed. The design and content of educational material for patients deserves careful consideration as it influences their satisfaction, adherence, and health outcomes (54) yet patients' needs are varied and their ability to independently assimilate this information determined by numerous factors including age, socio-economic status, education, and ethnicity (55–58). Some we spoke to described their antipathy toward aspects of existing diabetes educational material, including generic "diabetes" posters that failed to differentiate between T1D and Type II Diabetes. One particular source of frustration amongst patient participants was selecting elite sportspeople to tell their patient story[11]. Used appropriately these stories can be a powerful tool and through their familiarity, become especially vivid (35) yet many existing examples bore little resemblance to patients' everyday experience of living and exercising with T1D. Instead patients spoke of the value of peer-to-peer contact where the benefits of discussing relatable strategies and solutions would be more readily applicable. The benefits of this type of peer-to-peer mentoring in diabetes have been recognized previously and appear an underutilized resource in supporting those wishing to exercise (59).

CONCLUSION

Drawing on both patient and staff perspectives, our findings provide persuasive evidence of the need for a more responsive and directed education programme for patients with T1D that exercise regularly alongside a similar programme for providers to enable them to offer ongoing advice for this level of activity. Currently there is no such educational package available for patients with T1D and the findings we present here will inform the content and delivery of an educational package that can support patients not only in the UK but also internationally. The nascent EXTOD education package will be offered to all patients based on their interests and preferences and not dictated solely by the time since diagnosis. It will contain advice on

[11] http://www.diabetesadvice.co.uk/real-stories/sir-steve-redgraves-winning-ways-with-type-2-diabetes (accessed October 2017)

the management of regular and irregular bouts of aerobic and anaerobic exercise alongside how to prepare for specific events. The patient stories utilized will more closely reflect the everyday experiences of patients with T1D supported by group education that both facilitates peer-to-peer interaction and minimizes costs to the provider. Perhaps most importantly it will incorporate a section that trains staff across the diabetes care team to enable them to contribute to the course directly or more confidently offer applicable advice as part of their routine patient contact.

AUTHOR CONTRIBUTIONS

The overall concept of the project was devised by RA and PN. The data collection was conducted by IL and the analysis performed by IL and SG. IL produced the original draft this was then critically revised by SG, RA, and PN for important intellectual content. A further draft was produced and all authors approved the final submitted manuscript. Each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication. IL is the guarantor who takes full responsibility for the work as a whole, including, access to data, and the decision to submit and publish the manuscript.

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EXTOD EDUCATION PROGRAMME DEVELOPMENT TEAM

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2019.00076/full#supplementary-material

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REVIEW
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Exercise Management for Young People With Type 1 Diabetes: A Structured Approach to the Exercise Consultation

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Regular physical activity during childhood is important for optimal physical and psychological development. For individuals with Type 1 Diabetes (T1D), physical activity offers many health benefits including improved glycemic control, cardiovascular function, blood lipid profiles, and psychological well-being. Despite these benefits, many young people with T1D do not meet physical activity recommendations. Barriers to engaging in a physically active lifestyle include fear of hypoglycemia, as well as insufficient knowledge in managing diabetes around exercise in both individuals and health care professionals. Diabetes and exercise management is complex, and many factors can influence an individual's glycemic response to exercise including exercise related factors (such as type, intensity and duration of the activity) and person specific factors (amount of insulin on board, person's stress/anxiety and fitness levels). International guidelines provide recommendations for clinical practice, however a gap remains in how to apply these guidelines to a pediatric exercise consultation. Consequently, it can be challenging for health care practitioners to advise young people with T1D how to approach exercise management in a busy clinic setting. This review provides a structured approach to the child/adolescent exercise consultation, based on a framework of questions, to assist the health care professional in formulating person-specific exercise management plans for young people with T1D.

Keywords: Type 1 diabetes, exercise, physical activity, hypoglycemia, blood glucose, child, adolescent, consultation

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INTRODUCTION

Regular physical activity during childhood is essential to promote optimal physical (1, 2) and psychological (3, 4) development. Physical activity is a key part of childhood and is not limited to sport and other forms of structured exercise; it encompasses playing and being generally physically active. However, it is well-recognized that many families do not adopt the recommendations that children and adolescents should engage in 60 min or more of physical activity daily (5).

Many factors contribute to the fact that a majority of young people do not achieve recommended time spent in activity, including perceived lack of time, motivation and resources. In addition to these factors, children and young people with T1D must overcome specific challenges related to managing diabetes and exercise. These challenges include maintaining stable blood glucose levels before, during and after exercise (6) and fear of hypoglycemia (7), especially on the nights after exercise (8). Health professionals can play a key role in assisting families to overcome these challenges as physical activity confers many benefits for individuals with T1D including; improved glycemic control (9, 10), cardiovascular function (11), blood lipid profiles (10) and psychological well-being (3).

Patterns of physical activity in young people differ from adults and therefore they merit a different management approach. In young children, physical activity is usually unplanned, based- around play and often varies from day to day (12). Thus, in this young age group it can be difficult to make planned adjustments of insulin or carbohydrate, and caregivers need to be equipped to problem solve as challenges arise. In contrast, older children and adolescents may be engaging in more structured exercise such as school sports and extra-curricular activities which may involve competition (13, 14). This planned exercise provides an opportunity for sequential review and refinement of exercise strategies. In addition to changes in patterns and types of exercise during childhood, physiological responses such as changes in insulin sensitivity with growth and pubertal development impact on glucose levels (15). Furthermore, responsibilities for diabetes management change over time, with a transfer of responsibility from parents and caregivers to the increasingly independent young person.

Exercise management for young people with T1D is complex and one approach does not fit all. Many factors influence an individual's glycemic response to exercise including the type, intensity and duration of the activity (16, 17), the amount of insulin on board (18) and the person's stress/anxiety levels (19). To further complicate management, even when all these factors are kept constant, an individual's response to exercise may (20, 21) or may not be predictable on repeated exercise occasions (22).

Diabetes should not prevent individuals from achieving their exercise goals whether these are occasional fun activities or at a more high-performance level. Indeed, many individuals with T1D have gone on to accomplish extraordinary sporting achievements (23). Due to the complexity of the many factors affecting blood glucose levels, individuals often embrace a trial and error approach to manage their blood glucose levels. This approach may be compounded by the fact that health care professionals can lack the knowledge and skills or simply don't allocate time to address these challenges in a busy clinic setting. However, challenges can be overcome with appropriate training. This has been recognized most recently through the work of the JDRF sponsored Performance in Exercise and Knowledge (PEAK) initiative (24), but this excellent source of information is not pediatric specific.

There are established international pediatric exercise guidelines for the pediatric population (25) and a comprehensive pediatric-specific review of exercise in both T1D and Type 2 diabetes by Pivovarov et al. provides current perspectives and a decision tree-based approach for blood glucose management in children with T1D (26). However, it should be noted that significant gaps in the literature exist and further research is required to address these gaps. Collaborating with patients and their families at all stages of the research process should be considered when designing studies as this approach may help uptake of findings into clinical practice (27).

Although existing pediatric and general based guidelines comprehensively review the literature around diabetes management and exercise, and make recommendations for clinical practice, a gap in the literature remains in facilitating the healthcare professional to apply these evidenced- based recommendations to an exercise consultation.

The aim of this paper is to provide a structured approach for the health care professional to use in a child/adolescent exercise consultation. The goal of this approach is to facilitate the formulation of a person-specific exercise management plan. The key to this approach is ensuring recommendations are individualized and dynamic- with the use of feedback plans that are revisited and refined. A brief review of physiology is followed by the strategies or "exercise tools" commonly used in clinical practice. A series of targeted questions to structure the exercise consultation are then presented to enable selection of the appropriate exercise tool/s for the individual young person with T1D.

PHYSIOLOGY

The success of the healthcare professional in assisting patients with effective exercise plans is likely to be improved by the understanding of some of the basic physiological principles of exercise and diabetes. The physiology of exercise in T1D has been reviewed in depth elsewhere (24, 28).

In an individual without diabetes, glucose provision for exercise originates predominately from the liver as a result of increased levels of glucagon and reduced circulating levels of insulin. However, during exercise in insulin-treated people with T1D, the insulin level cannot be rapidly changed, counter regulatory hormone responses can be either blunted at times or can surge as a consequence of high intensity exercise or competition (29). These hormonal imbalances can result in hypo, hyper or euglycemia (see **Figure 1**), which adds challenge to the management approach to exercise and diabetes (30, 31).

High individual variability exists in the blood glucose responses to different forms of exercise. In general, aerobic exercise decreases blood glucose levels, anaerobic exercise or high intensity aerobic exercise increases blood glucose levels when performed under near basal insulinemic conditions, and resistance activities are associated with relative glucose stability

Abbreviations: T1D, Type 1 Diabetes; SMBG, Self-monitoring blood glucose; CGM, Continuous glucose monitoring; rtCGM, Real-time continuous glucose monitoring; SAP, Sensor Augmented Pump.

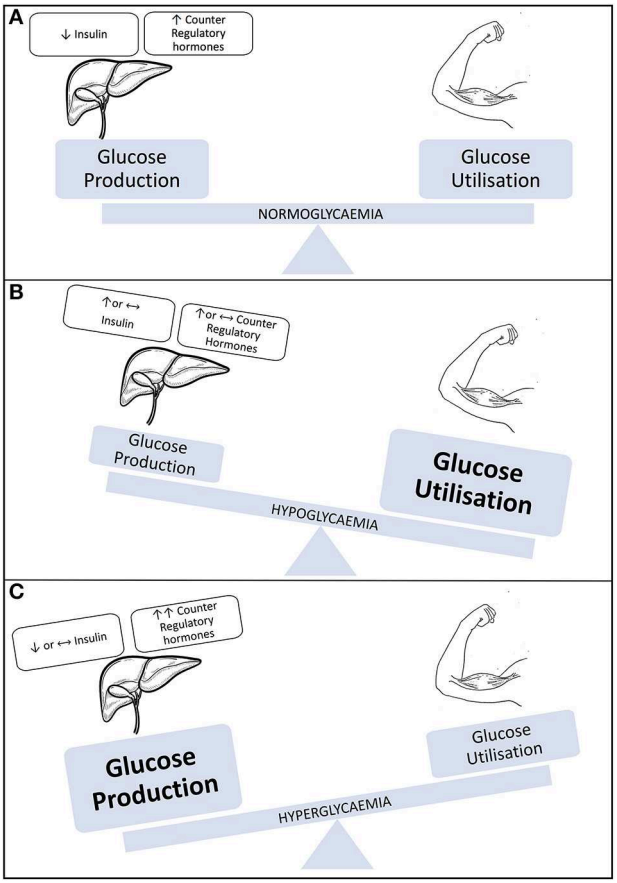

FIGURE 1 | Illustration representing blood glucose levels during exercise. **(A)** Individual without type 1 diabetes/well-managed T1D. **(B)** Individual with T1D engaging in sustained aerobic activity. **(C)** Individual with T1D engaging in aerobic activity. Modified with permission from Chu et al. (31).

(32). In addition to being affected by the type, duration and intensity of the activity, individual responses are dependent on additional factors, including initial blood glucose concentrations (33), individual fitness (34), concentrations of insulin glucagon, and other counter-regulatory hormones in the circulation (35), and the nutritional status of the individual (36).

Most clinicians are familiar with the concept that insulin facilitates movement of glucose into muscle cells, but it is less commonly appreciated that muscle contraction *per se* is an insulin-independent mechanism that promotes glucose uptake into skeletal muscle with consequent additive increased risk of hypoglycemia (37). Increased glucose uptake into muscle can persist for hours after exercise and impact on post-exercise glycaemia (38).

EXERCISE TOOLS AND MANAGEMENT STRATEGIES

Creating a specific exercise management plan for a young person with T1D involves understanding their pattern of physical activity, then selecting the appropriate strategy. There are a limited number of strategies available to manage blood glucose levels before, during and after exercise. These tools include glucose monitoring, carbohydrate intake, insulin adjustment, exercise strategies, and technology based tools. The choice of strategy is made easier by understanding some basic physiology of exercise and diabetes as described above.

Glucose Monitoring

Monitoring blood glucose either by self-monitoring (SMBG) or increasingly commonly, real-time continuous glucose monitoring (rtCGM) and intermittent scanning glucose monitoring, is important for managing glycemia before, during and after exercise. Information gathered from glucose monitoring allows refinement of future exercise strategies and can inform how different factors and behaviors influence blood glucose levels. Blood glucose levels at the onset of exercise can be used to tailor glycemic management strategies.

Expert opinion suggests that although blood glucose target levels at the start of exercise should be individualized, 7–10 mmol/l is an acceptable starting range for adult patients doing aerobic exercise for up to 60-min duration (24). There are no existing guidelines for target blood glucose levels at the onset of exercise in children. However, in adults, under hyperinsulinemic conditions, the rate of fall in blood glucose levels may result in hypoglycemia if prolonged exercise is initiated within this starting range, without any adjustment to insulin dose or carbohydrate intake. Thus, in addition to starting blood glucose level, it is important to consider the rate of change of blood glucose levels to inform management decisions. Of note, although anecdotal evidence suggests a blood glucose level > 10 mmol/L may adversely affect exercise performance, studies to date have failed to demonstrate a difference in sports skill performance during acute hyperglycemia compared to normoglycemia (39, 40). Currently the evidence base is limited on whether there is an optimal blood glucose target range for exercise performance.

Continuous Glucose Monitoring (CGM) provides detailed information on not only glucose levels but trends before, during and after exercise. Information gathered from CGM can help individuals learn how different factors and behaviors influence their blood glucose levels and plan for future activities. Moreover, strategies regarding correction of hyperglycemia and prevention of hypoglycemia can be refined as information obtained from CGM could be regarded as more complete than SMBG.

What SMBG adds, as a complementary method, is an increased point accuracy as there is a lag time between blood glucose and interstitial glucose levels when glucose levels are changing rapidly, such as during exercise. This lag-time, may lead to a marked overestimation of blood glucose levels when levels are falling rapidly (41, 42). However, advancement in CGM technology has made these devices increasingly accurate (43, 44) and user-friendly. Some devices now offer the option of sharing real-time glucose levels with others or "followers". This feature potentially allows parents/caregivers to alert their child to impending hypoglycemia during and after sports and physical activity. An observational study of 25 young people

with T1D aged 8-17 years in a camp-setting showed that use of a carbohydrate intake algorithm in response to sensor glucose levels and trends prevents hypoglycemia during exercise (45).

Given that regular blood glucose monitoring provides a highly effective means to prevent hypoglycemia during and after exercise, clinicians should strongly encourage their patients not only to monitor their blood glucose levels prior to engaging in any physical activity, but also to exercise only if their glucose monitors and enough test strips are readily available or near reach (unless on CGM), particularly for situations where carrying these devices might be impractical (e.g., contact sports, swimming). Finally, clinicians should encourage their patients to measure their blood glucose levels during as well as early and for several hours after exercise, and remind them that CGM tends to overestimate blood glucose levels when they are rapidly falling.

Carbohydrate Intake

Carbohydrate consumption before, during and after exercise can be used to prevent and treat exercise -mediated hypoglycemia (46). Factors influencing the amount of carbohydrate intake required to prevent exercise-mediated hypoglycemia include body mass, circulating insulin levels and the type, intensity and duration of exercise. The blood glucose level and trend at the start of exercise are other factors to consider and recommendations based on these parameters should be individualized.

The carbohydrate requirement to prevent exercise-mediated hypoglycemia increases with plasma insulin levels (47), with the pattern of blood glucose response to exercise being highly unpredictable under hyperinsulinaemic compared to near basal insulinaemic conditions (22).

If exercise is occurring when circulating insulin levels are high, such as within 3 h of a meal-time insulin bolus, then up to 1.0–1.5 g of carbohydrate/kg ideal body weight/ hour of sustained activity may be required (48, 49). In contrast, when exercise is taking place several hours after a meal-time bolus, or when the insulin bolus dose has been lowered pre-exercise, then carbohydrate requirements are lower (∼0.3–0.5 g/kg ideal body mass/h (47, 49). When insulin levels are close to basal levels, such as when exercise is performed before breakfast, the risk of hypoglycemia is minimal (50) and carbohydrate supplementation may not be required (51, 52). Given that categorizing carbohydrate requirements in a dichotomous manner (high vs. low insulin levels) is a simplified approach that does not take into account all the factors influencing glucose requirements, Francesco et al have developed an algorithm that estimates an individuals' glucose requirement during activity based on personalized situation specific information including insulin concentration (53).

In addition to being affected by insulin levels, the amount of carbohydrate to prevent exercise mediated hypoglycemia varies with the intensity and duration of exercise (18). A study in young people with T1D exercising under basal insulin levels reported that glucose requirements to maintain euglycemia during 40 min of exercise increase with intensity up to 50% and 65% VO_2 peak, but with no glucose required at 80% VO_2 peak (54). It remains to be established if this pattern is still observed when exercise is performed for a longer duration or under high circulating insulin levels.

The type and timing of carbohydrate ingestion should also be considered. Carbohydrates with a high glycemic Index (GI) such as glucose in liquid, tablet, and gel forms, are digested and absorbed more quickly, resulting in a rapid rise in blood glucose levels. In contrast, low GI foods, including fruits and wholemeal bread, are released more slowly causing a gradual and sustained rise in glycemia (55, 56).

A meal or snack containing low GI carbohydrate 1–4 h prior to exercise can increase hepatic glycogen stores and provide sustained carbohydrate release during exercise (57, 58). In contrast, high GI carbohydrates are preferable immediately prior to and during prolonged exercise (59). High GI snacks are also recommended in early recovery (1–2 h post exercise) to replenish glycogen stores (60) and to avoid hypoglycemia in this period of heightened insulin sensitivity. A bedtime snack containing carbohydrate, fat and protein may help reduce the risk of hypoglycemia on nights following exercise (61).

Clinical recommendations for carbohydrate intake will vary if the goal is hypoglycemia prevention, weight reduction, improving glycaemic control or optimal exercise performance. Since high carbohydrate intake is often recommended for healthy individuals without diabetes before and during prolonged exercise to optimize endurance performance (60), this strategy has recently been explored in adults with T1D (62), The authors report that increased carbohydrate supplementation, matched with increased insulin doses, is safe and allows the prevention of hypoglycemia during prolonged aerobic activity (62). This strategy has not been explored in the pediatric population. It is important to match insulin dose with extra CHO intake as excessive carbohydrate supplementation without matched insulin may result in hyperglycemia (63).

Insulin Adjustment

Insulin adjustment, along with balanced carbohydrate intake, is a key tool for managing blood glucose levels during and after exercise. The degree to which blood glucose levels fall during exercise is dependent on the amount of circulating insulin (47). Reduction in insulin doses to prevent exercise-mediated hypoglycemia is typically required for prolonged (>30 min) moderate intensity exercise, particularly if insulin is above basal levels (18, 64).

Options for insulin adjustment vary depending on insulin regimen. Insulin pumps allow greater flexibility in adjusting basal rates than injection regimens. Therefore, basal dose adjustments are most relevant to patients on insulin pumps, particularly for unplanned exercise, whereas bolus dose adjustment can be applied to most regimens. For those on Multiple Daily Injections (MDI), basal dose reduction can reduce the risk of nocturnal hypoglycemia on nights following afternoon exercise (25). However, this approach may result in hyperglycemia, and if this is the case, should be reserved for when participating in more activity than usual, such as sports camps.

TABLE 1 | Strategies to manage blood glucose levels during and after exercise.

Problem	Mechanism	Tool	Strategy
Hypoglycemia during exercise or recovery	• During sustained aerobic activity, relative insulin excess suppresses hepatic glucose production • Mismatch between glucose production by liver and increased glucose utilization by skeletal muscles	Carbohydrate intake	AMOUNT: Less than 3 h since last insulin bolus: up to 1.0–1.5 g of carbohydrate/kg ideal body weight/h Greater than 3 h since last insulin bolus: ∼0.3–0.5 g/kg ideal body mass/h TYPE: Low GI CHO 1–4 h prior to exercsie High GI CHO immediately prior, during and just after activity
		Insulin adjustment	Less than 3 h since last insulin bolus: Consider bolus dose reduction of 25–75% Greater than 3 h since last insulin bolus: basal rate reduction of 50–80% started 60–90 min prior to activity
		Exercise based strategies	10 s sprint before, during or after exercise
		Technology	CGM + carbohydrate intake algorithm SAP (LGS or PLGS) or closed loop therapy
Hypoglycemia on nights after exercise	• Relative insulin excess • Increased glucose uptake by skeletal muscles (increased insulin sensitivity) • Blunted counter regulatory response after exercise and during sleep	Carbohydrate intake	Meal after exercise to replenish glycogen stores Consider bedtime snack containing CHO, fat and protein
		Insulin adjustment	Pump: Basal rate reduction overnight (e.g., 20% reduction for 6 h) MDI: Consider basal analog reduction (e.g., 20% reduction in combination with bedtime snack)
		Technology	CGM with alarms SAP (LGS or PLGS) or closed loop therapy
Hypoglycemia during exercise or recovery	• Anaerobic activity causes increased lactate and counter regulatory hormones	Insulin adjustment	Consider conservative corrective bolus dose (e.g., 50% of usual dose)
		Exercise based strategies	Aerobic cool-down session

Exercise-Based Strategies

Utilization of the glycemic effects of specific types of exercise can play a role in managing blood glucose levels. The blood glucose rising effect of sprinting in young people with T1D suggests that this may provide a strategy to reduce hypoglycemia risk during and after exercise (65). Indeed, a series of studies in young adults with T1D have shown that a maximal 10 s sprint performed before (66) or after (67) moderate intensity exercise can prevent blood glucose levels from falling early after exercise. Furthermore, frequent short sprints (4 s sprints every 2 min) during moderate intensity exercise reduce the decline in blood glucose levels compared to continuous moderate intensity exercise during and early after exercise (68, 69). These strategies have been trialed in clinic-based studies, but real-world data are lacking.

In contrast, exercise induced hyperglycemia can be managed with moderate intensity exercise. Anecdotal evidence in adults suggests that moderate intensity exercise can be used as a strategy to counteract exercise-induced hyperglycemia, a technique known as an "aerobic cool down" (70). The mechanisms underlying this technique remain to be well-understood, they may include increased glucose (71) and lactate oxidation. Lactate is a substrate for gluconeogenesis and would potentially otherwise be converted to glucose in the liver resulting in hyperglycemia (72, 73).

Advances in Diabetes Technology

Diabetes technology is rapidly evolving and provides further tools to aid glucose management and reduce the burden of diabetes during exercise (74). Technology based tools include smart phone applications, insulin pumps, CGM, sensor augmented pump therapy and closed loop technology. Smart phone applications can help individuals to record exercise management and aid exercise management decisions (75). Insulin pumps enable greater flexibility in insulin adjustment as basal rates can be reduced or stopped before during or after exercise to prevent exercise mediated hypoglycemia. Despite some issues with sensor accuracy at times of rapid glucose flux, CGM can provide comprehensive dynamic real-time glucose information around exercise to help inform diabetes management decisions.

Perhaps the biggest game changer in current diabetes management is the ability to link sensor glucose readings to insulin delivery in sensor augmented and closed loop pump therapy. Sensor augmented pump (SAP) therapy includes low

glucose suspend and predictive low glucose suspend technology, where a mathematical algorithm suspends basal insulin delivery when sensor glucose levels fall below, or are predicted to fall below a pre-set threshold. Studies investigating the use of low glucose suspend and predictive low glucose suspend technology during exercise have shown a reduction in hypoglycemia (21, 76).

Closed loop systems expand on the concept of SAP therapy by using a control algorithm that continually increases or decreases hormone delivery in response to sensor glucose levels. Systems include dual hormone (insulin and glucagon) and single hormone (insulin only) pumps. Closed loop technology may be seen as the future of diabetes management, however physical activity remains one of the biggest challenges to fully automated systems (77). This is because physical activity in individuals with T1D induces rapid changes in glucose levels due to hormone imbalances that are dependent on the type, duration and intensity of the activity as well as individual factors such as fitness levels and the amount of circulating insulin on board. Furthermore, the glucose trends during physical activity may be variable within and between individuals. Further research is needed to guide exercise recommendations in patients using the current closed loop systems

For closed loop systems to be effective at this time of rapid and potentially unpredictable glucose fluctuations, several challenges must be overcome including sensor glucose lag-time (as previously discussed), pharmacokinetics of subcutaneous insulin administration and how to sense not only that physical activity is occurring but the intensity of the activity taking place (77).

In an individual without T1D, insulin levels rapidly decrease at the onset or exercise. This is difficult to replicate in T1D as insulin is administered subcutaneously and levels are not under endogenous control. Furthermore, absorption of insulin may be increased from stores of already administered subcutaneous insulin during exercise due to increased blood flow to the working muscle (78). Bihormonal pumps infusing both glucagon and insulin may help overcome this challenge (79).

Closed loop systems may be better able to manage blood glucose levels during exercise if the system could "sense" the intensity and duration of the physical activity. Future developments may include integration of physical activity monitoring such as heart rate and or accelerometery data into closed loop systems.

A STRUCTURED SERIES OF QUESTIONS FOR THE EXERCISE CONSULTATION

A structured approach to exercise management in young people with Type 1 diabetes involving targeted and clinically relevant questions can provide the framework for an effective consultation and aid selection of the most appropriate tools as described above. We recommend starting from the center of **Figure 2** and working outwards. Some health care professionals may find the use of a consistent template that addresses each of the 5 questions helpful. These questions can be re-visited in sequential consultations together with information from glucose monitoring to refine recommendations.

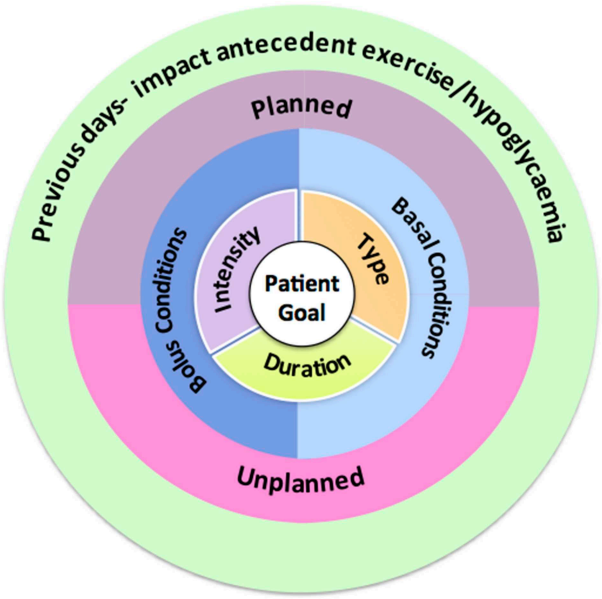

FIGURE 2 | Structured approach to the exercise consultation.

Q1. What Are the Individual's Exercise and Glycemic Goals?

The first step in formulating a patient's exercise management plan involves identifying the patient's exercise goal, as this will influence subsequent management decisions. Exercise goals may include: weight loss, exercise performance, socialization and fitness. Glycemic goals in addition to hypoglycemia prevention may include, maintaining blood glucose levels in target range, or achieving a specific blood glucose level to maximize exercise performance.

If the exercise goal is facilitating weight loss, it would be most appropriate to choose an insulin-reduction based strategy to manage blood glucose level during and after exercise so as to avoid excessive CHO intake particularly after exercise. If socialization and fun is the goal, then insulin dose reduction may be key to minimize time spent out of the activity to test blood glucose level and ingest CHO. In contrast, if the primary goal is exercise performance, then an individual may be aiming for increasing CHO intake before (e.g., CHO loading) and during exercise to maximize performance while managing their blood glucose levels so as to minimize or avoid any interruptions.

Strategies for exercise performance may focus on matching carbohydrate intake to the specific nutritional requirement of the activity (rather than hypoglycemia prevention) and insulin doses should be increased accordingly (62). If fitness is the goal, and the patient has a plan to incrementally increase physical activity over time, it will be important to anticipate a reduction in total daily insulin requirement to avoid hypoglycemia as insulin sensitivity increases in response to exercise training.

Q2. What Is the Exercise Type, Duration and Intensity?

The next step is to consider, the type, duration and intensity of the physical activity. This will allow anticipation of the expected effect on glucose levels (24). As mentioned above, continuous aerobic activity performed when insulin levels are high will result in a decrease in blood glucose levels and require a reduction in insulin and/or an increase in carbohydrate supplementation to avoid hypoglycemia. In contrast, short duration high intensity aerobic or anaerobic activity, a pattern typical of children's natural play (80), may maintain glucose levels during exercise and even result in early post-exercise hyperglycemia (16, 81) if performed while plasma insulin is close to basal level. Competition-induced anticipatory stress may also raise blood glucose levels as a result of elevated catecholamine levels.

Exercise-related hyperglycemia may require a conservative insulin correction dose (50% of usual dose) administered immediately after exercise (82). Alternatively, an aerobic cool-down session can be used to counteract post-exercise hyperglycemia (70). Since such a use of insulin or exercise as a means to oppose hyperglycemia post-exercise may increase the risk of hypoglycemia if the insulin dose or the duration of the cool-down session is excessive these strategies should be adopted only if accompanied by regular blood glucose monitoring.

Q3. Timing of Exercise Relative to the Last Insulin Bolus Dose?

Establishing the timing of exercise in relation to the last insulin bolus provides insight on relative insulin levels and will guide decisions on insulin adjustment, in particular if reductions should be made to basal or bolus insulin doses.

When exercise is planned to take place within 3 h of administration of an insulin bolus (high insulin levels), then a bolus dose reduction of 25-75% can be trialed (18, 83) It should be noted that the smaller the insulin dose administered, the shorter its duration of action (84). Recommendations for bolus reduction should be relative to the duration and intensity of the exercise (24). Alternatively, or in combination with insulin adjustment, pre-exercise carbohydrate intake to up to 1.0–1.5 g of carbohydrate/kg ideal body weight/ hour of sustained activity (85) may be required as discussed above.

Exercise performed when plasma insulin is close to basal levels (e.g., in the morning prior to breakfast) is less likely to result in hypoglycemia as circulating insulin levels are typically low. If hypoglycemia is occurring in this setting then management options include: carbohydrate consumption or reduction of basal insulin. Carbohydrate intake to prevent hypoglycemia when insulin levels are low is approximately 0.3-0.5 g/kg ideal body mass/hr; (47, 49). Reduction of basal insulin is more easily achieved for individuals on pump regimens and recommendations include a temporary basal rate reduction of 50-80% (64). To be effective, basal rates should ideally be reduced 60–90 min prior to the onset of activity. Other strategies to consider include use of automated basal insulin suspension functions during and after exercise, including: low glucose suspend (76) and predictive low glucose suspend technology (21).

Late onset post exercise hypoglycemia is the phenomenon of overnight hypoglycemia particularly occurring after late afternoon exercise (38, 86). A basal reduction; for those on insulin pumps a basal rate reduction of 20% for 6 h (87), or for those on MDI a 20% basal dose reduction in combination with a carbohydrate snack at bedtime (25), can reduce the incidence of nocturnal hypoglycemia in response to a prior bout of afternoon exercise.

Q4. Is the Exercise Planned or Spontaneous?

It is helpful to ascertain if the individual engages in mostly planned or spontaneous physical activity. If exercise is planned, then strategies based on insulin adjustment with or without carbohydrate supplementation can be implemented (see above). Furthermore, exploring if planned events involve the same type of activity at the same time of day will help establish if glycemic patterns are reproducible for that individual on different occasions when conditions are similar. If exercise is spontaneous and pre-exercise adjustment of bolus and basal insulin are not available in advance, then the options available are limited to basal insulin reduction, carbohydrate supplementation or use of glycemia-rising high intensity exercise (67, 81).

Q5. Have There Been any Episodes of Hypoglycemia and /or Exercise Prior to the Exercise Session?

When reviewing the glycemic response to a period of exercise it is helpful to find out if there have been any episodes of hypoglycemia or exercise prior to the exercise event. Both preceding exercise (88) and hypoglycemia (89) can attenuate the counter-regulatory response to subsequent exercise thereby increasing the risk of hypoglycemia.

The pattern and frequency of prior exercise is informative. Regular participation in aerobic activity increases insulin sensitivity and may consequently lower the total daily insulin requirement (90, 91). Therefore, if exercise is occurring on a day to day basis, further insulin dose reduction may be required.

CONCLUSION

It can be challenging for health care practitioners to advise young people with T1D how to approach exercise safely. Clinical guidelines and a recent comprehensive consensus statement on exercise and T1D provide thorough evidence-based recommendations. This paper aims to facilitate the healthcare professional in applying such evidence-based recommendations to clinical practice using a structured approach to the exercise consultation based on a framework of relevant questions. The tools or management strategies are provided as a starting base to help clinicians work with patients and families to achieve their exercise goals. This framework of questions together with information from blood glucose monitoring should be re-visited at sequential consultations to allow refinement of future exercise management strategies.

AUTHOR CONTRIBUTIONS

TC was responsible for the manuscript preparation. VS, PF, PA, TJ, and ED reviewed and edited the manuscript. All authors approved the final version of this article.

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REVIEW
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Resistance Isn't Futile: The Physiological Basis of the Health Effects of Resistance Exercise in Individuals With Type 1 Diabetes

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The importance of regular exercise for glucose management in individuals with type 1 diabetes is magnified by its acknowledgment as a key adjunct to insulin therapy by several governmental, charitable, and healthcare organisations. However, although actively encouraged, exercise participation rates remain low, with glycaemic disturbances and poor cardiorespiratory fitness cited as barriers to long-term involvement. These fears are perhaps exacerbated by uncertainty in how different forms of exercise can considerably alter several acute and chronic physiological outcomes in those with type 1 diabetes. Thus, understanding the bodily responses to specific forms of exercise is important for the provision of practical guidelines that aim to overcome these exercise barriers. Currently, the majority of existing exercise research in type 1 diabetes has focused on moderate intensity continuous protocols with less work exploring predominately non-oxidative exercise modalities like resistance exercise. This is surprising, considering the known neuro-muscular, osteopathic, metabolic, and vascular benefits associated with resistance exercise in the wider population. Considering that individuals with type 1 diabetes have an elevated susceptibility for complications within these physiological systems, the wider health benefits associated with resistance exercise may help alleviate the prevalence and/or magnitude of pathological manifestation in this population group. This review outlines the health benefits of resistance exercise with reference to evidence in aiding some of the common complications associated with individuals with type 1 diabetes.

Keywords: resistance exercise, type 1 diabetes, physical activity, strength training, weights

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INTRODUCTION

Notwithstanding their etiological, pathophysiological, and epidemiological complexities, the severity and incidence of complications associated with type 1 diabetes (T1D) are lower in physically active individuals (1, 2). Conversely, at a population level, sedentariness constitutes the fourth leading risk factor for mortality (3), such that individuals with the highest rates of sedentariness are up three times more likely to suffer premature mortality than their physically

active counterparts (4). Therefore, whilst pharmaceutical and technological therapies aid glycaemic management, the utility of simple, holistic approaches such as regular physical activity (PA) constitute attractive adjunct treatment options, that alongside standardised medical care facilitate the improvement of T1D related pathological complications. However, a research and advocatory emphasis has been placed on the implementation of sustainable moderate intensity continuous exercise (MICE) in those with T1D, with less discernible evidence exploring alternative exercise modalities such as resistance exercise (RE). Whilst the health benefits associated with MICE are by no means immaterial, longstanding T1D is often accompanied by complications that impact the ability of participants to comfortably perform their rhythmic and/or pounding nature. Furthermore, MICE often fails to maximise the development of skeletal muscle mass and strength, both of which are features that facilitate improvements in various metabolic, neuroendocrine, and osteopathic processes.

As such, the utility of incorporating RE to assist the functional development of skeletal muscle integrity constitutes an important feature of the current exercise guidelines for those with T1D (5).

METHODS

The authors undertook a detailed PubMed literature search for the following key words: "resistance exercise," "exercise," "physical activity," "strength training," "weight training," "type 1 diabetes," "T1DM." The reference lists of systematic reviews, reviews, and included as well as excluded articles were manually screened for studies considered to be relevant. The literature search was conducted by the corresponding and secondary lead authors with additional suggestions and/or missed literature being provided by co-authors when necessary.

IMPORTANCE OF PHYSICAL ACTIVITY AND EXERCISE IN PEOPLE WITH TYPE 1 DIABETES

Research has consistently demonstrated the inverse relationship between PA and a reduced risk of diabetes-related complications (6, 7), including both mental well-being (8), life-expectancy (4, 7), and health related quality of life (9). In addition to the advocation of frequent PA, there is considerable evidence supporting the inclusion of regular exercise as an adjunct therapeutic strategy in people with T1D (10). Definitively, exercise describes activities completed with a structured and intentional approach to maintaining or attaining improvements in physical fitness (11). The increased metabolic activity of skeletal muscle during exercise evokes an adaptive response of several integrative processes, including the cardio-respiratory, vascular, and metabolic systems. As a reflection of the integrative functions of these physiological systems, cardio-respiratory fitness (CRF) is often used as a barometer for physical fitness and reflects the ability of the circulatory-and-respiratory systems to supply the muscular system with the increasing oxygen (O_2) demand experienced during sustained PA. Although the topic remains controversial, lower CRF has been reported in individuals with-vs.-without T1D (12). However, this finding appears to be closely related to glycaemic control, which can considerably influence acute exercise tolerance (12–14). Whilst considerable shifts in both cellular and tissue homeostasis are observed following most exercise activities, these processes are magnified following higher-intensity exercise, which represents a potent physiological stress. In the long-term, this acute stressor functions to optimise the body for subsequent subjection to bouts of physiological or indeed pathophysiological insults. Therefore, the type and intensity of the exercise stimulus can considerably influence the acute physiological and chronic adaptive responses that occur.

EXERCISE DEFINITION AND CLASSIFICATION

The word "exercise" is often used interchangeably and encompasses several adjustable variables including modality, frequency, intensity, and duration. Metabolically speaking, the energy contribution to a given task is determined by the intensity of effort required for its performance. These metabolic disturbances activate several kinases and phosphatases, necessary not only for the immediate supply of energy to sustain contractional output, but also the synthesis of genetic transcriptions that produce an adaptive phenotype for subsequent functional demands. Generally, the pathways responsible for the provision of adenosine triphosphate (ATP) to skeletal muscle are categorised as aerobic i.e., with the use of O_2 or anaerobic i.e., without the use of O_2. In each pathway, muscle must convert free adenosine diphosphate (ADP) and inorganic phosphate (Pi) to ATP. The regenerated ATP is then made available to the myosin ATPase enzymes that facilitate the contractile processes that enable movement. During low to moderate intensity exercise, the rate of O_2 supply necessary for continued contraction is comfortably met via the oxidative metabolism of carbohydrates and lipids. During intense physical exercise conditions of cellular hypoxia are experienced, as the rate of O_2 demand far exceeds the rate of supply capable via oxidative phosphorylation. Under such circumstances, anaerobic metabolism becomes the predominate means via which ATP is produced. The process involves the degradation of phosphocreatine (PCr) i.e., the ATP-CP system and the production of lactate within the glycolytic pathway i.e., the glycolytic system (**Figure 1**).

Essentially, a continuum exists that enables physical exercise activities to be grouped into low, moderate, and high intensity efforts. However, it should be noted that no exercise is ever considered ''exclusively" aerobic or anaerobic, rather both pathways are activated simultaneously with one predominating fuel provision. Nonetheless, the terms provide reference guides that can be used generally to classify exercise intensities. Conventionally speaking, predominately aerobic exercise imposes a high-frequency (repetition), low power output (load) demand on muscular contraction. These characteristics are often observed during MICE including endurance orientated activities.

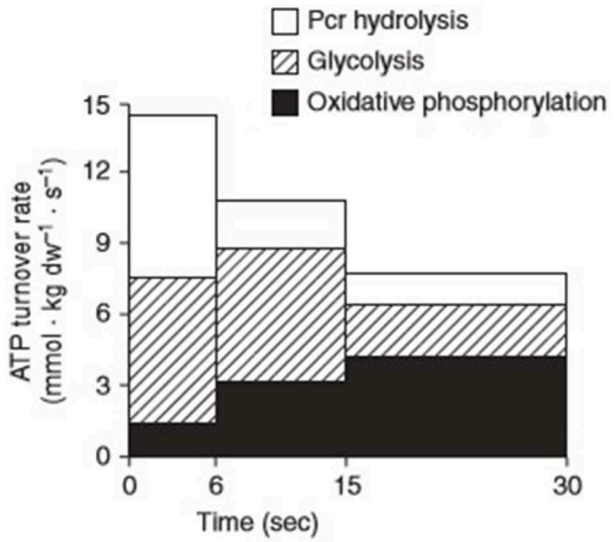

FIGURE 1 | Contributions of the three major energy pathways; phosphocreatine (Pcr), glycolysis, and oxidative phosphorylation to adenosine triphosphate (ATP) turnover during 30 s of maximal isokinetic cycling exercise. Reprinted from Parolin et al. [(15), Figure 7B]. Copyright ©1999 the American Physiological Society.

Conversely, predominately anaerobic exercise mandates a low-frequency, high-resistance power output including both high intensity exercise (HIIE) and RE.

Resistance Exercise Definition

Resistance exercise or "strength/weight" exercise is a term used to describe exercise that mandates the body's musculature to move against an opposing force, addressing the functional behaviours mandatory to human movement. Resistance exercise training (RET) is the process of developing strength, flexibility, coordination, and stamina through performing exercises (at self-selected, high-intensity efforts) that involve multiple joints and muscle groups. RE be implemented using a multitude of training modalities, including isokinetic resistance, variable resistance, isometric resistance, and explosive plyometrics. This is important, as the term "resistance exercise" is often strictly associated with the use of equipment-based/external loads placed on the body in a strength orientated fashion. However, it actually reflects the exercise continuum—from which program design allows variable adaptation. Fundamentally the acute program variables (muscle action, intensity and volume, exercise selection and order, rest interval, repetition velocity, and frequency) dictate the specific training outcome (i.e., muscular strength, hypertrophy, maximal strength, or power). As such, there appears to be a specific relationship between the training stimulus and the adaptive response. Due to its malleability RE can be easily adapted to suit the attainment of a specific exercise goal. Indeed, small adjustments in the load, velocity and duration of a typical RE movement can substantially alter the physiological response that occurs.

Resistance Exercise Guidelines

As per the latest position statement by the American Diabetes Association (ADA), the adoption and maintenance of PA are critical foci for blood glucose management and overall health maintenance in individuals with T1D (5). Indeed, as part of their core guidelines, the ADA state that individuals with diabetes should engage in 150 min or more of moderate-to-vigorous intensity activity weekly. Guidelines suggest spreading these minutes over 3 days per week, with no more than 2 consecutive days passing without activity. Shorter durations (minimum 75 min per week) of vigorous-intensity or interval sprint training may be sufficient for younger and more physically fit individuals. Furthermore, the specific advocation of RE is included, and details that adults with T1D should engage in 2–3 sessions per week on non-consecutive days. Encouragingly, this also aligns with the latest position stand by the American College of Sports Medicine, who advocate the implementation of RE for each of the major muscle groups on $\geq$2 days per week in healthy adults (11). Finally, considering the elevated susceptibility to diabetes related complications, the utility, safety and physiological adaptations associated with RE are increasingly important. Due to its ability to train the peripheral muscles without producing extensive cardiovascular stress, dynamic interval based RE, using loads of 50–60% 1-repetition maximum (1RM), has been established as a safe and effective mode of exercise in high cardiovascular disease (CVD) risk cohorts (16).

Despite these advocatory guidelines, there is currently a lack research comprehensively detailing the physiological responses to RE in individuals with T1D (**Table 1**). Moreover, in what little RE-focused research pertinent to T1D that does exist, there is often a lack of program variability, which may overlook important responses to alterations in acute program variables i.e., time under tension, repetition ranges and exercise selection. Furthermore, existing research has mostly explored acute sessions, with participant numbers failing to exceed 15. Finally, the cohorts used have been relatively homogenous, made up of predominately young, relatively healthy, Caucasian male participants. This not only makes wider generalisation difficult, but also overlooks important gender, ethnic and age-related variables.

MORPHOLOGICAL ADAPTATIONS—SKELETAL MUSCLE MASS: BENEFITS BEYOND SIZE

As an extremely heterogeneous tissue with immense plasticity, skeletal muscle influences locomotion, energy metabolism, thermodynamics, endocrine complexes, and cell signalling.

From a clinical perspective, the morphological adaptations induced by RET are associated with reduced rates of chronic inflammation (29–32), lowered global and central adiposity (31, 33), and a reduced risk of falls and fractures (34). Encouragingly, a recent article highlighted the credibility of RET in augmenting myocyte mitochondrial respiratory capacity and function (35). Considering both skeletal muscle insulin resistance and mitochondrial dysfunction are major features

TABLE 1 | Synopsis of the resistance exercise interventions in human participants with type 1 diabetes.

References	Title	Participant characteristics	Exercise characteristics	Main outcome
Durak et al. (17)	Randomized crossover study of effect of resistance training on glycaemic control, muscular strength, and cholesterol in type I diabetic men	***N*** = Eight adults **Age (years):** 31 ± 3.5 **BMI (kg/m^2):** 25.9 ± 0.48 **Gender:** ♂ 8 ♀ 0 **VO_{2max} (ml·kg·min^{-1}):** **HbA1c (%):** **Diabetes duration:** 12.3 ± 9.8	**Intervention:** Chronic **Intervention duration:** 10 weeks. 3* p/w. **Exercise duration**: 60 min **Exercise Modality**: Whole body RE 6 upper body and 4 lower body exercises Major to minor muscle group sequence **Exercise Intensity**: Heavy, progressive RE designed to reach muscular failure in the latter sets. <12 reps per exercise. Total of 40–50 sets during a typical session. Rests between sets ranged from 30 s to 2 min	Glycaemia
Jimenez et al. (18)	Insulin-sensitivity response to a single bout of resistive exercise in type 1 diabetes mellitus	***N*** = Fourteen adults TG: 7 CG: 7 **Age (years):** TG: 23.4 ± 4.0 CG: 26.3 ± 6.7 **BMI (kg/m^2):** TG: 28.3 CG: 24.2 **Gender:** ♂ 11 ♀ 3 **Co-morbidities: -** **Exercise**: Physically active **VO_{2max} (ml·kg·min^{-1}): -** **HbA1c (%):** 6.8 ± 1.5 **Diabetes duration: -**	**Intervention:** Acute **Exercise duration**: **Exercise Modality**: Lower limb **Exercise Intensity**: 80% 5 sets 6 repetitions **Exercise Classification:** Strength	Glycaemia, CVD biomarkers
D'hooge et al. (19)	Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial	***N*** = Sixteen Children **Age (years):** 10–18 **BMI (kg/m^2):** **Gender:** **VO_{2max} (ml·kg·min^{-1}):** **HbA1c (%):** **Diabetes duration:**	**Intervention:** Chronic **Intervention duration:** 20 weeks 2* p/w **Exercise duration**: 70 min **Exercise Modality**: Combined AE and RE **Exercise Intensity**: RE; - 20 RM 0–6 weeks - 17 RM 6–12 weeks - 12 RM 12–20 weeks	Glycaemia, CRF, Quality of Life
Yardley et al. (20) Yardley et al. (21)	Performing resistance exercise before vs. after aerobic exercise influences growth hormone secretion in type 1 diabetes Effects of performing resistance exercise before vs. after aerobic exercise on glycemia in type 1 diabetes	***N*** = Twelve adults **Age (years):** 31.8 ± 15.3 **BMI (kg/m^2):** 25.3 ± 3.0 **Gender:** Mixed ♂ 10 ♀ 2 **VO_{2max} (ml·kg·min^{-1})** 51.2 ± 10.8 **HbA1c (%):**7.1 ± 1.1 **Diabetes duration:** 12.5 ± 10.0	**Intervention:** Acute **Exercise duration**: 45 min **Exercise Modality**: AE before RE (AR) RE before AE (RA) **Exercise Intensity**: AE 60% VO_{2peak} RE: 67% 1RM. 3 sets 10 reps **RE Classification:** Hypertrophy	Glycaemia
Silveira et al. (22)	Acute effects of different intensities of resistance training on glycaemic fluctuations in patients with type 1 diabetes mellitus	***N*** = Twelve adults **Age (years):** 24.4 ± 6.4 **BMI (kg/m^2): 21.3 ± 2.9** **Gender:** ♂ 6 ♀ 6 **VO_{2max} (ml·kg·min^{-1}):** **HbA1c (%):** **Diabetes duration: 7.3 ± 6.8**	**Intervention:** Acute **Exercise duration**: 70 min **Exercise Modality**: RE **Exercise Intensity**: 60% 1RM vs. 89% 1RM	Glycaemia

(Continued)

TABLE 1 | Continued

References	Title	Participant characteristics	Exercise characteristics	Main outcome
Turner et al. (23)	Reductions in resistance exercise-induced hyperglycaemic episodes are associated with circulating interleukin-6 in Type 1 diabetes	***N*** = Eight adults **Age (years):** 38 **BMI (kg/m^2):** 26.9 ± 4.1 **Gender:** Mixed ♂ 7 ♀ 1 **VO_{2max} (ml·kg·min^{-1}):** **HbA1c (%):** 8.7 ±1.0 **Diabetes duration (years):** 15 ±13	**Intervention:** Acute **Exercise duration**: 42 min **Exercise Modality**: Circuit RE Eight whole body exercises **Exercise Intensity**: RE: 67% 1RM. 3 sets 10 reps **RE Classification:** Hypertrophy	Glycaemia and Inflammation
Turner et al. (24)	Impact of single and multiple sets of resistance exercise in type 1 diabetes	***N*** = Eight adults **Age (years):** 38 **BMI (kg/m^2):** 26.9 ± 4.1 **Gender:** Mixed ♂ 7 ♀ 1 **VO_{2max} (ml·kg·min^{-1}):** **HbA1c (%):** 8.7 ±1.0 **Diabetes duration (years):** 15 ±13	**Intervention:** Acute **Exercise duration**: 42 min Set 1 (14 min) Set 2 (28 min) Set 3 (42 min) **Exercise Modality**: Circuit RE Eight whole body exercises **Exercise Intensity:** RE: 67% 1RM. 3 sets 10 reps **RE Classification:** Hypertrophy	Glycaemia
Waclawovsky et al. (25)	Exercise on progenitor cells in healthy subjects and patients with type 1 diabetes	***N*** = Fourteen adults **Age (years):** 30.3 ± 1.6 **BMI (kg/m^2):** 26.2 ± 0.8 **Gender:** ♂ 14 **VO_{2peak} (ml·kg·min^{-1}):** 37.1 ± 1.4 **HbA1c (%):**7.7% ± 0.2 **Diabetes duration (years):** 30 ± 1.6	**Intervention:** Acute **Exercise duration:** 40 min **Exercise Modality:** Combined AE and RE AE (cycle ergometry) RE (four lower limb exercises) **Exercise Intensity:** AE: 40–60% VO_{2max} RE: 60% 1RM **RE Classification:** Hypertrophy	Microvascular
Turner et al. (26)	Similar magnitude of post-exercise hyperglycaemia despite manipulating resistance exercise intensity in type 1 diabetes individuals	***N*** = Eight adults **Age (years):** 34 ± 7 **BMI (kg/m^2):** 25.7 ± 1.6 **Gender:** Mixed ♂ 7 ♀ 1 **VO_{2max} (ml·kg·min^{-1}):** **HbA1c (%):** 8.7 ±1.0 **Diabetes duration (years):** 15 ±13	**Intervention:** Acute **Exercise duration:** 42 min **Exercise Modality**: Circuit RE Six whole body exercises **Exercise Intensity:** 2 sets of 20 reps @ 30% 1RM (LOW) 2 sets of 10 reps @ 60% 1RM (MOD) **RE Classification:** Muscular endurance vs. Hypertrophy	Glycaemia
Zaharieva et al. (27)	The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous vs. circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion	***N*** = Twelve adults **Age (years): 32 ± 11** **BMI (kg/m^2): 23.5** **Gender:** Mixed ♂ 6 ♀ 6 **VO_{2max} (ml·kg·min^{-1}): 50.1 ± 13.7** **HbA1c (%): 7.0 ± 0.9** **Diabetes duration (years):−2–43**	**Intervention:** Acute **Exercise duration:** 40 min **Exercise Modality**: Mixed AE: Treadmill walk RE: Circuit **Exercise Intensity**: AE: 40–50% VO_{2max} RE: HIIE circuit training **Exercise Classification:** Circuit	Glycaemia
Reddy et al. (28)	Effect of aerobic and resistance exercise on glycemic control in adults with type 1 diabetes	***N* =** Ten adults **Age (years):** 33 ± 6 **BMI (kg/m^2):** 24.4 ± 2.1 **Gender:** ♂ **4** ♀ **6** **Co-morbidities: -** **Exercise:** Physically active **VO_{2max} (ml·kg·min^{-1}):** 46.8 ± 11.55 **HbA1c (%):** 7.4% ± 1% **Diabetes duration:** 18 ± 10	**Intervention:** Acute/Training (1 week) Two sessions of RE. Two sessions of AE. Control (no exercise) **Exercise duration**: 45 min **Exercise Modality**: RE: Whole body (Leg press, bench press, leg extension, leg flexion and seated row) AE: Treadmill running **Exercise Intensity**: RE:60–80% 1RM. 3 sets 8-12 repetitions AE: 60% VO_{2max} **Exercise Classification:** RE: Hypertrophy AE: MICE	Glycaemia

N, number of participants; BMI, body mass index; HbA1c, Glycated haemoglobin; RE, Resistance exercise; AE, aerobic exercise; RM, repetition maximum; VO_2, Volume of oxygen consumed; Reps, repetitions.

in the pathogenesis of T1D (36), interventions aimed at stimulating skeletal muscle growth are increasingly important in a diabetic milieu. The importance of preserved skeletal muscle mass is perhaps most evident in reference to age related muscle wasting or "sarcopenia." This pathological derangement decreases the efficiency of several major metabolic processes, thereby accelerates the development risk of metabolic and mitochondrial abnormalities. Skeletal muscle mass is maintained when there is equilibrium between muscle protein synthesis (MPS) and muscle protein breakdown (37). A disturbance in this finite balance during which MPS exceeds the rate of protein breakdown induces skeletal muscle hypertrophy i.e., an increase in muscle size, whilst the opposite is said for atrophy i.e., a decrease in muscle size. The cellular mechanisms responsible for the initiation of growth involves the activation of various anabolic substrates including the phosphatidylinositol 3-kinase (P13K) signaling substrate mammalian target of rapamycin (mTOR) (38). mTOR is a serine/theronin kinase that integrates nutrient and metabolic stimuli to regulate cell growth and proliferation (39, 40). It's activation is dependent on sequential upregulations of P13K, phosphoinositide-dependent kinase (PDK)-1, 70-kDa ribosomal S6 kinase, and the Akt/PKB isoforms (41). Metabolically, mTOR increases glycolytic flux by activating the transcription and the translation of hypoxia inducible factor 1α (HIF1α) (42), whilst Akt facilitates the stimulation of glycogen synthase and formation by inhibiting glycogen synthase kinase-3 (31). HIF1α is an intermediate of several glycolytic and angiogenic genes including both vascular endothelial growth factor (VEGF) and erythropoietin (EPO) (43). VEGF triggers not only divisional but also phenotypical changes of the vascular endothelial cells to alter their migratory capacity and proliferation potential, whilst EPO stimulates erythropoiesis and therefore systemic O_2 delivery. The hypertrophic potential of RE is not novel and its efficacy in substantially increasing rates of MPS in the many hours after exercise engagement are well-established (44). Biochemically, RE is known to evoke a transient increases in the phosphorylation of several of the aforementioned anabolic signalling molecules including mTOR (41), Akt/PKB (45), and 70-kDa ribosomal S6 kinase (45). Conversely, due to its inhibitory effect on several biochemical mediators of MPS, rates are minimal and/or unapparent following MICE. Encouragingly, recent research has demonstrated significant increases in upstream mediators of mTOR (growth hormone) in a volume dependent manner following acute RE in individuals with T1D (24). Since mTOR deregulation (46) and low CRF (47) are reported features of T1D, the biochemical cascades activated in response to appropriately designed RE are particularly noteworthy.

Skeletal Muscle Strength and Fatigability

The functional significance of hypertrophied skeletal muscle is reflected by the accompanied increase in maximal strength and power (48). Muscular strength describes the amount of force a muscle can produce in a single effort, whilst muscular power describes the ability of the muscle to exert that force rapidly. The development of these two physical attributes extends to beyond enhancements in athletic performance. Strong, powerful muscles are necessary for the completion of simple, everyday tasks, which translate to greater independence and autonomy with aging, lower rates of all-cause mortality, enhanced fluidity of movement, and a decreased risk of injury (49). Beyond its pivotal role in locomotion, the clinical significance of hypertrophied muscle is also noted. The associations between reduced skeletal muscle strength and higher rates of clinical biomarkers of CVD are critically important in those with T1D, who are predisposed to a greater incidence of primary CVD throughout the lifespan (50). Indeed, research has highlighted a significantly lower muscle strength and fatigability in those with-vs.-without T1D (51). A physiological explanation for these declines may be evident within the muscle fibre type, since muscle fibre arrangement and/or type has a functional significance on the rate of force production and contraction velocity. Briefly, there exist two broad classifications of muscle fibres, Type 1, and Type II (the latter of which can be further subdivided to include Type IIa and IIx variations). However, it should be noted that whilst useful, these divisions are overly simplistic and do not reflect the reality of fibre type distribution—which includes a heterogenous mix within the skeletal muscle.

Structurally, there appears to be a reduced number of slow-twitch oxidative fibres (Type 1) coupled with an increased amount of the fast-twitch highly fatigable muscle fibres (Type II) in individuals with T1D. Combined, these increase the development of fatigue during maximal exercise and therefore necessitate earlier exercise cessation (52). Supporting these insights, previous work by Crowther and colleagues evidenced a significantly lower muscle pH at rest and at the end of exercise, indicating a greater reliance on glycolytic metabolism in the muscles of individuals with vs.-those-without T1D (53). Moreover, a significantly slower phosphocreatine (PCr) recovery time has been noted in adolescence with-vs.-without T1D, suggesting a reduced skeletal muscle oxidative profile with impaired recovery capacity (36). Whilst an altered skeletal muscle phenotype has been observed in T1D, the severity of these reductions appears to be magnified by the presence of diabetes-related complications. Recent work by Orlando and colleagues illustrated an impairment in the functionality of skeletal muscle in T1D patients with diabetic polyneuropathy (DPN) vs. those with complication free T1D (T1D) and healthy controls (C) (51). Findings revealed the DNP group had lower knee extensor muscle strength than both the T1D (−19%) and the C groups (−37.5%) as well as an elevated (22 and 45%) rate of lower body fatigability than the T1D and C groups, respectively. Critically, RE induces several neural adaptations, including disinhibition of inhibitory mechanisms, as well as improvements in both intra-and-inter-muscular co-ordination. This enhances the synchronisation of motor unit recruitment and firing capacity to facilitate greater levels of maximal force production. These adaptations are proportional to alteration in muscle morphology as seen by increases in muscle cross-sectional area (CSA) accompanied by increases in Type II muscle fibres and altered muscle architecture (fibre pennation) (37). A large part of this process is mediated by the central nervous system which acts as a highly complex

control centre that facilitates movement at the molecular level (54).

METABOLIC RESPONSES TO RESISTANCE EXERCISE

T1D is characterised by the progressive depletion and destruction of pancreatic β-cells accompanied with impaired glucagon-producing α-cell function. The resulting deficiency in endogenous insulin secretion manifests in chronic hyperglycemia, with the sequential need for a lifelong reliance on exogenous insulin therapy (55). On the other hand, hypoglycemia represents a perpetual clinical and conventional worry which independently constitutes a primary patient reported barrier to regular exercise participation (56). Therefore, a key consideration for those with T1D whom partake in any physical exercise is the maintenance of blood glucose (BG) control. However, whilst accounted for with little contemplation in regulatory metabolism, the attainment of this outcome requires a degree of diligent pre-planning in those with T1D, for whom variations in exercise modality, intensity, and duration require specific adjustments in therapeutic and feeding strategies in order to mitigate risk.

Glycaemic Responses to Resistance Exercise

The control of BG during exercise involves the integrative co-ordination of two physiological systems (1) the autonomic nervous system (ANS) with particular emphasis on its sympathetic branch (SNS) and (2) the endocrine system (48). At a simplistic level, biochemical mediators released via these systems provide the feed-forward mechanisms that dictate glucose homeostasis. During moderate-to-high-intensity exercise, this feed-forward mechanism induces a rise in glucose concentrations which is primarily driven by hepatic glucose production (HGP). When glucose concentrations begin to fall as a result of sustained exercise efforts, the body produces a strong counter-regulatory response in an attempt to avoid hypoglycemia. This response is driven by the release of counter-regulatory hormones i.e., those that exert opposing actions to those of insulin. Recent work exploring the impact of single and multiple sets of RE on acute glycemic and glucoregulatory parameters has provided valuable endocrinological information in those with T1D (24). Researchers found significant increases in BG concentrations compared to resting conditions following one (+21%) and two (+29%) but not 3 sets of RE. The increases in BG were concurrent with a significant time*interaction effects in plasma catecholamines (noradrenaline and adrenaline). Indeed, peak catecholamine values were 28% greater under the 2nd set than the 1st set, and 17% greater under the 3rd set than the 2nd set. An increase in these two hormones parallels the idea that sympathoadrenergic activity can modulate HGP during exercise (57). Moreover, peak concentrations in growth hormone (GH) were observed during the 3rd (and final) set, which also agrees with work by Kraemer et al. who support the use of high volume session for maximising potential for hypertrophic outcomes (38). Furthermore, the considerable disturbance in acid-base balance observed during this protocol supports the "anaerobic" classification of RE that utilises predominately non-oxidative fuel metabolism via gluconeogenic pathways. Interestingly, despite the increasing hormonal and BG trajectory during the first two sets, the inclusion of a 3rd set produced BG concentrations similar to that of a non-exercise trial (24). It should also be noted that during recovery from 1 to 3 sets of RE, researchers reported no evidence of either exercise-induced hypoglycaemia or requirement for exogenous carbohydrates (CHO) (24). These findings oppose those commonly associated with AE, which typically reduces BG concentrations to a much greater extent (28, 58). Physiologically, the metabolic consequences of non-oxidative glycolytic activity likely contribute to the associated elevations in BG during the post exercise period, thereby offering protection against the onset of post-exercise hypoglycaemia. As a cautionary note, recent research has illustrated an increase in meal intake and after dinner snacking during the 24 h following both aerobic-and-resistance exercise sessions in order to prevent hypoglycaemia (28). Notably, findings highlighted significant reductions in post RE bolus insulin dosing requirements, which were also accompanied by less severe drops in plasma BG concentrations comparative to those recorded following AE (28). Accordingly, current recommendations are to reduce rapid acting insulin dosages alongside side a CHO rich pre-exercise meal (59, 60). This reductive strategy offsets the degree of hyperinsulinemia in people with T1D, which constitutes an inevitable outcome associated with exogenous insulin administration. Metabolically speaking, hyperinsulinemia exerts an inhibitory effect on fat utilisation during exercise, with the subsequently overreliance on CHO oxidation and therefore glucose dependency by the exercising skeletal muscle. Moreover, irrespective of interventional dose manipulations, insulin concentrations often increase during exercise (61). Mechanistically, this is likely due to an increased absorption rate from the subcutaneous tissue depot, together with a decreased clearance rate from at the systemic level. Combined the elevated degree of concentration of circulating of insulin propagates an increased risk of exercise-induced hypoglycaemia, which unsurprisingly prevails as a major barrier to exercise participation (56). Previous work has shown that postprandial exercise is associated with an increased risk of hypoglycemia if the pre-meal insulin dose is not reduced (62). Physiologically, this dose reduction strategy can augment the clearance rate of BG following the digestion of a CHO rich meal, thereby preserving BG concentrations ahead of exercise (62). The avoidance of in-exercise hyperinsulinemia has also been shown to replicate patterns of substrate oxidation and glucose regulation similar to a non-T1D individual (61). Moreover, a reduction in insulin mediated glucose uptake, in combination with elevations in catecholamine concentrations lessens the uptake and subsequent combustion of BG. Consequently, the major fuel substrates can be provided for both HGP and replenishment of muscle glycogen stores (63), such that a preservation effect is observed (64). Directionally, the cost of a slightly higher plasma glucose level before exercise translates to an improved glycemic profile during-and immediately-post-exercise (62).

It should be noted that when the exercise session is predominately reliant on non-oxidative fuel metabolism, post-exercise hyperglycaemia is common (23). The degree to which BG concentrations rise is dependent on several variables and can differ considerably both within and between individuals. Work by Turner and colleagues noted that when matched for volume, a comparable degree of post exercise hyperglycaemia is experienced in both low-and-high intensity morning RE sessions (26). Subsequent work highlighted the efficacy of administering an individualised dose of post-exercise rapid acting insulin in reducing the magnitude and severity of post-exercise hyperglycaemia, without causing early post-exercise hypoglycaemia in those with T1D (65). However, this protective effect waned thereafter, when prevalence rates of hypoglycaemia ensued during the later hours (65). Research has also demonstrated that the omission of pre-exercise bolus, but continuation of basal insulin dosages offers a protective effect against the occurrence of hypoglycaemia during and soon after a fasted bout of morning RE. A direct comparison between glycaemic responses to evening AE and RE in T1D revealed a decline in plasma glucose during a three-set evening RE session (albeit to a lesser extent than observed in the AE trial). Notably, there was also a tendency towards more frequent nocturnal hypoglycaemia following RE which warrants acknowledgment when considering the implementation of post exercise insulin dosing strategies to avoid acute hyperglycaemia. The differences in methodology between these two studies provides potential clues for contrasting glycaemic responses. Nevertheless, the authors concluded that in comparison to AE, RE may result in greater glycaemic stability both during and after exercise in those with T1D (20). Collectively, these data emphasise the need to account for exercise modality for the governance of appropriate insulin and feeding strategies around physical exercise in people with T1D.

Relationships Between Skeletal Muscle, Obesity, and Insulin Resistance

The fact that skeletal muscle tissue is one of the largest organs in the human body, combined with the discovery that contracting skeletal muscle is a multifactorial control centre for the release of various genetic, cytokine and growth-related factors, supports the reasoning behind it's classification as an endocrine organ (31). Due to its mediatory role in promoting skeletal muscle vitality, integrity, and functionality, the potential of RE in influencing the progression or regression of several pathogenic disease states should not be overlooked. Although not historically a condition associated with obesity, there is an alarming percentage of individuals with T1D now categorised as either overweight or obese (66). Whilst intensive insulin therapy is often advocated to counteract poor glycaemic control, aggressive treatment can lead to weight gain, with the subsequent propensity to develop insulin resistance (IR). Worryingly, IR has become a recognised featured of T1D youth, accompanied by compromised exercise capacity and microvascular derangements (36). Moreover, in a study assessing the hemodynamic parameters to maximal exercise in patients with well-controlled T1D, researchers found IR to be inversely associated with cardiac output (67). IR occurs when an inadequate quantities of glucose transporter molecules (namely GLUT-4) migrate to the cell surface following insulin stimulation (31). The translocation site of GLUT-4 is the T-tubules found within the skeletal muscle, which highlights the potential of contracting skeletal muscle to uptake circulating glucose independently of insulin. Thus, whilst not novel, the "insulin-like" properties of skeletal muscle are extremely important in pathologies with metabolic abnormalities. As a fuel source, fat constitutes the most abundant energy pool in mammals and is stored in three major sites; adipose, skeletal muscle, and liver tissue. Each tissue contains depots of triacylglycerol molecules which are hydrolyzed to form fatty acids (FAs) and used as an energy source (31). However, an excessive accumulation of triacylglycerol leads to conditions of hyperlipidemia, with the subsequent propensity to develop IR (68). Skeletal muscle FA metabolism is acutely sensitive to physical exercise which causes substantial increases in intra and extra-cellular FA utilisation (31). Skeletal muscle is a leading consumer of FA from either lipoprotein-triacylglycerol or plasma non-essential fatty acids, and this consumption process rises exponentially during exercise. Finally, as a metabolically active tissue, skeletal muscle plays a pivotal role in maintaining body composition. Acutely, the prolonged window of increased MPS following RE induces elevations in thermogenesis and energy expenditure. Considering that skeletal muscle accounts for ∼40% of total body mass and ∼30% of basal metabolic rate (BMR) in adult humans (40), hypertrophied skeletal muscle may elevate resting muscle metabolism due to an increased ratio of skeletal muscle mass relative to body weight. Therefore, appropriately programmed exercise programmes that stimulate skeletal muscle hypertrophy may assist in weight reduction and/or management in those with T1D.

CARDIO-VASCULAR RESPONSES TO RESISTANCE EXERCISE

For individuals with T1D, CVD is a major cause of morbidity and mortality and unsurprisingly constitutes a serious health concern that demands a prevention rather than treatment approach (69–71). Encouragingly, recent research has acknowledged the credibility of RE in reducing several CVD risk factors as well as improving various biomarkers of cardio-metabolic health (albeit it in a non-T1D cohorts) (72, 73). Although sparse, research has emphasised the efficacy of RET in improving traditional indices of CVD in people with T1D, including glycaemic and lipid related parameters (17). Furthermore, increases in heart rate (24, 26) and forearm reactive hyperaemia (25) have been reported following RE in individuals with T1D. Physiologically, the hypertrophic and angiogenic potential of RE is perhaps magnified in importance during circumstances where blood flow maybe compromised due to pathological abnormalities. Supporting this concept, researchers observed greater improvements in blood flow following lower limb RE vs. AE in individuals with T1D (25). However, these peripheral based improvements have thus far failed to correspond

with improvements in cellular indices of vascular function. Indeed, a blunted circulating endothelial progenitor cell (cEPC) response has presented regardless of exercise modality, perhaps reflecting derangements in the microvascular domains. Although it should be noted that existing literature has thus far employed mostly MICE (74) and/or submaximal-lower limb RE (25).

SKELETAL MUSCLE: IMPORTANT MICRO-VASCULAR AND ANGIOGENIC POTENTIALS

Prevalence rates of circulatory disease in people with T1D are extensive and at a population level constitute a leading cause of mortality (50). The pathophysiological mechanism responsible for the compromised circulatory system is most evident by the presence of abnormalities in the form and function of the blood vessels (50, 75, 76). Thus, whilst the identification of classical CVD risk factors provides valuable information as to an individual's current CVD vulnerability, they often fail to identify risk in its infancy and/or in those who appear to be asymptomatic. As such, physiological defects can go unrecognised until manifested as irreversible and/or severe acute complications within blood vessels including the presentation of endothelial dysfunction. Whilst the pathogenesis of macro-and-micro-vascular disease is multifactorial, the common recipient of injury is the vascular endothelium; a monolayer of cells that lines the blood vessels. Occupying a strategically important location between circulating blood and the surrounding tissues, the endothelium modulates the tone of the underlying vascular smooth muscle, maintains a non-adhesive luminal surface, mediates homeostasis, evokes cellular proliferation, and modulates inflammatory and immune mechanisms within the vascular wall (77). The functionality of the endothelium is mediated by a tightly regulated balance between the intermediates that induce cell damage i.e., pro-constrictive, pro-inflammatory, pro-thrombotic, and pro-hypertensive factors and the intermediates that support cell vitality i.e., pro-relaxation, anti-inflammatory, anti-thrombotic, and anti-hypertensive factors. Skeletal muscle hosts several sources of these vitality promoting intermediates, including the erythrocytes (which produce ATP and Nitric Oxide [NO]), the endothelial cells (which produce ATP, NO, and Prostacyclin [PGI_2]), the skeletal muscle cells (which produce ATP, NO, and adenosine). Thus, during skeletal muscle contraction, there is an increased turnover of various vasodilatory factors that encourage blood flow and vascular repair processes. Indeed, the co-operative intimacy between skeletal muscle and its surrounding vasculature is made clear by the proximity of capillaries embedded in grooves indenting the sarcolemma and expanding the contact area between myocytes and endothelial cells (78). Muscle fibre mitochondria also appear to cluster along these groves, thereby shortening the travelling distance of O_2 and various nutrients required for diffusion (78). The complex and intermate interaction between the biochemistry of the vascular endothelium, the vascular smooth muscle cells (VSMCs) and the skeletal muscle fibres emphasises the importance of endothelial vitality. Endothelial derangements proposedly contribute to the chronic under perfusion of skeletal muscle, resulting in suboptimal delivery and uptake of various nutrients, hormones and gaseous exchange. Indeed, these findings are somewhat consistent within the literature with research detailing higher rates of leg muscle deoxygenation (79), and altered red blood cell dynamics associated with the T1D milieu (80).

Mechanistically, microvascular abnormalities may be a result of lower skeletal muscle capillary density in individuals with T1D (81) which would agree with the aforementioned muscle fibre phenotype associated with T1D. Collectively, these attributes may contribute to a reduced circulatory ability to increase O_2 delivery to exercising muscle. This may explain the lower rates of regular physical activity (56) as well as the earlier onset of fatigue observed in T1D during exercise testing where O_2 delivery contributes to fatigue (82). Inefficient O_2 and nutrient supply may also impact the vascular tone of skeletal muscle. Vascular responses to light exercise provide insight into the hierarchical regulation of muscle perfusion. With light exercise, vasomotion within the terminal arterioles appears to cease, and the number of perfused capillary increases without significant changes in total muscle blood flow. Thus, during MICE, there is less of an increase in shear stresses traversing over the vessel lumen than during higher intensity exercise. During higher intensity exercise, or following ischemia, under-perfused capillaries are recruited to ensure an increase muscle perfusion. Indeed, in people with T1D, 7 weeks of high-intensity sprint training has been shown reduced metabolic fluctuations and enhance muscle oxidative metabolism (83). Thus, as a major storage site of several nutrients including glucose, amino acids, and free fatty acids, skeletal muscle also plays an integral role in substrate provision during hypoxic or anaerobic conditions.

These insights suggest a credible role for exercise modalities that utilise compound movements performed at high intensity effort as a strategy for re-endothelisation. Perhaps, as a reflection of its capacity to induce ischemia and muscle microtrauma, exhaustive or eccentric exercise protocols including downhill running and RE appear to cause the greatest stress responses. The acute physiological "stress" experienced during these sessions augments the production and release of several mediators of re-endothelisation including stromal cell-derived factor 1 (SDF-1) (84) and VEGF (85). Upon activation, these proteins mediate progenitor cell mobilisation, proliferation, and migration (86). One of the most potent upstream mediators of EPC proliferation is VEGF, which is primarily known for its mediatory role in the (i) sprouting and (ii) intussusceptive splitting of capillary beds to form angiogenesis. Recent research has shown considerable elevations in VEGF concentrations within both skeletal muscle and the peripheral circulation following intense RE (87, 88). As such, the potential of exercise to induce local angiogenesis may assist in the prevention of ischemia within its surrounding tissue (43). Considering the decreased perfusion rates and increased atherosclerotic tendencies associated with T1D, the angiogenic potential of RE in this population is important.

OSTEOPATHIC RESPONSES TO RESISTANCE EXERCISE

The term "osteoporosis" describes inelasticity within the skeletal system when exposed to the habitual subjection of forces experienced during joint movement, locomotion, and loading. Bone mineral density (BMD) is used as a reference of bone mineralisation within bone tissue and is substantially influenced by endocrine activity. The endocrine and metabolic disturbances associated with T1D are hypothesised to contribute to higher rates of poor bone quality noted within the literature (89–91). Biochemically, T1D is associated with reductions in the anabolic agents of bone formation including IGF-1 and transforming growth factor beta 1 (TGFβ1), which initiate a potent stimulatory effect on the synthesis of bone-specific proteins and osteoblastic proliferation potential (92). Moreover, the downstream complications associated with hyperglycaemia including the direct inhibition of osteoblast activity, osmotic damage to osteoblasts, increased peroxisome proliferator-activated receptor activity and low microvascular proliferative capacity, may increase susceptibility to osteoporosis and fracture risk.

Physiologically, bones adapt to loading stimuli by upregulating osteoblast activity in the areas experiencing mechanical strain. With this in mind, the essence of RE may offer support against the poor bone quality sometimes observed in T1D. Supporting this concept, T1D centred paediatric research noted increases in both lean body mass (LBM) and BMD following 9-months of weight bearing activity (93). These physiological adaptations are mutually connected, since there seems to be a stoichiometric relationship between muscle and bone. Indeed, bone architecture depends critically on muscle CSA and tension development (94), whilst muscle immobilization, and/or detraining leads to bone mass loss (95). Moreover, exercises that require large rates of muscular force cause greater bone-related benefits than do isometric or low force exercises (94, 96–98). Conversely, extreme endurance and/or low load bearing activities may exasperate the degradation of bone quality and health (99, 100). Researchers have documented losses in bone mass during the competitive seasons in endurance cycling (100) whilst increases in bone mass are ascertained during the competitive seasons of gymnastics (95). Further research is needed to progress our understanding of the osteopathic responses to RE in individuals with T1D.

RECOMMENDATIONS FOR RESISTANCE EXERCISE IN TYPE 1 DIABETES

There are several acute manipulations which can substantially influence the outcome induced by RE. Indeed, DeLorme's classic work suggested that RET using low repetition/high resistance favoured adaptations for strength, power, and hypertrophy, whereas training with high repetition/low resistance increased muscular endurance and oxidative potential (101). From this, a repetition training continuum (102) or repetition maximum continuum (103) has been hypothesised such that the number of repetitions allowed by the resistance will result in very specific training adaptations. In order to enable a clear outline of program design, early work by Bird et al. (104) collated this information and created a visual representation of RE prescription. A modified version of this template that emphasises the points relevant to this review is included below (**Figure 2**).

Considering the focus of this review has emphasised the importance of skeletal muscle size the practical recommendations to follow will reflect the attainment of muscular hypertrophy. Skeletal muscle experiences the increases in size and strength when forced to contract at maximal or near-maximal efforts. Indeed, the rate of MPS is driven by the intracellular availability of amino acids—a factor which is influenced directly by the intensity and duration of muscle tension. With overall session intensity in mind, early research by Kramer and colleagues concluded that the combined effects of a higher volume, moderate intensity session with shorter rest periods provides a favourable hormonal milieu for promoting skeletal muscle growth (38). Thus, to maximise intensity, rests between exercises and sets should therefore be kept minimal (30–60 s) to maintain an elevated skeletal O_2 demand that requires the use of predominately non-oxidative fuel metabolism.

Furthermore, the duration of muscular contraction significantly contributes to the phenotypic response. This process describes the "*tempo*" or time of the muscular contraction and is typically expressed in seconds. Moderate (2 s CON; 2 s ECC) and fast (1 s CON; 1 s ECC) velocities have been shown to maximise hormonal responses (105) and result in substantial metabolic cost (106). Classically the optimal repetition range for muscular hypertrophy is between 8 and 12. Initially, 2–3 sets may be enough for the untrained individual, however this should progress to >3 sets as with progressive overload. Moreover, programs that demand the simultaneous recruitment of large muscle groups traversing multiple joints in both the lower and upper body segments are advised. In this context, a program that emphasises compound movements towards the start of the session (when the muscle is in a "rested" state so can produce maximal force without fatigue), with isolated work grouped towards the end of a session is advised. In terms of exercise frequency, recommendations provided by the ADA (5) state that RE sessions aimed at skeletal muscle hypertrophy should be performed a minimum of twice but ideally thrice weekly.

Undertaking divergent exercise i.e., RE and MICE in close proximity may cause an "interference" effect on several of the acute molecular responses that orchestrate the adaptive phenotype. For example, activation of AMPK signalling in response to endurance exercise can block or dampen rates of MPS via its inhibitory effect on translation initiation and elongation (107). Moreover, the activation of AMPK is augmented in response to nutrient stress; particularly glycogen depletion; emphasising the need to acknowledge dietary considerations around exercise sessions. Thus, in an attempt to maximise MPS, individuals may wish to avoid both energy stress (increases in carbohydrate and amino acid feeding around exercise) and the concurrent practice of endurance and resistive exercise in close proximity (108).

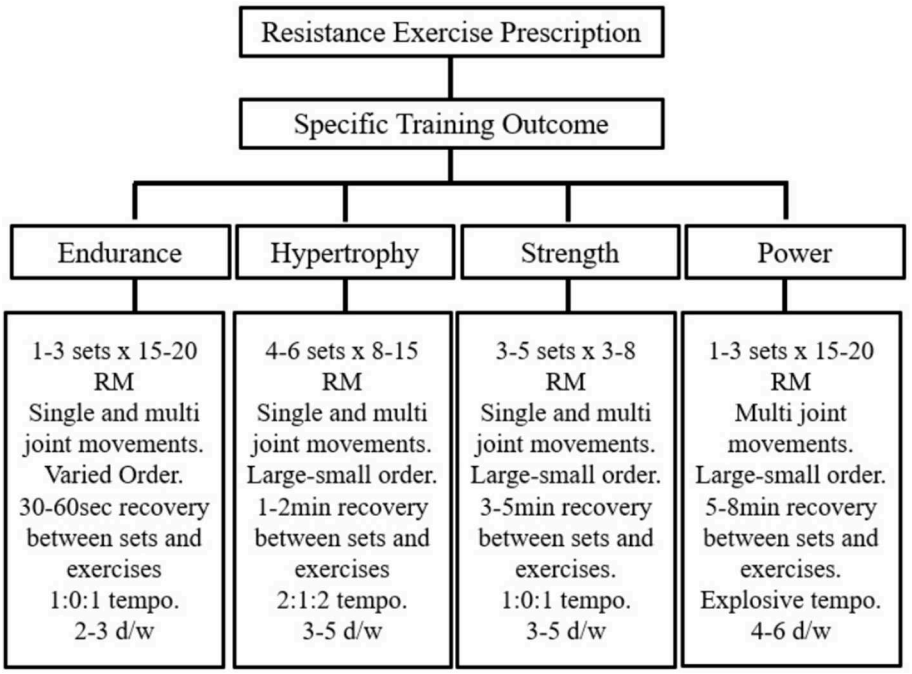

FIGURE 2 | Proper programme design of resistance exercise for specific training outcomes incorporates the acute programme variables and key training principles. ECC, Eccentric; CON, Concentric; ISO, Isometric; Ex, exercise; Sec, seconds; RM, repetition maximum; Btn, Between; d/wk, Days per week. Figure adapted from Bird et al. [(104), Figure 2]. Springer Nature. Copyright © (Jan 1, 2005).

Clearly exercise carries impactful glycaemic connotations for individuals with T1D. However, factors including the type, intensity and duration of exercise as well as the level of on-board exogenous insulin can considerably affect the glycemic responses that occur. Due to the pharmacological administration of exogenous insulin therapy, people with T1D frequently engage in exercise under markedly hyperinsulinemic conditions, thus are exposed to a greater risk of hypoglycaemia (62). As such, exercise often poses a glycaemic challenge which must be performed with a degree of contingency planning to both lifestyle and therapeutic strategies. It is prudent to suggest than insulin reductions and/or carbohydrate intake in the pre-and-post exercise periods are important features that need careful consideration with reference to BG values to appropriately manage glycemia. Exercise while fasting may produce a lesser decrease or indeed smaller increase in BG (65). It is advisory that BG is checked frequently in the hours pre, during and post exercise in order to govern safe and effective decisions regarding CHO feeding and insulin administration (5). RE induced hyperglycaemia risk can be abated by interspersing intense lifting efforts with lower intensity aerobic efforts (109) and/or combing RE (completed first) with AE (completed second) to optimize glycaemic stability (110). Further studies are needed to investigate the glycaemic impact of alterations in rapid-acting insulin strategies according to the type, intensity, and duration of the intended RE session.

FUTURE RESEARCH

Intuitively, the implementation of RE, a predominately glycolytic exercise that can be programmed to achieve global conditioning characterises a compelling therapeutic strategy that can be employed to improve several complications associated with T1D. However, despite the wider health merits associated with RE, a clear research emphasis has been placed on MICE with glycemia as its primary outcome.

In the existing RE specific research, program design has orientated around primarily hypertrophy or strength related outcomes, with less work investigating muscular endurance and/or power regimes for raising daily background levels of physical activity. In light of recent research emphasising the angiogenic potential of muscular endurance resistance exercise (MERE); during which healthy participants exercised to-or-near-to muscular failure (88), there presents a compelling rationale to employ these strategies in T1D by means of augmenting skeletal muscle angiogenesis. Indeed, the angiogenic and re-endothelialisation potential of MERE is particularly noted in this patient cohort, for whom circulatory complications are frequently observed (50). Moreover, considering the aforementioned alterations in the bioenergetics of skeletal muscle associated with T1D, the neuromuscular adaptations associated with moderate-to-heavy strength RE which incorporates a

mixture of isometric and isokinetic movements i.e., greater motor unit recruitment, increased discharge rate modulation, larger muscle cross section area and changes in muscle architecture, are duly noted. Future research that explores the physiological responses to RE that *varies* in several of the aforementioned acute and chronic training variables would not only deepen our understanding from a research perspective but offer much clinical and patient relevance that may help develop healthcare guidelines specific to those with T1D.

CONCLUSION

The importance of skeletal muscle strength and size extends far beyond it aesthetic and/or athletic performance value. Indeed, skeletal muscle plays an indispensable role in several key physiological processes including locomotion, hemodynamics, thermodynamics, cell signaling, and energy metabolism. Thus, the clinical merit of strategies that assist the maintenance and/or development of skeletal muscle are deserving of wider healthcare attention in patient populations. As a key determinant of muscle size and strength, the rate of MPS is critical for the development and/or preservation of skeletal muscle mass. This review has highlighted the potential of RE in upregulating the activity of several key biochemical and molecular signalling pathways that augment rates of MPS, including the PI3K/Akt/mTOR signalling pathway. Perhaps most importantly, the wider metabolic, vascular and respiratory roles of skeletal muscle each have particular relevance for individuals with T1D, whom are predisposed to greater pathological risk within these systems by virtue of the condition. Thus, the positive, adaptive health benefits associated with the hypertrophic and strength benefits accompanied with RE should be promoted as a necessary adjunct to standard diabetes care.

AUTHOR CONTRIBUTIONS

OlM: investigation and writing—original draft. OtM and RB: validation. OlM, RB, OtM, ME, RD, JP, and SB: writing—review and editing.

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Carbohydrate Loading Followed by High Carbohydrate Intake During Prolonged Physical Exercise and Its Impact on Glucose Control in Individuals With Diabetes Type 1—An Exploratory Study

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Background: Prolonged physical exercise (PE) is a challenge in type 1 diabetes with an increased incidence of both hypoglycemia and hyperglycemia.

Purpose: To evaluate the impact of two consecutive days of carbohydrate (CHO) loading, followed by high intermittent CHO-intake during prolonged PE, facilitated by a proactive use of Real-Time Continuous Glucose Monitoring (rtCGM), on glucose control in individuals with type 1 diabetes.

Methods: Ten physically active individuals with type 1 diabetes were invited to participate in a 3-day long sports camp with the objective to evaluate CHO-loading and high intermittent CHO-intake during prolonged PE. 1.5 months later the same procedure was evaluated in relation to a 90 km cross-country skiing race (Vasaloppet). Participants were instructed to act proactively using rtCGM with predictive alerts to maintain sensor glucose values within target range, defined as 72–180 mg/dl (4–10 mmol/l).

Results: Mean glucose values during CHO-loading were: day 1; 140.4 ± 45.0 mg/dl (7.8 ± 2.5 mmol/l) and day 2; 120.6 ± 41.4 mg/dl (6.7 ± 2.3 mmol/l). Mean sensor glucose at start of PE was 126.0 ± 25.2 mg/dl (7.0 ± 1.4 mmol/l) and throughout PE 127.8 ± 25.2 mg/dl (7.1 ± 1.4 mmol/l). Percentage of time spent in range (TIR) respective time spent in hypoglycemia was: CHO-loading 74.7/10.4% and during PE 94.3/0.6%.

Conclusions: High intermittent CHO-intake during prolonged PE combined with proactive use of rtCGM is associated with good glycemic control during prolonged exercise in individuals with diabetes type 1. However, the time spent in hypoglycemia during the 2-days of CHO-loading was 10.4% and therefore a lower insulin dose might be suggested to reduce the time spent in hypoglycemia.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT03722225

Keywords: blood glucose, carbohydrates, continuous glucose monitoring, insulin, physical activity, time in range, type 1 diabetes

INTRODUCTION

Studies have shown that individuals with diabetes type 1 have the same aerobic capacity as healthy individuals, provided that blood glucose (BG) is maintained in the euglycemic range (1, 2). However, in individuals with diabetes type 1, physical exercise (PE) is associated with an increased incidence of both hypoglycemia and hyperglycemia (3, 4). Whether the aim of PE is to have fun, become physically fit, lose weight or to increase the physical performance, the general glucose management strategy during PE is to avoid hypoglycemia. Depending on the specific aim, different strategies are required to obtain stable glucose control which could be achieved via alterations in the carbohydrate (CHO) intake or insulin adjustments or a combination of these.

In healthy subjects, new guidelines are available (5), with information on optimal CHO-intake for PE with various durations in order to ensure maximum performance and achieve stable blood glucose levels (5). A CHO-intake of 90 g/h during prolonged PE (>2.5/h) is recommended to maximize performance. The high CHO-intake contributes to a maintained high rate of CHO oxidation necessary to sustain the exercise intensity and to reach better performance (6).

For individuals with diabetes type 1 there are currently no recommendations concerning insulin adjustments and/or the CHO-intake during prolonged endurance sports when physical performance is to be considered. In the absence of such recommendations, the individuals must adopt a trial-and-error approach based on their past experience of BG responses to similar activities (7, 8).

In healthy individuals an increased intake of carbohydrates (CHO-loading) during the days before prolonged PE (>1.5 h) was shown to improve the physical performance (9). In healthy individuals an increased intake of carbohydrates, such as carbohydrate loading (CHO), is automatically accompanied by an increased insulin secretion with maintenance of a stable glucose level. In individuals with type 1 diabetes, this automatic regulation is missing and to our knowledge, only one study has been published investigating the effect of CHO-loading on physical performance and blood glucose control (10). In this study, the glucose control deteriorated along with impaired physical performance and it was concluded that a high CHO diet prior to PE was not recommended in the case that blood glucose control cannot be maintained in individuals with type 1 diabetes. Given the limited knowledge, it is therefore important to develop effective CHO-loading models for the individual with type 1 diabetes.

A common strategy prior to the prolonged PE in individuals with diabetes type 1 is to reduce the basal insulin doses by about 30–80% to reduce the risk of hypoglycemia. However, during competition, problems with hyperglycemia is often seen and is due to stress-induced release of glucose elevating stress hormones such as adrenaline and noradrenaline (7, 8, 11). A hyperglycemia at this time might result in avoidance of ingesting CHO at the start of the race and, which in turn can result in a late onset hypoglycemia, due to the increased requirements of CHO during the PE have not been met (8).

Furthermore, during prolonged PE, the carbohydrate intake has primarily been governed by the current blood glucose value or trend in previous studies (7, 8) instead of actually adding the amount of CHO required for the duration and intensity of the exercise. This reversed approach was evaluated when individuals with type 1 diabetes conducted a 90 km cross-country skiing race (Vasaloppet) (12). A fixed amount of CHO (75 g/h) was used corresponding to the duration of the PE aiming to maintain high intensity during the activity. In this study, the adjustments of insulin doses were individualized and slightly increased for the majority of participants. This strategy resulted in a maintained good glycemic control during the race.

With technological developments in recent years it is not only possible to accurately assess glucose control but also to take preventive actions. Real-Time Continuous Glucose Monitoring (rtCGM) has been shown to improve glycated hemoglobin (A1c) as well as reducing the risk of hypoglycemia (13). As hypoglycemia and hyperglycemia is associated with PE, rtCGM may therefore improve glucose management related to PE (12). The rtCGM allowed access to combined glucose information such as; actual value, glucose trend and direction and rate of the glucose changes. This information could be used to promote proactive actions, to reduce the glucose variability and if sustained also to reduce the A1c level (13–16).

The aim of this study was to evaluate CHO-loading prior to and intermittent high carbohydrate intake during prolonged PE in individuals with type 1 diabetes and its impact on glycemic control when applied along with rtCGM.

MATERIALS AND METHODS

Study Population

Physically active individuals with type 1 diabetes from different regions of Sweden reported their interest to participate in the study and 10 individuals were selected.

Inclusion criteria: age 18–50 years, type 1 diabetes with a diabetes duration >1 year, exercising regularly ≥3 workout/week, previous experience from long-distance cross-country skiing and willingness to follow the study according to the protocol.

Exclusion criteria: A1c 8.6% NGSP (70 mmol/mol IFCC) proliferative retinopathy, known nephropathy or cardiac failure, and presently following a low-carbohydrate diet.

Study Design

This is a descriptive, single arm, non-randomized interventional study. The intervention consisted of CHO-loading prior to and intermittent high CHO-intake during PE and a proactive use of rtCGM to achieve and maintain glucose control. A 3-day long sports camp was performed 1.5 months before a 90 km cross-country skiing race (Vasaloppet). The objective of this sport camp was to educate and prepare the participants on CHO-loading and

Abbreviations: A1c, Glycated Hemoglobin; BG, Blood Glucose; BMI, Body Mass Index; CHO, Carbohydrates; CSII, Continuous Subcutaneous Insulin Infusion; IFCC, International Federation of Clinical Chemistry; MDI, Multiple Daily Injections; NGSP, National Glycohemoglobin Standardization Program; PE, Physical Exercise; rtCGM, Real-Time Continuous Glucose Monitoring; TIR, Time in range.

the extended use of CHO during PE. All participants used rtCGM during the sports camp, the time between the sports camp and the Vasaloppet as well as during the race.

Preparation for Exercise—Glucose Control During 2 Days of Carbohydrate Loading

All participants conducted a 2-day CHO-loading twice, first during the time interval between the sports camp and the Vasaloppet and later during the 2 days prior to the race. The first occasion was used as an exercise in adjusting the insulin doses. The CHO-loading procedure consisted of the usual diet extended by 2 g of CHO/kg/day for 2 days in the form of a sports drink mixed in 1 liter of water which was ingested, 0.4 dl/h every half hour, intermittently for 12 h (08:00 a.m.−08:00 p.m.). The extended CHO-intake was simultaneously balanced with an increased amount of basal insulin where the individual carbohydrate to insulin ratio was used to find the appropriate dose to add as a basal dose during the subsequent 12 h. Furthermore, before bedtime after the start of CHO-loading the basal insulin was increased by ∼20% day 1 and 30% during day 2 lasting throughout the night until breakfast on both nights. The participants on multiple daily injection (MDI) therapy administered the long-acting insulin twice daily with a 50–50% distribution morning and evening. During the CHO-loading, the long-acting insulin taken in the evening was increased by 20% prior to night 1 and by 30% prior to night 2. Extra bolus doses were used during daytime corresponding to the added carbohydrate amount. **Supplementary File 1** illustrates the CHO-loading procedure including recommended insulin dose adjustments.

Preparation for Exercise—Glucose Control Between Meal and Start of the Race

To avoid the stress-induced hyperglycemia prior to the start of the Vasaloppet, the participants practiced to deliberately increase the mealtime insulin dose prior to PE during preparations prior to the race aiming to reach a glucose target of 90–144 mg/dl (5–8 mmol/l) at the start of PE. The breakfast was consumed at least 2 h before the start of PE and the participants were given a breakfast they were used to consume in relation to PE. The participants were informed to consume extra CHO (about 20–25 g) in the form of a sport drink, or to use a 30-min pump suspension, if the glucose level tended to decrease toward hypoglycemia before start, thus using the rtCGM proactively.

Implementation—Glucose Control During the Race

During all exercise sessions, the participants consumed a glucose–fructose containing liquid, three times per hour. The use of this mixed glucose-fructose sports drink enabled the extended use of CHO, corresponding to 1.00 ± 0.15 g CHO/kg body weight. The participants with type 1 diabetes were instructed to balance this CHO-intake with an appropriate insulin dose aiming at glucose values in range 72–180 mg/dl (4–10 mmol/l).

rtCGM

The Dexcom G5 Platinum system (Dexcom, San Diego, CA) was used during the study period. The sensors were inserted and calibrated according to company recommendation. The rtCGM devices and insulin pumps were downloaded via Diasend (Glooko Inc., Mountain View, CA) downloading system. HemoCue Glucose 201 RT (HemoCue, Ängelholm, Sweden), glucose measuring range 0–180 mg/dl (0–24.6 mmol/l), coefficient of variation (CV) 1.8%, was used for calibration of the rtCGM. All participants utilized the information they received via rtCGM but received no further instructions on glucose management during the race.

Each participant was informed to take proactive actions against hyperglycemia, >180 mg/dl (>10 mmol/l) as well as against hypoglycemia, <72 mg/dl (<4 mmol/l).

Hyperglycemia: Glucose value >180 mg/dl (>10 mmol/l) and stable alternatively increasing trend—Action: Bolus correction aiming at 108 mg/dl (6 mmol/l) taking into account a doubled Insulin Sensitivity Factor (ISF) during exercise.

Hypoglycemia: Glucose value 86.4–102.6 mg/dl (4.8–5.7 mmol/l) + arrow trend obliquely downwards, 102.6–117 mg/dl (5.7–6.5 mmol/l) + single arrow downwards and 117 mg/dl (>6.5 mmol/l) + double arrow downwards—Action: Immediate response by extra CHO-intake (about 20–25 g) or to use a 30-min insulin pump suspension.

Statistical Analysis

The statistical package for the social sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Glucose values are presented as mean ± standard deviation unless otherwise indicated.

RESULTS

Ten individuals, mean age 36.3 ± 4.9 years (range 31–43), mean diabetes duration 15.3 ± 10.9 years (range 1.6–30) and the mean A1c was 7.2% (55 mmol/mol) were included. The baseline characteristics of the study population is shown in **Table 1**.

TABLE 1 | Characteristics of study population.

Number (*n*)	10
Gender (female/male), number	2/8
Age (years), mean ± SD (range)	36.5 ± 4.9 (27–43)
BMI (kg/m^2), mean ± SD (range)	24.7 ± 2.6 (20.1–27.8)
Weight (lb), mean ± SD (range)	180.6 ± 26 (143.3–233.7)
Weight (kg), mean ± SD (range)	81.9 ± 11.8 (65–106)
Diabetes duration (years), mean ± SD (range)	15.3 ± 10.9 (1.6–30)
Treatment regimen (CSII/MDI), number	7/3
Total daily dose of insulin (IU/kg), mean (range)	0.47 (0.17–0.81)
A1C (NGSP, %), mean (range)	7.2 (6.3–8.3)
A1C (IFCC, mmol/mol), mean (range)	55 (45–67)

CSII, Continuous Subcutaneous Insulin Infusion; MDI, Multiple Daily Injections; NGSP, Glycohemoglobin Standardization Program; IFCC, International Federation of Clinical Chemistry.

Preparation for Exercise—Glucose Control During 2 Days of Carbohydrate Loading

During the CHO-loading prior to the Vasaloppet, one participant had problems with the rtCGM equipment during day 1 resulting in missing data. Mean glucose during the 2-day CHO-loading were: for both days; 129.6 ± 43.2 mg/dl (7.2 ± 2.4 mmol/l), day 1; 140.4 ± 45.0 mg/dl (7.8 ± 2.5 mmol/l) and day 2; 120.6 ± 41.4 mg/dl (6.7 ± 2.3 mmol/l) (**Table 2**). TIR defined as 72–180 mg/dl (4–10 mmol/l) was: for both days; 74.4%, day 1; 70.7% and day 2; 78.3%. Time spent in hypoglycemia <72 mg/dl (<4 mmol/l) was: for both days; 10.4%, day 1; 9.9% and day 2; 10.8%. The distribution of glucose values in TIR, hyperglycemia and hypoglycemia is shown in **Table 3**.

Glucose Control Before and During the Race

The mean insulin bolus dose before the race was increased by 55.5%, from the calculated dose of 5.4 ± 3.0 IU to 8.4 ± 4.0 IU. Mean sensor glucose levels at the start (07:00 a.m.) of the race was 126.0 ± 25 mg/dl (7.0 ± 1.4 mmol/l), with a range of 81–157 mg/dl (4.5–8.7 mmol/l) (**Table 4**). Thus, 100% of the sensor glucose values were within TIR prior to the race (**Table 3**).

Mean sensor glucose during the race was 127.8 ± 25.2 mg/dl (7.1 ± 1.4 mmol/l) (**Table 4**). The percentage of TIR was 94.3%, and time spent in hypoglycemia; 0.6% (**Table 3**).

Five of the participants experienced hyperglycemia during the race with a max sensor glucose value 220 mg/dl (12.2 mmol/l) and one subject had a hypoglycemia with a nadir sensor glucose value of 68 mg/dl (3.8 mmol/l). Each participant's glucose graph is shown in **Figure 1**.

The time needed to complete the race, CHO-intake and basal insulin dose adjustments are illustrated in **Table 4**.

DISCUSSION

In this study we have shown that it was possible to achieve and maintain good glycemic control, even during extraordinary challenges such as 2 days of CHO-loading followed by high intermittent CHO-intake during a 90 km long cross-country skiing race. A proactive use of rtCGM enabled individual insulin dose adjustments under these conditions.

To our knowledge few studies have been published regarding models for carbohydrate loading in type 1 diabetes individuals and the same also applies for the use of high carbohydrate intake during prolonged physical exercise. At the same time, we want to emphasize that attempts have been made exploring this area, for example via projects as "Team Novo Nordisk Pro Cycling," but published data are limited or missing.

Preparation for Exercise—Glucose Control During 2 Days of Carbohydrate Loading

In the study by McKewen et al. (10), who investigated the effect of increased CHO-intake and its effects on exercise performance and glycemic control in individuals with type 1 diabetes, the participants increased the CHO-intake by 10%, and the total daily dose of insulin by 14%. Despite this, the mean blood glucose increased 10% compared to normal diet 171 ± 25.2 mg/dl (9.5 ± 1.4 mmol/l) vs. 154.8 ± 30.6 mg/dl (8.6 ± 1.7 mmol/l), $p = 0.005$. In contrast to this we obtained preserved glucose control during a 2-day carbohydrate loading. An explanation to retained glucose control in our study may be due to the use of gradually increased levels of basal insulin during night 1 (+20%) and night 2 (+30%). Studies have suggested that increased muscular glycogen content increases insulin resistance which could explain why the participants required more insulin during night 2 (17–19). It might be suggested that a slightly lower basal insulin rate could be recommended in the present study considering

TABLE 2 | Mean glucose levels measured by rtCGM in individuals with type 1 diabetes during a 2-day carbohydrate loading prior to Vasaloppet.

Glucose control during two days of carbohydrate loading prior to Vasaloppet								
Participants	**Day 1**				**Day 2**			
	Glucose control mg/dl (mmol/l)				**Glucose control mg/dl (mmol/l)**			
	Mean	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
A	153 (8.5)	59 (3.3)	40 (2.2)	277 (15.4)	140 (7.8)	56 (3.1)	40 (2.2)	259 (14.4)
B	126 (7.0)	49 (2.7)	40 (2.2)	275 (15.3)	101 (5.6)	40 (2.2)	40 (2.2)	220 (12.2)
C	113 (6.3)	22 (1.2)	47 (3.6)	173 (9.6)	106 (5.9)	23 (1.3)	52 (2.9)	185 (10.3)
D	155 (8.6)	31 (1.7)	88 (4.9)	232 (12.9)	142 (7.9)	43 (2.4)	70 (3.9)	245 (13.6)
E	95 (5.3)	31 (1.7)	40 (2.2)	194 (10.8)	94 (5.2)	34 (1.9)	41 (2.3)	230 (12.8)
F	162 (9.0)	49 (2.7)	56 (3.1)	286 (15.9)	149 (8.3)	34 (1.9)	68 (3.8)	212 (11.8)
G	180 (10.0)	67 (3.7)	49 (2.7)	297 (16.5)	119 (6.6)	45 (2.5)	54 (3.0)	268 (14.9)
H	NA	NA	NA	NA	146 (8.1)	61 (3.4)	59 (3.3)	238 (13.2)
I	155 (8.6)	36 (2.0)	45 (2.5)	236 (13.1)	119 (6.6)	41 (2.3)	47 (2.6)	218 (12.1)
J	131 (7.3)	67 (3.7)	40 (2.2)	326 (18.1)	117 (6.5)	52 (2.9)	43 (2.4)	265 (14.7)
All	140 (7.8)	45 (2.5)	50 (2.8)	256 (14.2)	121 (6.7)	41 (2.3)	47 (2.6)	234 (13.0)

In addition to the usual diet, the participants added 2 g of carbohydrates/kg/day.

TABLE 3 | Glucose values in individuals with type 1 diabetes during 2 days of carbohydrate loading and during a 90 km cross-country skiing race (Vasaloppet).

Distribution of glucose values as percentage of total time during the carbohydrate loading and at start as well as during Vasaloppet					
	Two days of carbohydrate loading			Vasaloppet	
	Day 1	Day 2	Both days	At start of Vasaloppet	During Vasaloppet
Time in range (% of total time): 72–180 mg/dl (4–10 mmol/l)	70.7	78.3	74.7	100	94.3
Time spent in hypoglycaemia (% of total time): (<72 mg/dl) (<4 mmol/l)	9.9	10.8	10.4	0	0.6
Time spent in hyperglycemia (% of total time): (>180 mg/dl) (>10 mmol/l)	19.4	10.9	14.9	0	5.2

Time in glucose target range (TIR) (%), defined as 72–180 mg/dl (4–10 mmol/l).

TABLE 4 | Mean glucose levels, carbohydrate intake, and adjustment of basal insulin in individuals with type 1 diabetes during a 90 km cross-country skiing race (Vasaloppet) and the duration of the physical activity (A–J).

Glucose control and finishing time during a 90 km intensive cross-country skiing race								
Participants	Treat-ment (MDI/CSII)	Glucose value at start mg/dl (mmol/l)	Glucose control during Vasaloppet			CHO intake/h of activity (g)	Basal insulin percentage change (%)	Time from start to finish (hour:minutes)
			Mean	SD	Range			
A	MDI	94 (5.2)	86 (4.8)	8 (0.5)	74–99 (4.1–5.5)	90	0	05:33
B	MDI	140 (7.8)	138 (7.7)	9 (0.5)	119–158 (6.6–8.8)	75	0	05:21
C	CSII	104 (5.8)	129 (7.2)	33 (1.8)	86–194 (4.8–10.8)	75	0	07:00
D	MDI	157 (8.7)	110 (6.1)	22 (1.2)	77–196 (4.3–10.9)	75	0	08:23
E	CSII	153 (8.5)	138 (7.6)	18 (1.0)	99–162 (5.5–9.0)	84	0	05:54
F	CSII	119 (6.6)	150 (8.3)	26 (1.5)	104–184 (5.8–10.2)	84	0	06:45
G	CSII	81 (4.5)	141 (7.8)	31 (1.7)	81–187 (4.5–10.4)	100	0	06:24
H	CSII	142 (7.9)	132 (7.3)	39 (2.2)	68–203 (3.8–11.3)	75	0	07:20
I	CSII	128 (7.1)	128 (7.1)	21 (1.2)	85–158 (4.7–8.8)	75	+27	06:02
J	CSII	139 (7.7)	126 (7.0)	38 (2.1)	83–220 (4.6–12.2)	75	Start: 0 #01:00: −14 #05:30: −31	06:07
All		126 (7.0)	128 (7.1)	25 (1.4)	68-220 (3.8–12.2)	80.8		06:28

#*The participant J had to deviate from the planned CHO intake during the race due to gastrointestinal discomfort which resulted in a reduction of the basal insulin dose 01:00 respectively 5:30 h after start.*

that 10.4% of the time was spent in the hypoglycemic range. It should also be considered that individuals with type 1 diabetes usually face problems with hypoglycaemia on regular basis. This will affect the counterregulatory hormonal response and attenuate endogenous hepatic glucose production during exercise and might therefore result in an increased risk of hypoglycaemia during a subsequent physical activity (20). Thus, avoidance of a hypoglycemia the day before prolonged physical activity is most likely even more important with the approach presented in this study where the basal doses were not reduced before and during the race.

Preparation for Exercise—Glucose Control Between Meal and Start of the Vasaloppet

Prior to competitions, stress is common, causing increased release of adrenaline and noradrenaline (21). This stress results in hyperglycemia (7, 8, 11). Beyond this fact, individuals with type 1 diabetes often have a fear of hypoglycemia associated with PE, which often results in a reduction of the basal insulin dose before the start of the race (11). In a recent publication Riddell et al. showed that the variability of glucose control during aerobic exercise partially was explained by pre-exercise glucose level (22). Our approach was to reach a stable and good

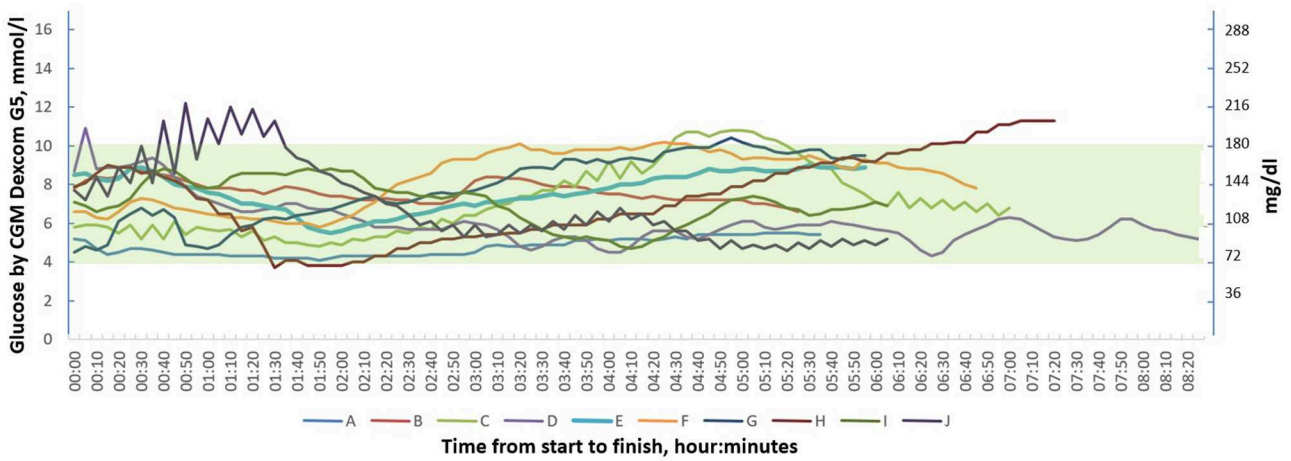

FIGURE 1 | Continuous glucose monitoring graphs of 10 individuals with type 1 diabetes during the 90 km cross-country skiing race (Vasaloppet).

glucose control prior to the start of the race. To reduce the risk of hyperglycemia in this study, first the participants did not have to reduce basal insulin before and during the competition due to the plan we had about using an extended amount of CHO throughout the race. Second, the participants increased the insulin dose to the meal taken 2.5 h before the start by mean 55.5%. To our knowledge there are no previous studies using this novel model. The rtCGM, used in our study, provided safety to this approach as the individual could be warned about pending hypoglycemia and consume a liquid CHO solution in such occasions.

Implementation—Glucose Control During the Race

Both hypoglycemia and hyperglycemia are important to avoid during PE when performance also is regarded as an important factor. Hyperglycemia increases the release of free fatty acids (FFA) (23). An increase in FFA has been shown to decrease both insulin-dependent and insulin-independent muscular glucose uptake (24–26). In one of these studies an increase in plasma FFA up to 31.1 mg/dl (1.1 mmol/l) was shown to decrease muscle glucose uptake by 42% (25). In addition, an increase in plasma FFA will reduce muscle CHO oxidation, which may adversely affect physical performance (27).

Despite the prolonged duration of the PE in the current study, the participants spent 94.3% of the TIR. Our results differ in comparison to a previous study in individuals with type 1 diabetes who performed a 75 km cross-country skiing race (>7 h) at two consecutive years (1986 and 1987), where a CHO-intake corresponding to 40 g of CHO/h appeared to prevent hypoglycemia in the majority of the participants (8 of 9) in both competitions (7). In the same study, mean plasma free insulin levels in the individuals with type 1 diabetes before the race were half (7.8 ± 2.0 mU/l) of that was seen in healthy control subjects (15.6 ± 3.1 mU/1, $p < 0.001$) while mean pre-race blood glucose for the participants with type 1 diabetes was 365.4 ± 32.4 mg/dl (20.3 ± 1.8 mmol/l). Thus, compared to this study, we were able to achieve a better glycemic control at start and then also to maintain this glucose control during prolonged PE.

A possible mechanism behind the good results in our study could be the combination of carbohydrate loading and subsequent high carbohydrate intake during prolonged physical exercise. This procedure ensured a relatively high glycogen content in the liver and muscles prior to exercise. Exercise performance/capacity and a stable plasma glucose level is often limited by endogenous carbohydrate availability during prolonged physical activity (28). In the current study, the participants consumed between 75 and 100 g CHO/h during the race. The main focus of this study was to continuously ingest increased amounts of carbohydrates to maintain a high carbohydrate availability throughout the race and thereby hopefully achieve a preserved blood glucose value. However, it should be highlighted that an increased intake of carbohydrates during exercise does not seem to spare muscle glycogen (29, 30). Instead, studies have shown that an increased carbohydrate intake spare the liver glycogen which likely supports both a stable blood glucose and performance in the latter stages of prolonged exercise (31, 32).

Gastrointestinal discomfort is very common symptom during exercise, especially in prolonged endurance races (33). The occurrence of gastrointestinal disturbances has been related to the CHO-intake during exercise (34). However, it has been shown that the gut is adaptable in that the intestinal capacity to absorb CHO can be increased by regularly consuming increasing amounts of CHO during exercise (35, 36). In the current study, the participants had a high intake of CHO corresponding to 75–100 g/h during the race. Unfortunately, one participant had to deviate from the planned CHO-intake during the race due to gastrointestinal discomfort. This deviation resulted in a reduction of the planned basal insulin dose. This participant had, due to an upper respiratory infection, 2 weeks prior to the Vasaloppet, only completed a few exercise sessions with a higher intake of CHO before the PE. It is likely that this

participant would have needed more exercise sessions with a high CHO-intake to increase the tolerance for high amounts of CHO.

Limitations

This study was performed as an exploratory study which includes the benefits of this being a real world situation. As opposed to this, there are of course also limitations as a control group is missing and where the environment made it difficult to carry out parallel sampling to evaluate the mechanisms behind the good glucose control achieved in the study.

Furthermore, the participants was not randomly selected and could thus limit the generalisability of the study. Vasaloppet is a 90 km long cross-country skiing race which is very demanding in terms of individual physical performance and the participants had to have relative high level of fitness to be able to complete the race. Therefore, the results could be seen as a description of real-world data in this specific group.

CONCLUSIONS

We conclude, that high intermittent CHO-intake during prolonged PE was associated with good glucose control in individuals with type 1 diabetes. However, the proportion of time spent in hypoglycemia during the 2-days of CHO-loading was 10.4% and a lower insulin dose might have been required to reduce time spent in hypoglycemia. rtCGM could be beneficial when used proactively to maintain sensor glucose values within target range before and during PE. These strategies and the mechanisms that create the conditions for good glucose control during prolonged physical exercise needs to be further evaluated in randomized controlled studies.

ETHICS STATEMENT

All procedures performed in this study involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments. Signed informed consent was collected from all participants prior to study start. This study was approved by the Regional Ethical Review Board in Uppsala, Sweden (DNR: 2012/159).

AUTHOR CONTRIBUTIONS

SM and PA conceived and designed research, conducted the experiments, and analyzed data. JJ participated in the planning of the study. SM, PA, and JJ did all participate during the preparatory sports camp. SM wrote the manuscript. PA and JJ reviewed the manuscript. All authors read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2019.00571/full#supplementary-material

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