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Lowering Physical Activity Impairs Glycemic Control in Healthy Volunteers

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Abstract

Introduction—Postprandial glucose (PPG) is an independent predictor of cardiovascular events and death, regardless of diabetes status. While changes in physical activity produce changes in insulin sensitivity, it is not clear whether changes in daily physical activity directly impact PPG in healthy, free-living persons.

Methods—We utilized continuous glucose monitors to measure PPG and PPG excursions (PPG; post- minus pre-meal blood glucose) at 30-min increments after meals in healthy, habitually active volunteers (n=12, Age 29±1 y, BMI 23.6±0.9 kg•m⁻², VO₂max 53.6±3.0 mL•kg⁻¹•min⁻¹) during three days of habitual (10,000 steps•d⁻¹) and reduced (<5,000 steps•d⁻¹) physical activity. Diets were standardized across monitoring periods, and fasting-state oral glucose tolerance tests (OGTT) were performed on the fourth day of each monitoring period.

Results—During three days of reduced physical activity (12,956±769 to 4,319±256 steps•d⁻¹), PPG increased at 30 and 60-min post-meal (6.31±0.19 to 6.68±0.23 mmol•L⁻¹ and 5.75±0.16 to 6.26±0.28 mmol•L⁻¹, P<0.05 relative to corresponding ACTIVE time point), and PPG increased by 42%, 97%, and 33% at 30, 60, and 90-min post-meal, respectively (P<0.05). Insulin and C-peptide responses to the OGTT increased after three days of reduced activity (P<0.05), and the glucose response to the OGTT did not change significantly.

Conclusions—Thus, despite evidence of compensatory increases in plasma insulin during an OGTT, PPG assessed by CGMS increased markedly during three days of reduced physical activity in otherwise healthy, free-living individuals. These data indicate that daily physical activity is an important mediator of glycemic control, even among healthy individuals, and reinforce the utility of physical activity in preventing pathologies associated with elevated PPG.

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The authors have nothing to disclose.

Keywords

exercise; glycemia; postprandial glucose; physical inactivity

INTRODUCTION

The prevalence of type 2 diabetes is increasing rapidly in the United States, with recent estimates indicating that 79 million Americans currently have prediabetes, and as many as one third of Americans will have type 2 diabetes by the year 2050 (9). Thus, efforts to identify strategies to prevent the development of type 2 diabetes are worthwhile. Elevated postprandial glucose (PPG) typically precedes the development of type 2 diabetes and is an independent risk factor for adverse cardiovascular events, regardless of diabetes status (22, 32, 34), making PPG a promising target for diabetes prevention. Physical inactivity is gaining acceptance as a key etiological factor in the development and progression of type 2 diabetes. However, despite physical activity guidelines recommending 10,000 steps per day (36), the majority of Americans acquire only half of the recommended dose (3).

Epidemiological evidence implicates low levels of physical activity in the development and progression of insulin resistance and type 2 diabetes (18, 25). While higher levels of physical activity are associated with reduced risk of developing insulin resistance and cardiovascular diseases (18, 25), individuals with type 2 diabetes consistently report lower levels of leisure time physical activity than their healthy counterparts (28) (see (4) for review). Bed rest, cessation of exercise training, and reduced ambulatory activity lead to declines in insulin sensitivity in healthy individuals (13, 17, 20, 29). Conversely, a single bout of moderate intensity exercise enhances insulin sensitivity in both healthy and insulin resistant individuals (17, 21).

Although the impact of physical inactivity on insulin sensitivity has been widely studied, classic experimental techniques to assess insulin sensitivity or glucose tolerance, including the hyperinsulinemic-euglycemic clamp, intravenous glucose tolerance testing, and oral glucose tolerance testing (OGTT), do not directly assess glycemic variability in free-living persons consuming mixed meals (6) and, therefore, fail to capture the day-to-day frequency, magnitude and duration of postprandial hyperglycemia (2, 5, 8). Thus, the direct impact of changes in physical activity on glycemic control is less clear. This is an important distinction given that postprandial glucose (PPG) is a strong, independent predictor of cardiovascular events and death, regardless of diabetes status (22, 32, 34).

Direct assessment of PPG is vital to determining the role of daily physical activity in maintaining normal glycemic control. Direct measures of PPG can now be made using continuous glucose monitoring systems (CGMS) capable of recording minute-to-minute measures of blood glucose over multiple days. From these measures, the magnitude and duration of PPG in free-living individuals consuming mixed meals can be determined (16, 23).

The specific effects of reducing physical activity on PPG are not well-defined. The purpose of this study was to evaluate the impact of reducing daily activity from the current physical

activity guidelines ($\geq 10,000$ steps per day) to the current norm ($\sim 5,000$ steps per day) for three days on PPG and glycemic variability in healthy, habitually active individuals. Given the powerful impact acute changes in physical activity have on experimental measures of insulin sensitivity and glucose disposal, we hypothesized that short-term reductions in physical activity would increase both PPG and glycemic variability in free-living individuals consuming mixed meals.

METHODS

All protocols were approved by the University of Missouri Health Sciences Institutional Review Board, and written informed consent was obtained from all volunteers. ClinicalTrials.gov number, NCT00881972.

Subjects

Young (20-35 years of age), generally healthy (determined by detailed medical history questionnaire), recreationally active (routinely acquire $\geq 10,000$ pedometer steps per day) volunteers were recruited for participation. Health status was determined by a detailed medical history questionnaire. Prior to enrollment in the study, participants were given pedometers and instructed to wear them for seven days while recording the number of steps taken each day. Volunteers who acquired $< 10,000$ steps per day were excluded from participation. Additional exclusion criteria included: body mass index $\geq 30 \text{ kg}\cdot\text{m}^{-2}$, smoking, pregnant, breast-feeding, consuming ≥ 14 servings of alcohol per week, or involvement in competitive endurance events.

Experimental Design

Following an overnight (10-12 hour) fast, participants were instrumented with CGMS (*iPro*TM CGM, Medtronic Diabetes, Northridge, CA), pedometers, and Intelligent Device for Energy Expenditure and Physical Activity monitors (IDEEA®, MiniSun, Fresno, CA) and were instructed to maintain habitual physical activity patterns while keeping detailed diet and physical activity records for three days (ACTIVE phase; Figure 1). Participants were also instructed to allot ≥ 2 hours between meals and snacks to allow for quantification of the 120 minute glucose response to meal ingestion (PPG and Δ PPG assessed via CGMS). On the morning of day four, a 2-hour OGTT (75 g glucose) was performed after an overnight fast (Figure 1).

Following a brief washout period (≥ 7 days), the protocol was repeated, and participants were instructed to reduce their physical activity to accumulate $\leq 5,000$ steps per day for three days (INACTIVE phase). Participants self-monitored physical activity during the INACTIVE phase using pedometers. Again, a 2-hour OGTT was performed following an overnight fast on the morning of day four. Four of the twelve participants completed the phases in reverse order (INACTIVE prior to ACTIVE) to reduce potential confounding effects of testing sequence.

In order to ensure that changes in PPG were due to changes in physical activity and not diet, participants were instructed to replicate their dietary patterns precisely (food and beverage

intake and timing) across the ACTIVE and INACTIVE phases. The OGTTs were performed at the same time in the morning across phases in order to eliminate diurnal influences.

Demographic measures

Height, weight, and body composition (dual energy x-ray absorptiometry, Hologic QDR 4500A, Waltham, MA) were measured at baseline. Diet records were analyzed for micro- and macronutrient content using Food Processor SQL (ESHA Research, Salem OR). Maximal oxygen consumption ($\text{VO}_{2\text{max}}$) was determined by indirect calorimetry (TrueOne 2400, Parvo Medics, Salt Lake City, UT) using the standard Bruce protocol (7).

Continuous Glucose Monitoring

At the onset of each CGMS monitoring period, a glucose sensor was inserted subcutaneously in the periumbilical region and connected to the CGMS for three days. Participants recorded precise periods of meal consumption and physical activity during the CGMS monitoring periods. Participants also recorded the timing and results of at least four finger stick glucose readings (Accu-check Compact Plus, Roche Diagnostics) each day for calibration against the CGMS recording. On the morning of the OGTTs, record books were collected, the glucose sensor was removed, and data from the CGMS were downloaded and processed using Solutions Software for CGMS *iPro* (Medtronic Diabetes). Using the start of meal times documented in the food records, glucose concentrations were extracted from the CGMS recordings at times corresponding to 5-min prior to meal ingestion and at 30 min intervals up to 120 min after meal ingestion [pre-meal and 30, 60, 90, and 120 min postprandial glucose (PPG), respectively]. Because, glycemic variability appears to be as important, if not more so, than absolute postprandial glucose concentrations, we also calculated ΔPPG , an index of glycemic variability, for the respective time points, where

$\Delta\text{PPG} = \text{post meal} - \text{pre meal blood glucose concentration; mmol}\cdot\text{L}^{-1}$. Peak ΔPPG was also calculated as: $\Delta\text{PPG}_{\text{peak}} = \text{peak post meal} - \text{pre meal blood glucose concentration; mmol}\cdot\text{L}^{-1}$, where the peak post-meal glucose value is the highest value recorded within 120 min of meal ingestion. Because we did not see an effect of meal or time on PPG or ΔPPG (PPG and ΔPPG were not different between meals or between day 1, 2 and 3 within each phase), PPG and ΔPPG were pooled across all meals and across all days within each phase for analysis.

Oral Glucose Tolerance Testing (OGTT)

On the fourth morning of each phase, OGTTs were performed following an overnight (10-12 h) fast. Blood samples were collected into serum separator or EDTA tubes at 0, 30, 60 and 120 min. Serum samples were allowed to clot for 10 min, and all samples were centrifuged at 2000 g for 15 min at 4°C. Serum and plasma were frozen at -80°C for subsequent analysis. Serum glucose was determined using the glucose oxidase method (Sigma), and serum insulin, C-peptide, cortisol, and growth hormone were measured by chemiluminescent enzyme immunoassay (Immulite 1000 Analyzer, Siemens Healthcare Diagnostics, Inc., Deerfield, IL). The area under curve (AUC) for glucose, insulin, C-peptide, cortisol, and growth hormone were calculated using the trapezoidal method.

Surrogate markers of insulin sensitivity and insulin resistance were calculated from the glucose and insulin responses to the OGTT using the Matsuda composite insulin sensitivity index (ISI) (26), with adjustments to exclude glucose and insulin measures at 90 min, and from fasting glucose and insulin values using the homeostasis model assessment of insulin resistance (HOMA-IR) (27), respectively.

Physical activity

Physical activity was quantified during each phase by pedometer and IDEEA monitors, which can recognize and distinguish the type, onset, duration, and intensity of fundamental movements with 98% accuracy (40). Participants were equipped with pedometers and IDEEA monitors at the time the CGMS monitors were inserted and activated. Similarly, the pedometers and IDEEA monitors were collected at the OGTT. IDEEA data were then downloaded and processed using Actview Software (MiniSun). Pedometer use is well-established as a valid index of physical activity levels and correlates strongly with those obtained by accelerometers (35, 37). Therefore, pedometers were used in the current study as previously described (20) to allow participants to self-monitor daily activity and to ensure compliance with reduced activity during the INACTIVE phase.

Statistical Analysis

Differences in repeated pre- and post-intervention measures were detected using 2-way repeated measures ANOVA. Where significant main effects were found, Tukey *post hoc* testing was applied to identify specific between phase differences. Paired t-tests were performed to detect between phase differences in paired observations. Statistical significance was set at $P < 0.05$, and all data are expressed as means $\pm$ SE. Statistical analyses were performed using SAS Version 9.1 (SAS Institute, Inc., Cary, NC)

RESULTS

Subjects

Twelve healthy volunteers (8 men, 4 women) participated in the study (Table 1).

Physical Activity

Participants acquired $12,956 \pm 769$ pedometer steps per day during the ACTIVE phase and $4,319 \pm 256$ steps/day during the INACTIVE phase (Figure 2A), indicating that they were highly compliant with reducing physical activity during the INACTIVE phase. On average, participants self-reported 38 ± 1 min of structured and/or planned physical activity per day during the ACTIVE phase, with approximately 19 ± 2 , 16 ± 4 , and 4 ± 2 minutes of activity being of self-reported as low, moderate, and high intensity, respectively each day. During the INACTIVE phase, participants reported only 3 ± 1 minutes of low intensity structured or planned walking per day.

Detailed physical activity data obtained from the IDEEA monitors is displayed in Table 2. Due to technical complications, accelerometer data is unavailable for five of the twelve participants. In agreement with the pedometer and self-reported data, the IDEEA analysis revealed significant reductions in the amount of time spent walking, climbing stairs, and

running ($P < 0.05$, versus ACTIVE phase). Similarly, ambulatory time decreased from $8 \pm 1\%$ of each day to $2 \pm 1\%$ ($P < 0.05$). It appears that during the INACTIVE phase, the majority of this time was spent sitting. However, the difference in sitting time between phases did not reach statistical significance ($P < 0.07$).

Glycemic Control

Three days of reduced physical activity in the healthy, previously active volunteers led to significant increases in PPG at 30 and 60 min and to increases in PPG of 30-50% at 30, 60 and 90 min post meal ($P < 0.05$; Figure 2B-C). Furthermore, peakPPG increased by 26% ($P < 0.05$; Figure 3). However, the reduction in physical activity did not influence pre-meal blood glucose concentrations measured by the CGMS (5.08 ± 0.09 vs. 4.93 ± 0.10 mmol•L⁻¹). The 24 hour average glucose concentration did not change (Table 3). However, the minimum and maximum glucose concentrations observed during each phase decreased and increased, respectively ($P < 0.05$). Similarly, the duration of time spent above target post-prandial blood glucose concentrations (> 8 mmol•L⁻¹) (19) increased during three days of reduced physical activity ($P < 0.05$).

Glucose tolerance

Following three days of reduced physical activity (INACTIVE), fasting plasma insulin (23.3 ± 3.2 to 34.2 ± 3.7 pmol•L⁻¹, $P < 0.05$) and C-peptide (0.43 ± 0.04 to 0.66 ± 0.09 nmol•L⁻¹, $P < 0.05$) were elevated, whereas fasting glucose (4.64 ± 0.13 to 4.75 ± 0.09) and the glucose responses to the 75g OGTT (Figure 3) were not significantly altered. Conversely, both insulin and C-peptide responses to the OGTT were increased significantly after the INACTIVE phase ($P < 0.05$; Figure 3), suggesting additional insulin was needed to dispose of the same glucose load. Correspondingly, the Matsuda ISI decreased from 14.26 ± 1.81 to 9.91 ± 0.76 ($P < 0.05$), and HOMA-IR increased from 0.83 ± 0.13 to 1.24 ± 0.14 after three days of reduced physical activity ($P < 0.05$).

Responses of the counter-regulatory hormones cortisol and growth hormone to the OGTT did not change in response to three days of reduced activity (data not shown).

DISCUSSION

Our data reveal robust changes in PPG and glycemic variability in response to short-term reductions in physical activity, providing new evidence that regular physical activity plays a key role in the day-to-day maintenance of glycemic control. Specifically, we demonstrate that PPG and PPG increase significantly during just three days of reduced physical activity (from ~12,000 to ~5,000 steps per day) in healthy individuals. Notably, these effects were not adequately captured by glucose responses to an OGTT, nor were they reflected by changes in fasting glucose concentrations.

Physical activity is widely recognized as an important component of a healthy lifestyle. Even a single bout of moderate to vigorous intensity exercise has been shown to improve insulin sensitivity in healthy individuals as well as those with type 2 diabetes (19, 23). More recently, CGMS has been used to demonstrate that a single bout of moderate intensity exercise significantly reduces the prevalence of hyperglycemia in patients with type 2

diabetes (24, 30). Conversely, transient physical inactivity, whether in the form of bed rest, exercise cessation, or reductions in ambulatory activity, can substantially reduce insulin sensitivity (13, 17, 20, 29). However, the impact of short-term reductions in physical activity on glycemic control is less clear. Findings from the present study indicate that as little as three days of reduced physical activity lead to increases in PPG by as much as two-fold in healthy individuals. Although additional studies are needed to evaluate the impact of chronic physical inactivity on PPG and PGG, these findings are particularly disturbing given the strong association between postprandial hyperglycemia and cardiovascular disease and death and in light of recent evidence that, on average, Americans acquire roughly 5,000 steps per day (3).

The health benefits of physical activity are commonly attributed to physiological adaptations to chronic exercise training, including increased cardiorespiratory fitness or lowered adiposity. However, previous work has established that adiposity and fitness are not significantly altered in response to ten days of physical inactivity in healthy volunteers (17), suggesting that they were not significantly impacted during three days of reduced activity in the present study. Although the importance of these factors in predicting health outcomes is widely accepted, the data presented here provide evidence that physical activity directly impacts postprandial glycemia, independent of altering fitness or adiposity. Accumulating evidence suggests large swings in blood glucose (glycemic variability) may be as deleterious as or potentially even more damaging than chronic hyperglycemia (10). Large fluctuations in blood glucose initiate the production of reactive oxygen species, increased leukocyte-endothelial interaction, and protein glycosylation (10, 38), which may contribute to the progression from insulin resistance to frank type 2 diabetes and may also drive micro- and macro-vascular complications in patients with insulin resistance and type 2 diabetes (8, 14, 34). Thus, maintenance of glycemic control may be one mechanism by which adequate physical activity protects against the development and progression of metabolic and cardiovascular diseases.

Disparities in energy intake and expenditure which result in an energy imbalance may contribute to changes in insulin sensitivity. However, reducing energy intake to maintain energy balance during one day of reduced ambulatory activity abrogates only a portion of the effects of reduced physical activity on insulin sensitivity (33), suggesting an imbalance in energy availability does not fully account for changes in insulin sensitivity during short-term changes in physical activity. Additionally, while overfeeding has been shown to reduce insulin sensitivity when combined with physical inactivity (12), short-term overfeeding alone does not produce significant changes in insulin sensitivity (1, 11). The complex interaction between short-term changes in physical activity and glycemic control is further supported by evidence that a single bout of low to moderate intensity exercise has a more robust impact on glycemic control than an isocaloric bout of high intensity exercise (24). Collectively these data suggest that the interaction between physical activity levels (and/or intensity) and short-term glycemic control may be more important than that between energy availability and glycemic control. Though confounding effects of an implied positive energy balance resulting from a decline in energy expenditure coupled with no change in energy intake cannot be explicitly ruled out in the present study, it is likely that these conditions

more appropriately mimic the physiological state of many individuals who acutely or chronically lower their activity levels but do not modify energy intake (3, 39).

We suspect that a reduction in skeletal muscle insulin sensitivity played a role in the increase in PPG and glycemic variability in the present study as a number of studies have demonstrated the deleterious effects of physical inactivity on skeletal muscle insulin signaling and sensitivity (13, 17, 20, 29). However, little is known about how reductions in physical activity influence the regulation of hepatic glucose production or pancreatic beta cell function, factors that may have played a role in the changes in PPG and PPG revealed in this study. Similar to our findings, Olsen et al. (29) recently reported no change in the glucose response to an OGTT coupled with a greater insulin response following two weeks of reduced ambulatory activity in healthy volunteers. Another study from the same group demonstrated that two weeks of reduced ambulatory activity altered skeletal muscle insulin signaling and sensitivity but not hepatic glucose production (20). These data support the premise that insulin secretion and/or clearance may adjust to compensate for decreases in skeletal muscle insulin signaling, at least during the early stages of reducing physical activity levels in an attempt to maintain euglycemia.

In the present study, despite evidence of enhanced insulin secretion (higher C-peptide concentrations) during the OGTT, PPG measured by CGMS increased by nearly two-fold in healthy individuals in response to reduced physical activity, suggesting the increases in circulating insulin following the OGTT were not replicated in response to mixed meals or were not sufficient to fully compensate for suspected declines in peripheral insulin sensitivity. Furthermore, fasting and pre-meal glucose concentrations were not elevated during three days of reduced activity, suggesting hepatic glucose production was not increased.

In agreement with previous reports, comparisons between PPG measured by CGMS and the laboratory-based OGTT revealed noteworthy differences in this study (15). We speculate that disparities between the two methodologies are likely attributable to differences in the macronutrient content of the 75 g glucose load ingested during the OGTT and the mixed meals consumed during CGMS monitoring. Unlike the OGTT, mixed meals contain fiber, lipids, amino acids, and micronutrients which impact enteric hormones, gastrointestinal motility, and neural impulses thereby influencing rates of absorption, gastric emptying and insulin secretion. As a result, mixed meals may produce a greater first phase insulin response and lower plasma glucose concentration relative to the OGTT (31). Additionally, OGTTs were performed in the morning after an overnight fast while participants remained supine, whereas CGMS captured PPG responses to meals consumed with and without prior periods of prolonged fasting with no restrictions on posture or movement during the postprandial period. Collectively, these data suggest CGMS may be a more sensitive method for detecting alterations in glycemic control in response to inactivity or other perturbations in free-living populations, including persons without diabetes.

A limitation of this study is the small sample size and homogeneous nature of the research participants. Further study with larger sample sizes is needed to evaluate the impact of transitioning to reduced physical inactivity in more diverse populations to determine if age,

sex, type of daily activity, body composition, glucose tolerance status, ethnicity, and other potential factors impact the degree to which changes in physical activity alter glycemic variability.

In summary, we demonstrate that physical activity plays a fundamental role in the day-to-day maintenance of PPG and glycemic control and that changes in PPG in response to reductions in physical activity levels occur rapidly and likely prior to changes in adiposity or fitness. These data also emphasize the need to look beyond common clinical measures of glycemic control when assessing the efficacy of interventions designed to improve this outcome. However, above all, our findings support a growing body of evidence implicating low levels of physical activity as an important etiological factor in the development of insulin resistance and reinforce the utility of physical activity in preventing pathologies associated with elevated PPG, including type 2 diabetes and cardiovascular disease.

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References

1. Adochio RL, Leitner JW, Gray K, Draznin B, Cornier MA. Early responses of insulin signaling to high-carbohydrate and high-fat overfeeding. *Nutr Metab (Lond)*. 6 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19781106>.
2. Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care*. 1997; 20(12):1822–6. [PubMed: 9405900]
3. Bassett DR Jr, Wyatt HR, Thompson H, Peters JC, Hill JO. Pedometer-measured physical activity and health behaviors in U.S. adults. *Med Sci Sports Exerc*. 2010; 42(10):1819–25. [PubMed: 20305579]
4. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *J Appl Physiol*. 2005; 99(3):1193–204. [PubMed: 16103522]
5. Bonora E, Corrao G, Bagnardi V, et al. Prevalence and correlates of post-prandial hyperglycaemia in a large sample of patients with type 2 diabetes mellitus. *Diabetologia*. 2006; 49(5):846–54.
6. Bonora E, Muggeo M. Postprandial blood glucose as a risk factor for cardiovascular disease in Type II diabetes: the epidemiological evidence. *Diabetologia*. 2001; 44(12):2107–14. [PubMed: 11793012]
7. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res*. 1971; 3(6):323–32. [PubMed: 5156892]
8. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J Clin Endocrinol Metab*. 2006; 91(3):813–9. [PubMed: 16352690]
9. Centers for Disease Control and Prevention. 2011 National Diabetes Fact Sheet. Atlanta, GA: Centers for Disease Control and Prevention, Centers for Disease Control and Prevention; Available from: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf [2011 May 05]

10. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008; 57(5):1349–54. [PubMed: 18299315]
11. Fox AK, Kaufman AE, Horowitz JF. Adding fat calories to meals after exercise does not alter glucose tolerance. *J Appl Physiol*. 2004; 97(1):11–6. [PubMed: 14978010]
12. Hagobian TA, Braun B. Interactions between energy surplus and short-term exercise on glucose and insulin responses in healthy people with induced, mild insulin insensitivity. *Metabolism*. 2006; 55(3):402–8. [PubMed: 16483886]
13. Hamburg NM, McMackin CJ, Huang AL, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *Arterioscler Thromb Vasc Biol*. 2007; 27(12):2650–6. [PubMed: 17932315]
14. Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T. Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD Study. Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes. *Diabet Med*. 2000; 17(12):835–40. [PubMed: 11168325]
15. Hasson RE, Freedson PS, Braun B. Use of continuous glucose monitoring in normoglycemic, insulin-resistant women. *Eur J Appl Physiol*. 2010; 108(6):1181–7. [PubMed: 20033205]
16. Hay LC, Wilmshurst EG, Fulcher G. Unrecognized hypo- and hyperglycemia in well-controlled patients with type 2 diabetes mellitus: the results of continuous glucose monitoring. *Diabetes Technol Ther*. 2003; 5(1):19–26. [PubMed: 12725703]
17. Heath GW, Gavin JR 3rd, Hinderliter JM, Hagberg JM, Bloomfield SA, Holloszy JO. Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J Appl Physiol*. 1983; 55(2):512–7. [PubMed: 6352578]
18. Hu FB, Sigal RJ, Rich-Edwards JW, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA*. 1999; 282(15):1433–9. [PubMed: 10535433]
19. International Diabetes Federation. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation, Clinical Guidelines Task Force; 2005. Available from: <http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf> [2011 May 05]
20. Krogh-Madsen R, Thyfault JP, Broholm C, et al. A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. *J Appl Physiol*. 2010; 108(5):1034–40. [PubMed: 20044474]
21. Larsen JJ, Dela F, Kjaer M, Galbo H. The effect of moderate exercise on postprandial glucose homeostasis in NIDDM patients. *Diabetologia*. 1997; 40(4):447–53. [PubMed: 9112022]
22. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch Intern Med*. 2004; 164(19):2147–55. [PubMed: 15505129]
23. Maia FF, Araujo LR. Efficacy of continuous glucose monitoring system (CGMS) to detect postprandial hyperglycemia and unrecognized hypoglycemia in type 1 diabetic patients. *Diabetes Res Clin Pract*. 2007; 75(1):30–4. [PubMed: 16806560]
24. Manders RJ, Van Dijk JW, van Loon LJ. Low-intensity exercise reduces the prevalence of hyperglycemia in type 2 diabetes. *Med Sci Sports Exerc*. 2010; 42(2):219–25. [PubMed: 19927038]
25. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA*. 1992; 268(1):63–7. [PubMed: 1608115]
26. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999; 22(9):1462–70. [PubMed: 10480510]
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28(7):412–9. [PubMed: 3899825]

28. Morrato EH, Hill JO, Wyatt HR, Ghushchyan V, Sullivan PW. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care*. 2007; 30(2):203–9. [PubMed: 17259482]
29. Olsen RH, Krogh-Madsen R, Thomsen C, Booth FW, Pedersen BK. Metabolic responses to reduced daily steps in healthy nonexercising men. *JAMA*. 2008; 299(11):1261–3. [PubMed: 18349087]
30. Praet SF, Manders RJ, Lieveverse AG, et al. Influence of acute exercise on hyperglycemia in insulin-treated type 2 diabetes. *Med Sci Sports Exerc*. 2006; 38(12):2037–44. [PubMed: 17146308]
31. Rijkkelijkhuizen JM, Girman CJ, Mari A, et al. Classical and model-based estimates of beta-cell function during a mixed meal vs. an OGTT in a population-based cohort. *Diabetes Res Clin Pract*. 2009; 83(2):280–8. [PubMed: 19097663]
32. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care*. 2001; 24(8):1397–402. [PubMed: 11473076]
33. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. *Metabolism*. 2011; 60(7):941–9. [PubMed: 21067784]
34. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care*. 2000; 23(12):1830–4. [PubMed: 11128361]
35. Tudor-Locke C, Ainsworth BE, Thompson RW, Matthews CE. Comparison of pedometer and accelerometer measures of free-living physical activity. *Med Sci Sports Exerc*. 2002; 34(12):2045–51. [PubMed: 12471314]
36. Tudor-Locke C, Bassett DR Jr. How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Med*. 2004; 34(1):1–8. [PubMed: 14715035]
37. Tudor-Locke C, Johnson WD, Katzmarzyk PT. Accelerometer-determined steps per day in US adults. *Med Sci Sports Exerc*. 2009; 41(7):1384–91. [PubMed: 19516163]
38. Wright E Jr, Scism-Bacon JL, Glass LC. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *Int J Clin Pract*. 2006; 60(3):308–14. [PubMed: 16494646]
39. Young LR, Nestle M. The contribution of expanding portion sizes to the US obesity epidemic. *Am J Public Health*. 2002; 92(2):246–9. [PubMed: 11818300]
40. Zhang K, Pi-Sunyer FX, Boozer CN. Improving energy expenditure estimation for physical activity. *Med Sci Sports Exerc*. 2004; 36(5):883–9. [PubMed: 15126725]

FIGURE 1. Study Design

Postprandial glucose responses were measured via continuous glucose monitoring systems (CGMS) during three days of habitual ($\geq 10,000$ step/d; ACTIVE phase) or reduced ($< 5,000$ steps/d; INACTIVE phase) physical activity in healthy volunteers. Participants also wore pedometers and IDEEA physical activity monitors and maintained detailed diet and physical activity records during each three-day period. Oral glucose tolerance tests (OGTT) were performed on the fourth day of each phase after an overnight fast. The phases were completed in reverse order in a subset ($n=4$) of participants.

FIGURE 2. (A) Daily pedometer steps

Number of steps taken each day by healthy volunteers (n=12) during three days of habitual (ACTIVE) or reduced physical activity (INACTIVE). □ Mean±SEM steps per day during the ACTIVE phase; ■ Mean±SEM steps per day taken during the INACTIVE phase. (B, C) Postprandial glucose (PPG) and glucose excursions (ΔPPG). Three days of reduced physical activity resulted in significant increases in (A) PPG and (B) PPG. PPG_{peak} was also significantly elevated. All data are expressed as means±SEM. *Significantly different from ACTIVE (P < 0.05).

FIGURE 3. Glucose Tolerance

Glucose (A, B), insulin (C,D), and C-peptide (E,F) responses to a 75 g oral glucose tolerance test in physically active, healthy volunteers before (ACTIVE) and after three days of reduced physical activity (INACTIVE). AUC – area under the curve. All data are expressed as means $\pm$ SEM. *Significantly different from baseline ($P < 0.05$).

TABLE 1**Participant Characteristics**

Age, y	29±1
Sex	8 male, 4 female
Weight, kg	75.0±4.4
BMI, kg•m ⁻²	23.6±0.9
Fat, %	21.0±2.0
VO ₂ max, mL•kg ⁻¹ •min ⁻¹	53.6±3.0
Energy intake, kcal•d ⁻¹	2742±170
Macronutrients, % kcals	
from carbohydrate	61±2
from fat	24±2
from protein	15±1

Characteristics of habitually active, healthy volunteers.

BMI – body mass index; VO₂max – maximal oxygen consumption; kcal – kilocalorie.

TABLE 2

Daily activities

	ACTIVE	INACTIVE
Ambulatory activities	111±6	29±6 [*]
Walking	90±8	28±5 [*]
Climbing stairs	6±2	1±1 [*]
Running or jogging	15±4	0 (0) [*]
Non-ambulatory activities	1359±25	1409±13 [†]
Reclining or lying down	432±58	388±80
Transitioning	8±1	5±1
Sitting	593±56	745±116 [†]
Standing	326±18	272±72

Time (minutes per day) spent performing ambulatory and non-ambulatory activities during three days of habitual (ACTIVE) or reduced (INACTIVE) physical activity in young, healthy subjects (n=7). All data are expressed as means±SE.

^{*} Significantly different from ACTIVE phase (P<0.05).

[†] Different from ACTIVE phase (P<0.10).

TABLE 3

Glycemic control

	Average blood glucose (mmol•L ⁻¹)	Minimum blood glucose (mmol•L ⁻¹)	Maximum blood glucose (mmol•L ⁻¹)	Duration below low limit (min)	Duration above high limit (min)
Day 1					
ACTIVE	5.42±0.17	3.99±0.15	7.60±0.26	24.58±19.36	8.08±4.90
INACTIVE	5.23±0.16	3.50±0.17*	7.7±0.33	44.17±14.48	18.46±7.02 [†]
Day 2					
ACTIVE	5.40±0.13	3.75±0.22	7.88±0.40	61.25±20.80	16.15±6.33
INACTIVE	5.48±0.10	3.46±0.20	7.79±0.40	57.08±19.18	19.62±8.89
Day 3					
ACTIVE	5.35±0.24	3.96±0.16	7.90±0.30	26.67±11.24	15.00±4.25
INACTIVE	5.48±0.29	3.59±0.19 [†]	8.39±0.58	40.33±23.66	55.00±23.35 [†]
Cumulative					
ACTIVE	5.44±0.10	3.32±0.17	8.58±0.36	112.50±33.20	40.42±12.78
INACTIVE	5.39±0.10	2.93±0.17*	9.38±0.51*	145.83±35.50	95.0±34.52*

Average, minimum, and maximal daily blood glucose and duration of blood glucose concentrations below 3.7 mmol•L⁻¹ or above 8 mmol•L⁻¹ during three days of habitual (ACTIVE) or reduced (INACTIVE) physical activity in young, healthy subjects (n=12). All data are expressed as means±SE.

* Significantly different from ACTIVE phase (P<0.05).

[†] Different from ACTIVE phase (P<0.10).