Insulin sensitivity and metabolic flexibility following exercise training among different obese insulin-resistant phenotypes

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Submitted 12 August 2013; accepted in final form 17 September 2013

Malin SK, Haus JM, Solomon TP, Blaszczak A, Kashyap SR, Kirwan JP. Insulin sensitivity and metabolic flexibility following exercise training among different obese insulin-resistant phenotypes. Am J Physiol Endocrinol Metab 305: E1292–E1298, 2013. First published September 24, 2013; doi:10.1152/ajpendo.00441.2013.—Impaired fasting glucose (IFG) blunts the reversal of impaired glucose tolerance (IGT) after exercise training. Metabolic inflexibility has been implicated in the etiology of insulin resistance; however, the efficacy of exercise on peripheral and hepatic insulin sensitivity or substrate utilization in adults with IFG, IGT, or IFG + IGT is unknown. Twenty-four older (66.7 ± 0.8 yr) obese (34.2 ± 0.9 kg/m²) adults were categorized as IFG (n = 8), IGT (n = 8), or IFG + IGT (n = 8) according to a 75-g oral glucose tolerance test (OGTT). Subjects underwent 12-wk of exercise (60 min/day for 5 days/wk at ~85% HRmax) and were instructed to maintain a eucaloric diet. A euglycemic hyperinsulinemic clamp (40 μM-m²·min⁻¹) with [6,6-²H]glucose was used to determine peripheral and hepatic insulin sensitivity. Nonoxidative glucose disposal and metabolic flexibility [insulin-stimulated respiratory quotient (RQ) minus fasting RQ] were also assessed. Glucose incremental area under the curve (iAUCOGTT) was calculated from the OGTT. Exercise increased clamp-derived peripheral and hepatic insulin sensitivity more in adults with IFG or IGT alone than with IFG + IGT (P < 0.05). Increased clamp-derived peripheral insulin sensitivity was also correlated with enhanced metabolic flexibility, reduced fasting RQ, and higher nonoxidative glucose disposal (P < 0.05). Adults with IFG + IGT had smaller gains in clamp-derived peripheral insulin sensitivity and metabolic flexibility, which was related to blunted improvements in postprandial glucose. Additional work is required to assess the molecular mechanism(s) by which chronic hyperglycemia modifies insulin sensitivity following exercise training.

obesity; prediabetes; insulin resistance; cardiometabolic; exercise

APPROXIMATELY 79 MILLION ADULTS IN THE US HAVE IMPAIRED FASTING GLUCOSE (IFG), IMPAIRED GLUCOSE TOLERANCE (IGT), OR BOTH (IFG + IGT) AND ARE COLLECTIVELY REFERRED TO AS HAVING PREDIABETES (2). FOCUSING ON ADULTS WITH IFG, IGT, AND IFG + IGT IS CLINICALLY IMPORTANT SINCE EACH PHENOTYPE HAS A UNIQUE PATHOLOGY THAT PROMOTES DIFFERENT DEGREES OF CARDIOVASCULAR DISEASE RISK (8, 31). THE EXACT CAUSE FOR THE DIFFERENCE IN DISEASE RISK IS UNCLEAR, BUT THE DEGREE OF INSULIN RESISTANCE IN SKELETAL MUSCLE OR THE LIVER IS A LIKELY CANDIDATE. INDIVIDUALS WITH IGT [2-h ORAL GLUCOSE TOLERANCE TEST (OGTT) VALUES BETWEEN 140 AND 199 MG/DL] ARE TYPICALLY CHARACTERIZED AS HAVING REDUCED SKELETAL MUSCLE INSULIN SENSITIVITY, WHEREAS ADULTS WITH IFG (FASTING GLUCOSE 100–125 MG/DL) GENERALLY HAVE IMPAIRED HEPATIC INSULIN SENSITIVITY (5). ADULTS DIAGNOSED WITH IFG + IGT HAVE MORE SEVERE INSULIN RESISTANCE SINCE BOTH SKELETAL MUSCLE AND LIVER GLUCOSE METABOLISM ARE DYSREGULATED (5). SINCE IFG, IGT, AND IFG + IGT ARE CHARACTERIZED BY DIFFERENT ABNORMALITIES IN GLUCOSE METABOLISM, IT STANDS TO REASON THAT THERAPIES ATTEMPTING TO NORMALIZE HYPERGLYCEMIA MAY IMPACT EACH PHENOTYPE DIFFERENTLY (14, 37).

Exercise reduces glucose intolerance and cardiometabolic risk factors by in part increasing insulin sensitivity (22, 26, 27, 35). However, there is high intersubject variability in response to exercise (9). Recently, we reported that adults with IFG + IGT have attenuated reductions in 2-h glucose concentrations following a 12-wk lifestyle intervention (33). However, the mechanism by which IFG blunts reductions in postprandial glucose concentrations is unknown. One possibility is that IFG attenuates improvements in skeletal muscle, hepatic, and/or adipose insulin sensitivity in adults with IGT. In addition, recent work suggests that the presence of IFG reduces carbohydrate utilization, particularly glycogen, during exercise in adults with IGT (32). But whether individuals with IFG + IGT are characterized by metabolic inflexibility (i.e., the inability to switch from predominantly fat use in the fasted state to mainly carbohydrate during insulin stimulation) or glycogen storage defects is unknown. Therefore, the primary objective of this study was to gain mechanistic insight into differences in insulin-stimulated glucose uptake across the prediabetes phenotypes following exercise. We hypothesized that exercise training would improve peripheral and hepatic insulin sensitivity in individuals with IFG or IGT more than adults with IFG + IGT matched on age, aerobic fitness, and weight. We also hypothesized that the blunted increase in insulin sensitivity would correlate with attenuated improvements in glycemic control and metabolic flexibility.

METHODS

Subjects. Twenty-four older (66.7 ± 0.8 yr) obese (34.2 ± 0.9 kg/m²) adults (see Table 1) were recruited from the Cleveland, OH, area for this study and matched relative to age, aerobic fitness, and
weight. Subjects were excluded if they were weight unstable (>2 kg in the previous 6 mo), physically active (>60 min/wk), or on anti-diabetic medications or had chronic disease (i.e., renal, hepatic, type 2 diabetes, cardiovascular, etc.). Women were postmenopausal, and all adults underwent a medical and physical examination that included both a resting ECG and maximally graded exercise stress test. We used an OGTT and the American Diabetes Association criteria to characterize prediabetes status (1). Subjects gave verbal and informed signed consent documents approved by the Cleveland Clinic Institutional Review Board.

**Cardiovascular fitness and body composition.** Maximum oxygen consumption (\( \text{VO}_{2\text{max}} \)) and heart rate (HR<sub>max</sub>) were determined using a continuous incremental treadmill exercise test (Jaeger OxygenPro; Viasys, Yorba Linda, CA) to describe cardiovascular fitness. Blood pressure was recorded in the seated position after ~10 min of rest. Body weight was recorded on a digital platform scale, and dual X-ray absorptiometry (GE Lunar Prodigy, Madison, WI) was used to quantify total fat mass and fat-free mass. Waist circumference was measured in the standing position 2 cm above the umbilicus using a Gulick tension tape measure.

**Control period.** Metabolic assessments were conducted during a 3-day inpatient stay at our Clinical Research Unit before and after the intervention. Resting metabolic rate was determined after subjects rested in the supine position for 30 min. Exhaled air (i.e., \( \text{VO}_{2} \) and \( \text{VCO}_{2} \)) was collected using a ventilated hood and indirect calorimetry (Vmax Encore; Viasys), and from this, subjects were provided eucaloric meals (resting metabolic rate \( \times 1.2 \) activity factor; 55% CHO, 30% fat, and 15% protein). Postintervention metabolic assessments were obtained 16–18 h after the last exercise session.

**OGTT.** After an overnight fast, a catheter was inserted into an antecubital vein for the collection of fasting triglyceride, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, and insulin. A 75-g oral glucose load was then administered for the determination of postprandial glucose and insulin concentrations at 30, 60, 90, 120, and 180 min. Glucose and insulin incremental area under the curve (iAUC) during the OGTT was calculated using the trapezoidal rule.

**Insulin sensitivity.** After an overnight fast, a euglycemic hyperinsulinemic clamp was performed. A primed (3.28 mg/kg) continuous (0.036 mg·kg<sup>-1</sup>·min<sup>-1</sup>) infusion of [6,6-\( ^2 \)H<sub>2</sub>]glucose was started at \( t = -120 \) min. Prior to insulin infusion, exhaled air was collected for 20 min, using a ventilated hood and indirect calorimetry to determine basal substrate oxidation. At \( t = 0 \), a constant infusion (40 mU·m<sup>2</sup>·min<sup>-1</sup>) of insulin was administered via an indwelling catheter placed in an antecubital vein. Glucose was infused for 120 min at a variable rate to maintain plasma glucose at 90 mg/dl. A retrograde hand catheter was also placed, and the hand was warmed to 60°C for collection of arterialized blood samples. Rates of glucose appearance (\( R_a \)) and glucose rates of disposal (\( R_d \)) were calculated using non-steady-state Steele equations, as we described previously (34).

\[
\text{glucose}\ R_a \text{(mg/min)} = \frac{F - V[(C1 + C2)/2][IE2 - IE1]/(t2 - t1)]}{[IE2 + IE1]/2} - \text{glucose}\ R_d\text{(mg/min)} = \text{R}_d = \frac{V[(C2 - C1)/2]}{[t2 - t1]}
\]

where \( F \) is the isotope infusion rate, \( IE_1 \) and \( IE_2 \) are enrichments of plasma glucose with isotope label at times \( t1 \) and \( t2 \), and \( C_1 \) and \( C_2 \) are plasma glucose concentrations, and \( V \) is the estimated volume of distribution for glucose (180 ml/kg). Rates of glucose disposal (\( \text{R}_d \)), which reflect mostly skeletal muscle glucose uptake, were averaged during the last 30 min of the clamp and used to characterize peripheral insulin sensitivity. Basal rates of endogenous glucose appearance (\( R_e \)), which is comprised primarily of hepatic glucose production (HGP), were averaged from \( t = -30 \) to \( t = 0 \) min. HGP during the clamp was calculated as the difference between \( \text{R}_d \) and the exogenous glucose infusion rate. The suppression of HGP was defined as \( [1 - (\text{HGP}_{\text{clamp}}/\text{HGP}_{\text{fast}}) \times 100\%] \) and used to estimate hepatic insulin sensitivity (34). Insulin-stimulated suppression of free fatty acids (FFA) was calculated as \( [1 - (\text{FFA}_{\text{clamp}}/\text{FFA}_{\text{fast}}) \times 100\%] \). Glucose kinetics and clamp-derived carbohydrate oxidation were determined by indirect calorimetry during the last 20 min of the clamp using standard equations (17). Nonoxidative glucose disposal (NOGD) was calculated (NOGD = \( R_e - \text{total carbohydrate oxidation} \)). Metabolic flexibility was also calculated as \( \text{R}_{Q\text{H}} - \text{R}_{Q\text{fast}} \).

**Exercise training.** Participants underwent a supervised exercise intervention for 60 min/day, 5 days/wk at ~85% of HR<sub>max</sub> for 12 wk. Subjects performed treadmill exercise for ~45 min, whereas cycling was permitted to facilitate exercise compliance. Thus, walking was the primary mode of exercise and was consistent between groups. This suggests that exercise energy expenditure is unlikely to explain metabolic differences between groups after the intervention. Appropriate exercise intensity was managed using heart rate monitors (Polar Electro, Woodbury, NY). Subjects met weekly with a dietician to review 3-day diet logs to ensure dietary compliance.

**Biochemical analysis.** Blood samples were centrifuged at 4°C for 10 min at 1,000 rpm and then stored at ~80°C until subsequent analysis. Plasma glucose was determined by a glucose oxidase assay (YSI 2300 STAT Plus; Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was measured using a radioimmunoassay (Millipore, Billerica, MA). Plasma triglycerides and cholesterol were analyzed using enzymatic methods with an automated platform (Roche Modular Diagnostics, Indianapolis, IN). Plasma FFAs were analyzed by a colorimetric assay (Wako Chemicals, Richmond, VA). Plasma samples for isotopic enrichment were deproteinized, extracted, and then derivatized before analysis by gas chromatography-mass spectrometry, as described previously (40).

**Statistical analysis.** Pre- and postgroup means were compared using R (Leopard build 64-bit; The R Foundation, Vienna, Austria). Nonnormally distributed data were log-transformed for statistical analysis. To compare the group effect, baseline characteristics and the change (i.e., post-pre) before and after the intervention were compared with a one-way analysis of variance. Baseline peripheral insulin

<table>
<thead>
<tr>
<th>Table 1. Body composition and aerobic fitness</th>
<th>IFG</th>
<th>IGT</th>
<th>IFG + IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n, males/females)</td>
<td>5/3</td>
<td>4/4</td>
<td>2/6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67.5 ± 1.6</td>
<td>67.0 ± 0.9</td>
<td>65.6 ± 1.6</td>
</tr>
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<td>Height, m</td>
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<td>1.71 ± 0.04</td>
<td>1.66 ± 0.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Pre 102.1 ± 6.8</td>
<td>95.2 ± 3.6</td>
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</tr>
<tr>
<td>Δ</td>
<td>-9.5 ± 2.2*</td>
<td>-5.9 ± 1.3*</td>
<td>-6.4 ± 0.8*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Pre 33.8 ± 1.3</td>
<td>32.6 ± 1.3</td>
<td>36.3 ± 1.8</td>
</tr>
<tr>
<td>Δ</td>
<td>-3.1 ± 0.6*</td>
<td>-2.1 ± 0.4*</td>
<td>-2.4 ± 0.3*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>Pre 110.3 ± 4.4</td>
<td>106.5 ± 3.4</td>
<td>108.4 ± 3.6</td>
</tr>
<tr>
<td>Δ</td>
<td>-5.5 ± 1.2*</td>
<td>-5.3 ± 1.2*</td>
<td>-5.5 ± 1.3*</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>Pre 42.7 ± 3.8</td>
<td>38.3 ± 3.8</td>
<td>45.3 ± 2.8</td>
</tr>
<tr>
<td>Δ</td>
<td>-6.8 ± 2.1*</td>
<td>-3.2 ± 1.0*</td>
<td>-4.5 ± 0.8*</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>Pre 58.7 ± 5.1</td>
<td>56.2 ± 4.6</td>
<td>53.2 ± 3.4</td>
</tr>
<tr>
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<td>-1.8 ± 0.7*</td>
<td>-1.9 ± 0.9*</td>
</tr>
<tr>
<td>( \text{VO}_{2\text{max}} ), l/min</td>
<td>2.3 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Δ</td>
<td>0.4 ± 0.1*</td>
<td>0.2 ± 0.3*</td>
<td>0.2 ± 0.1*</td>
</tr>
<tr>
<td>( \text{VO}_{2\text{max}} ), ml·kg&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>Pre 21.9 ± 1.3</td>
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<td>19.9 ± 0.6</td>
</tr>
<tr>
<td>Δ</td>
<td>6.2 ± 1.3*</td>
<td>3.5 ± 0.6*</td>
<td>4.2 ± 0.8*</td>
</tr>
</tbody>
</table>

Data are means ± SE. IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index. Data were log transformed for statistical analysis but are presented herein as raw values. ANOVA was performed to detect between-group differences. Within effect (paired t-test; *P < 0.05 and †P < 0.09).
sensitivity, sex, weight loss, and improved aerobic fitness were used as covariates to adjust for their influence on the change in peripheral insulin sensitivity across groups. Bonferroni’s post hoc analysis was used in the event of a significant main effect to assess group differences. Two-tailed paired t-tests were used to compare within-group exercise effects. Pearson’s correlation was used to examine associations. Data are means ± SE. Significance was accepted as $P \leq 0.05$.

**RESULTS**

**Body composition and cardiometabolic risk factors.** All subjects completed the intervention, and each group increased VO$_2$max ($P < 0.001$; Table 1). Exercise training reduced body weight/fat comparably across IFG, IGT, and IFG + IGT ($P < 0.001$; Table 1). Exercise reduced total cholesterol across all groups. However, exercise decreased triglycerides and LDL in those with IFG or IFG + IGT ($P < 0.05$; Table 2), whereas blood pressure was lowered in subjects with IGT or IFG + IGT ($P < 0.05$; Table 2).

**Plasma glucose and insulin.** By study design, baseline fasting plasma glucose was higher in people with IFG and IFG + IGT compared with IGT ($P < 0.05$), whereas 2-h glucose concentrations were higher in adults with IGT and IFG + IGT compared with IFG (Table 3). Exercise decreased fasting plasma glucose in those with IFG and IFG + IGT, whereas glucose iAUC was reduced in adults with IGT only ($P < 0.05$; Table 3). The intervention reduced fasting insulin and insulin iAUC across groups ($P < 0.05$; Table 3).

**Peripheral insulin sensitivity.** At baseline, insulin-stimulated glucose uptake was more statistically different across IFG, IGT, and IFG + IGT ($P = 0.15$). Exercise training increased insulin-stimulated glucose uptake more in adults with IFG or IGT than individuals with IFG + IGT (group × test, $P < 0.03$; Fig. 1A). Exercise increased NOGD in those with IFG or IGT compared with IFG + IGT (group × time effect, $P < 0.05$; Table 3) and lowered fasting respiratory quotient (RQ) in subjects with IFG (trend; $P = 0.09$) and IGT ($P < 0.05$) but not IFG + IGT ($P = 0.23$). Metabolic flexibility was also increased after exercise in those with IFG or IGT only ($P < 0.03$; Fig. 1B).

**Hepatic glucose production and FFA suppression.** Exercise led to statistically significant reductions in basal HGP in IFG (2.4 ± 0.3 vs. 1.8 ± 0.1 mg·kg$^{-1}$·min$^{-1}$, $P < 0.05$) but not IGT (2.4 ± 0.4 vs. 1.8 ± 0.3 mg·kg$^{-1}$·min$^{-1}$, $P = 0.13$) or IFG + IGT (3.1 ± 0.6 vs. 2.4 ± 0.5 mg·kg$^{-1}$·min$^{-1}$, $P = 0.23$). Exercise improved insulin-stimulated suppression of HGP in adults with IFG (1.2 ± 0.3 vs. 0.4 ± 0.2 mg·kg$^{-1}$·min$^{-1}$, $P < 0.01$) and IGT (1.4 ± 0.4 vs. 0.4 ± 0.2 mg·kg$^{-1}$·min$^{-1}$, $P < 0.03$) but not IFG + IGT (1.7 ± 0.4 vs. 0.9 ± 0.3 mg·kg$^{-1}$·min$^{-1}$, $P = 0.14$). Subsequently, individ-

| Table 3. Glucose homeostasis and substrate oxidation |
|----------------|-------|-------|-------|
|                | IFG   | IGT   | IFG + IGT |
| FPG, mg/dl     |       |       |       |
| Pre             | 105.2 ± 1.9$^*$ | 94.6 ± 1.6 | 104.9 ± 1.6$^*$ |
| $\Delta$       | −9.6 ± 1.8$^*$ | −0.8 ± 1.3 | −8.7 ± 2.8$^*$ |
| FPL, µU/ml      |       |       |       |
| Pre             | 18.6 ± 3.9 | 13.2 ± 2.2 | 22.2 ± 4.0 |
| $\Delta$       | −7.1 ± 2.4$^*$ | −2.9 ± 1.2$^*$ | −9.1 ± 3.2$^*$ |
| 2-h OGTT glucose, mg/dl |       |       |       |
| Pre             | 116.1 ± 4.0 | 153.7 ± 3.7$^*$ | 163.9 ± 7.9$^*$ |
| $\Delta$       | 6.0 ± 1.1 | −12.2 ± 6.5 | −9.5 ± 12.6 |
| GLC iAUC OGTT, mg·dl$^{-1}$·180$^*$ |       |       |       |
| Pre             | 2,508.5 ± 433.5 | 5,164.4 ± 465.7$^*$ | 4,530.5 ± 482.3$^*$ |
| INS iAUC OGTT, µU·ml$^{-1}$·180$^*$ |       |       |       |
| Pre             | 142.8 ± 772.5 | −1,027.4 ± 269.7$^*$ | −667.8 ± 718.7 |

Data are means ± SE. FPG, fasting plasma glucose; FPI, fasting plasma insulin; iAUC, incremental area under the curve; GLC, glucose; INS, insulin; RQ, respiratory quotient; NOGD, nonoxidative glucose disposal. *Data were log-transformed for statistical analysis but are presented herein as raw values. ANOVA was performed to detect between-group differences. Between-group effect (†$P < 0.05$ vs. IGT; ‡$P < 0.05$ and $\ddagger$P = 0.10 vs. IFG + IGT). Within effect (paired t-test; *$P < 0.05$, †$P < 0.05$, ‡$P < 0.03$).
uals with IFG or IGT increased hepatic insulin sensitivity after training ($P < 0.05$; Fig. 1C). There were no statistical differences in fasting FFA concentrations or insulin-stimulated FFA suppression after the intervention across groups (Table 2 and Fig. 1D).

Correlations. Decreased fasting glucose after training was significantly associated with a rise in glucose iAUC ($r = -0.43$, $P < 0.05$). Increased insulin-stimulated glucose uptake was associated with lower glucose iAUC ($r = -0.55$, $P < 0.01$), metabolic flexibility ($r = 0.41$, $P = 0.05$), RQfast ($r = -0.55$, $P < 0.01$), and NOGD ($r = 0.79$, $P < 0.0001$) after training. Improved hepatic insulin sensitivity was associated with fat loss ($r = -0.42$, $P < 0.05$) but not glucose iAUC ($r = -0.26$, $P = 0.27$).

CONCLUSIONS

The major finding in our study was that adults with IFG + IGT had smaller improvements in peripheral and hepatic insulin sensitivity after 12 wk of exercise training compared with age, weight, and aerobically fit matched adults with IFG or IGT alone. Consistent with prior work from our laboratory (33), we show here that the presence of IFG blunts reductions in postprandial glucose concentrations in adults with IGT. We also expand on our previous work (32, 33) and demonstrate that alterations in carbohydrate and fat utilization are present in adults with IFG + IGT compared with IGT after training. Together, these data suggest that the presence of IFG in adults with IGT modifies exercise training-induced improvements in glucose regulation. Although exercise generally increases insulin sensitivity in adults across the glucose continuum (11, 22, 26, 35), the data are consistent with carefully controlled studies reporting that people with metabolic syndrome or early-onset type 2 diabetes have less improvement in clamp-derived whole body insulin sensitivity following 12 wk of exercise compared with healthy age, weight, and fitness-matched counterparts (25, 30). In addition, the Diabetes Prevention Program Outcomes Study emphasized recently that adults with more severe forms of prediabetes were least likely to regress to normal glucose tolerance (37). Thus, our data highlight insulin resistance as an important factor contributing to the normalization of glucose in adults across the prediabetes spectrum.

There are several possible reasons why the presence of IFG blunted improvements in postprandial glucose concentrations in adults with IGT. Fasting hyperglycemia is typically ascribed to hepatic insulin resistance, and thus, it is possible that insulin failed to adequately suppress hepatic glucose production after exercise training (7). In the current study, adults with IFG + IGT had smaller improvements in hepatic insulin sensitivity after exercise training compared with subjects with IFG or IGT alone. However, we did not observe a statistically significant association between the change in hepatic insulin sensitivity and the blunted improvement in postprandial hyperglycemia. On the basis of this observation, it appears that improvements in postprandial glucose were not linked directly to changes in hepatic insulin sensitivity, and an alternative mechanism is more probable. Obesity is considered a causal factor in the development of lipotoxicity, and adults with IFG or IGT are...
characterized with adipose insulin resistance (4). Elevated FFA levels have been linked to increased hepatic glucose production and may partially explain hyperglycemia following glucose ingestion (5, 22). Previously, we reported that reductions in visceral fat were attenuated in adults with IFG + IGT after lifestyle modification compared with IFG or IGT alone (33). In the current study, however, we observed similar reductions in body fat and waist circumference, and these changes in fatness mirrored the changes in hepatic insulin sensitivity and circulating FFAs (5). Thus, the blunted improvement in glucose tolerance in this study is not likely related to hepatic or adipose insulin sensitivity.

Skeletal muscle is considered the chief tissue responsible for glucose disposal. Previously, we hypothesized that the presence of IFG blunts improvements in skeletal muscle insulin sensitivity in adults with IGT, and this in turn contributes to the lack of IGT normalzation (33). Since insulin-stimulated glucose uptake was blunted in adults with IFG + IGT after exercise training in the current study, we would expect little change in postprandial glucose concentrations. Indeed, improvements in postprandial glucose were directly correlated with increased peripheral insulin-stimulated glucose uptake. The cellular mechanism responsible for attenuated improvements in peripheral insulin sensitivity in adults with IFG + IGT is not readily apparent from our study design, but we propose that impaired mitochondrial oxidative capacity may play a role (16, 20, 29, 32, 49) since chronic hyperglycemia has been implicated in the dysregulation of mitochondrial capacity (28, 41). In our study, exercise training increased metabolic flexibility in subjects with IFG or IGT alone, whereas those with IFG + IGT remained metabolically inflexible. This observation is consistent with in vivo work reporting that IFG impairs carbohydrate utilization in adults with IGT (16, 32). In addition, in vitro work demonstrates that chronic hyperglycemia impairs metabolic flexibility by decreasing mitochondrial complex I activity in human myotubes (3). Skeletal muscle biopsies are needed to determine whether the presence of IFG alters in vivo mitochondrial oxidative capacity in adults with IGT (20, 29, 42). However, given that in vivo (29, 42) and in vitro studies (3) report that chronic hyperglycemia loads mitochondrial oxidative capacity, it appears plausible that exercising with a background of hyperglycemia impairs skeletal muscle glucose uptake through a metabolic stress/inflammatory-related pathway (36). This hypothesis is consistent with evidence that PGC-1α and AMPK expression are lower after exercise in insulin-resistant individuals (13, 24, 30).

Independent of substrate utilization, improving glycogen synthesis is an important mechanism by which exercise increases skeletal muscle insulin sensitivity (12). In our study, adults with IFG + IGT had smaller gains in nonoxidative glucose metabolism compared with individuals with IFG or IGT alone, and the increased nonoxidative glucose metabolism was linked to enhanced insulin-stimulated glucose uptake. This observation is consistent with our prior work reporting that adults with IFG + IGT have decreased muscle glycogen utilization during exercise compared with insulin-resistant and age-, fitness-, and weight-matched IGT counterparts (32). Our data are also consistent with animal work and human muscle cell studies demonstrating that hyperglycemia downregulates glycogen synthase (10, 21). Taken together, these observations suggest that glycogen storage may be a limiting factor for glucose clearance in hyperglycemic adults.

Adults with IFG + IGT have been characterized as having higher cardiometabolic disease risk than people with IGT or IFG (31). Because insulin resistance is an important underlying factor in the development of cardiometabolic disease, it is reasonable to expect that changes in insulin sensitivity after exercise mirror the change in cardiometabolic risk factors. In the present study, however, our data suggest that exercising with a background of hyperglycemia has little consequence on modifying cardiometabolic risk factors. Consistent with prior cross-sectional work, we observed significant blood pressure reductions in adults with IGT only, whereas plasma lipids were decreased in those with IFG (31). Interestingly, there did not appear to be any difference in these cardiometabolic risk factors between IGT only compared with IFG + IGT despite stark differences in insulin sensitivity responses to exercise. This observation suggests that improvements in insulin sensitivity are not essential for reductions in blood pressure or circulating lipids in these obese adults. It is also worth noting that we detected subtle reductions in HDL across all prediabetes phenotypes, although this did not reach statistical significance. Reductions in HDL might be considered an adverse response to exercise, and prior work has suggested that familial heritability in part explains the intersubject HDL variability in response to exercise (9). We did not design this study to determine the mechanism responsible for reductions in blood pressure or circulating lipids, but our data suggest that further work investigating the cardiovascular (e.g., capillary density) as well as lipid kinetic responses following exercise across the prediabetes phenotypes is warranted. We also recognize that no measurements of macrophage/systemic inflammation were made, which are important factors that are known to contribute to changes in skeletal muscle insulin sensitivity after exercise training (18, 19). It is also possible that weight/fat loss contributed to the improvements in cardiometabolic risk and masked the effect of preserved insulin resistance in adults with IFG + IGT.

There are limitations to the study that merit consideration. First, the uneven sex distribution across groups may have influenced the response to exercise. However, despite men and women potentially differing in the risk for developing IFG or IGT (15), both sexes appear to lower postprandial glucose in response to exercise (23, 27). In addition, we used sex as a covariate in our statistical model for peripheral insulin sensitivity, and this did not influence the results. We also recognize that our study had a relatively small sample size, and it is possible that we were underpowered to detect some group differences. In addition, we did not strictly control dietary intake throughout the study, although the glycemic index and/or energy content of the diet is unlikely to have major effects on insulin sensitivity when combined with exercise training (40, 43). Moreover, we cannot rule out the possibility that different exercise programs, including resistance exercise or lower aerobic exercise doses, could have different effects on glucose regulation in the prediabetes phenotypes (6). Longer-term exercise and/or diet studies are needed to rule this out. Finally, there was no true control group of normal glucose-tolerant (NGT) adults included in the current study. Previously, we reported (33) that NGT age- and weight-matched individuals increased whole body insulin sensitivity similarly to adults...
with IFG or IGT alone. As a result, we decided to focus on gaining mechanistic insight in individuals across the prediabetes spectrum. In our current study, individuals with IFG or IGT served as the control groups so that we could isolate the physiological response of adults with IFG + IGT to exercise. Despite these limitations, we are confident that our study allows for conclusions on the hyperglycemic phenotype response to exercise since we used precise means of characterizing prediabetes, the gold-standard euglycemic clamp technique with glucose kinetics to assess peripheral vs. hepatic insulin sensitivity, and a carefully controlled and supervised exercise program of sufficient intensity.

In conclusion, IFG + IGT contributes to attenuated improvements in peripheral and hepatic insulin sensitivity after exercise training. These findings may be clinically relevant since poor gains in peripheral insulin sensitivity were linked to small improvements in postprandial glucose concentrations. Moreover, a failure to improve insulin sensitivity in adults with IFG + IGT after exercise may over time lead to β-cell exhaustion and the development of type 2 diabetes (37). Our data raise the possibility that each prediabetes phenotype represents a unique pathophysiological condition that regresses to normal glucose tolerance via different mechanisms. Taken together, pharmacological treatment may be needed, in addition to exercise therapy, to combat hyperglycemia in adults with IFG + IGT (38). However, the best anti-diabetes medication treatment plan that should be combined with exercise therapy remains poorly understood and may not necessarily be beneficial for restoring glucose homeostasis (34). Further work is required to identify optimal strategies for treating hyperglycemia in the prediabetes phenotypes to normalize blood glucose.

ACKNOWLEDGMENTS

We thank the Clinical Research Unit nursing staff, the participants for their efforts, and the exceptional organizational assistance of Julianne Filion.

GRANTS

This research was supported by National Institute on Aging Grant RO1-AG12834 (to J. P. Kirwan) and National Institutes of Health National Center for Research Resources Grant 1UL1-RR-024989 (Cleveland, OH). S. K. Malin was supported by an National Institute of Diabetes and Digestive and Kidney Diseases T32-DK-007319 Training Grant.

DISCLOSURES

The authors report no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

S.K.M. and J.P.K. contributed to the conception and design of the research; S.K.M., T.P.S., and J.P.K. performed the experiments; S.K.M., J.M.H., T.P.S., A.B., and J.P.K. analyzed the data; S.K.M., J.M.H., T.P.S., S.R.K., and J.P.K. interpreted the results of the experiments; S.K.M. and J.P.K. prepared the figures; S.K.M. and J.P.K. drafted the manuscript; S.K.M., J.M.H., T.P.S., A.B., S.R.K., and J.P.K. edited and revised the manuscript; S.K.M., J.M.H., T.P.S., A.B., S.R.K., and J.P.K. approved the final version of the manuscript.

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