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Original article

Responses to oral glucose challenge differ by physical activity volume and intensity: A pilot study

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Abstract

Background: One-hour postprandial hyperglycemia is associated with increased risk of type 2 diabetes and cardiovascular disease. Physical activity (PA) 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 PA.

Methods: Thirty-one adults without diabetes (age 25.9 ± 6.6 years; body mass index 23.8 ± 3.8 kg/m^2; mean ± SD) were recruited and divided into 3 groups based on self-reported PA volume and intensity: low activity < 30 min/day of moderate-intensity activity (n = 11), moderately active ≥ 30 min/day of moderate-intensity PA (n = 10), and very active ≥ 60 min/day of PA at high intensity (n = 10). Participants completed an oral glucose tolerance test (50 g glucose) with capillary blood samples obtained at baseline, 15 min, 30 min, 45 min, 60 min, 90 min, and 120 min post-ingestion.

Results: There were no significant differences between groups for age or body fat percentage or glycated hemoglobin ($p > 0.05$). The groups were significantly different in terms of baseline glucose level ($p = 0.003$) and, marginally, for gender ($p = 0.053$) and BMI ($p = 0.050$). There was a statistically significant effect of PA on the 1-h postprandial glucose results ($p = 0.029$), with differences between very active and low activity groups ($p = 0.008$) but not between the moderately active and low activity groups ($p = 0.360$), even when baseline glucose level and gender differences were accounted for. For incremental area under the curve there was no significant effect of activity group once gender and body fat percentage had been accounted for ($p = 0.401$). Those in the low activity group took 15 min longer to reach peak glucose level than those in the very active group ($p = 0.012$).

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

Keywords: Blood glucose response; Incremental area under the curve; Oral glucose tolerance test; Physical activity; Time to peak; Type 2 diabetes

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 behavior is strongly predictive of type 2 diabetes (T2D).[2] Western populations have high rates of sedentary behavior and low levels of participation in physical activity (PA) combined with high rates of diagnosed and undiagnosed T2D.[1–3] It has been suggested that 30 min of PA a day may represent the cut-off point at which people begin to accrue benefits to blood glucose control.[4] PA 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 PA.[8] Participation in formal PA (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

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preventing T2D, may need to focus on avoiding sedentary behavior in addition to the promotion of planned exercise.

Previous randomized controlled trials have found interventions involving around 150 min a week of PA have lowered the risk of progressing from impaired glucose tolerance to T2D by over 50%.[6,12] PA 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.[12] Despite this connection between PA 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.[13,14]

Both chronic participation and acute bouts of PA clearly affect blood glucose control and in all probability frequency and intensity have an impact. An example from studies focusing on the effects of single bouts of exercise show insulin sensitivity is improved for only 1−3 days.[15,16] 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 PA 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 PA. 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, moderately 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-h 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 years, body mass index (BMI) 23.8 ± 3.8 kg/m^2, and body fat percentage 24.15% ± 4.21%; mean ± SD). Subjects were recruited via email advertisements, which specifically asked for individuals who undertook low, moderate, or high levels of habitual PA. 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/day of PA at or below moderate intensity; moderately active: ≥30 min/day of PA at moderate intensity; and very active: ≥60 min/day of PA at high intensity. Classification into "level of activity" group was based on the mean duration of PA, determined using the Scottish Physical Activity Questionnaire (SPAQ)[17] and the mean intensity of exercise calculated using a 1−10 Borg scale.[18] The SPAQ asks participants to report the PA they have undertaken at home and work during the last month via an interview with a data recorder familiar with the questionnaire. The estimated mean metabolic equivalents (METs) were calculated from the mean number of minutes of PA and the mean rating of perceived exertion values using the compendium of PAs.[19]

The exclusion criteria were age <19 years or >59 years, presence of diabetes (as per the World Health Organization (WHO) definition of diagnosis[20]), 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 were collected. The study was approved by Sheffield Hallam University Ethics Committee.

2.2. Procedures

All subjects attended the research laboratory after a 12-h fast on 2 occasions separated by a week. They were instructed to avoid alcohol and limit PA on the day prior to each test day and to eat the same meal at the same time in 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 Ltd., Birmingham, UK). 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 kg/m^2. 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 min of supine rest. Body fat percentage and lean weight (kg) were recorded to the nearest 0.1% and 0.1 kg, respectively. On the 1st test day, subjects provided a capillary blood sample for the determination of glycated hemoglobin (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 1st sip of glucose solution and further measurements were made at 15 min, 30 min, 45 min, 60 min, 90 min, and 120 min. Subjects returned to the laboratory 1 week later and the oral glucose test was repeated. The mean blood glucose responses of the 2 visits were used for subsequent statistical analysis. Capillary samples of blood were obtained using sterilized Softclix lancets (Roche Diabetes Care Ltd., Surrey England, UK) and blood glucose was measured with One-Touch Ultra 2 glucose meters (Johnson & Johnson, Livingstone, Scotland, UK). Each measurement was taken in duplicate. The proposed covariance for glucose meters suggests allowing an error margin of 5%−10%.[21] A control solution was used to verify the accuracy of the glucose meters and a covariance of 4.63% was calculated based on 10 replicates. Whole blood HbA1c was measured on

an Alere Afinion AS100 analyzer (Alere San Diego Inc., San Diego, CA, USA).

2.3. Data analysis

iAUC was calculated by the trapezoidal method outlined by Wolever et al.[22] Differences between the activity groups in BMI, age, HbA1c, body fat percentage, PA duration and intensity, and baseline glucose level were ascertained by one-way analysis of variance (ANOVA) while Fisher's Exact test was used to compare the sex composition of the groups. The primary outcomes of glucose concentration after 1 h and iAUC, together with time to peak, peak glucose level, and final glucose concentration (after 2 h) were compared across groups using one-way ANOVA. General linear models were then fitted to the primary outcomes to adjust for differences between the groups in baseline glucose level, gender, and BMI. Significance level was set at $\alpha = 0.05$, and all analyses were performed using SPSS Version 23.0 (IBM Corp., Armonk, NY, USA).

3. Results

One subject, in the low activity group, displayed values that 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 PA differed across the groups, both in intensity and duration ($p < 0.001$). There were, however, significant differences at baseline between groups for blood glucose level ($p = 0.003$) and, marginally, for BMI ($p = 0.050$), 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 PA were found to be highly correlated ($r = 0.903$) in the study sample.

Table 2 shows the outcome measures for blood glucose level across the 3 activity groups. All outcome measures differ significantly between groups with the exception of the 2-h post-test when blood glucose level 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, where the very active group has a much-reduced average level.

Fig. 1 shows the mean blood glucose responses for the 3 groups over 120 min. Blood glucose level peaked, on average, at around 30 min post-test for those in the very active and moderately active groups and somewhat later for the low active group. For those in the low activity group, the peak level was considerably higher than the other 2 groups and remained higher for the duration of the test.

Unadjusted model estimates in Table 3 show that higher 1-h blood glucose level is significantly associated with higher baseline glucose level ($p = 0.005$) and with the low activity group compared with the very active group ($p = 0.002$). This may relate to duration or intensity of PA, both of which are individually significant ($p = 0.004$ and $p = 0.001$, respectively). Although not statistically significant, higher HBA1c, higher body fat percentage, and being female as opposed to male may also be associated with higher 1-h blood glucose level. There does not appear to be an association between BMI ($p = 0.239$) or age ($p = 0.253$) and 1-h blood glucose level.

All variables were fitted into a forward stepwise model (Table 4) for 1-h glucose level (with the exception of PA dura-

Table 1
Baseline characteristics of participants (mean ± SD).

	Low activity ($n = 10$[a])	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 (year)	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/day)	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
Male (%)	70	100	50	0.053

[a] 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.
Abbreviations: BMI = body mass index; HbA1c = glycated hemoglobin; MET = metabolic equivalent.

Table 2
Blood glucose outcome measures (mean ± SD).

	Low activity ($n = 10$)[a]	Moderately active ($n = 10$)	Very active ($n = 10$)	p
1-h post-test (mmol/L)	7.50 ± 1.69	6.06 ± 0.97	5.55 ± 0.98	0.005
iAUC (mmol/L/120 min)	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
2-h post-test (mmol/L)	4.94 ± 0.99	4.40 ± 1.12	4.49 ± 0.63	0.401

[a] 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.
Abbreviation: iAUC = incremental area under the curve.

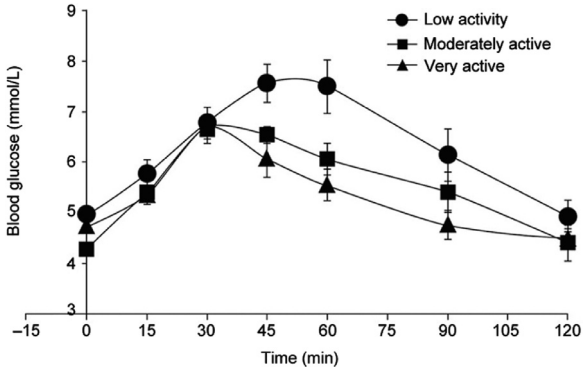

Fig. 1. Mean blood glucose by physical activity group. Error bars represent standard error of mean.

tion and intensity, which were determined by and highly correlated with activity group). Overall, activity group has a significant impact on 1-h blood glucose level ($p = 0.029$), even when baseline blood glucose level ($p = 0.005$) and gender ($p = 0.008$) are accounted for. The data suggest a mean increase in 1-h blood glucose level of 1.50 mmol/L (95% confidence interval (CI): 0.5−2.5) for each additional 1.0 mmol/L of baseline glucose level, and that, on average, females have 1-h blood glucose level of 1.35 mmol/L (95%CI: 0.4−2.3) higher than males. Even when these are taken into account, those in the low activity group have an average 1-h blood glucose level 1.35 mmol/L (95%CI: 0.4−2.3) higher than those in the very active group, though the difference between low activity and moderately active groups is not significant ($p = 0.360$). It should be noted that this model explains over 50% of the variation in 1-h glucose level in this sample.

Table 3
Unadjusted linear model parameter estimates for 1-h glucose level.

	Parameter	SE	*p*
BMI (kg/m^2)	0.085	0.071	0.239
Age (year)	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/day)	−0.440	0.139	0.004
Intensity (MET)	−0.025	0.007	0.001
Gender (female *vs.* male)	1.156	0.581	0.057
Activity group			0.050
Very active *vs.* low activity	1.950	0.564	0.002
Moderately active *vs.* low activity	0.515	0.564	0.369

Note: Each variable fitted in a univariate general linear model.
Abbreviations: BMI = body mass index; HbA1c = glycated hemoglobin; MET = metabolic equivalent.

Table 4
Linear model parameter estimates for 1-h glucose level.

	Parameter	SE	*p*
Intercept	−2.229	2.333	0.348
Baseline glucose (mmol/L)	1.499	0.484	0.005
Gender (female *vs.* male)	1.353	0.469	0.008
Activity group			0.029
Very active *vs.* low activity	1.350	0.472	0.008
Moderately active *vs.* low activity	0.513	0.550	0.360

Notes: All variables adjusted for all other variables in a single model. $R^2 = 0.601$; adjusted $R^2 = 0.537$.

Similar analyses were carried out on iAUC, peak blood glucose level, and time to peak. For iAUC there was no significant effect of activity group once gender and body fat percentage had been accounted for. For peak blood glucose level, the effect of activity group was not quite significant once gender and baseline glucose level 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 15 min longer to reach peak glucose level than those in the very active group ($p = 0.012$); the difference between the moderately active and very active groups was, on average, 13.8 min 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 PA, 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 level 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 2 groups are in the healthy range. However, there is no indication from this study that BMI in the healthy or overweight range is associated with blood glucose response, especially once baseline blood glucose levels are taken into account.

Only the low activity group did not meet the WHO target for adults to perform a minimum of 30 min PA on most days (their mean PA during the last month was 23 min/day). All subjects in all 3 groups also had healthy HbA1c values. In diabetic subjects there is often a reduction in HbA1c level when subjects undertake an exercise regimen.[11] 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 level reaches after 50 g 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 but this effect did not remain significant once baseline blood glucose level 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 PA and the failure to reach statistical significance may be due to small numbers in this pilot study. This discrepancy needs interpreting with caution and confirmed in a larger study of healthy individuals matched closely for factors potentially affecting blood glucose response but diverse in terms of PA volume and intensity.

In the present investigation, the time to peak is slower, the peak is higher, and the return to baseline is slower among the low activity subjects. This difference indicates poorer glucose tolerance in the low activity group versus the moderately active and very active groups.[23,24]

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 2 groups in response to 50-g dose of glucose; however, this difference did not remain significant once gender and body fat percentage 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 PA, 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 finding 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-h and 2-h post intake.[25] Alyass and colleagues[25] suggested that 1-h glucose levels are a key predictor in T2D risk and that a 1-h value of 8.9 mmol/L outperforms other key indicators of diabetes risk (age, gender, BMI, and family history of T2D). In the present study, the low activity group's blood glucose level rises were clearly greater than the 2 comparator groups, suggestive of lower insulin sensitivity in the least active. Alyass and colleagues[25] also suggested the 1-h value had a greater predictive accuracy for T2D than HbA1c. In the present study five of the 10 low activity subjects had values of $\geq$8.0 mmol/L at 1-h and nobody had values of $\geq$8.0 mmol/L at 1-h in both the moderately active and very active groups. Other work has suggested the shape of the glucose curve and elevated 1-h 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 comparted to those who had normal glucose tolerance 7−8 years post-testing.[26] 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 PA is the key determinant of blood glucose response to a 50-g 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-h), 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 PA, is extensive and compelling.[4,27−31] This protection is irrespective of whether the PA is aerobic or anaerobic in nature.[31] It has, however, been suggested that the modes of exercise combined (resistance training and aerobic exercise) may offer the greatest protection.[27] 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.[4]

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 (1) altering adipokine profiles[32] or (2) decreasing the concentrations of intramyocellular lipid intermediates, such as diacylglycerol and various ceramides that interfere with insulin signaling,[33−35] or both. Aerobic exercise also activates 5′-AMP-activated protein kinase-peroxisome proliferatoractivated receptor-γ co-activator-1α signaling, which promotes the expression of glucose transporter 4 in skeletal muscle thereby increasing glucose uptake.[36] The depletion of glycogen during aerobic exercise induces glycogen synthase and this enhances glucose disposal.[37] Resistance exercise also increases the expression of glucose transporter 4 (albeit through a different signaling pathway) and induces glycogen synthase; however, it seems to have benefits distinct from aerobic exercise.[31] For example, emerging evidence suggests that hypertrophy of type 2 muscle fibers increases glycolytic capacity and this enhances glucose clearance and hence blood glucose control.[29]

This study has some limitations. 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 level; however, these variations do not appear to explain the significant difference in blood glucose values at 1-h 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 PA, where these are highly correlated, and subjects with a wider range of PA patterns should be sought for further study. Further work could corroborate the PA 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 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 PA 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-h 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 that matters. Attention should be focused on the most effective methods for helping people become and maintain being physically active.

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Authors' contributions

TNS conceived the study design, carried out the data collection, and drafted the manuscript; CM and KK assisted in the drafting of the manuscript and the statistical analysis; AL and CO assisted in the drafting of the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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