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BRIEF REPORT

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Associations of sedentary time, physical activity, and fitness with muscle glucose uptake in adults with metabolic syndrome

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Objective: The objective of the study was to investigate the associations of sedentary time, physical activity, and cardiorespiratory fitness with skeletal muscle glucose uptake (GU).

Methods: Sedentary time and physical activity were measured with accelerometers and VO_2max with cycle ergometry in 44 sedentary adults with metabolic syndrome. Thigh muscle GU was determined with [^{18}F]FDG-PET imaging.

Results: Sedentary time ($\beta = -0.374$), standing ($\beta = 0.376$), steps ($\beta = 0.351$), and VO_2max ($\beta = 0.598$) were associated with muscle GU when adjusted for sex, age, and accelerometer wear time. Adjustment for body fat-% turned all associations non-significant.

Conclusion: Body composition is a more important determinant of muscle GU in this population than sedentary time, physical activity, or fitness.

KEYWORDS

insulin resistance, physical activity, positron emission tomography, sedentary behavior, skeletal muscle

Section Specialty Area: Health, Disease & Physical Activity.

1 | INTRODUCTION

Physical activity and cardiorespiratory fitness are known to protect against type 2 diabetes,[1] whereas sedentary time is associated with an increased diabetes risk.[2] Insulin resistance precedes type 2 diabetes, and skeletal muscles are in a central role in the development of insulin resistance, as they are responsible for ~80%–85% of total insulin-stimulated glucose uptake (GU).[3]

Exercise training has been shown to improve whole-body and skeletal muscle GU,[4] but the effects of sedentariness, standing, and non-exercise physical activity on GU are less known, particularly on the tissue level. Therefore, the aim was to investigate the associations of sedentary time, physical activity, and fitness with insulin-stimulated skeletal muscle GU in sedentary adults with metabolic syndrome. GU was assessed with ^{18}F-fluorodeoxyglucose ([^{18}F]FDG)-positron emission tomography (PET) imaging, combined with hyperinsulinemic-euglycemic clamp. The results can provide novel insights into the associations between lifestyle habits and tissue-specific insulin resistance.

2 | MATERIALS AND METHODS

The data were collected at the Turku PET Centre (Turku, Finland) 2017–2019. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (16/1810/2017), and good clinical practice and the Declaration of Helsinki were followed. All participants gave written informed consent before entering the study.

Participants were recruited from the local community according to the inclusion and exclusion criteria presented in Supplementary file S1. In short, the target population was 40–65 years old, sedentary, and physically inactive adults with metabolic syndrome.

The accelerometer data collection and analysis methods have been described in detail previously.[5] In summary, accelerometers (UKK AM30, UKK Institute, Tampere, Finland) were worn on the right hip during waking hours (except when exposed to water) for four consecutive weeks, and wear time of 10–19 h/day and at least 4 days of measurement were considered valid. The accelerometer data were analyzed with validated mean amplitude deviation and angle for posture estimation methods.[6,7] Sedentary time and standing were defined as ≤ 1.5, and light-intensity and moderate-to-vigorous physical activity as 1.5–2.9 and ≥ 3.0 metabolic equivalents, respectively.

Fitness was assessed by a progressive maximal cycle ergometer test (eBike EL Ergometer + CASE v6.7, GE Medical Systems Information Technologies Inc.) with direct respiratory gas measurements (Vyntus CPX, CareFusion). Test protocol and VO_2max determination criteria have been described in detail previously.[5]

Whole-body insulin-stimulated GU (μmol·kg body weight^{-1}·min^{-1}) was measured with a hyperinsulinemic-euglycemic clamp after fasting overnight. To quantify skeletal muscle insulin-stimulated GU (μmol·kg tissue^{-1}·min^{-1}), the clamp was combined with [^{18}F]FDG-PET imaging of the femoral region with a PET/CT scanner (GE D690, GE Healthcare) as previously described.[4] Detailed descriptions of the whole-body and muscle GU measurements are provided in Supplementary file S1.

Venous blood samples were drawn on the morning of PET imaging after at least 10 hours of fasting, and the samples were analyzed at the Turku University Hospital Laboratory as described in Supplementary file S1. Blood pressure was measured digitally. Weight, body fat-% and fat-free mass were estimated by air displacement plethysmography (Bod Pod, COSMED USA, Inc.) after fasting at least 4 hours. Height, BMI, and waist circumference were determined with standard methods.

Means (SD) or medians (Q1, Q3) were calculated, and differences between sexes were tested with unpaired t-test. The associations of sedentary time, physical activity, and fitness with GU outcomes were examined with linear regression models including the GU of quadriceps femoris, hamstrings, or the whole body as the dependent variable, and one activity/fitness outcome at a time as the independent variable. Model 1 was adjusted for sex and age, and Model 2 additionally for body fat-%. All models with activity outcomes were adjusted for accelerometer wear time. The results are expressed as standardized β coefficients (95% CI). Sedentary time was stratified into quartiles and the differences in GU between groups were examined with one-way ANOVA. Statistical significance was set at $p < 0.05$ (two-tailed). Analyses were performed with JMP Pro 15.1.0 (SAS Institute Inc.), and figures were created with JMP Pro 15.1.0 and GraphPad Prism 5.01 (GraphPad Software). Further details on statistical analyses are provided in Supplementary file S1.

3 | RESULTS

The mean age of the participants (n = 44; 25 women) was 58.2 (SD 6.7) years and mean BMI 32.2 (4.5) kg·m^{-2}. Participants wore accelerometers for 14.6 (1.0) h, spent 10.2 (1.0) h sedentary, 1.8 (0.5) h standing, and took 5075 (1770) steps and 28 (8) breaks in sedentary time daily. Participant characteristics are presented in Table S1 in Supplementary file S2.

Quadriceps femoris and hamstrings GU strongly correlated with whole-body GU: $r = 0.85$ and $r = 0.91$, respectively ($p < 0.001$ for both). When adjusted for sex, age, and

TABLE 1 Associations of sedentary time, physical activity, and cardiorespiratory fitness with skeletal muscle and whole-body glucose uptake

	Quadriceps femoris GU[a] (μmol·kg tissue^{-1}·min^{-1})				Hamstrings GU[a] (μmol·kg tissue^{-1}·min^{-1})				Whole-body GU (μmol·kg body weight^{-1}·min^{-1})			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Sedentary time, h/day	−0.271 (−0.625, 0.084)	0.13	−0.109 (−0.448, 0.230)	0.52	−0.374 (−0.728, −0.019)	**0.04**	−0.199 (−0.531, 0.132)	0.23	−0.362 (−0.712, −0.012)	**0.04**	−0.180 (−0.498, 0.138)	0.26
Standing, h/day	0.295 (−0.062, 0.651)	0.10	0.156 (−0.180, 0.493)	0.35	0.376 (0.017, 0.734)	**0.04**	0.224 (−0.105, 0.553)	0.18	0.405 (0.061, 0.749)	**0.02**	0.253 (−0.054, 0.560)	0.10
Steps/day	0.287 (−0.031, 0.606)	0.08	0.088 (−0.238, 0.414)	0.59	0.351 (0.031, 0.672)	**0.03**	0.133 (−0.188, 0.455)	0.41	0.343 (0.032, 0.653)	**0.03**	0.107 (−0.197, 0.412)	0.48
Breaks in sedentary time/day	0.209 (−0.158, 0.576)	0.26	0.099 (−0.237, 0.435)	0.55	0.352 (−0.013, 0.717)	0.06	0.233 (−0.092, 0.559)	0.16	0.363 (0.011, 0.716)	**0.04**	0.244 (−0.062, 0.550)	0.12
VO_2max, mL·kg^{-1}·min^{-1}[b]	0.566 (0.216, 0.915)	**0.002**	0.266 (−0.193, 0.724)	0.25	0.598 (0.256, 0.940)	**0.001**	0.286 (−0.160, 0.732)	0.20	0.614 (0.299, 0.929)	**<0.001**	0.332 (−0.122, 0.786)	0.15

Note: Values expressed as standardized β coefficients (95% CI); all values on log10-scale.

Abbreviation: GU = glucose uptake.

Bold *p*-values indicate statistical significance ($p < 0.05$).

Model 1 adjusted for sex, age, and accelerometer wear time (for activity outcomes). Model 2 adjusted for sex, age, body fat-%, and accelerometer wear time (for activity outcomes).

[a]= data available for 43 participants.

[b]= data available for 41 participants.

accelerometer wear time, sedentary time was detrimentally, and standing time and step count beneficially associated with hamstring muscle and whole-body GU, whereas breaks in sedentary time associated only with whole-body GU. Cardiorespiratory fitness (VO_2max [mL·kg^{-1}·min^{-1}]) was associated with all three GU outcomes, when adjusted for sex and age (Table 1). Hamstrings and whole-body GU were lower with sedentary time ≥ 10.5 h/day compared with less sedentary time (Figure 1), and whole-body GU was higher with standing time ≥ 2.0 h/day compared with < 1.5 or 1.5- < 2.0 h/day (Figure S2 in Supplementary file S3). Correlations of steps and breaks in sedentary time with GU outcomes are illustrated with scatterplots in Figures S3 and S4 in Supplementary file S3. Additional adjustment for body fat-% turned all above-mentioned associations non-significant (Table 1).

The associations of GU outcomes with different intensities of physical activity (light, moderate-to-vigorous), VO_2max per fat-free mass (mL·kg$_{FFM}$$^{-1}$·min^{-1}), maximal power output in the fitness test, and fasting blood lipids were also examined (Tables S3 and S4 in Supplementary file S2). Both muscle and whole-body GU were associated with free fatty acids, and muscle GU also associated with triglycerides and HDL.

4 | DISCUSSION

The findings suggest that sedentary time, standing, step count, and fitness are associated with skeletal muscle and whole-body GU. However, body adiposity appears to be a more important determinant of GU in this population of sedentary adults with metabolic syndrome, which again emphasizes the importance of healthy body composition in individuals at risk of developing metabolic diseases.

To our knowledge, this is the first study to investigate the associations between insulin-stimulated skeletal muscle GU and accelerometer-measured sedentary time and physical activity. Previously, muscle GU has been shown to increase acutely during exercise,[8] as well as following longer high- or moderate-intensity exercise training periods.[4,9] A few mechanisms have been proposed for the exercise training-induced enhancements in muscle insulin sensitivity, including increased glucose transporter GLUT4 concentration, mitochondrial volume, and glycogen synthase and oxidative enzyme activity.[10,11] Similar mechanisms may partly explain the associations between muscle GU and (in)activity outcomes in our study.

Our results regarding whole-body GU are similar to our previous results from a larger sample,[5] and this study extends those findings into tissue-level. The associations between muscle GU and activity outcomes were different in quadriceps femoris and hamstrings, which may be explained by the localized effects of muscular activity, as exercise studies have shown improved GU only in contracting muscles, both acutely and after 2 weeks of training.[4,12] Higher-intensity activities activate primarily quadriceps femoris, whereas hamstrings are considered postural muscles. Moreover, high body mass requires increased activation of postural muscles to support upright positions.[13] It is thus logical that in our sedentary and overweight/obese population, who did virtually no vigorous activity, hamstring GU was 55% greater than quadriceps femoris GU, and more hamstring-related associations were observed.

However, adjustment for body adiposity eliminated all associations between GU and activity/fitness outcomes. The importance of adiposity in the GU regulation has also been indicated by previous PET studies, as abdominal obesity and obesity-induced elevation in plasma free fatty acids have been shown to decrease both whole-body and muscle GU,[14,15] and contribution of adipose tissue to whole-body GU is larger with higher fat mass.[16] Furthermore, individuals with obesity, metabolic syndrome, or type 2 diabetes often have increased intramuscular fat content and significantly fewer insulin-sensitive

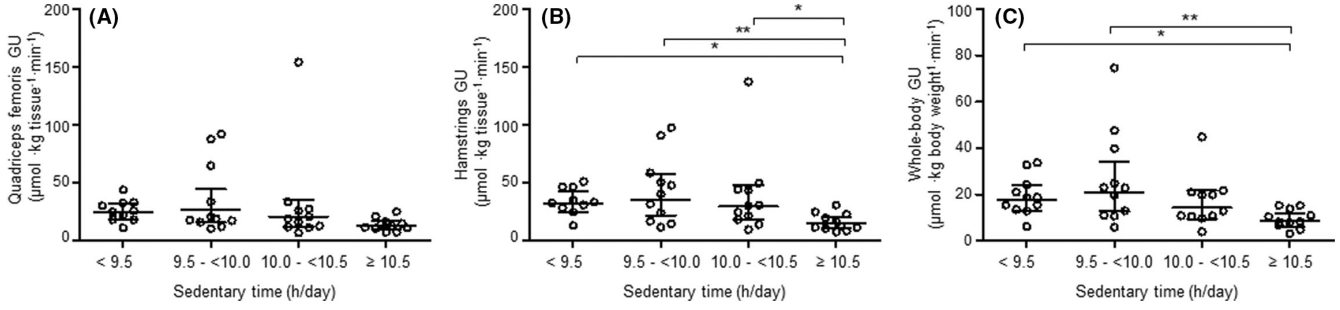

FIGURE 1 Differences in skeletal muscle and whole-body glucose uptake between quartiles of sedentary time (h/day) in inactive and sedentary adults with metabolic syndrome ($n = 44$). A) quadriceps femoris GU (µmol·kg tissue^{-1}·min^{-1}), B) hamstrings GU (µmol·kg tissue^{-1}·min^{-1}), C) whole-body GU (µmol·kg body weight^{-1}·min^{-1}). GU-values backtransformed from log10-scale and expressed as geometric means (95% CI). GU = glucose uptake. * = $p < 0.05$, ** = $p < 0.01$ between groups

type 1 muscle fibers than healthy adults, which promotes skeletal muscle insulin resistance.[17–19] Indeed, our participants had considerably lower whole-body and muscle GU in comparison with normal-weight adults.[20] Overall, our findings suggest that body adiposity is a major regulator and a more important determinant of both whole-body and muscle GU than sedentary time, physical activity, or fitness in sedentary adults with metabolic syndrome.

Major strengths of our study include the combination of PET imaging and hyperinsulinemic-euglycemic clamp, and the 4-week accelerometer measurement. The cross-sectional setting and the relatively small sample size can be considered limitations.

5 | CONCLUSION

Sedentary time, standing, step count, and cardiorespiratory fitness are associated with glucose uptake of hamstring muscles and the whole body in sedentary adults with metabolic syndrome. However, body adiposity appears to be a more important determinant of glucose uptake in this population, which further emphasizes the importance of focusing preventive efforts on attaining and maintaining healthy body composition in populations at increased risk of metabolic diseases.

AUTHOR CONTRIBUTIONS

I.H., J.K., K.K., T.V., and T.S. contributed to conception and design of the study. T.S., M.K., S.L., T.G., M.S., P.K., and N.H. contributed to data acquisition. O.E. and J.R. contributed to radiochemistry and isotope production. H.V-Y., T.S., T.G., S.L., E.L., and I.H. contributed to analysis and interpretation of data. T.G. drafted the manuscript, and all authors edited and revised the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

J.K. has received consultancy fees from GE Healthcare and AstraZeneca and speaker fees from GE Healthcare, Bayer, Lundbeck, Boehringer-Ingelheim and Merck, outside of the submitted work. The other authors declare that they have no competing interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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