



Daily Energy Expenditure, Cardiorespiratory Fitness and Glycaemic Control in People with Type 1 Diabetes

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Abstract

Objective: Encouraging daily physical activity improves cardiorespiratory fitness and many cardiovascular risk factors. However, increasing physical activity often creates a challenge for people with type 1 diabetes, because of difficulties maintaining euglycemia in the face of altered food intake and adjustments to insulin doses. Our aim was to examine the triangular relationship between glucose control measured by continuous glucose monitoring system (CGMS), objective measures of total daily energy expenditure (TEE) recorded by a multi-sensory monitoring device, and cardiorespiratory fitness (CRF), in free-living subjects with type 1 diabetes.

Research Design and Methods: Twenty-three individuals (12 women) with type 1 diabetes who were free from micro- and macrovascular complications were recruited. TEE and glucose control were monitored simultaneously for up to 12 days, using a multi-sensory device and CGMS respectively. CRF was recorded as V_{O2} max from a maximal treadmill test with the Bruce protocol.

Results: Subjects (mean ± SD) were aged 37 ± 11 years, with BMI = 26.5 ± 5.1 kg.m⁻², HbA_{1c} = 7.7 ± 1.3% (61 ± 14 mmol/mol) and V_{O2} max (ml.min⁻¹.kg⁻¹) = 39.9 ± 8.4 (range 22.4 – 58.6). TEE (36.3 ± 5.5 kcal.kg⁻¹.day⁻¹) was strongly associated with CRF (39.9 ± 8.4 ml.min⁻¹.kg⁻¹) independently of sex (r = 0.63, p < 0.01). However, neither TEE (r = -0.20, p = 0.36) nor CRF (r = -0.20, p = 0.39; adjusted for sex), were significantly associated with mean glycaemia measured by CGMS.

Conclusion: Higher levels of energy expenditure (due to a more active lifestyle) are associated with increased cardiorespiratory fitness, but not necessarily better glycaemic control. Since increased levels of energy expenditure and good glycaemic control are both needed to protect against diabetes-related complications our data suggest they need to be achieved independently.

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Introduction

The health and general well-being benefits of high levels of cardiorespiratory fitness (CRF) and physical activity are well documented in people with diabetes [1,2]. Often, however, physical activity levels are sub-optimal in people with type 1 diabetes because of a fear of hypoglycaemia or low levels of CRF [3,4]. Additionally, a further challenge facing people with type 1 diabetes is how best to ensure good glucose control in the presence of varying levels of food intake and insulin doses throughout the day. Too little or too much exogenous insulin causes erratic glucose control, particularly when individuals have varying levels of physical activity energy expenditure (PAEE). Such erratic control can have adverse effects on the individual's overall glycaemic control, thereby increasing the predisposition to vascular complications [5].

Most of the studies reported to date have studied the effect of specific exercise interventions (typically moderate intensity aerobic activities) on cardiovascular risk factors and glycaemic control.

Physical activity interventions in people with type 1 diabetes have been linked to improved CRF [6–13], insulin sensitivity [6,10], lipid profile [6–9,13] and endothelium function [12,14], but results investigating the association between levels of physical activity and glycaemic control have been contradictory [15]. Similar inconsistent results have been reported in observational studies that used questionnaires to quantify levels of physical activity. For example, long-term glucose control assessed by HbA_{1c} has been shown to be lower in people with type 1 diabetes engaging in increased levels of physical activity [16,17], but Waden *et al.* [18] found that such an association was only present in women; while others found no correlation [19], and some even reported a positive relationship between HbA_{1c} and CRF [20]. Recently, Kennedy *et al.* [21] concluded in their meta-analysis of 13 studies that there was no evidence of glycaemic benefit, measured by HbA_{1c}, of exercise and further suggested that HbA_{1c} may not be a sufficiently sensitive indicator of glycaemic control.

It is plausible that these discrepant results between studies might have originated from imprecision in the measurements of energy

expenditure, combined with a failure to accurately take account of potential confounders affecting the relationship between physical activity levels and glycaemic control (e.g. body fatness, energy intake and insulin dose). Energy expenditure quantified by validated questionnaires is only poorly-to-moderately accurate, with correlation coefficients ranging from $r=0.1$ to 0.6 when compared to double labelled water (DLW) [22]. The accuracy of questionnaires in representing an individual's pattern of daily energy expenditure is therefore debatable. Due to advances in wearable sensing technologies and pattern recognition algorithms, light multi-sensory physical activity armbands can nowadays be used to obtain an objective measure of energy expenditure, and with a correlation coefficient of $r=0.86$ with DLW [23], such devices offer clear advantages over questionnaires and/or simple accelerometers. Continuous glucose monitoring systems (CGMS) have lately given researchers a tool to obtain more precise estimates of short-term mean glycaemia and variability, which infrequent finger-prick measurements could not reveal. Using a multi-sensory physical activity armband combined with CGMS monitoring it is therefore possible to obtain estimates of 24 hr glucose control and energy expenditure in free-living people.

The aim of our pilot study was to examine the triangular relationship between glucose control measured by CGMS, levels of energy expenditure measured by a multi-sensory monitoring device, and cardiorespiratory fitness, in a heterogeneous group of free-living subjects with type 1 diabetes.

Research Design and Methods

Participants

Twenty-five complications-free people with type 1 diabetes were recruited in our open, non-randomised and observational study. The object of the study was to observe a varied cohort spanning the spectrum of energy expenditure from sedentary to more active individuals. Potential volunteers were identified from those attending the Diabetes Resource Centre at the Royal South Hants Hospital, Southampton, England. Subject selection criteria were non-stringent only requiring the participant to be on multiple insulin injections (and not on an insulin pump) and have no other acute problems. Invitation to participate was made directly by letter with a verbal explanation and patient information sheet before recruitment. Data from 23 (12 women) subjects are reported (one individual withdrew for personal reasons after recruitment and one individual had problems using the CGMS) as reported in the CONSORT diagram in Figure 1. The study protocol and TREND checklist are available as supporting information (Protocol S1 and Checklist S1). After giving signed consent, the participants undertook a number of clinical tests to determine total body fat and CRF. The participants were then issued with a multi-sensory physical activity monitoring device and CGMS for free-living monitoring. Volunteers were recruited between 8th July 2008 and 4th December 2009 – there was no period of follow up.

Ethics Statement

The ethical content of the study was reviewed by the Southampton and South West Hampshire Research Ethics Committee (LREC:07/H0502/134), and conforms to the principles outlined in the Declaration of Helsinki.

Daily Energy Expenditure and Glucose Control in a Free-Living Environment

Daily energy expenditure was monitored by a SenseWear Pro2/3 armband (BodyMedia, PA, USA), while blood glucose (BG) was

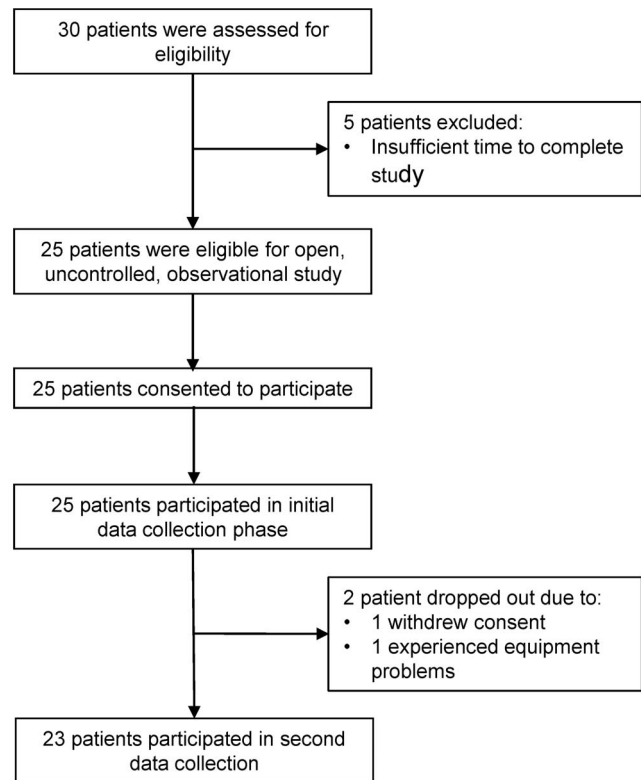


Figure 1. CONSORT flow diagram showing enrollment and retention of volunteers in the study of energy expenditure in type 1 diabetes.

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monitored by a Guardian® Real-Time CGMS (Medtronic MiniMed Inc., CA, USA). Both devices were issued to the participants after being taught how to use them, and instructed to contact the researcher should there be any problem in operating them. Particular emphasis was placed on abiding to the manufacturer's guidelines on calibrating the CGMS (2 h after sensor insertion, again after 6 h, then at least one calibration within every 12 h period). Frequent calibrations avoid issues with sensor drifts and thus improve the quality of the data. The multi-sensory physical activity armband and CGMS were worn simultaneously and continuously for up to 12 days, in order to obtain a snapshot of the individual's daily lifestyle and corresponding glucose control. The participants were free to partake in any activity and make any therapeutic decision which would affect their BG.

Average total daily, energy expenditure (TEE) in $\text{kcal kg}^{-1} \text{day}^{-1}$ was used to quantify the volunteer's lifestyle and the Metabolic Equivalent ($1 \text{ MET} = 1 \text{ kcal kg}^{-1} \text{hour}^{-1}$) to compute the mean daily percentage of time spent engaging in activities of different intensity levels. The intensity categories used were sedentary ($<2 \text{ METs}$), light ($2\text{--}3 \text{ METs}$), moderate ($3\text{--}6 \text{ METs}$) and vigorous ($>6 \text{ METs}$) [24]. Short-term glycaemic control was quantified by the daily, mean (MBG), standard deviation (SD) and coefficient of variation (CV, standard deviation normalised by the mean) of BG. We also estimated the percentage of time spent at risk of hypoglycaemia ($< 4 \text{ mmol/l}$), with normoglycaemia ($4\text{--}11 \text{ mmol/l}$) and with hyperglycaemia ($> 11 \text{ mmol/l}$). HbA_{1c} was measured to give an estimate of each individual's glycaemic control over the preceding 2–3 months prior to the research study. For all individuals between two and eight measurements of HbA_{1c}

were available for the 2-year period prior to recruitment in the study.

The participants were also asked to keep a food and insulin diary throughout the monitoring period. Average daily carbohydrate intake was estimated by converting the self-reported meals into equivalent grams of carbohydrates using food databases, or for specific branded foods, the producer's stated nutritional facts. All of our volunteers were treated with multiple daily insulin injection (MDII) regimes. Insulin diaries were used to estimate the typical daily insulin dosage.

Body Composition and Cardiorespiratory Fitness

Body composition was estimated by a dual X-ray absorptiometry (DEXA) scan using a Hologic Delfia W 4500 (Hologic, Bedford, USA). CRF was assessed by a maximal treadmill test. The Bruce protocol was chosen so as to challenge even the fittest people in our heterogeneous group, which spanned a wide spectrum of lifestyles, from fairly sedentary to very active people. The volunteer wore an air-tight mask (Hans Rudolph Inc., MO, USA), which had a gas sensor (Metalyzer 3B, Cortex Biophysik GmbH, Germany) attached to it, while heart rate was monitored using a Polar Electro T61 chest heart rate monitor (Polar Inc., Lake Success, NY, USA). The participant was asked to run on a treadmill (Woodway, GmbH, Germany) until exhaustion, unless they experienced chest pain or felt unwell. $\text{VO}_{2\text{max}}$ was taken to be the final steady-state value for oxygen consumption. The Foster [25] and Pollack [26] equations, which are functions of the time spent on the treadmill under the Bruce protocol, were used for men and women respectively, to estimate CRF.

Statistical Analysis

Free-living physical activity and CGMS measurements were averaged over 24 h periods and over the total number of days in order to obtain a single data point for each participant in the study. Univariate correlation analyses were performed using the Pearson correlation for normally distributed variables. Multiple linear regression modelling was undertaken to identify factors that were independently associated with CRF. All statistical analyses were performed on IBM® SPSS® Statistics 21. A value of $p < 0.05$ was taken as statistically significant.

Results

Table 1 shows the baseline characteristics of the 23 (12 women, age = 37 ± 11 years) participants with type 1 diabetes recruited to the study. No participants had evidence of microvascular or macrovascular complications. Univariate associations between the three key study variables (MBG, TEE and CRF), and glycaemic control metrics (MBG, SD, CV, HbA_{1c}) and lifestyle measures (TEE, CRF, total body fat, mean daily carbohydrate intake, mean daily insulin dosage) are summarised in Table 2.

MBG, which represents the average blood glucose concentration over a 24 hr period as measured by CGMS, was associated with SD ($r = 0.62$, $p < 0.01$) but not with CV ($r = -0.30$, $p = 0.17$) of BG. MBG (short-term glycaemic control measure) and HbA_{1c} (long-term glycaemic control measure) were poorly correlated and did not achieve conventional statistical significance ($r = 0.36$, $p = 0.09$). No significant associations were found between MBG and lifestyle.

TEE is an objective measurement of the average energy expended by an individual during their daily routine. TEE was not associated with any of the glycaemic control metrics. However, TEE was strongly correlated with CRF ($r = 0.63$, $p < 0.01$; adjusted for sex), percentage total body fat ($r = -0.71$, $p < 0.001$; adjusted

for age and sex) and average daily carbohydrate intake ($r = 0.69$, $p < 0.001$; adjusted for body weight). Average daily carbohydrate was strongly associated with both levels of sedentary activity ($r = -0.53$, $p < 0.05$; adjusted for body weight) and moderate activity ($r = 0.53$, $p < 0.05$; adjusted for body weight). Carbohydrate intake was also associated with average daily insulin dosage ($r = 0.58$, $p < 0.01$; adjusted for body weight), but not with glycaemic control metrics.

CRF quantifies the efficiency of the human body to transport and use oxygen during aerobic exercise and is therefore conceptually different from the energy expended by an individual during day-to-day activities. CRF was not correlated with glycaemic control metrics. It was however associated with diabetes duration ($r = -0.43$, $p < 0.05$; adjusted for age), TEE ($r = 0.63$, $p < 0.01$; adjusted for sex), percentage total body fat ($r = -0.78$, $p < 0.0001$; adjusted for age and sex) and time spent at moderate activity levels ($r = 0.58$, $p < 0.05$; adjusted for age and sex). The amount of time spent at high activity in this cohort is very small and thus we have inadequate power to assess relationships with high versus low intensity activity further.

Because CRF is a strong predictor of cardiovascular disease, the factors associated with CRF were further explored using multiple regression modelling. Age is a known non-modifiable factor affecting CRF. However in a model with CRF as the outcome and age and TEE as explanatory variables, age was found to be statistically non-significantly associated with CRF ($\beta = 0.01$, $p = 0.94$), whereas TEE was associated with CRF ($\beta = 0.69$, $p = 0.001$); and this regression model explained 47% of the variance in CRF ($R^2 = 0.47$, $p < 0.01$). In a second regression model with CRF as outcome, 56% of the variance in CRF was explained by TEE ($\beta = 0.41$, $p = 0.054$) and percentage body fat ($\beta = -0.40$, $p = 0.059$) ($R^2 = 0.56$, $p < 0.001$).

We examined further the relationships between CRF, TEE and MBG concentrations. The 3-D scatter plot in Figure 2 shows the relationship between CRF and TEE with the corresponding MBG for the participants in this study. At the extremes, relatively unfit and inactive individuals show markedly different MBG while similar albeit smaller variations are observable in the fitter and more active participants.

Discussion

In this observational pilot study of a cohort of people with type 1 diabetes of different ages and lifestyles, we found that: a) daily energy expenditure was negatively associated with total body fat and positively correlated with CRF and mean carbohydrate intake; b) daily energy expenditure was not strongly correlated with the various measures of glycaemia, and in our relatively small data-set these correlations were not statistically significant. Figure 3 summarises pictorially the main findings of our study.

The main strength of our study was the use of an objective quantitative measure of energy expenditure, when compared to subjective lifestyle questionnaires, and the use of CGMS data captured over 8 ± 3 days, (mean \pm SD) to obtain typical minute-by-minute variability in each individual's glycaemic control. The SenseWear Pro2/3 physical activity armband has been found to underestimate energy expenditure by $117 \text{ kcal day}^{-1}$ [23], which is only about 5% of the recommended calorific intake of an average adult man. Whilst CGMS has been shown to have a consistent range-dependent bias, with overestimation of glucose concentrations within the hypoglycaemic range, no bias in the normoglycaemic range, and underestimation during hyperglycaemia [27].

Table 1. Baseline characteristics of N=23 participants with type 1 diabetes.

Age (years)	37±11
Diabetes Duration (years)	17±11
BMI (kg.m ⁻²)	26.5±5.1
Total Body Fat (%)	27.9±9.2
Maximal Oxygen Consumption (ml.min ⁻¹ .kg ⁻¹) (V02 max)	39.9±8.4
Total Cholesterol (mmol/l)	4.7±0.9
LDL Cholesterol (mmol/l)	2.8±0.9
HDL Cholesterol (mmol/l)	1.5±0.4 (1.0 – 2.8)
Triglyceride (mmol/l)	0.7±0.4 (0.4 – 2.7)
Fasting Glucose (mmol/l)	10.1±4.7
HbA _{1c} (%)	7.7±1.3
HbA _{1c} (mmol/mol)	61±14
Mean Daily Insulin Dosage (IU/day)	53±20
Mean Daily Carbohydrate Intake (g/day)	227±62
Mean Daily Energy Expenditure (kcal.kg ⁻¹ .day ⁻¹)	36.3±5.5
Time Spent Sedentary (<2 METs) (%)	69.8±9.3
Time Spent in Light Activities (2 – 3 METs) (%)	17.5±6.3
Time Spent in Moderate Activities (3 – 6 METs) (%)	11.8±4.9
Time Spent in Vigorous Activities (> 6 METs) (%)	0.2±1.4 (0 – 4.8)
Time Spent Blood Glucose < 4 mmol/l (%)	3.5±8.6 (0 – 24.6)
Time Spent Blood Glucose 4 – 11 mmol/l (%)	72.3±16.0
Time Spent Blood Glucose > 11 mmol/l (%)	15.4±18.6 (0 – 76.3)

Data are mean ± SD for normally distributed variables and median ± IQR (range) for non-normally distributed variables. HDL cholesterol, triglyceride and time spent in vigorous activities, BG<4 and BG>11 were non-normally distributed.
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No exercise intervention was prescribed for our volunteers, who were monitored in a free-living environment. Consequently the data captures routine behaviour for the people in our cohort. Although we acknowledge that the size of the cohort in our detailed physiological study has limited the power of the statistical methods used to detect associations, it is important to stress that

associations between all of the measures of glycaemic control and physical activity were weak. The largest r-value computed was 0.2, which represents a small effect size if this association is real. A retrospective sample size calculation shows that we would have needed a cohort of 194 people to show statistical significance at the 0.05 level with 80% power to detect this effect.

Table 2. Partial correlation coefficients for daily mean blood glucose (MBG), average total daily energy expenditure (TEE) and cardiorespiratory fitness (CRF), with glycaemic control metrics and lifestyle measures.

	MBG (mmol/l)	TEE (kcal.kg ⁻¹ .day ⁻¹)	CRF* (ml.min ⁻¹ .kg ⁻¹)
Glycaemic Control Metrics			
MBG (mmol/l)	1.0	-0.20 (p=0.36)	-0.20 (p=0.39)
SD (mmol/l)	0.62 (p<0.01)	0.07 (p=0.76)	-0.09 (p=0.68)
CV (%)	-0.30 (p=0.17)	0.23 (p=0.28)	-0.003 (p=0.99)
HbA _{1c} (%)	0.36 (p=0.09)	-0.10 (p=0.65)	-0.03 (p=0.89)
Lifestyle Measures			
TEE (kcal.kg ⁻¹ .day ⁻¹)	-0.20 (p=0.36)	1.0	0.63 (p<0.01)
CRF (ml.min ⁻¹ .kg ⁻¹)*	-0.20 (p=0.39)	0.63 (p<0.01)	1.0
Total Body Fat (%)†	0.31 (p=0.18)	-0.71 (p<0.001)	-0.78 (p<0.0001)
Mean Daily Carbohydrate Intake (g.day ⁻¹) ‡	-0.07 (p=0.76)	0.69 (p<0.001)	0.18 (p=0.44)
Mean Daily Insulin Dosage (IU.day ⁻¹) ‡	-0.14 (p=0.54)	0.35 (p=0.11)	-0.21 (p=0.36)

* adjusted for sex
†adjusted for age and sex
‡adjusted for body weight
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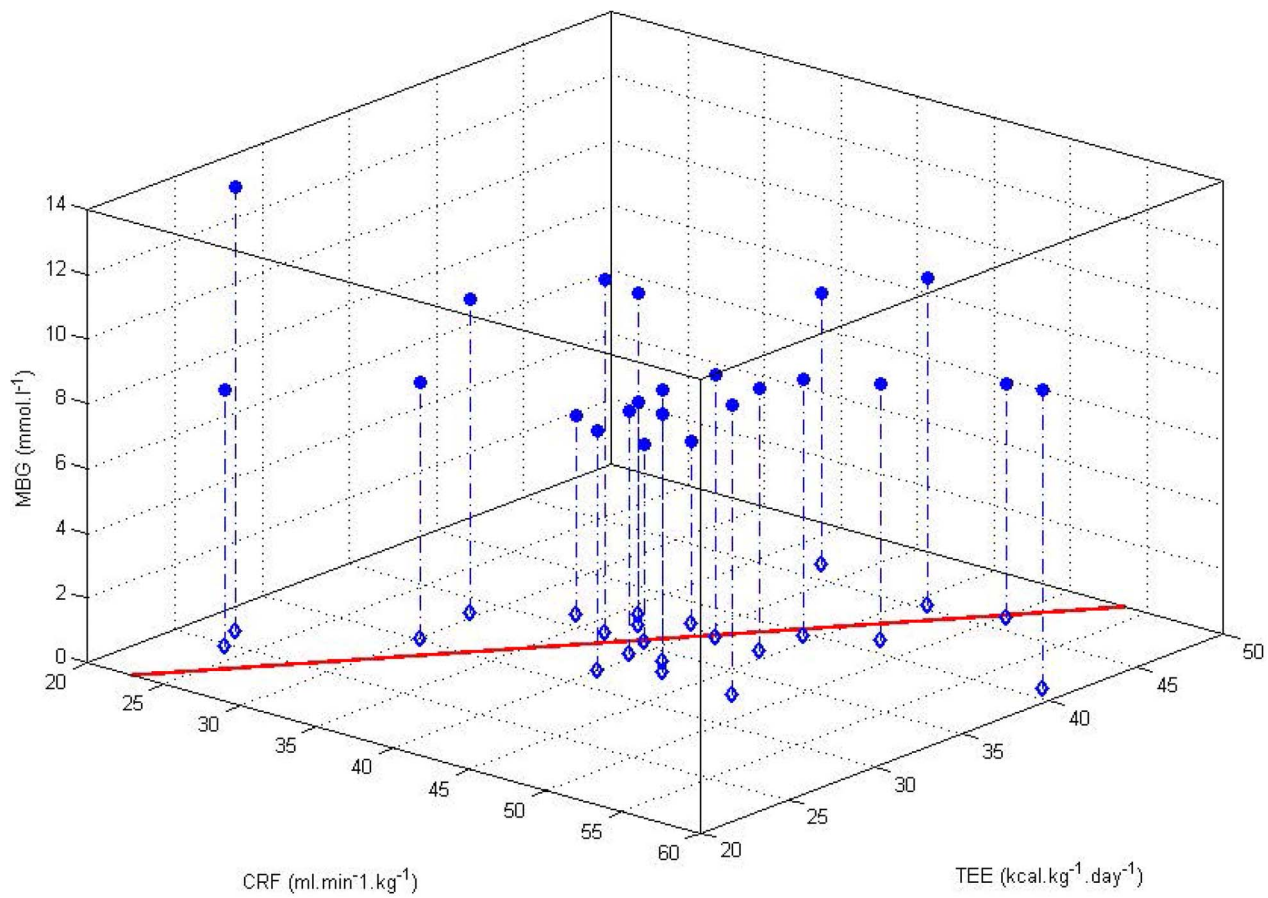


Figure 2. 3-D Scatter plot for cardiorespiratory fitness (CRF), mean daily total energy expenditure (TEE) and mean blood glucose (MBG) of study participants. Blue diamonds show the relationship between CRF and TEE with the solid red line showing the linear fit ($CRF = TEE + 2.3$, $R^2 = 0.47$). Blue circle markers show the corresponding MBG for each individual. doi:10.1371/journal.pone.0097534.g002

We have shown that levels of daily energy expenditure were associated with body fat and CRF. Ekelund *et al.* [28] reported an inverse relationship between physical activity energy expenditure, estimated from heart rate monitoring, and fat mass in a large middle-aged healthy group. Similar results were reported by den Hoed and Westerterp [29] who found an association between body composition and physical activity in a study of 134 healthy individuals, measured by a triaxial accelerometer. In a healthy, but non-athlete group of thirty-eight people, habitual physical activity was associated with mitochondrial capacity [30]; this could have contributed for the association with CRF found in our group. CRF was found to be positively associated with both duration and intensity of incidental physical activity in a cohort of inactive and abdominally obese adults [31]. In a large longitudinal study of healthy individuals, Lakoski *et al.* [32] reported that 56% of the variance in CRF was explained by age, gender, BMI and physical activity, the latter being quantified by self-reported questionnaires. Our multiple regression results, (acknowledging our limited sample size), showed striking similarity with data from Lakoski *et al.* [32]. In our study, we showed that 56% of the variance in CRF in individuals with type 1 diabetes was explained by TEE and percentage total body fat, and we found that age did not contribute to this relationship. The normalised β -coefficients for TEE ($\beta = 0.41$) and percentage body fat ($\beta = -0.40$) suggest that these modifiable factors have similar weights on the relationship with CRF, albeit in opposite directions. The difference between

daily energy expenditure and CRF in their contribution towards health and general wellbeing is still a topic of active research [33]. The cardio-protective effects of physical activity are however undisputed [34] and recent results from a large study on adults aged over 60 years have shown a strong inverse correlation between physical fitness and all-cause mortality independent of fat distribution [35].

In our study group, carbohydrate intake was positively correlated with daily energy expenditure when adjusting for body weight. The positive correlation could be in part possibly explained by fear of hypoglycaemia [3] in those individuals who have a more active lifestyle, and possibly confounding the relationship between mean glycaemia and energy expenditure. There was a strong negative association between carbohydrate intake and sedentary levels of energy expenditure and a strong positive association with moderate levels of energy expenditure. This may suggest that more active individuals consume more carbohydrate and that in itself potentially causes some difficulties in maintaining glycaemic control.

The majority of previous studies have tested the effect of specific lifestyle intervention programmes on long-term glycaemic control quantified by HbA_{1c}. The results from those studies have been contradictory, with a number of studies reporting no improvement in HbA_{1c} following the training program [6,8–12,14,19,35–37], while in others an association was found between physical activity and long-term glycaemic control [7,13,16,17] as reported here

analysis and interpretation of results, which is primarily aimed at explaining the inter-subject variation. Averaging data to characterise an individual's quality of glycaemic control and lifestyle obscures within day and between day changes in both variables. It is therefore debatable how to quantify the *typical* lifestyle and glycaemic control. HbA_{1c} is the *de facto* mean which clinicians use to assess their patients overall glycaemic control, and this was not found to be statistically significantly or strongly associated with MBG. Although the HbA_{1c} assay and CGMS measure different entities, glycated haemoglobin and interstitial glucose respectively, they should in theory return similar estimates for the average blood glucose concentrations. HbA_{1c} values for our cohort were fairly constant two years prior to being recruited in the study, with an average coefficient of variation (SD normalised by the mean, expressed as a percentage) of $6.2 \pm 3.5\%$ (2.1 – 15.4%). One would have expected therefore that when observing the individuals for up to 12 days, the mean recorded by the CGMS would be strongly associated with HbA_{1c}. There are however several other unaccounted factors that could have affected BG significantly in the short-term, such as psychological stress [39,40], menstrual cycle [41] and the effect of the previous day, for example the initial state of glycogen depots in the liver and muscle.

Conclusions

Our novel data show that in people with type 1 diabetes, daily energy expenditure is positively and strongly associated with cardiorespiratory fitness and cardiorespiratory fitness declines with diabetes duration. In contrast, the measures of daily energy expenditure were only weakly associated with several measures of glycaemic control. Our results suggest that people with type 1

diabetes who have a more active lifestyle exhibit both better cardiorespiratory fitness and less body fat, but not necessarily better glycaemic control. Since increased levels of energy expenditure and good glycaemic control are both needed to protect against diabetes-related complications and they are only weakly related, our data suggest they may need to be achieved independently as we have found no evidence of a strong relationship between energy expenditure and levels of glycaemia.

Supporting Information

Checklist S1 TREND checklist.

(PDF)

Protocol S1 Study protocol.

(DOC)

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Author Contributions

Conceived and designed the experiments: AJC CDB. Performed the experiments: JJV GFC. Analyzed the data: JJV AJC GFC CDB. Wrote the paper: JJV AJC CDB.

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