Relationships Between Glucose Metabolism and Thermogenesis With and Without Prior Exercise in Obese Women With Non–Insulin-Dependent Diabetes Mellitus

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The rate of insulin-stimulated glucose disposal is reduced in individuals with insulin resistance, and is associated with a blunted or absent increase in energy expenditure in response to a glucose load. The magnitude of the effect of glucose on energy expenditure (EGEE) may be a function of opposing changes in the rate of glucose disposal (Rd) and hepatic glucose production (HGP). In this study, six women with non–insulin-dependent diabetes mellitus (NIDDM) were studied on a metabolic ward in each of three conditions. On days 1 and 2, they did no exercise (NX) or else performed low-intensity exercise ([LO] 3,118 kJ [745 kcal]) at 50% maximal oxygen consumption [Vo_2max]) or high-intensity exercise ([HI] 3,114 kJ [744 kcal] at 75% Vo_2max). On day 3, infusion of 6,6^{2}H-glucose in the basal state was immediately followed by infusion of glucose, 6,6^{2}H-glucose, and insulin at fixed rates. Indirect calorimetry was performed during the last 30 minutes of each infusion. EGEE was not different among the three conditions (mean ± SEM: NX −0.18 ± 0.11, LO −0.08 ± 0.05, and HI −0.08 ± 0.07 kJ/min) and was inversely related to steady-state plasma glucose concentration, a direct measure of insulin resistance ($r = -.89$, $P < .05$). EGEE was positively correlated with glucose Rd ($r = .94$, $P < .001$) and negatively correlated with HGP ($r = -.91$, $P < .05$). The data indicate that the glucose effect on energy expenditure was slightly positive in the more insulin-sensitive individuals, but negative in the more insulin-resistant subjects. The EGEE appears to be determined by the relative balance between energy required to store glucose and energy saved by suppression of glucose production.

IN HUMANS WITH normal insulin sensitivity, energy expenditure increases in response to oral glucose or glucose/insulin infusion.[1-4] Energy expenditure increases by approximately 10% in lean individuals, but is markedly lower (0% to 5%) in obese insulin-resistant individuals with or without non–insulin-dependent diabetes mellitus (NIDDM).[4-7] The energy required to store glucose as glycogen, which is approximately 0.82 kJ/g glucose stored (2 mol ATP · 74 kJ/mol ATP, divided by glucose molecular weight [180 g/mol],[8]), is thought to account for much of the thermogenic effect.[6,7] Ravussin et al[4,5] showed a strong correlation between subnormal rates of glucose disposal and smaller increases in energy expenditure in people with insulin resistance.[4,5]

Individuals with NIDDM have elevated rates of hepatic glucose production (HGP) in the basal state, much of which has been attributed to gluconeogenesis, an energy-requiring process.[9-11] Increased rates of gluconeogenesis probably account for part (50%, according to Consoli et al[11]) of the elevated resting metabolic rate observed in this population.[11] An infusion of glucose and insulin inhibits hepatic glycogenolysis and gluconeogenesis, in addition to stimulating storage of glucose as glycogen.[3,5-7] Suppression of gluconeogenesis should decrease energy expenditure. The direction and magnitude of the change in energy expenditure induced by a glucose/insulin infusion is probably determined by the net balance between energy required to store glucose and energy saved by suppression of gluconeogenesis.[5,6,12] In people with NIDDM, a relatively large reduction in the energy expended to maintain high rates of basal gluconeogenesis could offset energy expended for storage of glucose, resulting in reduced net thermogenesis in response to glucose and insulin.[6,12]

Devlin et al[13,14] observed that a single bout of exercise increased the glucose rate of disposal and restored the thermic response to a glucose/insulin infusion in obese men with NIDDM. Recently, we reported the effects of low- and high-intensity exercise on glucose production and disposal, in the basal and insulin-stimulated states, in obese women with NIDDM.[15,16] The purpose of this paper is to compare the effect of a glucose infusion on energy expenditure in three conditions, and explain the results in the context of opposing changes in glucose production and disposal.

SUBJECTS AND METHODS

The study was approved by the Human Research Committees at the Universities of California at Berkeley and San Francisco. Data from this study were collected in the same subjects and at the same time as other data reported previously.[15,16] Six women with NIDDM signed informed-consent documents and were carefully screened before participation in the study. The inclusion criterion of NIDDM was based on a fasting plasma glucose concentration of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) measured during the screening session. All subjects were obese and physically untrained. Subjects were excluded from the study if they smoked cigarettes, took insulin, or were hypertensive. NIDDM in five subjects was managed with oral sulfonylurea drugs, which were discontinued 7 days before each admission. Subjects refrained from exercise for at least 5 days before each admission. Anthropometric and metabolic characteristics of the subjects are shown in Table 1.

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Table 1. Anthropometric and Metabolic Characteristics of Subjects

	Age (yr)	Height (cm)	Weight (kg)	Fat (%)	BMI (kg/m²)	FPG (mmol/L)	FPI (pmol/L)	$\dot{V}O_2$max (mL/kg/min)
Mean	44.3	165.5	83.9	41.2	30.7	9.85	128	27.0
SD	5.2	6.7	8.2	4.3	3.5	1.31	29	2.7

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose concentration; FPI, fasting plasma insulin concentration.

Protocol

On the morning of day 1, subjects were admitted to the inpatient facility of the General Clinical Research Center (GCRC) at San Francisco General Hospital. Body composition was assessed by dual-energy x-ray absorptiometry (Lunar DPX, Madison, WI). Subjects received a controlled diet containing energy equal to 1.3 times their basal energy requirements, composed of 50% carbohydrate, 20% protein, and 30% fat, with at least 250 g carbohydrate per day.

On the afternoon of day 1, subjects either rested (no exercise [NX]) or performed the first two bouts of exercise at either low intensity (LO) or high intensity (HI). In the LO condition, subjects walked on a motor-driven treadmill (model Q50; Quinton Instruments, Seattle, WA) at 50% of their previously determined maximal oxygen consumption ($\dot{V}O_2$max). In the HI condition, treadmill walking was performed at 75% $\dot{V}O_2$max. During exercise, the subjects' expired breath was diverted by a one-way valve through a calibrated pneumotachometer and oxygen and carbon dioxide analyzers (Quinton Q-Plex 1 metabolic cart). Treadmill speed and grade were manipulated (mean ± SD: LO, 3.7 ± 0.1 km/h and 6.7% ± 1.4%, and HI, 4.1 ± 0.2 km/h and 14.5% ± 2.9%, respectively) so that oxygen consumption was steady at the desired percentage of $\dot{V}O_2$max (50.4% ± 1.7% for LO and 74.4% ± 3.0% for HI). The duration of each exercise bout was adjusted so that energy expenditure was approximately 523 kJ (125 kcal). There was a 15- to 20-minute rest period between the two exercise bouts. Subjects performed two more exercise bouts in the same way on the morning of day 2 and again on the afternoon of day 3. The duration of each exercise bout was 23.8 ± 3.8 minutes (LO) and 15.0 ± 1.3 minutes (HI) (total for the six exercise bouts, LO, 143 ± 23, and HI, 90 ± 8). Total exercise energy expenditure was 3,118 ± 63 kJ (LO) and 3,114 ± 90 kJ (HI).

Infusions

Subjects fasted overnight, and basal and insulin-stimulated infusions were performed on the morning of day 3. At 4:30 AM on day 3, 6,6-^{2}H-glucose was infused (70 μg/kg fat-free mass [FFM]/min) into an antecubital vein for 300 minutes. Blood samples obtained during the last hour of infusion were used to measure HGP. During minutes 270 to 300, a ventilated hood was placed over the subject's head, and expired breath was directed to the O_2 and CO_2 analyzers of a Delta-Trac metabolic monitor (Sensor Medics, Anaheim, CA). Immediately following the basal infusion, insulin and glucose (2.5% of which was 6,6-^{2}H-glucose) were infused at rates of 40 mU/m²/min and 4 mg/kg FFM/min, respectively. Blood samples were obtained every 15 minutes for 180 minutes and those collected during the last 30 minutes were used to measure glucose rate of appearance (Ra). During minutes 150 to 180, indirect calorimetry was performed as described earlier.

Subjects were discharged, and they reported back to the GCRC 4 and 8 weeks later (always in the follicular phase of the menstrual cycle) to undergo the identical procedures in the other two conditions. The order of the three conditions was balanced across subjects.

Biochemical Assays

Glucose concentration in whole blood was determined with a Yellow Springs Instruments 23A glucose analyzer (Yellow Springs, OH). Values for whole blood were corrected for hematocrit to calculate plasma glucose concentration. Concentrations of insulin and C-peptide in plasma were measured by radioimmunoassay using Coat-A-Count kits (Diagnostic Products, Los Angeles, CA). Plasma samples taken during the last 30 minutes of each infusion were used for measurement of glucose isotopic enrichment. Glucose in plasma was derivatized as described previously[15] and reconstituted in 100 μL ethyl acetate. The sample (2 μL) was injected, and mass spectra were recorded on a model 5970 gas chromatograph–mass spectrometer (Hewlett-Packard Analytical, Wilmington, DE). Selected ion monitoring was used to compare the abundance of the unlabeled fragment (mass/charge, 331) with that of the dideuterated isotopomer (mass/charge, 333). After correction for background enrichment (mean, .06%; range, .02% to .12%), the abundance of 6,6-^{2}H-glucose was expressed as a percent of total glucose species.

Calculations

In the steady-state condition (constant isotopic enrichment and concentration of plasma glucose), Ra of unlabeled glucose into plasma equals (isotope isotope infusion rate/isotopic enrichment of glucose in plasma) − isotope infusion rate. In the steady state, Ra equals the rate of glucose disposal (Rd). In the basal state, Ra equals HGP. During the glucose/insulin infusion, Ra equals HGP + glucose rate of infusion. Energy expenditure during basal and glucose/insulin infusions was calculated from the respiratory exchange ratio (RER) and $\dot{V}O_2$. Measured RER values were not corrected for urinary nitrogen, but in the range of our measurements, even large deviations in nonprotein RER (± 0.04 U) would have a negligible effect on measured energy expenditure (± 0.5%). The effect of glucose on energy expenditure (EGEE) was defined as (energy expenditure during the glucose/insulin infusion) − (basal energy expenditure), and expressed as kilojoules per minute.

Statistical Methods

Statistical comparisons among condition means were made with repeated-measures ANOVA. Tukey's studentized range test was used when significant ($P < .05$) F ratios were obtained. Pooled correlation coefficients (r_p) were calculated for each set of variables from single linear regression analyses for each condition (NX, LO, and HI), which were transformed to z values using the formula, $z = 1/2 \ln (1 + r/1 - r)$. The mean z value was retransformed to a pooled correlation coefficient using the formula, $r_p = (e^{2z} - 1)/(e^{2z} + 1)$. The correlations were then tested for statistical significance using analysis of covariance with repeated measures. Use of these procedures accounts for the nonindependent nature of the samples, ie, 18 data points from six subjects.

RESULTS

RER

The RER in the basal state was the same among conditions (Fig 1). During the insulin/glucose infusion, RER was significantly higher than in the basal state in all three conditions, but there were no differences among conditions.

Energy Expenditure

Energy expenditure rates during the infusions are shown in Fig 2. Energy expenditure was not statistically different

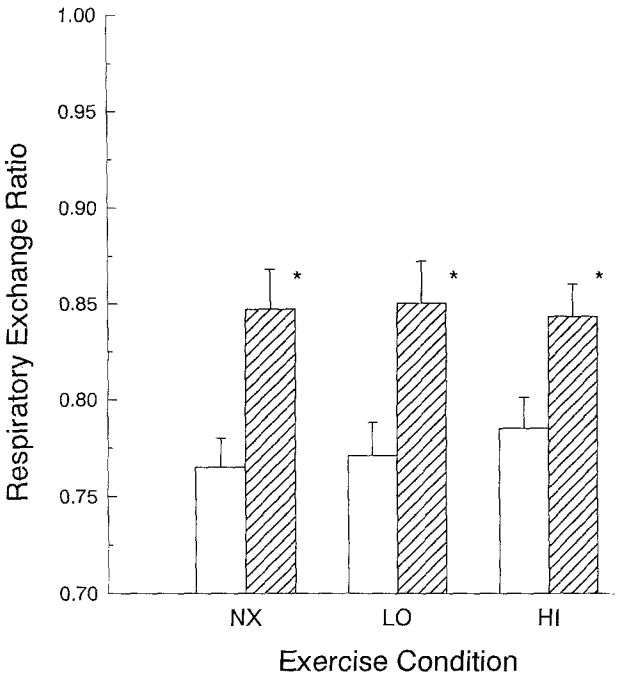

Fig 1. RER in the basal state (□) and during the glucose/insulin infusion (▨) in the 3 exercise conditions. *$P < .05$ *v* basal state.

among conditions in either the basal or insulin-stimulated states.

Thermic Effect of Glucose and Insulin

Mean energy expenditure tended to be lower during the glucose/insulin infusion relative to the basal state in all three conditions (NX −0.18 ± .11 kJ/min, LO −0.08 ± .05, and HI −0.08 ± .07), but the changes were not significantly different from zero or from each other.

Correlations Between EGEE and Glucose Metabolism

Figures 3 and 4 show the relationship between the EGEE and the change in glucose Rd or HGP. Using data from all three conditions, there was a positive correlation between EGEE and change in Rd ($r = .94, P < .001$; Fig 3) and an inverse relationship between EGEE and change in HGP ($r = -.91, P < .05$; Fig 4).

Relationship Between EGEE and Insulin Resistance

The relationship between insulin resistance, defined as the steady-state plasma glucose concentration (SSPG) attained during infusion of glucose and insulin at constant rates,[16,17] and EGEE is shown in Fig 5. There was a strong negative correlation between the measures ($r = -.89$, $P < .05$) using data from all three conditions. Indirect measures of insulin resistance, ie, fasting plasma glucose concentration and basal hepatic glucose output, were also negatively correlated with EGEE, with coefficients of −.82 ($P < .05$) and −.73 ($P < .05$), respectively.

DISCUSSION

In this study, infusion of glucose and insulin at fixed rates did not increase mean energy expenditure above basal values in obese women with NIDDM. There was a strong negative correlation between the degree of insulin resistance, which was directly assessed by SSPG during insulin/glucose infusion (NX 10.2 ± 2.9 mmol/L, LO 8.7 ± 3.1, and HI 8.6 ± 3.2), and the magnitude of glucose-induced change in energy expenditure. EGEE was positive in four of

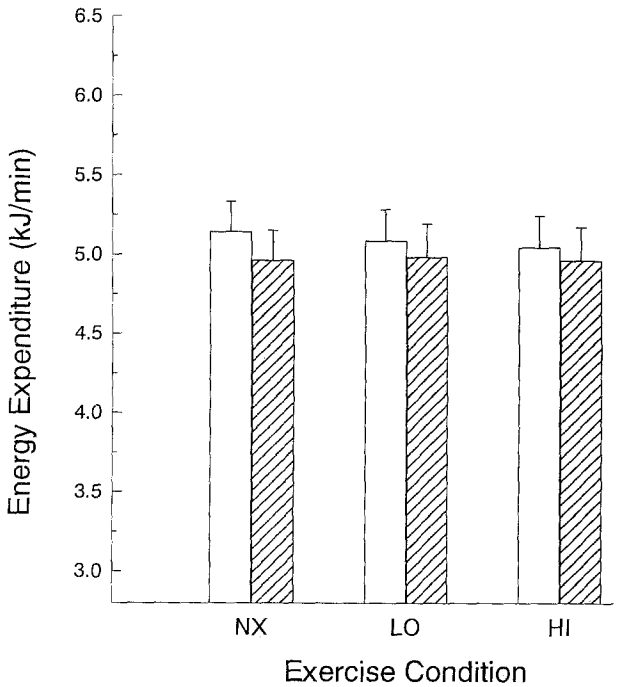

Fig 2. Energy expenditure in the basal state (□) and during the glucose/insulin infusion (▨) in the 3 exercise conditions.

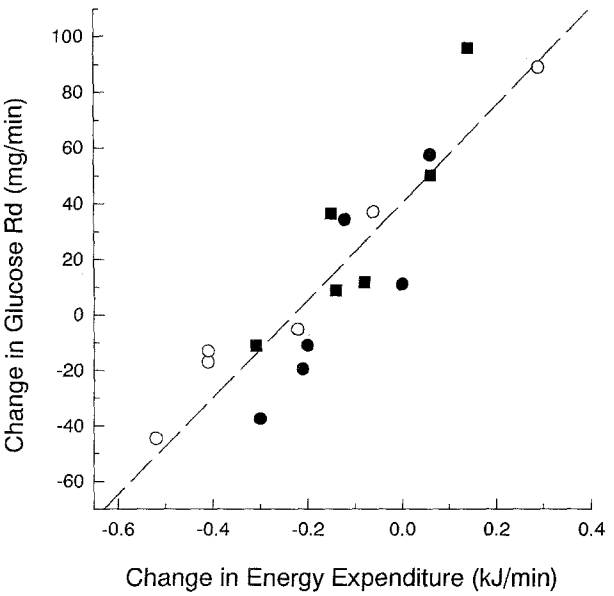

Fig 3. Change in energy expenditure versus change in glucose Rd during the glucose/insulin infusion relative to the basal state. (○) NX; (●) LO; (■) HI. Linear regression equation: change in EE = 0.0057 (change in Rd) − 0.228.

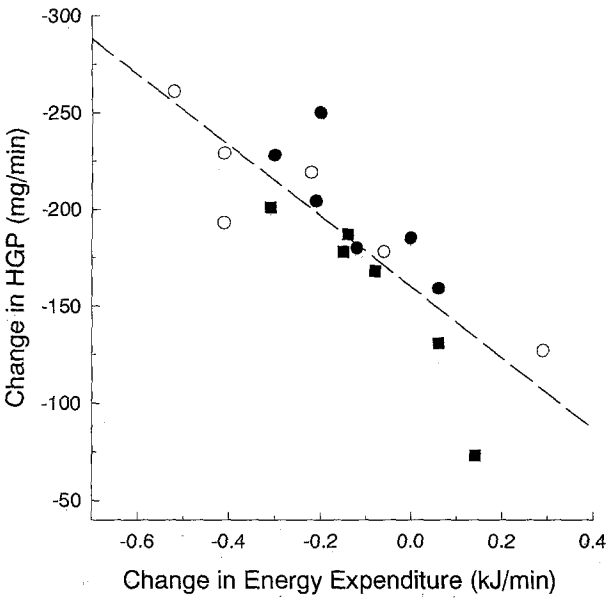

Fig 4. Change in energy expenditure versus change in HGP during the glucose/insulin infusion relative to the basal state. (○) NX; (●) LO; (■) HI. Linear regression equation: change in EE = 0.005 (change in HGP) + 0.825.

five cases when SSPG was not greater than 7 mmol/L (the exception had an EGEE of −0.06). Conversely, EGEE was negative in 12 of 13 cases when SSPG was at least 7 mmol/L (the exception had an EGEE of 0.00). These data indicate that, as noted previously,[4,5] there is an inverse relationship between insulin resistance and the effect of glucose to increase energy expenditure.

Individuals with the largest increase in glucose Rd during the infusion were those who showed the greatest EGEE

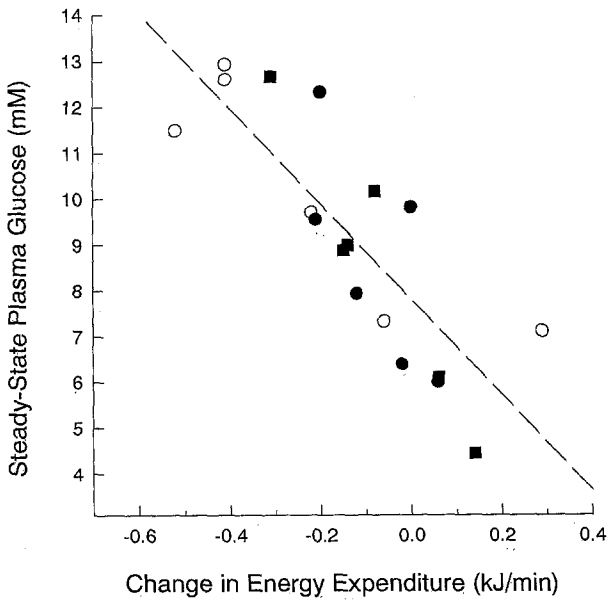

Fig 5. Change in energy expenditure versus SSPG during the glucose/insulin infusion. (○) NX; (●) LO; (■) HI. Linear regression equation: change in EE = −0.10 (SSPG) + 0.78.

(mean increases for the three conditions: NX 7.4 ± 2.9 mg/min, LO 10.3 ± 3.9, and HI 29.9 ± 7.8). A prior study by Ravussin et al[5] clearly demonstrated this relationship: when glucose Rd was artificially normalized by infusing large quantities of insulin, the thermic effect of glucose in obese and insulin-resistant (but not diabetic) subjects was restored. Simonson et al[18] found that substitution of fructose for glucose restored normal thermogenesis both in obese subjects and in those with NIDDM. They suggested that thermogenesis was normalized because fructose metabolism, which is mainly independent of insulin action, was not affected by insulin resistance. Schwarz et al[12] corroborated these findings, and extended them with the observation that infusion of fructose in lean and obese subjects did not suppress HGP. With no reduction in energy required to make glucose de novo, the energy cost of carbohydrate storage was not offset by energy savings, resulting in a net increase in total energy expenditure. Schwarz et al hypothesized, as did others,[5-7] that in subjects with NIDDM, suppression of abnormally high basal HGP (specifically the energy-requiring process of gluconeogenesis) could explain why thermogenesis was absent in this population. Data from the present study, showing an inverse relationship between suppression of HGP and the effect of glucose administration to increase energy expenditure for glucose storage, strongly support that hypothesis.

A major limitation of this study is that total HGP, not gluconeogenesis, was actually measured. Interpretation of our data is based on the assumption that suppression of total HGP (mean changes: NO −195 ± 41 mg/min, LO −192 ± 38, and HI −155 ± 44) is at least partly attributable to suppression of gluconeogenesis. Several observations make this assumption appear reasonable. In the present study, plasma concentrations of glucagon were 60% to 85% lower during glucose/insulin infusion than in the basal state (230 ± 21 to 139 ± 11 pmol/L for NX, 226 ± 23 to 121 ± 13 for LO, and 190 ± 31 to 118 ± 22 for HI). Coupled with large elevations in plasma insulin concentrations (124 ± 13 to 379 ± 31 pmol/L for NX, 98 ± 10 to 351 ± 28 for LO, and 100 ± 9 to 337 ± 20 for HI), the ratio of plasma insulin to glucagon increased from approximately 0.5 in the basal state to approximately 3.0 during insulin infusion. This ratio has a profound influence on the rate of hepatic gluconeogenesis,[10] and these data strongly suggest that gluconeogenesis was largely suppressed during the infusion. Confirmation of these data awaits new techniques to measure gluconeogenesis accurately in humans.[19]

Six bouts of exercise performed at either low or high intensity (last bout, 12 hours before the infusion) did not restore EGEE in obese women with NIDDM. In contrast, Devlin and Horton[14] observed that a single bout of high-intensity exercise completely restored the thermic effect of a low-dose glucose/insulin infusion in men with NIDDM.[14] Surprisingly, in obese men with insulin resistance but without NIDDM, thermogenesis was essentially zero with or without prior exercise.[14] The obese women with NIDDM who participated in our study responded to prior exercise like the obese insulin-resistant men in the study by Devlin et al, rather than the men with NIDDM. This could be a

real gender difference, or the women in our study could share metabolic traits with the obese insulin-resistant men that account for the discrepancy between the two studies.

Obesity and aerobic capacity are related to both insulin resistance and the thermic effect of glucose or a meal.[2,3,20-22] Segal et al[20,21] have shown that obese men with a high percentage of body fat have a lower thermic effect of a meal than lean men with the same absolute fat mass. Similarly, groups of men with the same percentage of body fat have the same thermic effect of a meal, even when they differ in absolute fat mass. Hollenbeck et al[22] showed a direct relationship between insulin-stimulated glucose disposal and $\dot{V}O_2$max ($r = .74$, $P < .001$) in older males, which was independent of percentage body fat. The women in our study, with 41.2% body fat and a $\dot{V}O_2$max of 2.70 L/min, were more similar to the obese men with insulin resistance (30.4% and 2.70 L/min) than the men with NIDDM (27.8% and 2.98 L/min) from the studies by Devlin et al.[13,14,23] The effect of prior exercise on fasting glucose metabolism was also different in the women in our study. Fasting hyperglycemia in men with NIDDM was markedly reduced after exercise in the study by Devlin et al (from 197 ± 12 to 164 ± 9 mg/dL), but not in the women with NIDDM who participated in our study (NX 209 ± 41, LO 204 ± 37, and HI 192 ± 27 mg/dL). Differences between the groups could also be related to different patterns of body fat distribution in women and men.[7]

Prior exercise changes the dose-response relationship between plasma insulin concentration and both suppression of HGP and stimulation of glucose Rd.[24,25] However, the effects are not necessarily equal, and at a given concentration of plasma insulin, stimulation of glucose Rd and suppression of HGP could be differentially affected. Glucose-induced thermogenesis in individuals with severe peripheral insulin resistance but relatively mild hepatic resistance could be less responsive to prior exercise than that in subjects with frank NIDDM (because HGP is greatly suppressed without a concomitant increase in Rd). In a comprehensive study by Segal et al,[26] glucose Rd was not increased by 12 weeks of exercise training in either lean, obese, or diabetic men.[26] There was a decrease in basal HGP in men with NIDDM. Exercise training did not increase the effect of infused glucose on energy expenditure in any group, with mean values slightly lower (although not statistically different from zero) after exercise training in the NIDDM group, possibly reflecting the decline in basal HGP and no increase in Rd. A mismatch between hepatic and peripheral insulin resistance is also apparent in our subjects. Women with the greatest insulin sensitivity (largest stimulation of glucose Rd and lowest SSPG) had the smallest suppression of HGP. Looking closely at the data, it is clear that the relative suppression of HGP was similar in all subjects (range, 65% to 80%) and the higher absolute values in the most insulin-resistant subjects are due to their grossly elevated rates of basal HGP. This suggests that hepatic insulin sensitivity (defined as percent suppression of basal HGP at a given submaximal plasma insulin concentration) was similar among subjects and unaffected by acute exercise. Therefore, it is probable that differences in peripheral insulin sensitivity (defined as stimulation of glucose Rd at a given submaximal plasma insulin concentration) accounted for much of the observed relationship between insulin resistance and EGEE. Although the results should be viewed only as estimates due to the small sample size, multiple regression analysis showed that changes in glucose Rd alone accounted for approximately 40% of the variance in EGEE. HGP alone accounted for less than 25% of the variance, and adding HGP to Rd alone did not improve the correlation.

Data from Devlin et al[13,23] provide further support for the importance of glucose storage to EGEE. Energy expenditure was only increased when the glucose/insulin infusion resulted in net glycogen deposition. This was the case with but not without exercise in men with NIDDM.[13] However, glycogen deposition was minor with or without exercise in nondiabetic men with insulin resistance, and EGEE was essentially zero.[23] Changes in muscle glycogen were not measured in our subjects, but in light of the data presented herein, the mean change would likely have been negligible, with individual increases positively related to EGEE.

In summary, the effect of infused glucose on energy expenditure was markedly reduced (and in many cases, negative) in obese women with NIDDM, relative to reported values for lean subjects. Prior exercise had no significant effect on thermogenesis. The effect of glucose on energy expenditure was inversely related to the degree of insulin resistance, directly related to the rate of glucose disposal, and inversely related to the suppression of HGP. These data support the hypothesis that the magnitude of glucose-induced thermogenesis is determined by the balance between glucose disposal and glucose production. Reduced or absent thermogenesis in individuals with insulin resistance may be due to offsetting changes in energy expenditure: the energy saved by suppression of elevated basal gluconeogenesis balances the energy cost of glucose storage at subnormal rates.

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REFERENCES

1. Pittet P, Chappuis P, Acheson K, et al: Thermic effect of glucose in obese subjects studied by direct and indirect calorimetry. Br J Nutr 35:281-292, 1976

2. Golay A, Schutz Y, Meyer HU, et al: Glucose-induced thermogenesis in non-diabetic and diabetic obese subjects. Diabetes 31:1023-1028, 1982

3. Thiebaud D, Schutz Y, Acheson K, et al: Energy cost of glucose storage in human subjects during glucose-insulin infusions. Am J Physiol 244:E216-E221, 1983

4. Ravussin E, Bogardus C, Schwartz RS, et al: Thermic effect of infused glucose and insulin in man: Decreased response with increased insulin resistance in obesity and non–insulin-dependent diabetes mellitus. J Clin Invest 72:893-902, 1983

5. Ravussin E, Acheson K, Vernet O, et al: Evidence that insulin

resistance is responsible for the decreased thermic effect of glucose in human obesity. J Clin Invest 76:1268-1273, 1985

6. Tappy L, Felber JP, Jequier E: Energy and substrate metabolism in obesity and postobese state. Diabetes Care 14:1180-1188, 1991

7. Felber JP, Acheson KJ, Tappy L: From Obesity to Diabetes. New York, NY, Wiley, 1994

8. Flatt JP: The biochemistry of energy expenditure, in Bray G (ed): Advances in Obesity Research. London, UK, Neumann, 1978, pp 211-228

9. Bogardus C, Taskinen M-R, Zawadzki J, et al: Increased resting metabolic rates in obese subjects with non–insulin-dependent diabetes mellitus and the effect of sulfonylurea therapy. Diabetes 35:1-5, 1986

10. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM: A balanced overview. Diabetes Care 15:318-368, 1992

11. Consoli A, Nurjhan N, Capani F, et al: Predominant role of gluconeogenesis in increased hepatic glucose production in NIDDM. Diabetes 38:550-557, 1989

12. Schwarz JM, Acheson KJ, Tappy L, et al: Thermogenesis and fructose metabolism in man. Am J Physiol 262:E591-E598, 1992

13. Devlin JT, Hirshman MS, Horton ED, et al: Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after a single bout of exercise. Diabetes 36:434-439, 1987

14. Devlin JT, Horton ES: Potentiation of the thermic effect of insulin by exercise: Differences between lean, obese, and non–insulin-dependent diabetic men. Am J Clin Nutr 43:884-890, 1986

15. Braun B, Zimmermann MB, Kretchmer N: Effects of exercise intensity on insulin sensitivity in women with NIDDM. J Appl Physiol 78:300-306, 1995

16. Zimmermann MB, Braun B, Kretchmer N: Effects of exercise intensity and duration on post-absorptive glucose metabolism in women with NIDDM. (submitted)

17. Franssila-Kallunki A, Rissanen A, Ekstran A, et al: Effects of weight loss on substrate oxidation, energy expenditure, and insulin sensitivity in obese individuals. Am J Clin Nutr 55:356-361, 1992

18. Simonson DC, Tappy L, Jequier E, et al: Normalization of carbohydrate-induced thermogenesis by fructose in insulin-resistant states. Am J Physiol 254:E210-E207, 1988

19. Neese RA, Schwarz JM, Faix D, et al: Gluconeogenesis and intrahepatic triose phosphate flux in response to fasting or substrate loads. Application of the mass isotopomer distribution analysis technique with testing of assumptions and potential problems. J Biol Chem 270:14452-14466, 1995

20. Segal KR, Gutin B, Albu J, et al: Thermic effects of food and exercise in lean and obese men of similar lean body mass. Am J Physiol 252:E110-E117, 1987

21. Segal KR, Lacayanga I, Dunaif A, et al: Impact of body fat mass and percent fat on metabolic rate and thermogenesis in men. Am J Physiol 256:E573-E579, 1989

22. Hollenbeck CB, Haskell W, Rosenthal M, et al: Effect of habitual physical activity on regulation of insulin-stimulated glucose disposal in older males. J Am Geriatr Soc 33:273-277, 1984

23. Devlin JT, Horton ES: Effects of prior high-intensity exercise on glucose metabolism in normal and insulin-resistant men. Diabetes 34:973-979, 1985

24. Mikines KJ, Sonne B, Farrel PA, et al: Effect of training on the dose-response relationship for insulin action in men. J Appl Physiol 66:695-703, 1989

25. Mikines KJ, Sonne B, Farrel PA, et al: Effect of physical exercise on sensitivity and responsiveness to insulin action in humans. Am J Physiol 254:E248-E259, 1988

26. Segal K, Edano A, Abalos A, et al: Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. J Appl Physiol 71:2402-2411, 1991