Effects of Prior High-Intensity Exercise on Glucose Metabolism in Normal and Insulin-resistant Men

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SUMMARY

The effects of prior high-intensity cycle exercise (85% $VO_{2\ max}$) to muscular exhaustion on basal and insulin-stimulated glucose metabolism were studied in obese, insulin-resistant, and normal subjects. Six obese (30.4% fat) and six lean (14.5% fat) adult males underwent two separate, two-level hyperinsulinemic-euglycemic clamp studies (100-min infusions at 40 and 400 mU/m²/min), with and without exercise 12 h earlier. Carbohydrate oxidation was estimated by indirect calorimetry using a ventilated hood system, and endogenous glucose production by D-(3-³H)-glucose infusion. Glycogen content and glycogen synthase activity (GS %I) were measured in vastus lateralis muscle biopsies before and at the end of each insulin clamp procedure.

After exercise, the obese and lean subjects had comparably low muscle glycogen concentrations (0.10 versus 0.08 mg/g protein, respectively), and equal activation of muscle GS activity (54.4 versus 45.3 GS %I, respectively). In the obese subjects, insulin-stimulated glucose disposal was increased significantly, but not totally corrected to normal. In both groups there was a comparable increase in nonoxidative glucose disposal (NOGD), whereas glucose oxidation was decreased and lipid oxidation was increased. Thus, the major effect of prior exercise was to increase insulin-stimulated glucose disposal in the obese subjects and to alter the pathways of glucose metabolism to favor NOGD and decrease glucose oxidation.

No correlation was found between the exercise-induced increase in GS %I and NOGD, except in the normal subjects during maximal insulin stimulation. Thus, glycogen synthase activity does not appear to be rate-limiting for NOGD at physiologic insulin concentrations.

Our findings suggest that a single bout of glycogen-depleting exercise can increase glucose disposal for at least 12–14 h in obese subjects with insulin resistance.
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Obesity is the most common cause of insulin resistance, and an increased prevalence of type II, non-insulin-dependent diabetes mellitus in obese subjects has long been recognized.[1] Obese subjects with hyperinsulinemia have been characterized as insulin resistant by a variety of techniques including the hyperinsulinemic, euglycemic clamp technique.[2] Even in the absence of weight loss, exercise training has been shown to improve insulin sensitivity in obesity.[3] It has been suggested that a single bout of exercise can also result in significant improvements in insulin sensitivity in these subjects, but this has not been clearly demonstrated.

Recently, Bogardus et al.[4] have shown that normal subjects have significant increases in both total glucose uptake and in nonoxidative glucose disposal 12 h after acute, glycogen-depleting exercise. Furthermore, they found significant correlations between the increases in glucose disposal and the conversion of glycogen synthase to its active (glucose-6-phosphate-independent) form, and postulated that glycogen synthase might function as a rate-limiting enzyme for glucose disposal after intense exercise in man.

The present study was undertaken to extend these observations by comparing the responses to acute, glycogen-depleting exercise in normal volunteers to a group of obese subjects with insulin resistance. Specifically, we wished to determine the extent to which a single bout of glycogen-depleting exercise would improve insulin sensitivity and responsiveness in insulin-resistant subjects. The roles of glycogen depletion and activation of glycogen synthase in regulating the changes in glucose disposal after acute exercise were also examined in these two groups.

MATERIALS AND METHODS

Six male subjects were selected on the basis of obesity (>130% IBW, based on Metropolitan Life Insurance Tables,

TABLE 1
Patient characteristics and results of oral glucose tolerance tests (mean ± SEM)

	Lean	Obese
Age	27.8 ± 1.9	33.8 ± 2.3
(Range)	(23–33)	(25–39)
% Fat	14.5 ± 1.7	30.4 ± 2.2‡
Fat-free mass (kg)	66.8 ± 2.7	80.8 ± 3.7*
% IBW	109	179‡
(Range)	(100–118)	(154–257)
OGTT results		
Glucose (mg/dl)		
Basal	90.0 ± 1.7	109.0 ± 5.7*
Peak	151 ± 19	200 ± 18†
Insulin (μU/ml)		
Basal	13 ± 2	34 ± 13
Peak	112 ± 13	261 ± 48†
$VO_{2\,max}$		
L/min	3.55 ± 0.22	2.69 ± 0.10†
ml/kg FFM/min	53.75 ± 2.23	33.05 ± 2.16‡
Exercise duration (min)	65.5 ± 3.4	33.1 ± 2.2‡

*$P < 0.05$, †$P < 0.02$, and ‡$P < 0.01$, lean versus obese subjects.

1959) and glucose intolerance and/or hyperinsulinemia during a 75-g oral glucose tolerance test.[5] Six control male subjects were within 18% IBW and had normal glucose and insulin responses to the same glucose challenge.

All subjects were free of medical illnesses, including hypertension, cardiovascular disease, or exercise limitations, and were on no regular medications. None were engaged in a physical training program. Their diets contained at least 250 g of carbohydrate/day for the 3 days before each of their two admissions to the Clinical Research Center.

On admission each subject received a maintenance diet (35 kcal/kg IBW/day, 50–55% carbohydrate) and physical activity was limited. On the first day of the "exercise" admission, maximum aerobic capacity ($VO_{2\,max}$) was determined using intermittent exercise on an electromagnetically braked cycle ergometer.[6] On the second day, beginning at 1900 h, each subject was exercised at 85% of the measured $VO_{2\,max}$. Two-minute bouts of exercise were interrupted by 3-min rest periods, and the subjects continued until muscle fatigue prevented further exercise. One-half the subjects were exercised on their first admission, and the other half on their second admission.

On the "nonexercise" admission, body composition was estimated from body density, determined by underwater weighing with simultaneous measurement of residual lung volume by helium dilution using the formula of Siri.[7]

On the third hospital morning of each admission, a "two-step" hyperinsulinemic-euglycemic clamp procedure was performed.[8] At 0700 h, a 19-gauge indwelling catheter was inserted into a right antecubital vein, and a 25-μCi bolus of D-(3-^{3}H)-glucose was given, followed by a constant infusion at 0.25 μCi/min. A 19-gauge indwelling needle was inserted in a contralateral hand vein and the hand was warmed in a heated box (70°C) for obtaining "arterialized" blood specimens.[9]

A ventilated hood system was used for continuous indirect calorimetry determinations[10] in the basal period and during both insulin infusions. Expired air was continuously withdrawn and delivered to a zirconium cell oxygen analyzer, an infrared carbon dioxide analyzer (Applied Electro-chemistry, Sunnyvale, California), and a Vertek flowmeter (Burlington, Vermont). The electrical outputs were interfaced to a desktop computer (Hewlett-Packard 85, Palo Alto, California), and integrated readings of O_2 consumption, CO_2 production, RQ, and energy expenditure were printed out every 5 min.

A muscle biopsy was obtained from the vastus lateralis muscle approximately 15 cm above the patella[11] using a 5-mm Bergstrom needle and local anesthesia, 10–15 min before and immediately after completion of the insulin clamp procedure. Muscle was dissected free of surrounding fat and fascia, and the sample was cut in half. One piece was immediately placed in liquid nitrogen for later determination of glycogen synthase activity and protein; the other piece was weighed serially over 1–2 min on a Mettler balance, with the weight extrapolated to time 0, before being placed in 30% KOH for later glycogen determination.

At 0900 h, a primed, continuous insulin infusion was begun at 40 mU/m^2/min ("low-dose") and continued for 100 min. After this, a second primed, continuous insulin infusion was begun at 400 mU/m^2/min ("high-dose") and continued for an additional 100 min. Plasma glucose was measured every 5 min, and a variable rate infusion of 20% dextrose was given

TABLE 2
Glucose, insulin, and C-peptide concentrations during euglycemic clamp studies (mean ± SEM)

	Lean		Obese	
	Nonexercise	Exercise	Nonexercise	Exercise
Glucose (mg/dl)				
Basal	95 ± 3	83 ± 4*	104 ± 8	95 ± 5
40 mU/m^2/min	89 ± 1	89 ± 1	91 ± 2	90 ± 2
400 mU/m^2/min	90 ± 1	91 ± 1	89 ± 1	89 ± 0
Insulin (μU/ml)				
Basal	9 ± 1.3	5 ± 1.0	28 ± 5.5	26 ± 5.6
40 mU/m^2/min	97 ± 5	95 ± 10	153 ± 19	150 ± 23
400 mU/m^2/min	4171 ± 775	3275 ± 533	4944 ± 309	4435 ± 235
C-peptide (pmol/ml)				
Basal	0.40 ± 0.06	0.27 ± 0.09†	1.38 ± 0.14	1.17 ± 0.20
40 mU/m^2/min	0.18 ± 0.03	0.16 ± 0.01	0.77 ± 0.20	0.82 ± 0.27
400 mU/m^2/min	0.08 ± 0.02	0.11 ± 0.03	0.39 ± 0.11	0.47 ± 0.14

*$P < 0.05$ and †$P < 0.02$, nonexercised versus exercised.

TABLE 3
Pathways of glucose disposal in lean and obese subjects (mean ± SEM)

	Total glucose disposal (mg/kg FFM/min)		Glucose oxidation (mg/kg FFM/min)		Nonoxidative glucose disposal (mg/kg FFM/min)	
	Lean	Obese	Lean	Obese	Lean	Obese
Basal						
Nonexercise	2.69 ± 0.13	2.20 ± 0.06	1.86 ± 0.29	1.68 ± 0.23	0.83 ± 0.30	0.52 ± 0.23
Exercise	2.30 ± 0.03*	2.30 ± 0.09	1.06 ± 0.10*	0.78 ± 0.12*	1.24 ± 0.08	1.52 ± 0.17*
40 mU/m²/min (60–100 min)						
Nonexercise	6.99 ± 0.51	2.88 ± 0.40	3.12 ± 0.08	2.02 ± 0.22	3.87 ± 0.52	0.85 ± 0.29
Exercise	7.18 ± 0.54	3.92 ± 0.51*	1.61 ± 0.29‡	1.43 ± 0.07	5.57 ± 0.62‡	2.49 ± 0.49‡
400 mU/m²/min (160–200 min)						
Nonexercise	13.37 ± 0.74	7.72 ± 0.60	5.32 ± 0.35	3.48 ± 0.26	8.05 ± 1.00	4.24 ± 0.42
Exercise	15.49 ± 0.82	9.67 ± 0.94‡	4.06 ± 0.18*	3.04 ± 0.23	11.43 ± 0.75†	6.63 ± 0.81*

*$P < 0.05$, †$P < 0.02$, and ‡$P < 0.01$, nonexercised versus exercised.

to maintain the plasma glucose at 90 mg/dl. During the high-dose insulin infusion, serum potassium was determined every 30 min, and a saline infusion containing 20 meq KCl/L was given at a rate of 20 cm³/h throughout the study to maintain serum postassium in the range of 3.3–4.5 meq/L. Plasma samples for D-(3-³H)-glucose, insulin, and C-peptide were drawn every 10 min.

Urinary urea nitrogen was determined on a sample collected throughout the period of the clamp (6–7 h), and this was used to calculate the nonprotein RQ. Using the tables of Lusk,[12] the carbohydrate and lipid oxidation rates were then calculated every 5 min during the study.

D-(3-³H)-glucose samples were deproteinized with perchloric acid, and the tritiated water was evaporated. The D-(3-³H)-glucose was then counted to determine the rates of appearance of glucose during the study, using the one-compartment model of Steele's equations,[13] as validated by Radziuk.[14] Endogenous glucose production during the 60–100-min low-dose steady-state period was taken to be the difference between the rate of appearance of glucose and the known rate of infusion of exogenous, unlabeled glucose.

Plasma glucose was measured by the glucose-oxidase method using a Yellow Springs Instrument glucose analyzer (Yellow Springs, Ohio). Insulin and C-peptide were measured by radioimmunoassay.[15] Glycogen synthase was measured using the filter paper method of Thomas.[16] Glycogen was determined by the *o'*-toluidine method,[17] and protein by the Bio-Rad Coomassie blue method.[18]

Data are expressed as the mean ± SEM. Student's paired and unpaired *t*-tests, and, where appropriate, two-way analysis of variance were used for statistical analysis.

RESULTS

The patient characteristics and oral glucose tolerance results are given in Table 1. The obese and lean subjects did not differ significantly with respect to age (mean age 33.8 versus 27.8 yr). The obese subjects had an increased percent body fat and increased fat-free mass (FFM) compared with the lean group. Of the six obese subjects, three had impaired glucose tolerance (IGT) as defined by the National Diabetes Data Group criteria,[5] and the rest had normal glucose tolerance with marked hyperinsulinemia (peak >186 μU/ml) after glucose ingestion. Since there were no significant differences in any aspect of glucose metabolism between the two subsets of obese patients (IGT and hyperinsulinemic), their data were pooled. The obese subjects had a significantly reduced $VO_{2\ max}$ (Table 1) compared with the lean subjects, whether expressed in liters/minute or milliliters/kilogram FFM/minute. The obese subjects also had a

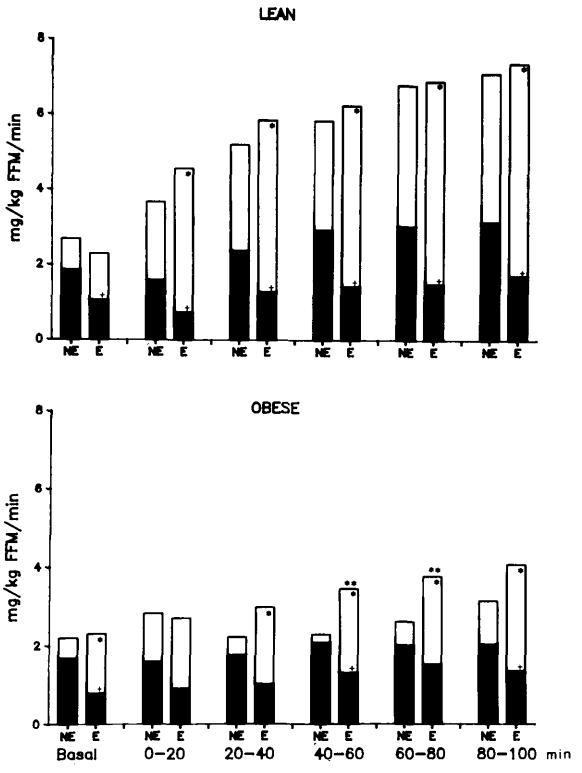

FIGURE 1. Glucose disposal rates (mg/kg fat-free mass/min), without (NE) and with (E) prior exercise, in the basal state and during each 20-min interval of the 40 mU/m²/min (low-dose) insulin infusion. Solid areas represent glucose oxidation; open areas represent nonoxidative glucose disposal (NOGD). +, Significant decrease in glucose oxidation ($P < 0.05$); *, significant increase in NOGD ($P < 0.05$); and **, significant increase in total glucose disposal ($P < 0.05$), comparing the postexercise to the nonexercised state.

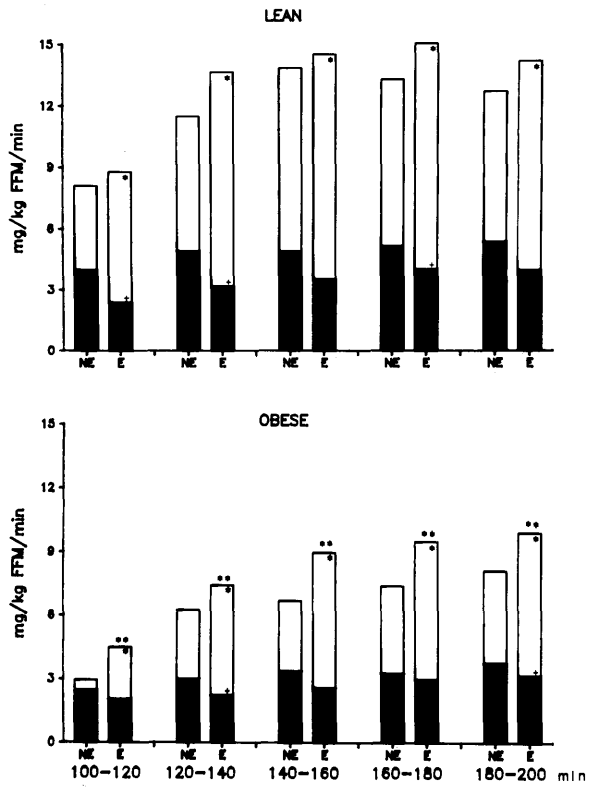

FIGURE 2. Glucose disposal rates (mg/kg fat-free mass/min), without (NE) and with (E) prior exercise, during each 20-min interval of the 400 mU/m²/min (high-dose) insulin infusion. Solid areas represent glucose oxidation; open areas represent nonoxidative glucose disposal (NOGD). +, Significant decrease in glucose oxidation ($P < 0.05$); *, significant increase in NOGD ($P < 0.05$); and **, significant increase in total glucose disposal ($P < 0.05$), comparing the postexercise to the nonexercised state.

significantly reduced endurance time to exhaustion during intermittent exercise at 85% of $VO_{2\ max}$ (Table 1).

Glucose, insulin, and C-peptide concentrations during euglycemic clamp studies (Table 2). During insulin infusions, plasma glucose concentrations were maintained close to 90 mg/dl, with no differences between groups in the studies. Compared with the lean controls, plasma insulin concentrations were significantly higher in the obese subjects in the basal state and during the low-dose insulin infusion. There was no significant difference, however, in steady-state plasma insulin concentrations during the high-dose clamp.

Compared with the lean group, plasma C-peptide concentrations were always significantly ($P < 0.05$) higher in the obese subjects under comparable conditions. However, the percent suppression of the basal C-peptide concentration was similar in the two groups during both the low- and high-dose insulin infusions.

Endogenous glucose production (EGP). The basal endogenous glucose production, determined by D-(3-³H)-glucose measurement, was significantly lower after exercise in the lean subjects (nonexercise: 2.73 ± 0.13, exercise: 2.30 ± 0.03 mg/kg FFM/min, $P < 0.05$) but not in the obese subjects (nonexercise: 2.20 ± 0.06, exercise: 2.30 ± 0.09 mg/kg FFM/min). During the low-dose insulin infusion, the lean subjects had >95% suppression of EGP, both with (0.09 ± 0.03 mg/kg FFM/min) and without (0.09 ± 0.03 mg/kg FFM/min) prior exercise. In contrast, the obese subjects had significantly ($P < 0.01$) less suppression of EGP during the low-dose insulin infusion, which was 49% of basal (1.13 ± 0.49 mg/kg FFM/min) with and 53% of basal (1.16 ± 0.23 mg/kg FFM/min) without prior exercise, respectively. Within each group there was no significant difference between the nonexercise and postexercise EGP values during the low-dose infusion.

Total glucose disposal (Table 3 and Figures 1 and 2). Before exercise, the obese subjects had decreased sensitivity and responsiveness to insulin. Although we have only a single, intermediate dose of insulin and cannot construct an insulin dose-response curve, the low-dose insulin infusion in the obese subjects resulted in glucose disposal rates that were only 37% of maximal, compared with 52% of maximal in the lean subjects. Insulin responsiveness, measured as the maximum insulin-stimulated rate of glucose disposal, was also reduced to 58% of normal in the obese group before exercise. After exercise, total glucose disposal was significantly increased compared with the nonexercised state in the obese subjects during the 40–60- and 60–80-min time periods of the low-dose insulin infusion (Figure 1) and during each 20-min time period of the high-dose insulin infusion (Figure 2). The lean subjects showed slight, but not statistically significant, increases in total glucose disposal during both low- and high-dose infusions. Insulin sensitivity was not improved in either lean or obese subjects after exercise, since the low-dose infusions resulted in 46% and 41% of maximal rates of glucose disposal, compared with 52% and 37% without prior exercise, in lean and obese subjects, respectively.

Glucose oxidation (Table 3 and Figures 1 and 2). In the nonexercised state, the obese subjects had normal basal rates of glucose oxidation. However, glucose oxidation was

TABLE 4
Muscle biopsy results in lean and obese subjects (mean ± SEM)

Glycogen (mg/g protein)		
Resting		
Preclamp	0.22 ± 0.05	0.26 ± 0.04
Postclamp	0.22 ± 0.03	0.22 ± 0.04
Exercise		
Preclamp	0.08 ± 0.01†	0.10 ± 0.01‡
Postclamp	0.13 ± 0.02	0.13 ± 0.01*
Glycogen synthase %I		
Resting		
Preclamp	12.3 ± 1.3	17.6 ± 3.3
Postclamp	27.4 ± 1.9	31.0 ± 3.5
Exercise		
Preclamp	45.3 ± 2.4‡	54.4 ± 4.8‡
Postclamp	51.2 ± 2.8‡	63.9 ± 3.2‡
Glycogen synthase I (μmol/min/g protein)		
Resting		
Preclamp	4.5 ± 0.5	7.0 ± 2.2
Postclamp	10.0 ± 1.4	10.3 ± 2.1
Exercise		
Preclamp	18.9 ± 2.9‡	17.9 ± 2.3‡
Postclamp	19.0 ± 3.0*	22.6 ± 1.5‡

*$P < 0.05$, †$P < 0.02$, and ‡$P < 0.01$, nonexercised versus exercised.

only 65% of normal during steady-state submaximal (60–100 min) and maximal (160–200 min) insulin infusions ($P < 0.05$ compared with lean controls).

After exercise, lean subjects showed significant ($P < 0.05$) decreases in basal and insulin-stimulated glucose oxidation rates compared with the nonexercised state, in each time period during the low-dose insulin infusion and in three of the five intervals during the high-dose infusion. Prior exercise also resulted in further reductions of the already low insulin-stimulated glucose oxidation rates in the obese subjects. This was statistically significant in two of the five time periods measured during both the low- and high-dose insulin infusions.

Nonoxidative glucose (NOGD) (Table 3 and Figures 1 and 2). In the lean and obese subjects, there were significant increases in NOGD after exercise during both the low- and high-dose insulin infusions ($P < 0.05$). Only the obese subjects had a significant increase in NOGD in the basal state. The postexercise increase in NOGD was nearly the same in the obese and lean subjects. However, the obese subjects continued to demonstrate a significant ($P < 0.01$) reduction in maximal responsiveness in NOGD compared with lean subjects (58% and 53% of the lean controls, with and without prior exercise, respectively).

Glycogen and glycogen synthase activity (Table 4). Vastus lateralis muscle glycogen concentration was significantly lower after exercise in both the lean and obese subjects, and muscle glycogen content was not significantly different between the two groups at any time under comparable conditions. In the nonexercised state, the baseline glycogen synthase percent I (GS %I) activity was similar in lean and obese subjects, and increased comparably after the insulin infusions in both groups ($P < 0.01$). After exercise, baseline GS %I activity was markedly increased in both the lean and obese subjects, with only a slight further increase after insulin infusion. Similar results were obtained when glycogen synthase I (GS I) was expressed as μmol/min/g protein.

Urinary urea nitrogen (UUN). The UUN excretion rate was higher in the postexercise state than in the resting state in both the lean (0.61 ± 0.07 versus 0.51 ± 0.09 g/h, respectively) and obese subjects (0.60 ± 0.08 versus 0.50 ± 0.05). Although this is not a significant difference in either group alone, if the data from lean and obese subjects are pooled, the difference is significant (0.61 ± 0.05 versus 0.50 ±0.05, $P < 0.05$).

Correlations. We examined the correlation coefficients between increments in NOGD and increase in preinsulin infusion GS %I and GS I activities, comparing the nonexercised and postexercise states. The correlations between the increments in NOGD and GS %I (lean, 0.47; obese, 0.17) during low-dose insulin infusions were insignificant. However, the increment in NOGD during the high-dose insulin infusion was highly correlated with the increments in both GS %I (0.94, $P < 0.01$, Figure 3) and in GS I (0.88, $P < 0.01$) in the lean subjects, but not in the obese subjects (GS %I, 0.42; GS I, 0.27).

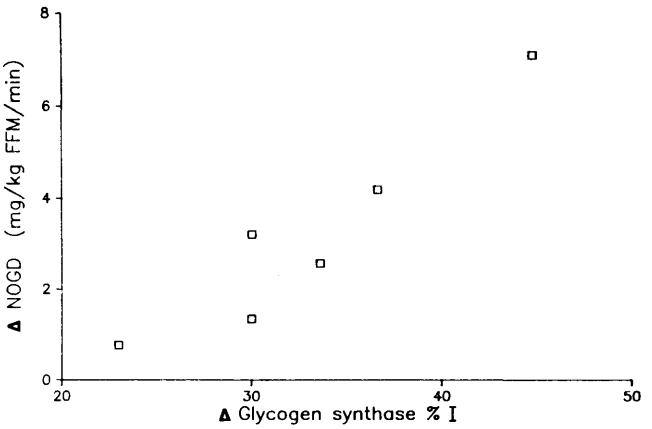

FIGURE 3. The relationship between the increase from the nonexercised to the postexercise state in preinsulin infusion glycogen synthase %I activity, and the increase in nonoxidative glucose disposal (NOGD) (mg/kg fat-free mass/min) during the 400 mU/m²/min (high-dose) insulin infusion in lean subjects. r = 0.94, P < 0.01.

DISCUSSION

Obesity has been associated with a state of insulin resistance.[1] Our group of obese subjects, selected on the basis of glucose intolerance and/or hyperinsulinemia, demonstrated decreased sensitivity and responsiveness to infused insulin. This was true for total glucose disposal, glucose oxidation, nonoxidative glucose disposal, and suppression of endogenous glucose production by insulin. However, insulin converted glycogen synthase to its active, glucose-6-phosphate-independent (I) form normally seen in obese subjects before exercise, suggesting that insulin stimulation of glycogen synthase is independent of changes in insulin-mediated glucose disposal, as suggested by Chiasson.[19] In addition, our results show that glycogen-depleting exercise also activates glycogen synthase normally in obese, insulin-resistant subjects.

Acute exercise has been shown to improve glucose uptake for several hours after exercise, both in humans[4] and in rats.[20] Heath[21] demonstrated that much of the beneficial effect of exercise training on glucose tolerance could be produced by a single bout of exercise in previously trained subjects. Using an exercise protocol similar to ours, Bogardus et al.[4] found that in normal subjects 12 h after intense, glycogen-depleting exercise, there were significant increases in total and nonoxidative glucose disposal, and a close correlation between the increases in glucose disposal and activation of glycogen synthase to the active (I) form. They postulated that glycogen synthase may be a rate-limiting enzyme for glucose disposal after glycogen depletion.

In our study, only the obese subjects showed significant increases in both submaximal and maximal insulin-stimulated glucose disposal after exercise. Although increases in total glucose disposal were also observed in the lean subjects, these did not reach statistical significance, possibly because of the relatively small sample size. The greater total glucose uptake during the high-dose insulin infusion after exercise was similar (2.12 mg/kg FFM/min) to that reported by Bogardus et al.[4] The absolute increase in glucose disposal after exercise was similar in obese and lean subjects, but constituted a larger percentage of preexercise values in the obese. This suggests that the effect of exercise to increase glucose uptake is relatively greater in obese, insulin-resistant

subjects than in normals. Furthermore, lean controls may have a more limited capacity to increase total glucose uptake after exercise, since their already high levels may be closer to the maximal rates of glucose transport. Although improved, total glucose disposal was not normalized in the obese subjects by prior exercise, since they remained less responsive to infused insulin than did the lean subjects (62% of normal). In addition, the resistance of endogenous glucose production to suppression by insulin in obese subjects was little affected by prior exercise.

As previously shown by Bogardus et al.[4] in lean subjects, a major effect seen 12 h after acute glycogen-depleting exercise in obese subjects was an alteration of the pathways for glucose metabolism (oxidative versus nonoxidative). The pattern of increased NOGD and decreased carbohydrate oxidation remained fairly constant throughout the time course of the insulin infusions (Figures 1 and 2). Glucose oxidation was significantly reduced after glycogen-depleting exercise in both lean and obese subjects in the basal state. During insulin infusion, the decreased rates of glucose oxidation persisted, but this change was greater in lean than in obese subjects. Since the total energy expenditure in both groups was little affected by prior exercise (data not shown), this represents a shift from glucose to free fatty acids as an oxidative fuel in the glycogen-depleted state. In addition to increased lipid oxidation, protein catabolism was probably also increased 12 h after exercise, as reflected by the higher urinary urea production rates seen in both groups. At submaximal insulin concentrations, the lean subjects showed a greater shift from glucose to lipid oxidation after exercise, so that there was no longer a significant difference in glucose oxidation rates between lean and obese subjects after exercise. Thus, the pattern of fuels oxidized in normal subjects after intense exercise more closely approximates the pattern seen in insulin-resistant subjects.

The increases in total glucose disposal observed in both the lean and obese subjects after exercise were due to increased rates of NOGD, presumably reflecting increased rates of glycogen synthesis.

To test the hypothesis that glycogen synthase might act as a rate-limiting enzyme for NOGD after acute exercise in man, as suggested by Bogardus et al.,[4] we examined the correlations between the increment in NOGD after exercise and the increases in baseline (preinsulin infusion) GS %I and GS I activity induced by the acute exercise. We did find that the exercise-induced increases in both GS I and GS %I correlated with the increment in NOGD observed in lean subjects during the high-dose insulin infusion. However, during the high-dose infusion in obese subjects, and during the low-dose infusion in both groups, the correlations were not significant. These data suggest that glycogen synthase may be rate limiting for NOGD only in subjects without insulin resistance and under maximal insulin stimulation. Since glycogen synthase is activated normally in obese subjects by both insulin infusions and prior exercise, with NOGD remaining less than normal, obese subjects appear to have a defect in NOGD that is proximal to the glycogen synthase step. For example, glucose transport may be impaired, as suggested by Richter et al. and Garetto et al.[22,23] from studies in the rat. Our data suggest that, at submaximal insulin concentrations, factors other than glycogen synthase are also rate limiting in normal subjects.

In summary, we found that acute exercise significantly increased, but did not completely normalize, insulin-stimulated rates of total glucose disposal in obese subjects for at least 12–14 h. Increases in glucose disposal were also observed in lean subjects, but these did not reach statistical significance. In both lean and obese subjects, the major effect of prior exercise was to increase nonoxidative glucose disposal and decrease glucose oxidation. Glycogen synthase increased normally in response to insulin and to exercise in obese subjects, despite their lower rates of insulin-stimulated glucose disposal. Thus, glycogen synthase does not appear to be the rate-limiting step for NOGD after exercise in insulin-resistant subjects. These findings suggest that physical exercise, even in untrained subjects, may significantly improve the insulin resistance frequently associated with obesity and impaired glucose tolerance.

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