HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2014 May 01.

Published in final edited form as:

Obesity (Silver Spring). 2013 November ; 21(11): 2272–2278. doi:10.1002/oby.20411.

A low glycemic diet lifestyle intervention improves fat utilization during exercise in older obese humans

Thomas P.J. Solomon[1,*], **Jacob M. Haus**[1,*], **Marc A. Cook**[1], **Chris A. Flask**[4,5], and **John P. Kirwan**[1,2,3]

[1]Department of Pathobiology, Cleveland Clinic, Cleveland, OH

[2]Department of Physiology & Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH

[3]Metabolic Translational Research Center, Endocrine and Metabolism Institute, Cleveland Clinic, Cleveland, OH, 44195

[4]Department of Radiology, Case Western Reserve University, Cleveland, OH

[5]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

Abstract

Objective—To determine the influence of dietary glycemic index on exercise training-induced adaptations in substrate oxidation in obesity.

Design and Methods—Twenty older, obese individuals undertook 3-months of fully-supervised aerobic exercise and were randomised to low (LoGIX) or high glycemic (HiGIX) diets. Changes in indirect calorimetry (VO_2; VCO_2) were assessed at rest, during a hyperinsulinemic-euglycemic clamp, and during submaximal exercise (walking: 65% VO_2max, 200 kcal energy expenditure). Intramyocellular lipid (IMCL) was measured by ^{1}H-magnetic resonance spectroscopy.

Results—Weight loss (−8.6±1.1%) and improvements ($P<0.05$) in VO_2max, glycemic control, fasting lipemia, and metabolic flexibility were similar for both LoGIX and HiGIX groups. During submaximal exercise, energy expenditure was higher following the intervention ($P<0.01$) in both groups. Respiratory exchange ratio (RER) during exercise was unchanged in the LoGIX group but increased in the HiGIX group ($P<0.05$). However, fat oxidation during exercise expressed relative

Corresponding Author: John P. Kirwan, Ph.D., Lerner Research Institute, Department of Pathobiology, Cleveland Clinic, 9500 Euclid Avenue / NE4, Cleveland, Ohio 44120, kirwanj@ccf.org.

*TPJS and JMH contributed equally to this work

Current address for TPJS: Thomas Solomon, Ph.D., Centre of Inflammation and Metabolism, Rigshospitalet, Section 7641 Blegdamsvej 9, 2100 København Ø Denmark : thomas.solomon@inflammation-metabolism.dk

AUTHOR CONTRIBUTIONS

TPJS, JMH, CAF, and JPK designed the research; TPJS, JMH, MAC, CAF, and JPK conducted the research; TPJS, JMH, CAF, and JPK analyzed the data; TPJS, JMH, and JPK discussed the data; TPJS and JMH wrote the paper; and JPK had primary responsibility for the final content. All authors read and approved the final manuscript.

DISCLOSURES

The authors declare no conflicts of interest.

to changes in body weight was increased in the LoGIX group (+10.6±3.6%; P<0.05). Fasting IMLC was unchanged, however extramyocellular lipid was reduced (P<0.05) after LoGIX.

Conclusions—A low glycemic diet/exercise weight-loss intervention increases fat utilization during exercise independent of changes in energy expenditure. This highlights the potential therapeutic value of low glycemic foods for reversing metabolic defects in obesity.

Keywords

glycemic index; weight loss; obesity; type 2 diabetes; exercise training; energy expenditure; fat oxidation

INTRODUCTION

In view of the growing obesity epidemic, lifestyle interventions must be developed to aid not only weight loss but also to reverse the underlying metabolic impairments present in overweight individuals. Several published exercise and diet interventions have yielded promising results with regards to improving body composition, insulin sensitivity and glucose tolerance in such populations (1, 2), and while the mode of exercise can influence these outcome variables (3, 4) it is also clear that dietary composition plays an important role (5, 6).

We recently reported that a 3-month exercise training intervention when combined with a low glycemic diet induces a more favourable metabolic state in older obese humans when compared to a high glycemic intervention (7–10). Further, our short-term (7-day) lifestyle intervention that combined a low glycemic index diet with daily aerobic exercise caused an increase in fasting intramyocellular lipid (IMCL) and a decrease in extramyocellular lipid (EMCL), suggestive of preferential substrate oxidation (10). Prior experiments conducted on lean healthy individuals suggest that low glycemic index (GI) meals may alter substrate oxidation during acute exercise bouts, towards increased fat utilization (11–16). In addition, ingesting meals with a low glycemic response has been shown to reduce fasting respiratory exchange ratios in some (17, 18) but not all (19, 20) studies. Such findings have clinical implications in that the prescription of low glycemic meals in an obese population may increase weight loss via increases in fat oxidation rates. However, no prior study has examined the effect of dietary glycemic index on substrate metabolism during exercise in obese individuals following diet and exercise induced weight loss.

This investigation examines the effects of a combined exercise training and low glycemic diet intervention on energy expenditure and substrate utilization at rest, during a hyperinsulinemic euglycemic clamp, and during submaximal exercise. In addition, we measured fasting skeletal muscle lipid using proton magnetic resonance spectroscopy (^{1}H-MRS) prior to and following the intervention period. Given the evidence that low GI meals can increase exercise-induced fat utilization, we hypothesized that following 3-months of exercise training a low glycemic diet would increase fat oxidation rates during submaximal exercise.

EXPERIMENTAL PROCEDURES

Participants

Twenty older, obese men and women (age 65±1 years; BMI 35.0±1.0 kg/m^2; mean±S.E.M.) volunteered to participate in a 3-month lifestyle intervention. All participants were weight stable and sedentary. The study was conducted using a randomized, parallel-group, repeated measures design. We previously described the design in detail in Ref (8). The variables in this current paper have not been published previously. Medical screening excluded individuals with heart, kidney, liver, thyroid, intestinal, and pulmonary diseases, or those taking medications known to affect our outcome variables. Resting ECG and sub-maximal exercise stress tests excluded individuals contraindicated to increments in physical activity. At the screening visit, volunteers also underwent a 30 minute assessment of resting energy expenditure using ventilated-hood indirect calorimetry. Resting energy expenditure was multiplied by a physical activity factor of 1.2 to calculate the caloric load of the subjects' diets during inpatient testing and study interventions. The study was approved by the Cleveland Clinic Institutional Review Board, and all subjects provided informed written consent in accordance with our guidelines for the protection of human subjects.

Intervention

All participants performed fully-supervised aerobic exercise (treadmill walking and cycle ergometry) 60 minutes/day, 5 days/week for 3-months at ~65% of their VO_2max (full details of the exercise intervention are available in Ref. (21)). In addition, participants were randomized to receive either a low GI diet (40 GI units, LoGIX; n = 10) or a high GI diet (80 GI units, HiGIX; n = 10). The two diets were macronutrient matched. For the duration of the 3-month intervention, all food and drink items were provided to participants on a daily basis by a registered dietitian. We have previously published full details of the dietary interventions and sample menus in Ref.(7). Dietary analysis was performed using Nutritionist Pro software (Axxya Systems, Stafford, TX).

Inpatient Control Period

Pre- and post-study assessments of body composition (dual-energy x-ray absorptiometry; iDXA; Lunar, Madison, WI), oral glucose tolerance (OGTT), insulin sensitivity (40 mU/m^2/min hyperinsulinemic euglycemic clamp, as previously described (7)), aerobic fitness (VO_2max; as previously described (21)) and substrate metabolism (as described below) were performed during a 3-day inpatient stay in the Clinical Research Unit at the Cleveland Clinic. During the pre-study inpatient stay, participants received a diet with a moderate GI (55–60 GI units). During the post-study inpatient stay, subjects continued their corresponding LoGIX or HiGIX interventions. Post-study metabolic measures (clamp and calorimetry) were performed ~16 h after the last exercise bout. Although energy balance was not measured directly, we ensured that all subjects received a daily caloric amount that was relative to their own caloric requirements as assessed by indirect calorimetry. Therefore, any deviations from energy balance would be equal between groups and not influence the metabolic outcomes of the study.

Substrate Metabolism

Resting and insulin-stimulated (clamp-derived) energy expenditure (22) and substrate oxidation rates (23) were determined via indirect calorimetry (Vmax Encore, Viasys, Yorba Linda, CA). Expired air was collected over a 30 min period immediately upon waking after an overnight fast and during the final 30 min of the clamp. Metabolic flexibility was calculated as the insulin-stimulated change in respiratory exchange ratio (RER) from resting conditions. In addition, following an overnight fast, each subject completed a steady-state submaximal treadmill walking exercise test at 65% of their VO_2max until 200 kcal of energy had been expended. VO_2 was continuously monitored via indirect calorimetry (Jaeger Oxycon Pro, Viasys, Yorba Linda, CA) so that EE could be assessed real-time. The data reported are calculated as the mean of the final 5 minutes of exercise. Following the 3-month intervention, subjects' repeated the submaximal exercise test. No blood samples were collected during these exercise tests. To control for the acute effects of exercise, pre-intervention exercise tests were conducted >48 h prior to metabolic measures.

IMCL and EMCL Assessments

^{1}H-MRS was used to quantify fasting lipid levels in the soleus (slow-twitch) muscle before and after the lifestyle intervention. Briefly, the right calf of each subject was positioned in a knee coil and positioned near isocenter within a 4T Bruker Medspec MRI scanner (Siemens, Malvern, PA). Following manual shimming to improve the spectral resolution of the acquisition (water linewidth (FWHM) ≤ 50 Hz (~0.3ppm)), a single-voxel Point-Resolved Spectroscopy (PRESS) acquisition (TR/TE = 1500/135ms, 128 averages, voxel size = 1 cm^3, water suppression, ADC BW = 10.5 ppm) was used to acquire the MRS data. Repeatability of the voxel placement following the intervention period was facilitated with anatomic landmarks. Following the acquisition, all spectra were reconstructed and exported to Matlab (The Mathworks, Natick, MA) for quantitative analysis of the lipid peaks. Fiber orientation modeling (FOM), previously described by Khuu *et al*. (24), was then applied to the MRS spectra. The IMCL and EMCL methylene and methyl residues were calculated and the relative concentrations of intra- ([IMCL]) and extramyocellular lipid levels ([EMCL]) were derived using the creatine signal as a concentration standard, assuming the skeletal muscle creatine concentration is approximately equal to 30 mmol/kg muscle wet weight. We have reported the use of this method previously (10). A total of 34 subjects were originally randomized to our HiGIX/LoGIX intervention. Of these 34, substrate oxidation data during exercise was collected in 20 subjects (10 HiGIX, 10 LoGIX); this manuscript presents that data. ^{1}H-MRS data was collected in the original cohort but due to a computer failure a large amount of spectroscopy data was lost leaving us with MRS data in 15 subjects (11 HiGIX, 4 LoGIX). Of these 15, a total of 10 subjects (8 HiGIX, 2 LoGIX) also had substrate oxidation measurements during exercise.

Biochemical Analyses

Plasma glucose was determined on a YSI 2300 STAT Plus analyzer (Yellow Springs, OH); plasma insulin via radioimmunoassay (Millipore, Billerica, MA). Plasma triglycerides and cholesterol were analyzed by enzymatic methods on an automated platform (Roche Modular

Diagnostics, Indianapolis, IN). Glycated hemoglobin (HbA1c) was measured via nonporous ion exchange HPLC (G7 HPLC Analyzer, Tosoh Bioscience, San Francisco, CA).

Statistics

Analyses were carried out using Prism v4 (GraphPad, San Diego, CA) and Statview v5.0.1 (SAS Institute, Cary, NC). Unpaired t-tests were used to compare group differences at baseline. Two-way (group × time) repeated measures ANOVA was used to identify between-group (LoGIX vs. HiGIX) differences. Bonferroni *post hoc* tests were used when significant group × time interactions arose. Additional ANCOVA analyses revealed that gender did not affect any variable in this intervention, nor were changes in RER influenced by the baseline differences between HiGIX and LoGIX groups. Between group changes in non-normally distributed variables were examined via Mann-Whitney tests. Bivariate correlation analyses were used to identify relationships between baseline variables and changes (Δ) in variables following the intervention period using Spearman's rank correlation. Statistical significance was accepted when $P<0.05$ and data are expressed as mean ± S.E.M.

RESULTS

Intervention

During pre-study inpatient studies, subjects consumed 1733±137 kcal/d with a macronutrient composition of 53±1, 30±1, 17±0 % of kcal from carbohydrate, fat and protein. During the intervention subjects consumed 1880±105 kcal/d with a macronutrient composition of 54±0, 29±1, 17±0 % of kcal from carbohydrate, fat and protein. The total energy intake and macronutrient composition was not different between LoGIX and HiGIX groups, as previously reported in full in Ref. (25). Dietary adherence was 97±1% (percent calories consumed relative to calories provided), and the mean study GI for the LoGIX group was 39.8±0.3 while GI for the HiGIX group was 80.0±0.6. In addition, subjects completed 95±1% of all exercise sessions, with a mean duration of 56±5 minutes/day, performed at 83.4±0.6% of maximum heart rate.

Subject Characteristics

Both LoGIX and HiGIX groups showed equal weight loss (−8.6±1.1%) and equal decreases in whole body adiposity (Table 1: both $P<0.05$), plus equal improvements in glycemic control (Table 1: reduced fasting plasma glucose [FPG] and hemoglobin A1c [HbA1c]; increased glucose disposal rates [GDR] during euglycemic hyperinsulinemia, all $P<0.05$) and fasting lipemia (Table 1: decreased triglycerides and cholesterol, both $P<0.05$). Maximal oxygen uptake (VO_2max) during exhaustive aerobic exercise was also equally increased in both LoGIX and HiGIX groups (+18.9±3.1%; Table 1: $P<0.05$).

Resting and Insulin-Stimulated Energy Metabolism

Energy expenditure (EE, kcal/kg/min) during resting and insulin-stimulated conditions increased following the 3-month intervention in both groups (Table 2: $P=0.05$). Absolute changes in EE (kcal/min) showed the same trends but the effect of time was not significant ($P=0.13$). Respiratory exchange ratios (RER) were equally decreased in both LoGIX and

HiGIX groups during resting conditions, while equally increased in both groups under insulin-stimulated conditions (Table 2: P<0.05). Finally, a statistically-significant increase in insulin-stimulated metabolic flexibility was found in both groups (Table 2: P<0.05).

Submaximal Exercise Energy Metabolism

Time to completion of sub-maximal exercise (200 kcal energy expenditure) was 31±2 and 27±2 minutes, pre- vs. post-intervention in all subjects (P<0.05). This was not different between groups. No differences in exercise intensity between groups or trials were found: submaximal exercise was performed at 65.1±0.7% of the subjects' VO_2max (Table 3). Compared to pre-study measures, the rates of oxygen uptake (VO_2, l/min and ml/kg/min) and energy expenditure (EE, kcal/min) during submaximal exercise were higher following the 3-month intervention (Table 3 and Fig. 1 Panel [A]: PRE vs. POST, P<0.05). The increases in EE and VO_2 were identical in both the LoGIX and HiGIX groups. Respiratory exchange ratios (RER) during exercise were unchanged in the LoGIX (P>0.05) following the study but increased in the HiGIX group (Fig. 1 [B], P<0.05). This change in RER in the HiGIX was significantly different from the LoGIX group (P<0.05). Rates of carbohydrate oxidation during exercise expressed relative to changes in body mass (mg/kg/min) were increased in both groups following the intervention (Fig. 1 [C], P<0.05), while fat oxidation rates during exercise were increased in the LoGIX group only (mg/kg/min; Fig. 1 [D], P<0.05). To further examine these changes in carbohydrate and fat oxidation, we calculated the percentage of total caloric energy expenditure that is derived from the two substrates (Fig. 2). Following the intervention, calories derived from either carbohydrate or fat sources during exercise were unchanged in the LoGIX group (P>0.05), while in the HiGIX group a significant increase in carbohydrate utilization (Fig.2 [A], P<0.05) and decrease in fat utilization was found (Fig.2 [B], P<0.05).

Skeletal Muscle Lipids

We had complete MRS measurements in n=15 subjects (4 LoGIX; 11 HiGIX). The 12 week lifestyle intervention did not significantly (P>0.05) affect resting skeletal muscle [IMCL] (change from pre-study, LoGIX vs. HiGIX: −2.3±1.2 vs. −1.0±1.3 mmol/kg muscle wet weight) or [IMCL/EMCL] (change from pre-study, LoGIX vs. HiGIX: 0.21±0.23 vs. −0.18±0.16) in either group. However, the change in resting [EMCL] following the intervention period was significantly different between groups (P=0.01) (change from pre-study, LoGIX vs. HiGIX: −14.9±6.4 vs. 11.4±6.7 mmol/kg muscle wet weight). No main effects were seen for muscle creatine values. In addition, relationships between skeletal muscle lipids and substrate oxidation rates at rest, insulin-stimulation and submaximal exercise were explored via correlation analyses in 10 subjects (2 LoGIX; 8 HiGIX) who had complete data-sets from both MRS and indirect calorimetry measures. At baseline, [EMCL] was inversely correlated (Rho=−0.704, P=0.02) with the rate of resting carbohydrate oxidation (mg/kgFFM/min) and resting RER (Rho=−0.642, P=0.04). Following the intervention, the change in [EMCL] was positively correlated (Rho=0.726, P=0.02) with the change in carbohydrate oxidation (mg/kgFFM/min) measured during submaximal exercise, and inversely correlated with the change in fat oxidation during submaximal exercise (Rho = −0.808, P=0.003). The changes in [IMCL]/[[EMCL] were also correlated with the changes in carbohydrate (Rho = −0.862, P=0.001) and fat oxidation (Rho = 0.748, P=0.01) during

submaximal exercise. Due to low subject numbers in these comparisons, we acknowledge these data as preliminary observations and they must be interpreted with caution until they can be verified in a larger cohort.

DISCUSSION

Our data indicate that exercise-induced alterations in body composition, insulin sensitivity, and energy expenditure are not influenced by dietary glycemic index in obese subjects. However, substrate metabolism during submaximal exercise was differentially altered between the dietary glycemic index groups. A high glycemic diet increased the respiratory exchange ratio during exercise and increased the reliance on carbohydrate oxidation to sustain exercise performed at a moderate intensity. Conversely, consumption of a low glycemic diet during the exercise training intervention led to increased partitioning of fat towards energy expenditure during exercise in our older, obese subjects.

Clapp *et al*. previously showed that prolonged habituation (20 days) to a low GI diet reduces fasting respiratory exchange ratios and increases fat oxidation in healthy women (17). Similar findings have been obtained in animal models (25, 26). In addition, Bouche *et al*. and Pittas *et al*. have demonstrated improved weight loss following a low-glycemic diet (27, 28). In this study, weight loss and increases in fasting respiratory exchange ratio induced by the combination of diet and exercise were equal among older obese individuals consuming either a low or high glycemic diet. Thus, when a negative energy balance is induced by diet and exercise, the overall changes in body composition are not influenced by the glycemic responses of the diet. While weight loss is a surrogate marker of improved metabolic health, it may not be indicative of all metabolic variables. As we have previously demonstrated from this same intervention, variables such as insulin secretion and inflammation show divergent trends between the LoGIX and HiGIX interventions in the presence of equal improvements in body composition (8–10). Further to this dietary group disparity, we now demonstrate that substrate metabolism during submaximal exercise is also influenced by dietary GI. However, due to our study design we cannot determine whether this disparity is due to the last meal or a metabolic adaptation to 3-months of meal feeding. That said, submaximal exercise tests were performed following an overnight fast, limiting the possible acute effects of meal GI. The larger reliance on lipid as a fuel during exercise following the intervention in the LoGIX group indicates that carbohydrate is being spared. Previous work has shown low glycemic feeding prior to aerobic exercise elevates fat oxidation during exercise (11–16), and that this may occur due to lower postprandial insulin responses compared to high glycemic meals, thus increasing the availability of free fatty acids for oxidation in the mitochondria (29, 30). These findings highlight dietary glycemic responses as an important consideration with regard to substrate oxidation during physical activity.

Several prior weight loss interventions have examined changes in energy metabolism (31–33). Our data indicates an increase in resting energy expenditure in the presence of ~9% weight loss, as well as increased energy expenditure during submaximal exercise. In this study, subjects' aerobic fitness (VO_2max) was measured every 2-weeks throughout the intervention such that the work load of each exercise training session could be adjusted to maintain the same relative exercise intensity throughout the study. As a result the

submaximal exercise tests were therefore performed at the same relative intensity as the exercise training sessions, allowing us to directly extrapolate data collected in these tests to reflect the physiological adaptations occurring during the training sessions.

Previous studies indicate that low glycemic diets may enhance weight loss (27, 28). The current study combines exercise training with either a low or high glycemic diet. We hereby show that when energy balance is equal between a group receiving a low vs. high-glycemic index diet, body composition is not differentially influenced between groups. While no group divergence in body composition was found, we did find group differences in skeletal muscle ectopic lipid accumulation. It appears that extramyocellular lipid stores may be sensitive to the glycemic index of the diet as indicated by our correlations between extramyocellular lipid and substrate oxidation rates. However, we must acknowledge that these correlations data are under powered and, given the unequal group distribution, should only be interpreted as a preliminary observation that must be verified in a larger cohort and by more detailed mechanistic studies. With reference to changes in resting and insulin-stimulated metabolism, it was found that following the intervention both groups demonstrated equal decreases in resting respiratory exchange ratios and equal increases in metabolic flexibility. Decreased RER at rest and increased metabolic flexibility has been demonstrated following exercise and diet-induced weight loss in obese subjects, by our group and others (31, 33). We confirm this finding and additionally show that dietary glycemic index does not influence these trends. However, during submaximal exercise, substrate metabolism was differentially altered between groups, but this could not be expected to extrapolate to a between-group difference in weight loss because we matched between-group energy balance during the study.

Following this exercise training intervention, we found a marked increase in caloric energy expenditure during exercise in both groups. This is primarily driven by the higher absolute workload in the post-intervention test (performed at the same percentage of VO_2max). However, independent of the increase in energy expenditure, there was an interesting divergence between the dietary groups with respect to substrate utilization. The respiratory exchange ratio was unchanged in subjects who had consumed a low glycemic diet (LoGIX) throughout the intervention while RER was increased during submaximal exercise in subjects consuming a high glycemic diet (HiGIX). Further to this, carbohydrate oxidation rates during exercise corrected for weight loss (mg/kg/min) were increased in both groups, while fat oxidation rates (mg/kg/min) were increased only in subjects consuming a low glycemic diet. When expressed as a percentage of total energy expenditure during exercise, no change in the percentage of calories derived from carbohydrate or fat oxidation was seen in the LoGIX group, while in the HiGIX group energy derived from carbohydrate was increased and energy from fat was decreased. In summary, this indicates that in older obese individuals undergoing diet and exercise induced weight loss, a high glycemic diet actually impairs fat oxidation during exercise training sessions such that reduced fat oxidation occurs. These divergent group effects are perhaps a result of the intervention effects upon the compensatory hyperinsulinemia present in our obese cohort: we previously reported that following this intervention only the LoGIX group showed significant reduction in hyperinsulinemia (reported in Ref (8)). Therefore, the underlying circulatory insulin levels may have been higher during submaximal exercise tests in the HiGIX group, thus

suppressing lipolysis to a greater degree than the LoGIX group, limiting free-fatty acid availability for oxidation. This hypothesis cannot be tested in this study as no blood/muscle samples were collected during the exercise bout, but a previous study by Wee *et al*. strongly supports this interpretation (29).

In summary, these novel data further highlight the importance of dietary intake during exercise and diet-induced weight loss interventions in obese populations. We have shown that while dietary glycemic index does not influence body composition following exercise training in obese individuals, a low glycemic diet is more favourable with respect to increasing fat oxidation during physical activity. Furthermore, it appears that a high glycemic diet actually prevents these beneficial exercise training responses. To conclude, while weight loss induced by a combination of diet and exercise may be a good marker of reduced disease progression in obese individuals, the dietary carbohydrate quality employed in such interventions must be carefully considered to address metabolic dysfunction in its entirety.

Acknowledgments

The authors wish to thank the research volunteers for their outstanding dedication and effort, and the nursing staff of the Clinical Research Unit and the staff and students who helped with the implementation of the study and assisted with data collection.

GRANTS

This research was supported by NIH grant RO1 AG12834 (JPK), and was supported in part by the National Institutes of Health, National Center for Research Resources, CTSA 1UL1RR024989, Cleveland, Ohio. JMH was supported by National Institutes of Health grant T32 HL00787.

REFERENCE LIST

1. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997; 20(4):537–44. [PubMed: 9096977]
2. Uusitupa M, Lindi V, Louheranta A, Salopuro T, Lindstrom J, Tuomilehto J. Long-term improvement in insulin sensitivity by changing lifestyles of people with impaired glucose tolerance: 4-year results from the Finnish Diabetes Prevention Study. Diabetes. 2003; 52(10):2532–8. [PubMed: 14514637]
3. Slentz CA, Tanner CJ, Bateman LA, et al. Effects of exercise training intensity on pancreatic beta-cell function. Diabetes Care. 2009; 32(10):1807–11. [PubMed: 19592624]
4. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation. 2008; 118(4):346–54. [PubMed: 18606913]
5. Newsom SA, Schenk S, Thomas KM, et al. Energy deficit after exercise augments lipid mobilization but does not contribute to the exercise-induced increase in insulin sensitivity. J Appl Physiol. 2010; 108(3):554–60. [PubMed: 20044472]
6. Melanson EL, Gozansky WS, Barry DW, Maclean PS, Grunwald GK, Hill JO. When energy balance is maintained, exercise does not induce negative fat balance in lean sedentary, obese sedentary, or lean endurance-trained individuals. J Appl Physiol. 2009; 107(6):1847–56. [PubMed: 19833807]
7. Solomon TP, Haus JM, Kelly KR, et al. Randomized trial on the effects of a 7-d low-glycemic diet and exercise intervention on insulin resistance in older obese humans. Am J Clin Nutr. 2009; 90(5): 1222–9. [PubMed: 19793849]

8. Solomon TP, Haus JM, Kelly KR, et al. A low-glycemic index diet combined with exercise reduces insulin resistance, postprandial hyperinsulinemia, and glucose-dependent insulinotropic polypeptide responses in obese, prediabetic humans. Am J Clin Nutr. 2010; 92(6):1359–68. [PubMed: 20980494]

9. Kelly KR, Haus JM, Solomon TP, et al. A low-glycemic index diet and exercise intervention reduces TNF(alpha) in isolated mononuclear cells of older, obese adults. J Nutr. 2011; 141(6):1089–94. [PubMed: 21525252]

10. Haus JM, Solomon TP, Lu L, et al. Intramyocellular lipid content and insulin sensitivity are increased following a short-term low-glycemic index diet and exercise intervention. Am J Physiol Endocrinol Metab. 2011; 301(3):E511–E516. [PubMed: 21712533]

11. Kirwan JP, O'Gorman D, Evans WJ. A moderate glycemic meal before endurance exercise can enhance performance. J Appl Physiol. 1998; 84(1):53–9. [PubMed: 9451617]

12. Kirwan JP, Cyr-Campbell D, Campbell WW, Scheiber J, Evans WJ. Effects of moderate and high glycemic index meals on metabolism and exercise performance. Metabolism. 2001; 50(7):849–55. [PubMed: 11436193]

13. Stevenson EJ, Williams C, Mash LE, Phillips B, Nute ML. Influence of high-carbohydrate mixed meals with different glycemic indexes on substrate utilization during subsequent exercise in women. Am J Clin Nutr. 2006; 84(2):354–60. [PubMed: 16895883]

14. Stevenson EJ, Astbury NM, Simpson EJ, Taylor MA, Macdonald IA. Fat oxidation during exercise and satiety during recovery are increased following a low-glycemic index breakfast in sedentary women. J Nutr. 2009; 139(5):890–7. [PubMed: 19321590]

15. Febbraio MA, Keenan J, Angus DJ, Campbell SE, Garnham AP. Preexercise carbohydrate ingestion, glucose kinetics, and muscle glycogen use: effect of the glycemic index. J Appl Physiol. 2000; 89(5):1845–51. [PubMed: 11053335]

16. Wee SL, Williams C, Gray S, Horabin J. Influence of high and low glycemic index meals on endurance running capacity. Med Sci Sports Exerc. 1999; 31(3):393–9. [PubMed: 10188743]

17. Clapp JF, Lopez B. Low-Versus High-Glycemic Index Diets in Women: Effects on Caloric Requirement, Substrate Utilization and Insulin Sensitivity. Metab Syndr Relat Disord. 2007; 5(3): 231–42. [PubMed: 18370777]

18. Scazzina F, Del RD, Benini L, et al. The effect of breakfasts varying in glycemic index and glycemic load on dietary induced thermogenesis and respiratory quotient. Nutr Metab Cardiovasc Dis. 2011; 21(2):121–5. [PubMed: 19836218]

19. Diaz EO, Galgani JE, Aguirre CA, Atwater IJ, Burrows R. Effect of glycemic index on whole-body substrate oxidation in obese women. Int J Obes (Lond). 2005; 29(1):108–14. [PubMed: 15505637]

20. Diaz EO, Galgani JE, Aguirre CA. Glycaemic index effects on fuel partitioning in humans. Obes Rev. 2006; 7(2):219–26. [PubMed: 16629877]

21. O'Leary VB, Marchetti CM, Krishnan RK, Stetzer BP, Gonzalez F, Kirwan JP. Exercise-induced reversal of insulin resistance in obese elderly is associated with reduced visceral fat. J Appl Physiol. 2006; 100(5):1584–9. [PubMed: 16373444]

22. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949; 109(1–2):1–9. [PubMed: 15394301]

23. Frayn KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. J Appl Physiol. 1983; 55(2):628–34. [PubMed: 6618956]

24. Khuu A, Ren J, Dimitrov I, et al. Orientation of lipid strands in the extracellular compartment of muscle: effect on quantitation of intramyocellular lipids. Magn Reson Med. 2009; 61(1):16–21. [PubMed: 19097207]

25. Isken F, Klaus S, Petzke KJ, Loddenkemper C, Pfeiffer AF, Weickert MO. Impairment of fat oxidation under high- vs. low-glycemic index diet occurs before the development of an obese phenotype. Am J Physiol Endocrinol Metab. 2010; 298(2):E287–E295. [PubMed: 19934403]

26. Scribner KB, Pawlak DB, Aubin CM, Majzoub JA, Ludwig DS. Long-term effects of dietary glycemic index on adiposity, energy metabolism, and physical activity in mice. Am J Physiol Endocrinol Metab. 2008; 295(5):E1126–E1131. [PubMed: 18780772]

27. Bouche C, Rizkalla SW, Luo J, et al. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. Diabetes Care. 2002; 25(5):822–8. [PubMed: 11978675]

28. Pittas AG, Das SK, Hajduk CL, et al. A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion but not in overweight adults with low insulin secretion in the CALERIE Trial. Diabetes Care. 2005; 28(12):2939–41. [PubMed: 16306558]

29. Wee SL, Williams C, Tsintzas K, Boobis L. Ingestion of a high-glycemic index meal increases muscle glycogen storage at rest but augments its utilization during subsequent exercise. J Appl Physiol. 2005; 99(2):707–14. [PubMed: 15831796]

30. Coyle EF, Jeukendrup AE, Wagenmakers AJ, Saris WH. Fatty acid oxidation is directly regulated by carbohydrate metabolism during exercise. Am J Physiol. 1997; 273(2 Pt 1):E268–E275. [PubMed: 9277379]

31. Goodpaster BH, Katsiaras A, Kelley DE. Enhanced fat oxidation through physical activity is associated with improvements in insulin sensitivity in obesity. Diabetes. 2003; 52(9):2191–7. [PubMed: 12941756]

32. Nicklas BJ, Rogus EM, Goldberg AP. Exercise blunts declines in lipolysis and fat oxidation after dietary-induced weight loss in obese older women. Am J Physiol. 1997; 273(1 Pt 1):E149–E155. [PubMed: 9252491]

33. Solomon TP, Sistrun SN, Krishnan RK, et al. Exercise and diet enhance fat oxidation and reduce insulin resistance in older obese adults. J Appl Physiol. 2008; 104(5):1313–9. [PubMed: 18323464]

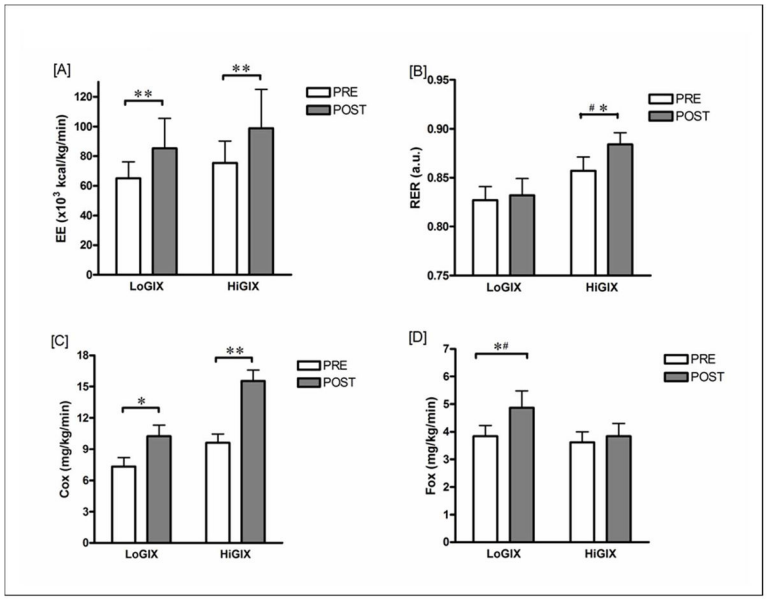

Figure 1. Energy metabolism during submaximal exercise

Whole body energy metabolism was measured via indirect calorimetry during a treadmill walking exercise bout performed at 65% of VO_2max, before and after a 3-month lifestyle intervention involving daily exercise training plus either a low glycemic (LoGIX) or high glycemic (HiGIX) diet. The exercise bout was performed before the intervention (PRE) and immediately following the intervention at (POST). Panel [A]: Following the intervention, energy expenditure (EE, kcal/kg/min) during exercise was increased in both LoGIX and HiGIX groups (PRE vs. POST: **P<0.01). Panel [B]: Respiratory exchange ratio (RER) during exercise was unchanged in LoGIX after the study, but increased in the HiGIX group (PRE vs. POST, *P<0.05; LoGIX vs. HiGIX, #P<0.05). Panel [C]: Carbohydrate oxidation rates expressed relative to changes in body weight (Cox, mg/kg/min) were increased in both groups after the study (PRE vs. POST, *P<0.05 **P<0.01), but this change was not different between groups. Panel [D]: Fat oxidation rates expressed relative to changes in body weight (Fox, mg/kg/min) were increased at in the LoGIX group only (PRE vs. POST, *P<0.05; LoGIX vs. HiGIX, #P<0.05).

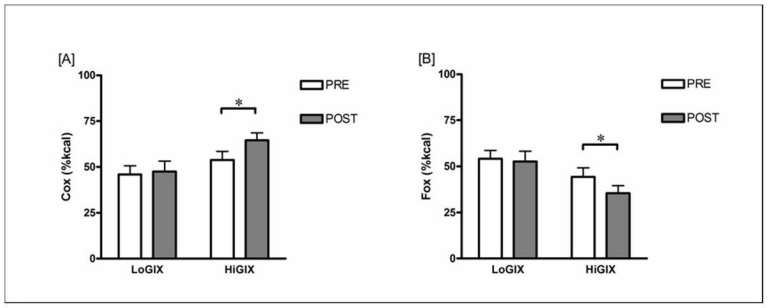

Figure 2. Metabolic substrate oxidation during submaximal exercise

Changes in caloric energy expenditure derived from carbohydrate and fat metabolism were expressed as a percentage of total energy expenditure. Panel [A]: Caloric expenditure from carbohydrate sources was increased in the HiGIX group (PRE vs. POST, *P<0.05) and unchanged in the LoGIX group following the study. Panel [B]: Caloric expenditure from fat sources was decreased in the HiGIX group (PRE vs. POST, *P<0.05) and unchanged in the LoGIX group following the study.

Table 1

Subject Characteristics.

Variable	LoGIX		HiGIX	
	PRE	POST	PRE	POST
n	10	-	10	-
Sex, ♂/♀	4/6	-	5/5	-
Age, y	66±2	-	63±1	-
Weight, kg	96.9±5.2	89.7±4.4*	97.8±6.1	88.4±4.8*
BMI, kg/m^2	35.3±1.5	32.7±1.3*	34.8±1.4	32.3±1.4*
Whole Body Adiposity, %	47.7±1.3	43.9±1.5*	45.7±2.3	40.5±3.5*
FPG, mg/dl	107.0±2.4	97.2±3.5*	103.6±3.9	98.2±3.4*
2h-OGTT, mg/dl	146.7±10.9	137.4±9.6	139.3±11.8	133.9±16.4
HbA1c, %	5.91±0.26	5.68±0.26*	5.57±0.15	5.48±0.14*
HOMA-IR, a.u.	4.62±0.67	3.86±0.45*	3.93±0.28	3.34±0.28*
Clamp GDR, mg/kg/min	2.03±0.29	3.47±0.36*	2.53±0.41	4.11±0.45*
Fasting TG, mg/dl	150.3±20.0	106.7±10.8*	144.6±24.3	105.1±18.8*
Fasting Cholesterol, mg/dl	200.5±13.2	181.7±10.5*	200.9±9.9	183.5±9.9*
VO_2max, l/min	1.95±0.17	2.36±0.22*	2.27±0.22	2.66±0.28*
VO_2max, ml/kg/min	20.0±1.0	26.3±2.0*	23.2±1.4	30.5±2.6*

Data represent mean ± S.E.M. LoGIX, low glycemic diet and exercise training group; HiGIX, high glycemic index diet and exercise group; PRE, baseline variables collected prior to intervention; POST, variables measured following the 12 week intervention; BMI, body mass index; FPG, fasting plasma glucose; 2h-OGTT, plasma glucose two hours following ingestion of 75 g of glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance calculated as the product of fasting glucose (mM) and insulin (μU/ml) divided by 22.5; a.u., arbitrary units; Clamp GDR, glucose disposal rate required to maintain euglycemia during 40 mU/m^2/min hyperinsulinemia; TG, triglycerides, VO_2max, maximal oxygen consumption during incremental treadmill walking test to exhaustion. Statistical analysis using two-way ANOVA indicated significant pre- vs. post-study differences (*P<0.05), but no significant effects of trial or time^{x}trial interactions.

Table 2

Resting and Insulin-Stimulated Energy Metabolism.

Energy Metabolism		LoGIX		HiGIX	
		PRE	POST	PRE	POST
Rest	RER, a.u.	0.861±0.008	0.838±0.011*	0.866±0.018	0.831±0.014*
	EE, $\times 10^3$ kcal/kg/min	10.6±0.2	11.1±0.3§	10.8±0.3	11.5±0.2§
	Cox, mg/kg/min	1.29±0.08	1.08±0.19	1.26±0.18	1.22±0.16
	Fox, mg/kg/min	0.334±0.047	0.420±0.069	0.360±0.072	0.378±0.106
Insulin	RER, a.u.	0.885±0.009	0.905±0.014	0.860±0.011	0.908±0.012
	EE, $\times 10^3$ kcal/kg/min	10.7±0.2	11.5±0.6	11.4±0.4	11.7±0.6
	Cox, mg/kg/min	1.58±0.08	1.95±0.13	1.49±0.12	2.04±0.16
	Fox, mg/kg/min	0.307±0.042	0.289±0.060	0.439±0.044	0.271±0.055
Metabolic Flexibility, a.u.		0.023±0.012	0.067±0.012*	0.006±0.017	0.077±0.017*

Data represent mean ± S.E.M. RER, respiratory exchange ratio; a.u., arbitrary units; EE, energy expenditure; Cox, carbohydrate oxidation; Fox, fat oxidation; % of EE, percentage of energy expenditure derived from either Cox or Fox; Insulin, measurements made during the final 30 min of 40 mU/m^2/min hyperinsulinemic euglycemic clamp; Metabolic Flexibility; the difference between the RER during insulin-stimulated conditions and at rest. Statistical analysis using two-way ANOVA indicated significant pre- vs. post-study differences (*P<0.05), but no significant effects of trial or $time^x$trial interactions. A P=0.05 increase in EE is represented by §.

Table 3

Oxygen consumption (VO_2) during Submaximal Exercise performed at 65% of VO_2max.

Exercise Intensity		LoGIX		HiGIX	
		PRE	POST	PRE	POST
VO_2	l/min	1.32±0.11	1.59±0.15*	1.52±0.15	1.77±0.18*
	ml/kg/min	13.5±0.6	17.7±1.3*	15.5±0.9	20.2±1.7*
% VO_2max		66.8±1.0	65.6±0.7	66.9±0.7	66.5±0.9

Data represent mean ± S.E.M.. Submaximal exercise was performed before (PRE) and after (POST) the intervention at 65% of pre-study VO_2max until 200 kcal of energy had been expended. VO_2, steady state rate of oxygen consumption measured by indirect calorimetry; %VO_2max, steady state oxygen consumption during exercise expressed as a percentage of maximal oxygen uptake. Statistical analysis using two-way ANOVA indicated significant effects of time: pre- vs. post-study differences are indicated by

*P<0.05.