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Metabolic inflexibility during submaximal aerobic exercise is associated with glucose intolerance in obese older adults

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Abstract

Objective—People with type 2 diabetes have reduced cardiorespiratory fitness and metabolic impairments that are linked to obesity and often occur prior to the development of type 2 diabetes. We hypothesized that obese, older adults with impaired glucose tolerance (IGT) have lower ability to shift from fat to carbohydrate oxidation when transitioning from rest to submaximal exercise than normal glucose tolerant (NGT) controls.

Design and Methods—Glucose tolerance, body composition, and substrate oxidation (measured by RER: respiratory exchange ratio) during submaximal exercise (50% and 60% VO_{2max}) and insulin infusion (3-hour hyperinsulinemic-euglycemic clamp) were assessed in 23 sedentary, overweight-obese, older men and women.

Results—Obese subjects with NGT (n=13) and IGT (n=10) had similar resting RER, but during submaximal exercise those with IGT had a lower RER and less transition to carbohydrate oxidation than the NGT group ($P<0.05$). The IGT group also oxidized less carbohydrate during insulin infusion than NGT ($P<0.05$). RER at each exercise intensity independently correlated with120-minute postprandial glucose ($r= {}^{-}0.54–{}^{-}0.58$, $P<0.05$), but not with body composition, VO_{2max}, or RER during insulin infusion.

Conclusions—Obese, older adults have metabolic inflexibility during exercise that is associated with the degree of glucose intolerance independent of age and body composition.

Keywords

type 2 diabetes; metabolism; exercise physiology; substrate oxidation

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Introduction

Over 26% of older Americans have diagnosed or undiagnosed impaired glucose tolerance (IGT) (1), placing them at high risk for development of type 2 diabetes. Obesity is a major risk factor for IGT and type 2 diabetes, and is often accompanied by metabolic dysfunction such as abnormal fat and carbohydrate oxidation (2). These impairments may contribute to metabolic inflexibility, previously defined as the inability to switch from fat to carbohydrate oxidation in response to a meal or insulin administration (2). Obese, insulin resistant individuals and those with IGT are metabolically inflexible in response to insulin infusion, while lean, insulin sensitive subjects are metabolically flexible (2, 3). The concept of metabolic inflexibility also may extend to metabolism during aerobic exercise, wherein the normal response in the fasted state is to shift from utilizing fat to carbohydrate during the transition from rest to exercise of increasing intensity. Because fat cannot be oxidized at high enough rates to supply all of the energy for moderate to vigorous exercise, this shift from fat to carbohydrate oxidation supplies the necessary energy as exercise intensity increases (4). Previous studies show lower cardiorespiratory fitness levels in type 2 diabetes (5), and this may extend to obese, older adults with metabolic inflexibility and IGT.

Middle-aged and older, overweight-obese subjects with IGT often have metabolic abnormalities such as impaired glucose uptake in response to insulin, and also have lower glycogen content in skeletal muscle and higher intramyocellular lipid levels in the postabsorptive state. These metabolic abnormalities may affect the ability to switch from fat to carbohydrate oxidation when going from rest to exercise of increasing intensity. The results of studies examining substrate oxidation during exercise in obese young and middle-aged subjects vary (6–9), but two studies in insulin resistant subjects report lower carbohydrate oxidation during exercise in young insulin-resistant women (10) and middle-aged subjects with type 2 diabetes (6). While these studies indicate that abnormalities in fat and carbohydrate oxidation during exercise are related to obesity and/or insulin resistance, the metabolic response to exercise of increasing intensity has not been established in obese, older subjects with a clinically-relevant designation of IGT or normal glucose tolerance (NGT) to our knowledge. Therefore, this study was designed to test the hypothesis that the ability to shift from fat to carbohydrate oxidation during submaximal exercise (metabolic flexibility during exercise) is lower in overweight-obese older subjects with IGT compared with NGT controls. To accomplish this, we assessed metabolic flexibility during aerobic exercise at 50% and 60% of maximal cardiorespiratory fitness (VO_{2max}) levels and used a hyperinsulinemic-euglycemic clamp to confirm metabolic inflexibility during insulin infusion in obese, older adults with IGT compared with NGT controls.

Research Design and Methods

Subjects

Twenty-three sedentary (self-reported moderate-intensity activity less than 20 minutes on 2 or fewer days per week), overweight-obese (BMI 25–38 kg/m^2) men and women between the ages of 45 and 80 years old were recruited from the Baltimore metropolitan area. All subjects were non-smokers and had no previous diagnosis of diabetes or cardiovascular disease. Additional exclusion criteria included 1) cancer, thyroid, renal, hematological, or

pulmonary diseases; 2) taking medications such as beta-blockers, steroids, or medications normally prescribed for diabetes; and 3) poorly controlled hypertension or dyslipidemia, anemia, or recent weight change of more than 2kg. Prior to participation, all subjects had an asymptomatic screening treadmill exercise test. All subjects provided written informed consent. All study procedures were approved by the Institutional Review Board at the University of Maryland School of Medicine.

Study Protocol

Prior to research testing, all subjects received instruction on maintaining a weight-stable, Therapeutic Lifestyle Changes (TLC) diet (11), by a Registered Dietitian one day per week for 6–8 weeks. All subjects were weight-stable (±2%) for at least two weeks prior to research testing and were provided an isocaloric diet for two days before testing to control nutrient intake. Subjects were also asked to refrain from any moderate-to-vigorous physical exercise during this two-day period.

Maximal oxygen consumption (VO_{2max})

VO_{2max} was measured by indirect calorimetry (Quark, Cosmed USA, Chicago, IL) during a graded exercise test on a motorized treadmill as previously described (12). Briefly, subjects walked at a constant velocity throughout the protocol and grade was initially set to 0% and increased every 2 minutes thereafter to maximal effort. VO_{2max} was defined as the highest oxygen consumption value obtained for a full 30-second increment. All subjects attained VO_{2max} as evidenced by standard physiological criteria (respiratory exchange ratio >1.10 or a plateau in VO_2 with an increase in workload).

Oral glucose tolerance test (OGTT)

Subjects underwent a 2-hour OGTT after a 12-hour overnight fast. A catheter was placed in an antecubital vein and blood samples were drawn before and every 30 minutes after the ingestion of a 75-gram glucose solution for 2 hours. Blood samples were centrifuged and plasma was separated and stored at −80°C until analysis. Plasma glucose levels were analyzed with a glucose analyzer (2300 STAT Plus, YSI, Yellow Springs, OH). Plasma insulin levels were determined by radioimmunoassay (Millipore, St. Charles, MO). Glucose (G_{AUC}) and insulin (I_{AUC}) areas under the curve during the OGTT were calculated using the trapezoidal method. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as described by Matthews et al. (13), and the insulin sensitivity index (ISI_M) was calculated using the method of Matsuda and DeFronzo (14). Subjects were classified as having NGT or IGT by American Diabetes Association criteria (15). Two subjects with a 120-minute postprandial glucose greater than 11.1 mmol/l were included in the IGT group because their fasting plasma glucose concentrations were less than 7 mmol/l (i.e., isolated post-challenge hyperglycemia).

Resting and insulin-stimulated substrate utilization (hyperinsulinemic-euglycemic clamp)

All subjects reported for testing between 7:00 and 9:00am after a 12-hour overnight fast. Subjects underwent measurement of resting respiratory exchange ratio (RER) for determination of resting substrate utilization prior to the hyperinsulinemic-euglycemic

clamp. The subjects were instructed to lay supine and were covered with a canopy to capture expired air. VO_2 and VCO_2 were measured by indirect calorimetry (Quark, Cosmed USA, Chicago, IL) and recorded for 20 minutes, with the 20-minute averages used to calculate resting RER. Twenty of the twenty-three subjects (10 NGT and 10 IGT) underwent a three hour hyperinsulinemic–euglycemic glucose clamp (16, 17) as implemented in our laboratory with an insulin infusion rate of 555 pmol*m^{-2}*min^{-1}. Insulin-stimulated RER was measured during the last 30 minutes of the insulin infusion using the same procedure as that used for resting RER. Plasma insulin levels were determined by radioimmunoassay (Millipore, St. Charles, MO). Mean insulin levels during the clamp were 1214 ± 73 pmol/L and did not differ between groups (p = 0.75).

Measurement of substrate utilization during submaximal exercise

On a subsequent visit, subjects underwent submaximal exercise testing. All subjects reported for testing between 7:00 and 9:00am after a 12-hour overnight fast. Prior to the start of the test, RER values were confirmed to match resting RER (±2%). After a five-minute warm-up, data were collected during two continuous, 10-minute, steady state treadmill exercise bouts at 50% VO_{2max} and 60% VO_{2max} (calculated as % VO_2 reserve) as determined by breath-to-breath VO_2 measurements. The mean intensities achieved for each bout were 49.4 ± 0.5% VO_{2max} and 60.2 ± 0.6% VO_2 reserve, respectively. Data collected during the last five minutes of each workload were analyzed when subjects were at a steady state of exercise (VO_2 mean CV = 3.4%; CV was ≤6% in all subjects). Likewise, RER was stable during the 5-minute measurement period in each workload (RER mean CV = 1.1%, CV was <2% in all subjects. Data are reported as the average of this 5-minute period and the amount of kilocalories derived from fat and carbohydrate were calculated using the Weir equation (18).

Body mass index and body composition

Body mass index (BMI) was calculated by dividing body weight (kg) by height (m^2). Body weight was measured to the nearest 0.1 kg with an electronic scale and standing height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body composition (fat mass, lean mass, and percent body fat) was determined by dual energy X-ray absorptiometry (iDXA, LUNAR Radiation Corp., Madison, WI). Intra-abdominal (IAF) and subcutaneous abdominal fat (SAF) areas were determined by a computed tomography scan at the L_4–L_5 region using a Siemens Somatom Sensation 64 Scanner (Fairfield, CT) and Medical Image Processing, Analysis and Visualization software (MIPAV v.7.0.0, NIH, Bethesda, MD). Three subjects did not undergo computed tomography scans.

Statistical analysis

Data are presented as means ± SEM. All statistical analyses were performed using SPSS v12.0 (IBM, Armonk, NY). Repeated measures ANCOVA was used to test for differences between subjects with IGT and NGT, using sex as a covariate where appropriate. Pearson product-moment correlations and multivariable regression analyses were used to determine relationships between metabolic variables. A type I error rate of α=0.05 was selected and two-tailed probabilities are reported for all analyses.

Results

Subject characteristics are presented in Table 1. There were no differences in age, weight, or body composition, nor were there differences in the distribution of sex and race between the IGT and NGT groups. As expected, the 13 subjects with IGT had higher fasting plasma glucose, 120-minute postprandial glucose (G_{120}), and G_{AUC} compared to the 10 subjects with NGT ($P \leq 0.001$ for all). Subjects with IGT also had significantly lower ISI_M values, as well as higher HOMA-IR values, fasting plasma insulin concentrations, 120-minute postprandial insulin levels, and I_{AUC} than subjects with NGT ($P \leq 0.05$ for all). VO_{2max} was lower in subjects with IGT compared to those with NGT when expressed relative to lean body mass ($P = 0.03$).

Metabolic responses to submaximal exercise and insulin infusion

VO_2 and heart rate responses to submaximal exercise are also shown in Table 1. There were no statistically significant differences between the IGT and NGT groups for actual VO_2 and heart rate attained during submaximal exercise. At rest, RER was similar between the IGT and NGT groups. During sub-maximal aerobic exercise at 50% VO_{2max} and 60% VO_{2max}, the IGT group had a significantly lower RER than the NGT group in analyses accounting for sex (Figure 1A, $P = 0.03$ and $P = 0.01$, respectively). In the NGT group, RER increased over resting by 0.14 ± 0.02 and 0.16 ± 0.02 at 50% VO_{2max} and 60% VO_{2max}, respectively; in the IGT group, RER only increased over resting by 0.09 ± 0.02 and 0.10 ± 0.02 at 50% VO_{2max} and 60% VO_{2max}, respectively. Despite similar energy expenditure (kcal/kgLBM/min) between groups at each workload, the amount energy derived from fat was greater in the IGT at both intensities compared with the NGT group (Figure 1B, $P < 0.05$). At 50% VO_{2max}, the IGT group utilized 44% carbohydrate and 56% fat, while the NGT group utilized 57% carbohydrate and 43% fat ($P = 0.04$). When the intensity was increased to 60% VO_{2max}, the difference in carbohydrate utilization between the IGT and NGT groups was maintained (49% vs. 65% carbohydrate, respectively, $P = 0.02$).

In response to the insulin infusion during a hyperinsulinemic-euglycemic clamp, IGT subjects (n = 10) were metabolically inflexible compared with the NGT subjects (n=10). RER increased in response to insulin within each group ($P < 0.01$ for both groups); however, the increase in the IGT group was significantly less than the increase in the NGT group (0.07 ± 0.02 vs. 0.12 ± 0.02, $P < 0.05$).

Associations of metabolic responses to exercise with glucose tolerance

In bivariate analyses that included all subjects (n=23), RER at 50% and 60% VO_{2max} correlated with G_{120}, VO_{2max}, age, and percent body fat ($|r| > 0.41$ and $P < 0.05$ for all), but not IAF, SAF, insulin concentrations, ISI_M and HOMA-IR ($r = -0.26 – 0.19$, $P > 0.27$ for all). In addition, there was no correlation between the change in RER during insulin infusion (metabolic flexibility during insulin) and the change in RER during exercise (metabolic flexibility during exercise) at either intensity ($r = 0.00 – 0.07$, $P > 0.78$, n=20). Adjustment for insulin-stimulated glucose uptake during the clamp did not significantly affect these results.

We then performed multivariable regression analyses that included percent body fat, age, VO_{2max}, and G_{120} as potential predictors of RER during exercise, to determine which variables were independently related to metabolic responses during submaximal exercise (Table 2). Models including all four of these independent variables explained 44–46% of the variance in RER during exercise at 50% VO_{2max} and 60% VO_{2max} ($P \leq 0.02$). At 50% VO_{2max}, RER independently and inversely correlated only with G_{120} (Figure 2A, $P = 0.01$), but not with percent body fat nor VO_{2max}. Results were similar at 60% VO_{2max}, with RER independently and inversely correlated only with G_{120} (Figure 2B, $P = 0.008$), but not with age, percent body fat, nor VO_{2max}. The inclusion of either ISI_M or HOMA-IR in these regression models did not affect our results. Thus, the finding that higher fat oxidation during submaximal exercise is independently associated with glucose intolerance is consistent across these exercise intensities.

Discussion

The current study shows that glucose intolerant, obese, older adults at high risk for type 2 diabetes exhibit metabolic inflexibility in response to aerobic exercise transitioning from rest to 50% and 60% VO_{2max}, as well as metabolic inflexibility during insulin infusion when compared with older adults with NGT. We also show that the lower carbohydrate utilization during exercise of increasing intensity is related to the degree of postprandial hyperglycemia, but not to metabolic inflexibility in response to insulin infusion. Higher fat oxidation during exercise may seem advantageous to obese older adults; however, the normal response is to increase carbohydrate oxidation in order to supply sufficient energy to exercising muscle during acute aerobic exercise of increasing intensity. Thus, the inability to effectively regulate fat and carbohydrate oxidation during aerobic exercise could limit the ability to supply sufficient energy at higher levels of aerobic exercise in obese adults with IGT.

Our findings are concordant with previous reports of lower carbohydrate oxidation during submaximal exercise in younger insulin-resistant subjects (6, 10). The present report adds that carbohydrate oxidation is reduced during submaximal exercise in a larger group of older men and women with IGT, that the metabolic inflexibility is manifest prior to the development of type 2 diabetes, and that this abnormality persists as exercise intensity increases. Previous research shows that VO_{2max} is lower in subjects with type 2 diabetes (5) and we find that VO_{2max} also is lower in IGT compared with controls. In the present study, we chose not to measure substrate utilization at workloads higher than 50–60% VO_{2max} because VCO_2 rises disproportionately and confounds the interpretation of substrate utilization from RER. However, if this inflexibility persists beyond 60% VO_{2max}, it is possible that the lower shift to carbohydrate oxidation in subjects with IGT could contribute to the limitation of VO_{2max}. Although our IGT subjects were metabolically inflexible during exercise, the IGT and NGT groups did not differ with respect to their resting RER. A higher resting RER was previously described as a component of metabolic inflexibility in some subjects (19), but this was not observed in all cohorts (20). Similar resting RER values in our IGT and NGT groups may indicate that IGT subjects still suppress glucose oxidation normally under fasting conditions, or that defects in muscle glucose metabolism present at

rest are masked because skeletal muscle accounts for a smaller proportion of whole body metabolism at rest than during exercise.

Other studies report discordant results when examining substrate utilization during submaximal exercise in overweight or insulin-resistant and normal subjects (8–10, 21, 22). Goodpaster et al. (8) found that obese young men had lower rates of carbohydrate oxidation and higher fat oxidation during exercise compared with lean controls. Conversely, Hickner et al. (9) reported higher rates of carbohydrate oxidation during exercise in obese compared with lean, young, Caucasian women. We did not study lean subjects, but our assessment of percent body fat as a continuous variable in regression analyses indicates that within overweight-obese, older adults, the degree of obesity itself was not associated with reduced carbohydrate oxidation independent of glucose tolerance. Interestingly, the obese and lean young subjects studied by Goodpaster et al. (8) had fasting plasma glucose levels (5.5 vs. 5.0 mmol) similar to the IGT and NGT groups in this study, respectively. While Hickner et al. (9) did not report plasma glucose or insulin concentrations, it is possible that differences in glucose metabolism contribute to these disparate findings. Russell et al. (21) reported no difference in metabolic flexibility during passive stretching between subjects with or without type 2 diabetes and controls; however, VO_2 and RER did not significantly increase during the stretching protocol. Although Numao et al. (22) reported differences between overweight men and postmenopausal women in RER during submaximal cycling exercise at 50% VO_{2peak}, there were no differences between the men and women in the present study.

Similar studies have used stable isotopes to elucidate contributions of specific sources (i.e., muscle glycogen, plasma glucose, plasma fatty acids, and intramyocellular triglycerides) to substrate oxidation during exercise. Blaak et al. (23) reported higher oxidation of intramyocellular triglycerides during cycling exercise at 50% VO_{2max} in obese middle-aged men with type 2 diabetes compared to controls; however, oxidation of plasma-derived fatty acids was lower in type 2 diabetes and overall fat oxidation was not different between groups. In a subsequent report, Mensink et al. (24) reported numerically lower RER and numerically higher fat oxidation during exercise at 50% VO_{2max} in 7 middle-aged obese men with IGT compared to controls, but these differences did not reach statistical significance in the relatively small sample. One limitation of the present study is that stable isotope tracers were not used to assess specific substrate sources; thus, we cannot comment on specific limitations from each source during exercise.

The metabolic inflexibility observed during exercise may be the result of several metabolic abnormalities present in adults with IGT, including reduced glucose uptake by exercising muscle, the presence of ectopic fat and reduced glycogen stores, and mitochondrial dysfunction. Galgani et al. show that reduced glucose uptake may explain the differences observed in insulin-stimulated metabolic flexibility between subjects with type 2 diabetes and normal controls (20). We showed that skeletal muscle capillarization is lower in otherwise healthy older adults with IGT compared to those with NGT (25, 26), and levels of glucose transporter-4 (GLUT4) also may be lower in insulin resistant older adults with IGT. While these could both limit glucose uptake by muscle during exercise (27, 28), research shows similar levels of glucose uptake by skeletal muscle during exercise in subjects with type 2 diabetes and normal controls (29). Thus, the contribution of glucose uptake to

differences in metabolic flexibility may differ between insulin-stimulated and exercise conditions. We and others report higher intramyocellular lipid (30–32), as well as reduced glycogen synthesis and content in insulin resistant subjects (33, 34), but it is unclear whether a moderate reduction in glycogen stores would limit carbohydrate oxidation as seen in this study during a relatively short bout of exercise. Mitochondrial defects are also implicated in insulin-stimulated metabolic inflexibility [for review see (35)]; however, one would anticipate these mitochondrial defects would not preferentially limit fat or carbohydrate oxidation during exercise because the metabolic pathways of fatty acid oxidation and carbohydrate oxidation converge as they enter the mitochondria and are converted to acetyl-CoA.

The results of this study indicate that the strongest predictor of substrate oxidation during submaximal aerobic exercise in obese, older adults was glucose tolerance, and not age, body composition, or the degree of metabolic inflexibility during insulin infusion. While definitive conclusions cannot be drawn from our data at this time, the mechanisms underlying metabolic inflexibility during exercise may be distinct from those observed in insulin-stimulated metabolic inflexibility, and could be caused by other defects in the ability to metabolize carbohydrate during exercise. One possibility is at the point of pyruvate transport into the mitochondria or at the point of pyruvate conversion to acetyl-CoA by the pyruvate dehydrogenase complex. Pyruvate dehydrogenase expression is lower, and there is increased expression of pyruvate dehydrogenase kinase-4 (PDK-4) and PDK -2 (both inhibitors of pyruvate dehydrogenase) in insulin-resistant individuals and people with type 2 diabetes (36, 37). Constantin-Teodosiu et al. demonstrated that PDK-4 may inhibit carbohydrate oxidation during exercise, and that upregulation of pyruvate dehydrogenase may attenuate this inhibition (38). Conversely, it is possible that the present findings could simply reflect a preference for fat oxidation as a compensatory mechanism for higher intramyocellular lipid levels in IGT. In general, there are conflicting reports on mitochondrial and transport mechanisms affecting metabolic flexibility during both insulin administration and exercise. Future studies are needed to determine specific mechanisms underlying metabolic inflexibility during aerobic exercise in IGT and type 2 diabetes.

In conclusion, these findings suggest that the ability to shift from fat to carbohydrate oxidation when going from rest to submaximal aerobic exercise of increasing intensity is reduced in overweight and obese, older subjects with IGT, and is related to the degree of postprandial hyperglycemia. This limitation in obese, older adults with IGT may affect the ability to supply energy to skeletal muscle during moderate-vigorous aerobic activities. Because regular exercise training and weight loss can improve glucose tolerance and reduce progression to type 2 diabetes (39, 40), we postulate that these lifestyle interventions may improve metabolic flexibility in response to exercise in subjects with IGT, but future investigations will be required to confirm this.

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S.J.P, A.S.R., and A.P.G. conceived and designed the research. S.J.P., A.S.R. and T.G.S. performed the experiments and analyzed the data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

References

1. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care. 2009; 32(2):287–94. [PubMed: 19017771]
2. Kelley DE, Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes. 2000; 49(5):677–83. [PubMed: 10905472]
3. Faerch K, Vaag A. Metabolic inflexibility is a common feature of impaired fasting glycaemia and impaired glucose tolerance. Acta Diabetol. 2011; 48(4):349–53. [PubMed: 21207234]
4. Coyle EF. Substrate utilization during exercise in active people. Am J Clin Nutr. 1995; 61(4 Suppl): 968S–79S. [PubMed: 7900696]
5. Regensteiner JG, Sippel J, McFarling ET, Wolfel EE, Hiatt WR. Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise. Med Sci Sports Exerc. 1995; 27(6):875–81. [PubMed: 7658949]
6. Colberg SR, Hagberg JM, McCole SD, Zmuda JM, Thompson PD, Kelley DE. Utilization of glycogen but not plasma glucose is reduced in individuals with NIDDM during mild-intensity exercise. J Appl Physiol. 1996; 81(5):2027–33. [PubMed: 8941525]
7. Geerling BJ, Alles MS, Murgatroyd PR, Goldberg GR, Harding M, Prentice AM. Fatness in relation to substrate oxidation during exercise. Int J Obes Relat Metab Disord. 1994; 18(7):453–9. [PubMed: 7920869]
8. Goodpaster BH, Wolfe RR, Kelley DE. Effects of obesity on substrate utilization during exercise. Obes Res. 2002; 10(7):575–84. [PubMed: 12105277]
9. Hickner RC, Privette J, McIver K, Barakat H. Fatty acid oxidation in African-American and Caucasian women during physical activity. J Appl Physiol. 2001; 90(6):2319–24. [PubMed: 11356798]
10. Braun B, Sharoff C, Chipkin SR, Beaudoin F. Effects of insulin resistance on substrate utilization during exercise in overweight women. J Appl Physiol. 2004; 97(3):991–7. [PubMed: 15133003]
11. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. Circulation. 2007; 114(1):82–96. [PubMed: 16785338]
12. Prior SJ, Joseph LJ, Brandauer J, Katzel LI, Hagberg JM, Ryan AS. Reduction in midthigh low-density muscle with aerobic exercise training and weight loss impacts glucose tolerance in older men. J Clin Endocrinol Metab. 2007; 92(3):880–6. [PubMed: 17200170]
13. 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]
14. 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]
15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012; 35(Suppl 1):S64–S71. [PubMed: 22187472]
16. Andres R, Swerdloff RS, Pozefsky T, Coleman D. Manual feedback technique for the control of blood glucose concentration. Automation in analytical chemistry (Technician Symposium). 1966:489–491.MediadNew York
17. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979; 237(3):E214–E223. [PubMed: 382871]
18. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949; 109(1–2):1–9. [PubMed: 15394301]

19. Kelley DE. Skeletal muscle fat oxidation: timing and flexibility are everything. J Clin Invest. 2005; 115(7):1699–702. [PubMed: 16007246]
20. Galgani JE, Heilbronn LK, Azuma K, et al. Metabolic flexibility in response to glucose is not impaired in people with type 2 diabetes after controlling for glucose disposal rate. Diabetes. 2008; 57(4):841–5. [PubMed: 18285553]
21. Russell RD, Kraemer RR, Nelson AG. Metabolic dysfunction in diabetic offspring: deviations in metabolic flexibility. Med Sci Sports Exerc. 2013; 45(1):8–15. [PubMed: 22811035]
22. Numao S, Hayashi Y, Katayama Y, Matsuo T, Tanaka K. Sex differences in substrate oxidation during aerobic exercise in obese men and postmenopausal obese women. Metabolism. 2009; 58(9):1312–9. [PubMed: 19501865]
23. Blaak EE, van Aggel-Leijssen DP, Wagenmakers AJ, Saris WH, van Baak MA. Impaired oxidation of plasma-derived fatty acids in type 2 diabetic subjects during moderate-intensity exercise. Diabetes. 2000; 49(12):2102–7. [PubMed: 11118013]
24. Mensink M, Blaak EE, van Baak MA, Wagenmakers AJ, Saris WH. Plasma free Fatty Acid uptake and oxidation are already diminished in subjects at high risk for developing type 2 diabetes. Diabetes. 2001; 50(11):2548–54. [PubMed: 11679433]
25. Prior SJ, McKenzie MJ, Joseph LJ, et al. Reduced skeletal muscle capillarization and glucose intolerance. Microcirculation. 2009; 16(3):203–12. [PubMed: 19225985]
26. Prior SJ, Ryan AS. Low clonogenic potential of circulating angiogenic cells is associated with lower density of capillaries in skeletal muscle capillarization in patients with impaired glucose tolerance. Diabetes Metab Res Rev. 2013; 29:319–25. [PubMed: 23390082]
27. Hespel P, Vergauwen L, Vandenberghe K, Richter EA. Important role of insulin and flow in stimulating glucose uptake in contracting skeletal muscle. Diabetes. 1995; 44(2):210–5. [PubMed: 7859943]
28. Vollus GC, Bradley EA, Roberts MK, et al. Graded occlusion of perfused rat muscle vasculature decreases insulin action. Clin Sci (Lond). 2007; 112(8):457–66. [PubMed: 17147515]
29. Martin IK, Katz A, Wahren J. Splanchnic and muscle metabolism during exercise in NIDDM patients. Am J Physiol. 1995; 269(3 Pt 1):E583–E590. [PubMed: 7573437]
30. Ho RC, Hirshman MF, Li Y, et al. Regulation of IkappaB kinase and NF-kappaB in contracting adult rat skeletal muscle. Am J Physiol Cell Physiol. 2005; 289(4):C794–C801. [PubMed: 15888549]
31. Phillips DI, Caddy S, Ilic V, et al. Intramuscular triglyceride and muscle insulin sensitivity: evidence for a relationship in nondiabetic subjects. Metabolism. 1996; 45(8):947–50. [PubMed: 8769349]
32. Krssak M, Falk PK, Dresner A, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia. 1999; 42(1):113–6. [PubMed: 10027589]
33. Bogardus C, Lillioja S, Stone K, Mott D. Correlation between muscle glycogen synthase activity and in vivo insulin action in man. J Clin Invest. 1984; 73(4):1185–90. [PubMed: 6423666]
34. Levin K, Daa SH, Alford FP, Beck-Nielsen H. Morphometric documentation of abnormal intramyocellular fat storage and reduced glycogen in obese patients with Type II diabetes. Diabetologia. 2001; 44(7):824–33. [PubMed: 11508266]
35. Galgani JE, Moro C, Ravussin E. Metabolic flexibility and insulin resistance. Am J Physiol Endocrinol Metab. 2008; 295(5):E1009–E1017. [PubMed: 18765680]
36. Morino K, Petersen KF, Dufour S, et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. J Clin Invest. 2005; 115(12):3587–93. [PubMed: 16284649]
37. Kulkarni SS, Salehzadeh F, Fritz T, Zierath JR, Krook A, Osler ME. Mitochondrial regulators of fatty acid metabolism reflect metabolic dysfunction in type 2 diabetes mellitus. Metabolism. 2012; 61(2):175–85. [PubMed: 21816445]
38. Constantin-Teodosiu D, Constantin D, Stephens F, Laithwaite D, Greenhaff PL. The role of FOXO and PPAR transcription factors in diet-mediated inhibition of PDC activation and carbohydrate oxidation during exercise in humans and the role of pharmacological activation of PDC in overriding these changes. Diabetes. 2012; 61(5):1017–24. [PubMed: 22315317]

39. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346(6):393–403. [PubMed: 11832527]

40. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001; 344(18):1343–50. [PubMed: 11333990]

What is already known about this subject?

- Insulin resistant adults have metabolic inflexibility (impaired ability to switch from fat to carbohydrate oxidation) in response to insulin infusion.
- Obese adults may oxidize more fat and less carbohydrate during exercise when compared with lean controls, but results across studies are discordant.

What this study adds

- Obese, older adults with impaired glucose tolerance exhibit metabolic inflexibility (a lower shift from fat to carbohydrate oxidation) during submaximal aerobic exercise at 50% and 60% VO_{2max}.
- Metabolic inflexibility during exercise in obese subjects is related to the degree of glucose intolerance, independent of age, body composition, and fitness level.

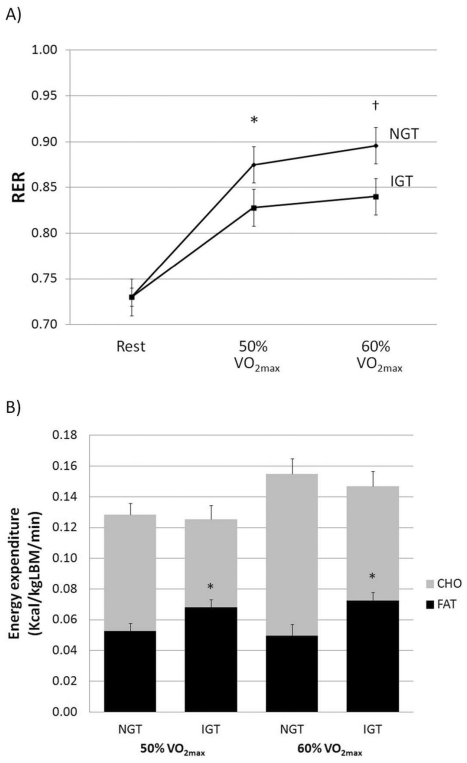

Figure 1.

Attenuated increase in respiratory exchange ratio (A), and higher kilocalories derived from fat (B) during submaximal exercise in older adults with impaired glucose tolerance (IGT) compared to controls with normal glucose tolerance (NGT). Data are means ± SEM. *,†Significant difference in RER, fat oxidation rate, or kcal derived from fat between NGT and IGT groups, *$p < 0.05$, †$p = 0.01$. RER: respiratory exchange ratio, CHO: carbohydrate, LBM: lean body mass.

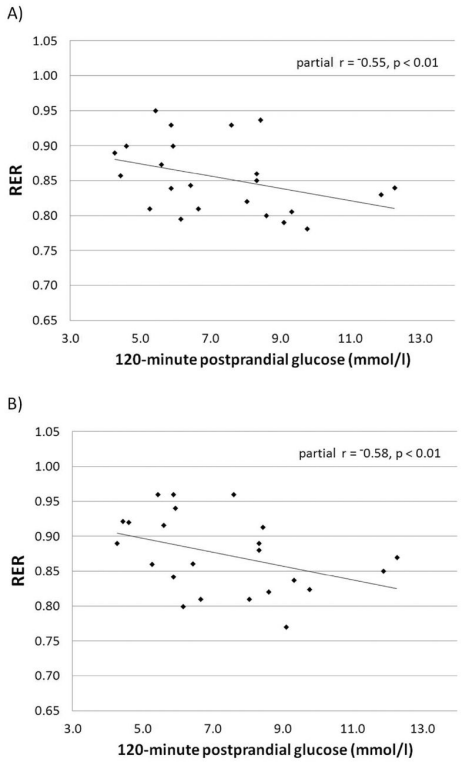

Figure 2.

Glucose intolerance (120-minute postprandial plasma glucose) is associated with lower respiratory exchange ratio (RER) (i.e., lower carbohydrate oxidation) during aerobic exercise at (A) 50% and (B) 60% VO_{2max}.

Table 1

Physical and metabolic characteristics of subjects and responses to submaximal exercise

	NGT (n=13)	IGT (n=10)
Sex (men/women)	5/8	3/7
Race (black/white)	5/8	3/7
Age (yr)	63 ± 2	62 ± 3
Body Composition		
Weight (kg)	86 ± 3	89 ± 4
Body Mass Index (kg/m^2)	29 ± 1	30 ± 1
Body Fat (%)	37.0 ± 2.7	36.5 ± 2.7
Fat Mass (kg)	32 ± 3	33 ± 3
Lean Body Mass (kg)	48 ± 2	51 ± 3
Intra-abdominal fat area (cm^2)	159 ± 21 *(n=10)*	190 ± 22 *(n=10)*
Subcutaneous abdominal fat area (cm^2)	223 ± 25 *(n=10)*	278 ± 26 *(n=10)*
Cardiorespiratory Fitness		
VO_{2max} (L/min)	2.3 ± 0.08	2.2 ± 0.09
VO_{2max} (ml/kgLBM/min)	49.0 ± 1.2	45.0 ± 1.3 *
Oral Glucose Tolerance Test		
Fasting Plasma Glucose (mmol/l)	5.0 ± 0.1	5.6 ± 0.2 ‡
Fasting Plasma Insulin (pmol/L)	83 ± 8	127 ± 14 †
120-min Glucose (mmol/l)	5.7 ± 0.3	9.4 ± 0.5 ‡
120-min Insulin (pmol/l)	425 ± 65	860 ± 147 †
G_{AUC} (mmol/l/120min)	817 ± 45	1121 ± 54 ‡
I_{AUC} (pmol/l/120min)	51247 ± 6473	74597 ± 9750 *
ISI_M	4.1 ± 0.5	2.0 ± 0.2 ‡
HOMA-IR	2.65 ± 0.30	4.62 ± 0.59 †
Submaximal Exercise		
Actual VO_2 at 50% VO_{2max} workload (ml/kgLBM/min)	27.3 ± 0.8	26.1 ± 1.4
HR at 50% VO_{2max} workload (beats/min)	112 ± 5	106 ± 3
Actual VO_2 at 60% VO_{2max} workload (ml/kgLBM/min)	32.3 ± 1.2	30.5 ± 1.8
HR at 60% VO_{2max} workload (beats/min)	125 ± 5	116 ± 4

Data are means ± SEM. VO_{2max}: maximal oxygen consumption, LBM: lean body mass, G_{AUC}: glucose area under the curve, I_{AUC}: insulin area under the curve, ISI_M: insulin sensitivity index, HOMA-IR: homeostatic model assessment for insulin resistance, HR: heart rate. *,†,‡ Statistically significant difference compared to the NGT group,

* $p < 0.05$,

† $p \leq 0.01$,

$^{\ddagger}p \leq 0.001$.

Table 2

Results of multivariable regression analyses to determine variables associated with respiratory exchange ratio (RER) during submaximal treadmill exercise

RER at 50% VO_{2max}					
Model r	**Model P-value**	**Independent Variable**	**β-coefficient**	**Partial r**	**P-value**
0.67	**0.01**	G_{120}	−0.499	−0.54	**0.01**
		Age	−0.594	−0.41	0.07
		% Fat	−0.351	−0.28	0.23
		VO_{2max}	−0.107	−0.07	0.77

RER at 60% VO_{2max}					
Model r	**Model P-value**	**Independent Variable**	**β-coefficient**	**Partial r**	**P-value**
0.68	**0.02**	G_{120}	−0.533	−0.58	**0.008**
		Age	−0.428	−0.32	0.18
		% Fat	−0.371	−0.30	0.20
		VO_{2max}	0.047	0.03	0.90

G_{120}: 120-minute postprandial glucose concentration, % Fat: percent body fat, VO_{2max}: maximal oxygen consumption.