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Responses to oral glucose challenge differ by physical activity volume and intensity: a pilot study. By Trevor N. Simper^{a*}, Cecile Morris^a, Anthony Lynn^a, Ciara O'Hagan^b, Karen Kilner^c

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Abstract

Background: One hour postprandial hyperglycaemia is associated with increased risk of type 2 diabetes and cardiovascular disease. Physical activity has short-term beneficial effects on post-meal glucose response. This study compared the oral glucose tolerance test results of 3 groups of people with habitually different levels of physical activity.

Methods: Thirty-one adults without diabetes (age 25.9 ± 6.6 years; body mass index $23.8 \pm 3.8 \text{ kg.m}^{-2}$) were recruited into 3 groups based on self-reported physical activity volume and intensity: Low Activity = $< 30 \text{ min.day}^{-1}$ of 'moderate' intensity activity (n = 11), Moderately Active = $\geq 30 \text{ min.day}^{-1}$ of 'moderate' intensity physical activity (n = 10), and Very Active = $\geq 60 \text{ min.day}^{-1}$ of 'intense' physical activity (n = 10). Participants completed an oral glucose tolerance test (50 g glucose) with capillary blood samples obtained at baseline, 15, 30, 45, 60, 90 and 120 minutes post-ingestion.

Results: There were no significant differences between groups for age or percentage body fat or glycated haemoglobin ($p > 0.05$). The groups were significantly different in terms of baseline glucose, gender and BMI and this was accounted for in the analysis. There was a statistically significant effect of physical activity on the one hour postprandial glucose results ($p = 0.029$), with differences between Very Active and Low Activity ($p = 0.008$) groups but not between the Moderately Active and Low Activity groups ($p = 0.360$), even when baseline glucose and gender differences were accounted for. For iAUC there was no significant effect of activity group once gender and bodyfat % had been accounted for. Those in the Low Activity group took an average 13.2 (95% CI: 2.8 – 23.5) minutes longer to reach peak glucose level than those in the Very Active group and this was significant ($p = 0.015$).

Conclusion: The results suggest that high levels of physical activity have a beneficial effect on postprandial blood glucose profiles when compared to low and moderate levels of activity.

Keywords: Type 2 diabetes, Oral glucose tolerance test, Physical activity, Incremental area under the curve, Blood glucose response

1. Introduction

In the UK, 3.2 million people are diagnosed with type 2 diabetes and an approximate 630,000 remain undiagnosed. This number has risen from 1.4 million in 1996.¹ Sedentary behaviour is strongly predictive of type 2 diabetes (T2D).² Western populations have high rates of sedentary behaviour and low levels of participation in physical activity combined with high rates of diagnosed and undiagnosed T2D.^{1,2,3} It has been suggested that 30 minutes of physical activity a day may represent the cut-off point at which people begin to accrue benefits to blood glucose control.⁴ Physical activity is seen as an effective preventative measure and a therapeutic intervention post-diagnosis.^{5,6} Even slow postprandial walking has an immediate effect on lowering blood glucose.⁷ There is a positive effect on glucose tolerance from either reducing weight by diet or by increasing physical activity.⁸ Participation in formal physical activity (gyms, walking, exercise classes etc.) may, however, form only part of the solution to effective blood glucose control. Some studies indicate being sedentary is a risk factor for T2D, independent of participation in bouts of planned exercise.⁹⁻¹¹ Therefore, public health interventions, aimed at preventing T2D, may need to focus on avoiding sedentary behaviour in addition to the promotion of planned exercise.

Previous randomised controlled trials have found interventions involving around 150 minutes a week of physical activity have lowered the risk of progressing from impaired glucose tolerance to T2D by over 50%.^{12,13} Physical activity intensity and subsequent fitness levels also have stark implications for diabetes sufferers; Church et al. 12 found that those in the lowest, second and third quintiles for cardiorespiratory fitness had 4.5, 2.8 and 1.6 fold greater risk of all-cause mortality respectively than men in the highest quintile for fitness.¹⁴ Despite this connection between physical activity and diabetes other work suggests the effects of exercise training on key health indicators: such as blood pressure and lipids in non-diabetic populations are mild.^{15,16}

Both chronic participation and acute bouts of physical activity clearly affect blood glucose control and in all probability frequency and intensity have an impact. An example from studies focussing on the effects of single bouts of exercise show insulin sensitivity is

improved for only 1-3 days.^{16, 17} This supports the notion that it is advisable to not go longer than 3 consecutive days without being active.

Although the above studies reflect the broad finding that physical activity is helpful in controlling blood glucose to our knowledge work still needs to be carried out to identify any observable differences in healthy individuals carrying out different volumes and intensities of physical activity. The present study investigates the blood glucose responses of healthy individuals undertaking different volumes and intensities of activity. It remains unclear whether there is a detectable or clinically significant difference in blood glucose response between low activity, active and very active non-diabetic people following a 50 g intake of carbohydrate. Our hypothesis was that responses would differ by volume and intensity of activity with those doing the most activity and at the greatest intensity having the lowest 1-hour blood glucose value and the lowest incremental area under the curve (iAUC).

2. Methods

2.1 Participants

A purposeful sample of 31 subjects were recruited (23 females and 8 males aged 25.9 ± 6.6 y; BMI 23.8 ± 3.8 kg.m² and body fat 24.15 ± 4.21 %). Subjects were recruited via email advertisements, which specifically asked for individuals who undertook low, moderate or high levels of habitual physical activity. The email advertisements were circulated to approximately 1600 people within a large university faculty. A total of 40 volunteers (2.5%) responded, all of whom were invited to take part; 31 presented for data collection. Subjects were classified by 3 'level of activity' groups: Low Activity: people who did < 30 min of physical activity per day at or below moderate intensity; Moderately Active: ≥ 30 min per day of physical activity at moderate intensity; and Very Active: ≥ 60 min per day of physical activity at high intensity. Classification into 'level of activity' group was based on the mean duration of physical activity, determined using the Scottish Physical Activity Questionnaire (SPAQ)¹⁸ and the mean intensity of exercise calculated using a 1-10 Borg scale.¹⁹ The SPAQ asks participants to report the physical activity they have undertaken at home and work during the last month via interview with a data recorder familiar with the questionnaire. The estimated mean metabolic equivalents (METs) were calculated from the mean number of minutes of physical activity and the mean RPE values using the compendium of physical activities.²⁰

The exclusion criteria were: age <19 years or >59 years, presence of diabetes (as per the WHO definition of diagnosis²¹), chronic illness, acute infections, food allergies, smoking and being pregnant. All participants were informed of the risks and benefits of taking part in the study and provided written informed consent before any data was collected. The study was approved by Sheffield Hallam University Ethics committee.

2.2 Procedures

All subjects attended the research laboratory after a 12 hour fast on two occasions separated by a week. They were instructed to avoid alcohol and limit physical activity on the day prior to each test day and to eat the same meal at the same time the evening before.

Prior to the physical measurements, participants were asked to void their bladders. Height (without shoes) and weight (indoor clothing) were recorded to the nearest 0.1 cm and 0.1 kg respectively (SECA 709 mechanical column scales with SECA 220 telescopic measuring rod; SECA Birmingham, United Kingdom). For consistency, participants were asked to wear the same clothes at each visit. Height measurements were made at the point of normal breath inspiration with the head orientated in the Frankfort horizontal plane. From these measures, BMI was calculated and rounded to the nearest 0.1. Bioelectrical impedance analysis was undertaken on non-conducting foam matting using a BodyStat 1500 (BodyStat Ltd., Isle of Man, British Isles). Measurements were made as per the manufacturer's instructions following 5 minutes of supine rest. Percentage body fat and lean weight (kg) were recorded to the nearest 0.1% and 0.1 kg respectively. On the first test day, subjects provided a capillary blood sample for the determination of HbA1c. A baseline blood glucose measure was then taken. Within 15 min of the baseline glucose test, subjects consumed a 50 g dose of glucose made up to 200 ml with water. A timer was started from the first sip of glucose solution and further measurements were made at 15, 30, 45, 60, 90 and 120 minutes. Subjects returned to the laboratory one week later and the oral glucose test was repeated. The mean blood glucose responses of the two visits were used for subsequent statistical analysis. Capillary samples of blood were obtained using sterilised softclix lancets (Roche Diabetes Care Ltd, Surrey England) and blood glucose was measured with One-Touch Ultra 2 glucose meters (Johnson & Johnson, Livingstone, Scotland). Each measurement was taken in duplicate. The proposed CV for glucose meters suggests allowing an error margin of 5–10%.²² A control solution was used to verify the accuracy of the glucose meters and a CV of 4.63% was calculated

based on 10 replicates. Whole blood HbA1c was measured on an Alere Afinion AS100 analyser (California, USA).

2.3 Data analysis

iAUC was calculated by the trapezoidal method outlined by Wolever et al.²³ Differences between the activity groups in BMI, age, HbA1c, body fat %, physical activity duration and intensity and baseline glucose were ascertained by 1-way ANOVA while Fisher's Exact test was used to compare the sex composition of the groups. The primary outcomes of glucose concentration after 1 hour and iAUC, together with time to peak, peak glucose and final glucose concentration (after 2 hours) were compared across groups using 1-way ANOVA. General linear models were then fitted to the primary outcomes to adjust for differences between the groups in baseline glucose, gender and BMI. Significance level was set at $\alpha=0.05$ and all analyses were performed using SPSS version 23 (IBM Corp. Armonk, NY, USA) Chicago.

3. Results

One subject, in the Low Activity group, displayed values which were commensurate with impaired glucose control (>11 mmol/l) and was removed from the analysis as an outlier. The baseline characteristics of all other subjects are summarized in Table 1. By definition physical activity differed across the groups, both in intensity and duration. There were, however, significant differences at baseline between groups for blood glucose and, marginally, for BMI, with the moderately active group having the lower mean scores in each case; such differences could impact upon post-test glucose results. The gender composition of the groups also differed, though this was not quite statistically significant ($p=0.053$). Duration and intensity of physical activity were found to be highly correlated ($r=0.903$) in the study sample.

Table 1: Baseline Characteristics of Participants

	Low Activity (n=10 [†])	Moderately Active (n=10)	Very Active (n=10)	p
BMI (kg/m ²)	25.8 ± 5.4	21.7 ± 1.7	24.0 ± 2.5	0.050
Age (years)	28.5 ± 9.1	22.8 ± 2.3	26.9 ± 6.2	0.147
HbA1c (%)	5.3 ± 0.2	5.3 ± 0.3	5.3 ± 0.3	0.959
Body fat (%)	25.2 ± 5.6	23.7 ± 3.6	21.3 ± 3.0	0.125
Baseline glucose (mmol/l)	5.0 ± 0.6	4.3 ± 0.2	4.7 ± 0.3	0.003
Physical activity (min/d)	23.4 ± 3.3	76.3 ± 5.3	101.3 ± 5.9	<0.001
Intensity (MET*)	3.1 ± 0.8	5.0 ± 0.7	6.9 ± 0.6	<0.001
Gender	7♀ 70%	10♀ 100%	5♀ 50%	0.053

*Average metabolic equivalent

[†]One subject, in the Low Activity group, displayed values which were commensurate with impaired glucose control and was removed from the analysis as an outlier

All values except gender are mean ± standard deviation.

HbA1c= glycosylated haemoglobin, BMI= Body mass index.

Table 2: Blood glucose outcome measures

	Low Activity (n=10)	Moderately Active (n=10)	Very Active (n=10)	p
One-hour post-test (mmol/l)	7.50 ± 1.69	6.06 ± 0.97	5.55 ± 0.98	0.005
iAUC (mmol/l.120 min ⁻¹)	171.53 ± 85.15	161.59 ± 83.63	73.71 ± 45.98	0.011
Time to peak (min)	46.50 ± 11.07	45.00 ± 14.14	31.50 ± 8.51	0.012
Peak glucose (mmol/l)	8.10 ± 1.30	7.05 ± 0.54	6.80 ± 0.74	0.009
Two-hours post-test (mmol/l)	4.94 ± 0.99	4.40 ± 1.12	4.49 ± 0.63	0.401

All values are mean ± standard deviation

Table 2 shows the outcome measures for blood glucose across the three activity groups. All outcome measures differ significantly between groups with the exception of two-hours post-test when blood glucose has largely fallen back to baseline levels for most individuals. On all significant measures, the worst outcomes are seen in the Low Activity group, while in general

the results in the Moderately Active and Very Active groups are similar, with the exception of iAUC and time to peak glucose, where the Very Active group has a much-reduced average level.

Figure 1 shows the mean blood glucose responses for the three groups over 120 minutes. Blood glucose peaked, on average, at around 30 minutes post-test for those in the Very Active group and somewhat later for the Low and Moderately Active groups. For those in the Low Activity group the peak was considerably higher than the other two groups and remained higher for the duration of the test.

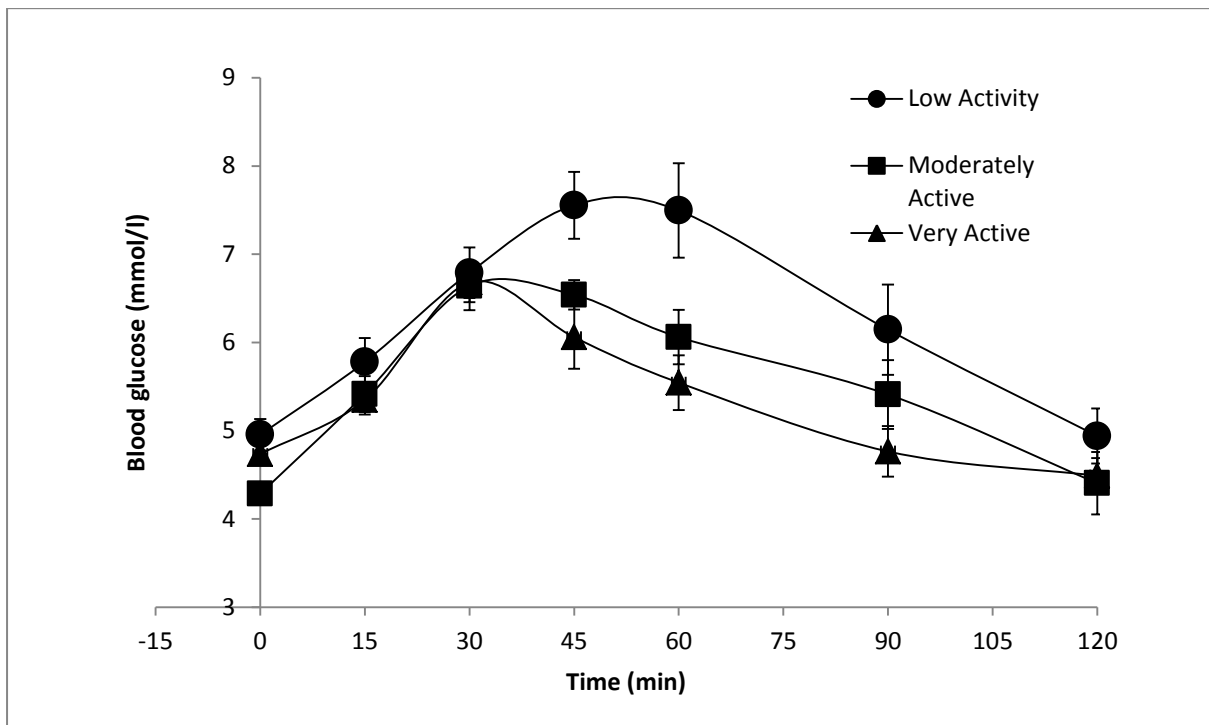


Figure 1: Mean blood glucose by physical activity group.

Error bars represent standard error of mean.

Table 3: Unadjusted linear model parameter estimates for one-hour glucose

	Parameter	SE	p
BMI (kg/m ²)	0.085	0.071	0.239
Age (years)	0.047	0.041	0.253
HBA1c (%)	2.177	1.149	0.069
Body fat (%)	0.106	0.061	0.090
Baseline			
glucose (mmol/l)	1.532	0.507	0.005
Physical			
activity (min/d)	-0.440	0.139	0.004
Intensity (MET)	-0.025	0.007	0.001
Gender (F v M)	1.156	0.581	0.057
Activity group			0.050
Very Active	1.950	0.564	0.002
v Low Activity			
Moderately Active	0.515	0.564	0.369
v Low Activity			

Each variable fitted in a univariate general linear model

Unadjusted model estimates in Table 3 show that higher one-hour blood glucose is significantly associated with higher baseline glucose and with Low Activity group compared with Very Active group. This may relate to duration or intensity of physical activity, both of which are individually significant. Although not statistically significant, higher HBA1c, higher body fat % and being female as opposed to male may also be associated with higher one-hour blood glucose. There does not appear to be an association between BMI and one-hour blood glucose.

Table 4: Linear model parameter estimates for one-hour glucose

	Parameter	SE	p
Intercept	-2.229	2.333	0.348
Baseline			
glucose (mmol/l)	1.499	0.484	0.005
Gender (F v M)	1.353	0.469	0.008
Activity group			0.029
Very Active v	1.350	0.472	0.008
Low Activity			
Moderately Active	0.513	0.550	0.360
v Low Activity			

All variables adjusted for all other variables in a single model.
R-Squared = 0.601 (Adjusted R-Squared = 0.537)

All variables were fitted into a forward stepwise model (Table 4) for one-hour glucose (with the exception of physical activity duration and intensity, which were determined by and highly correlated with activity group). Overall, activity group has a significant impact on 1-hour blood glucose ($p=0.029$), even when baseline blood glucose ($p=0.005$) and gender ($p=0.008$) are accounted for. The data suggest a mean increase in one-hour blood glucose of 1.50 mmol/l (95% CI: 0.5 – 2.5 mmol/l) for each additional 1.0 mmol/l of baseline glucose, and that, on average, females have one-hour blood glucose 1.35 mmol/l (95% CI: 0.4 – 2.3 mmol/l) higher than males. Even when these are taken into account, those in the Low Activity group have an average one-hour blood glucose 1.35 mmol/l (95% CI: 0.4 – 2.3 mmol/l) higher than those in the Very Active group, though the difference between Low Activity and Moderately Active groups is not significant. It should be noted that this model explains over 50% of the variation in 1-hour glucose in this sample.

Similar analyses were carried out on iAUC, peak blood glucose and time to peak. For iAUC there was no significant effect of activity group once gender and bodyfat % had been

accounted for. For peak blood glucose, the effect of activity group was not quite significant once gender and baseline glucose had been accounted for. Activity group was significantly associated with time to peak ($p=0.009$), with HbA1c not quite significant ($p=0.065$). Those in the Low Activity group took an average 14.8 (95% CI: 4.8 - 24.9) minutes longer to reach peak glucose level than those in the Very Active group and this was significant ($p=0.005$); the difference between the Moderately Active and Very Active groups was, on average, 13.8 (95% CI: 3.8 - 23.9) minutes and this was also significant ($p=0.009$).

4. Discussion

The main finding from this study is that healthy groups who are similar in terms of body composition, age and HbA1c but different in terms of volume and intensity of habitual physical activity, also have different responses to an oral glucose challenge indicating lower risk for T2D in the most physically active, even when differences in baseline blood glucose and gender are taken into account.

It is of note that only the Moderate Activity group had a statistically lower BMI than the Low Activity and Very Active groups. The Low Activity group, on average, would be classified as "overweight" whereas the other two groups are in the healthy range. However, there is no indication from this study that BMI in the healthy/overweight range is associated with blood glucose response, especially once baseline blood glucose levels are taken into account.

Only the Low Activity group do not meet the World Health Organization's target for adults to perform a minimum of 30 minutes physical activity on most days (their mean PA during the last month was 23 min/day). All subjects in all three groups also had healthy HbA1c values. In diabetic subjects there is often a reduction in HbA1c when subjects undertake an exercise regime¹¹. In the present investigation the blood glucose responses do not appear to be matched by commensurately 'poor' HbA1c values.

The peak values reflect how high an individual's blood glucose reaches after 50g of carbohydrate and this was highest in the present investigation in the Low Activity Group, lower in the Moderately Active group and lower still in the Very Active group ($P=0.009$), but this effect did not remain significant once baseline blood glucose and gender were accounted for. Even in groups of healthy individuals there appears to be a disparity in blood glucose response determined by volume and intensity of physical activity and the failure to reach statistical significance may be due to small numbers in this pilot study. This needs

interpreting with caution and confirming in a larger study of healthy individuals matched closely for factors potentially affecting blood glucose response but diverse in terms of physical activity volume and/or intensity.

In the present investigation, the time to peak is slower, the peak is higher and the return to baseline slower amongst the low activity subjects. This indicates poorer glucose tolerance in the Low Activity group versus the Moderately Active and Very Active groups.²⁴²⁵

There was no significant difference in the iAUCs of the Moderately Active and Low Activity groups. There was a significant difference between the Very Active and the other two groups in response to 50g dose of glucose; however this difference did not remain significant once sex and % body fat had been accounted for. It is possible, however, that there is an increasing level of blood glucose control commensurate with the increase in volume and intensity of physical activity which again might be easier to detect with a larger number of subjects.

The baseline glucose concentrations and HbA1c levels recorded for all our participants fell in the healthy-normal range. As a standalone measure this would not tell the full story of someone's response to carbohydrate intake, because the baseline glucose levels only partly predict the value at 1 and 2 hours post intake.²⁶ Alyass and colleagues suggest that 1 hour glucose levels are a key predictor in T2D risk and that a 1 hour value of 8.9 mmol/l outperforms other key indicators of diabetes risk (age, sex, BMI, family history of type 2 diabetes). In the present study, the Low Activity group's blood glucose rises were clearly greater than the two comparator groups, suggestive of lower insulin sensitivity in the least active. Alyass and colleagues also suggest the 1 hour value has a greater predictive accuracy for T2D than HbA1c ²⁶. In the present study 5 of the 10 Low Activity subjects had values of ≥ 8.0 mmol/l at 1 hour and this was zero out of ten in both the active and very active groups. Other work has suggested the shape of the glucose curve and elevated one hour values are predictive of risk for T2D, for example subjects with curves similar to those found in the Low Activity group for the present investigation, were found to be at 5 times the risk for T2D of those who had normal glucose tolerance 7-8 years post-testing.²⁷ It seems unlikely with age and body fat percentage being so closely matched that these factors would explain the difference. It is more likely that the amount and intensity of physical activity is the key determinant of blood glucose response to a 50g dose of glucose. In the present investigation, there are signs of comparatively impaired glucose tolerance in the low activity subjects (i.e.

close to 8 mmol/l at 1 hour) which may suggest a continuum from high risk to low risk by duration/frequency and intensity of PA.

The evidence that the risk of T2D is lowered, and that in diabetics the control of their condition is positively affected by physical activity is extensive and compelling.²⁸⁻³³ This protection is irrespective of whether the physical activity is aerobic or anaerobic in nature.³³ It has, however, been suggested that the two modes of exercise combined (resistance training and aerobic exercise) may offer greatest protection.²⁸ More activity than being sedentary is helpful but intense activity is probably best in terms of dramatically affecting blood glucose dynamics. In this respect, activity and more critically, intense activity have been shown to be valuable tools in the prevention of T2D.³²

The mechanisms through which aerobic and resistance exercise improve blood glucose control have yet to be fully elucidated, but several mechanisms have been proposed. Aerobic exercise increases insulin sensitivity possibly through: (i) altering adipokine profiles.³⁴ and/or (ii) decreasing the concentrations of intramyocellular lipid intermediates, such as diacylglycerol and various ceramides that interfere with insulin signalling.³⁵⁻³⁷ Aerobic exercise also activates AMPK-PGC-1 α (5'-AMP-activated protein kinase -peroxisome proliferator-activated receptor- γ co-activator-1 α) signalling, which promotes the expression of GLUT4 in skeletal muscle thereby increasing glucose uptake.³⁸ The depletion of glycogen during aerobic exercise induces glycogen synthase and this enhances glucose disposal.³⁹ Resistance exercise also increases the expression of GLUT4 transport proteins (albeit through a different signalling pathway) and induces glycogen synthase, however, it seems to have benefits distinct from aerobic exercise.³³ For example, emerging evidence suggests that hypertrophy of type 2 muscle fibres increases glycolytic capacity and this enhances glucose clearance and hence blood glucose control.³⁰

Study limitations and further work:

The small number of participants in this study limits generalizability of the results and future work should be carried out with a greater number of participants. Subjects could also be better matched with reference to BMI, gender and baseline glucose; however, these variations do not appear to explain the significant difference in blood glucose values at 1 hour or a 53% disparity in the iAUC between the Low Activity and Very Active groups. It is difficult to

differentiate the effects of duration from those resulting from the intensity of physical activity, where these are highly correlated, and subjects with a wider range of physical activity patterns should be sought for further study. Further work could corroborate the physical activity data with a validated objective measure such as accelerometry.

5. Conclusion

This work confirms that, in seemingly healthy (non-diabetic) subjects more exercise is better than less and that high intensity exercise is best in terms of blood glucose control. Fasted blood glucose values and HbA1c do not identify or predict the overall iAUC in this study but higher baseline blood glucose values are associated with higher blood glucose response. Participants with a BMI meeting the WHO definition of 'healthy' and who undertake more than the minimum number of minutes recommended by expert committees on physical activity have more effective blood glucose control than those who do not; however it is the group with the highest intensity and volume of activity who have the lowest 1 hour postprandial blood glucose values, lowest iAUC values and shortest time to peak. Higher intensity exercise shows the most protective effects in relation to blood glucose control and diabetes risk; yet it is the exercise that individuals find most readily repeatable which matters. Attention should be focussed on the most effective methods for helping people become and maintain being physically active.

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