# Glucoregulatory and metabolic response to exercise in obese noninsulin-dependent diabetes

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MINUK, HOWARD L., MLADEN VRANIC, ERROL B. MARLISS, AMIR K. HANNA, A. M. ALBISSER, AND BERNARD ZINMAN. *Glucoregulatory and metabolic response to exercise in obese noninsulin-dependent diabetes.* Am. J. Physiol. 240 (Endocrinol. Metab. 3): E458–E464, 1981.—The metabolic response to exercise in obese postabsorptive noninsulin-dependent diabetics was compared to that of obese nondiabetics. Exercise consisted of 45 min on a cycle ergometer at 60% maximum oxygen consumption. Six diabetic subjects were studied during oral hypoglycemic therapy and four on diet alone. The sulfonylurea therapy had no effect on the response. Glycemia was elevated at rest in both diabetic subgroups (192 ± 24 mg/dl for diet alone, 226 ± 36 mg/dl for sulfonylurea treatment) and a similar fall (35 and 37 mg/dl, respectively) occurred with exercise. In control subjects, glycemia was 86 ± 4 mg/dl and did not change with exercise. In the diabetics at rest, glucose production was elevated (220 ± 25 mg/min), whereas the metabolic clearance of glucose was suppressed. During exercise the increase in glucose utilization was similar to that in controls, but glucose production failed to increase significantly, thus accounting for the decline in plasma glucose. At rest, plasma immunoreactive insulin (IRI) was elevated to 0.90 ng/ml in the controls and decreased to 0.65 ng/ml with exercise. In the diabetics IRI was similarly elevated (0.89 ng/ml) but failed to decrease normally with exercise. Lactate, pyruvate, alanine, and free fatty acids increased similarly in diabetics and controls, whereas the increase in 3-hydroxybutyrate during recovery was less in diabetics. The sustained insulinemia, the basal overproduction of glucose, and hyperglycemia itself may all contribute to the observed differences in glucose flux during exercise in noninsulin-dependent diabetics.

glucose turnover; lactate; pyruvate; sulfonylureas; cycle exercise; 3-hydroxybutyrate; insulin

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NONINSULIN-DEPENDENT (maturity-onset type) diabetes is a problem of increasing magnitude in Western populations (22). Altered dietary habits, decreased physical activity, and obesity contribute to the increasing incidence of this common form of diabetes. Physical activity is often recommended as an adjunctive therapeutic modality to diet and sulfonylureas (38). However, the effects of acute exercise on glucoregulation in noninsulin-dependent diabetics remain to be defined in detail.

The glycemic lowering effect of physical exercise in diabetic subjects receiving subcutaneous insulin was recognized as early as 1926 (17). However, it was not until recently that the mechanism of exercise-induced hypoglycemia was more clearly defined. Studies in animals (4, 14) and man (15, 16, 33, 39, 40) have shown that exercise following subcutaneous insulin administration may result in hyperinsulinemia, impaired hepatic glucose production concurrent with increased utilization (14, 39), and hence a decline in glycemia. The reason for hyperinsulinemia is either increased absorption of insulin from its subcutaneous depot during exercise (4, 14, 16, 39) or increased levels of immunoreactive insulin (IRI) already present during the preexercise period (15). In contrast, when exercise is performed by hyperglycemic diabetics withdrawn from insulin, low levels of IRI are present and impaired glucose utilization in the face of increased production (34) results in a further increase in glycemia (3, 8, 37).

Much less information is available on the effects of exercise in noninsulin-dependent diabetics. Several studies have suggested that exercise programs in these diabetics result in enhanced insulin sensitivity (6, 7, 37). Saltin (29) demonstrated improved oral glucose tolerance despite unchanging insulin levels in normal weight diabetics with abnormal glucose tolerance after 3 mo of physical training. Although Björntorp (7) was not able to demonstrate improved oral glucose tolerance in five obese noninsulin-dependent diabetic subjects undergoing an 8-wk exercise program, he did demonstrate a lowered fasting level of insulin, suggesting increased insulin sensitivity. A short duration of the effect of training on insulin sensitivity was reported by Ruderman (26), who found that 2 wk after maturity-onset diabetic subjects stopped training, fasting glucose and insulin levels tended to increase and glucose tolerance had decreased significantly. The present study was undertaken to examine the glucoregulatory and other metabolic and hormonal responses to exercise in obese diabetic subjects treated with diet or diet and sulfonylureas. Nondiabetic obese individuals were studied as controls.

## MATERIALS AND METHODS

*Subjects.* Seven obese diabetic subjects (four male and three female) and seven obese nondiabetic control subjects (three male and four female) were studied in the Clinical Investigation Unit and the Respiratory Research Laboratory of the Toronto General Hospital. The subjects were normotensive and had normal renal, hepatic,


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and cardiac function as assessed by clinical examination and standard laboratory tests. All patients were on weight-maintaining diets prior to study and no recent weight changes had occurred. They were actively employed but none participated in regular sports or fitness programs. All patients had a normal exercise electrocardiogram. After careful explanation of the nature, purpose, and possible risks involved in the study, consent was obtained, as prescribed by University and Hospital Human Experimentation Committees.

Anthropomorphic and exercise load data are shown on Table 1. Diabetic *subject 1* participated in two studies separated by 1 yr and on the same treatment. *Subjects 2* and *4* were studied both on diet alone and after oral hypoglycemic therapy was instituted.

*Protocol.* All studies were performed in the morning after a 12- to 15-hour overnight fast. Six studies were performed in diabetic subjects while receiving sulfonylureas (5 on chlorpropamide, 1 glyburide), the last dose of which was given 24 h before the study. Four studies were performed in subjects during treatment with diet alone. Within 7 days before the study, maximum work capacity was estimated during exercise on a vertical cycle ergometer (Siemens-Elema model 380, Stockholm, Sweden) at two different submaximal work loads, during which heart rate and oxygen uptake were monitored. After correcting for age, standardizing for weight, and grading for cardiovascular fitness, the level of exercise predicted to give approximately 60% of maximum oxygen uptake was selected (2) (Table 1).

The exercise studies were performed in the following manner. The morning of the experiment, an 18-gauge catheter (Angiocath 1, Deseret Pharmaceutical, Sandy, UT) with a three-way stopcock was introduced into an antecubital vein for sampling of blood for glucose, hormones, metabolic substrates, and [3-$^3$H]glucose. The patency of the catheter was assured by slow infusion of 0.45% saline between sampling intervals. In a contralateral forearm, a second 20-gauge cannula was inserted for the infusion of [3-$^3$H]glucose through a Lambda pump (Harvard Apparatus, Millis, MA). For the measurement of glucose turnover, a priming bolus (33 $\mu$Ci) of [3-$^3$H]glucose (New England Nuclear, Boston, MA) was injected at the start of the experiment followed by a continuous infusion of labeled glucose (3 $\mu$Ci/ml 0.9% saline) at a rate of 0.112 ml/min throughout the rest of the study.

The protocol consisted of a 100-min period of rest during which steady-state glycemia was obtained, followed by 45 min of exercise and a recovery period of 60 min. Electrocardiographic monitoring was performed during rest, exercise, and recovery. Blood samples were drawn at intervals during each period and distributed immediately into tubes containing cold perchloric acid (PCA, 10% wt/vol) in a volume equal to that of blood, aprotinin (Trasylol, 10,000 KIU/ml, FBA Pharmaceuticals, Pte. Claire, Quebec) in a volume one-tenth that of blood (with heparin), into a capillary tube for hematocrit determination, and into heparinized microcentrifuge tubes for immediate glucose analysis. Samples for glucose turnover determination were placed into tubes that contained heparin and sodium fluoride and were processed as previously described (39). The values reported begin with the sample drawn 20 min after catheter insertion and rest is shown as an 80-min period.

*Analytical methods.* Plasma glucose was estimated by a glucose-oxidase method during the studies using a glucose analyzer (Beckman Instruments, Fullerton, CA). Samples for IRI, glucagon, substrates, and [3-$^3$H]glucose were centrifuged at 4°C within 30 min of the conclusion of the study, and supernatants frozen at −20° until assay. IRI was determined with an antibeef insulin antiserum

TABLE 1. *Anthropomorphic exercise load data*

| Subjects | No. of Studies Performed | Age | Sex | Ht, cm | Wt, kg | % Ideal Wt | Treatment | Duration of Diabetes, yr | Work Load, W | Predicted Max $\dot{V}O_2$, $m \cdot kg^{-1} \cdot min^{-1}$ | % Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetic | | | | | | | | | | | |
| *1* | 2 | 57 | M | 167 | 84.1 | 119 | Chlorpropamide, 250 mg/day | 9 | 60 | 22.6 | 61 |
| | | 58 | | | 86.4 | 121 | Chlorpropamide, 250 mg/day | 10 | 60 | 23.5 | 57 |
| *2* | 2 | 49 | M | 165 | 92.5 | 135 | Diet | 1.5 | 40 | 19.0 | 61 |
| | | 49 | | | 93.0 | 135 | Chlorpropamide, 250 mg/day | | 40 | 19.0 | 64 |
| *3* | 1 | 49 | M | 183 | 140.9 | 168 | Chlorpropamide, 250 mg/day | 4 | 70 | 17.6 | 66 |
| *4* | 2 | 47 | F | 168 | 81.4 | 133 | Diet | 12 | 60 | 23.2 | 56 |
| | | 47 | | | 85.0 | 139 | Glyburide, 10 mg/day | | 60 | 23.0 | 52 |
| *5* | 1 | 44 | F | 152 | 65.9 | 124 | Chlorpropamide, 250 mg/day | 15 | 50 | 27.0 | 47 |
| *6* | 1 | 54 | M | 177 | 90.6 | 117 | Diet | 7 | 60 | 22.6 | 64 |
| *7* | 1 | 34 | F | 108 | 103.6 | 157 | Diet | 12 | 60 | 19.3 | 81 |
| $\bar{x} \pm$ SE | | 49 ± 3 | | 160.0 ± 9.4 | 92.3 ± 6.2 | 135 ± 5 | | | 56 ± 9.6 | 21.7 ± 0.9 | 60.9 ± 2.9 |
| Nondiabetic | | | | | | | | | | | |
| *1* | 1 | 19 | M | 182 | 116.0 | 171 | | | 80 | 24.0 | 58 |
| *2* | 1 | 31 | M | 185 | 150.5 | 143 | | | 70 | 15.6 | 57 |
| *3* | 1 | 39 | F | 147 | 73.2 | 117 | | | 40 | 21.8 | 63 |
| *4* | 1 | 31 | M | 190 | 132.7 | 150 | | | 100 | 25.0 | 52 |
| *5* | 1 | 40 | F | 159 | 91.5 | 154 | | | 60 | 21.7 | 54 |
| *6* | 1 | 43 | F | 163 | 131.4 | 210 | | | 70 | 18.0 | 66 |
| *7* | 1 | 50 | F | 152 | 71.1 | 120 | | | 40 | 19.7 | 59 |
| $\bar{x} \pm$ SE | | 36 ± 3 | | 168.2 ± 6.5 | 109.5 ± 11.8 | 152 ± 12 | | | 65 ± 8.1 | 20.8 ± 1.2 | 58.4 ± 1.8 |

(courtesy of Dr. Peter Wright) purified human insulin standard (25.7 μU/ng), $^{125}$I-labeled pork insulin (Novo Research Institute, Copenhagen, Denmark), and a dextran-coated charcoal separation of free from bound hormone, as detailed previously (18).

The determination of immunoreactive glucagon (IRG) was performed on unextracted plasma with 30 K antiserum (received from Dr. R. H. Unger, Dallas, TX), purified pork glucagon standard, $^{125}$I-labeled pork glucagon (Novo), and a similar dextran-coated charcoal separation technique (18). Lactate, pyruvate, alanine, and 3-hydroxybutyrate were assayed in PCA supernatants by enzymic microfluorometric methods, and free fatty acids (FFA) in plasma by a radiochemical microtechnique (18). Glucose production, utilization (disappearance), and metabolic clearance were calculated by a validated nonsteady-state tracer method (25) during control, exercise, and recovery periods. The pool fraction was taken to equal 0.65 (11). Glucose space was taken to equal 19% body wt, as assessed by injections of [3-$^3$H]glucose in the postabsorptive obese man (32). Respiratory gas measurements were made by previously detailed methods (21) in which the subjects breathed through a low-resistance, low dead-space pulmonary-function breathing valve (E. W. Collins, Boston, MA). Standard statistical methods were employed with a Student's paired *t* test being used to examine the significance of the changes during exercise and recovery compared with rest and the unpaired *t* test to compare the diabetic and control responses. Analysis of variance and Duncan's new multiple-range test was used when comparisons were made among three groups (31).

## RESULTS

*Respiratory gas exchange and heart rate responses.* Table 2 presents oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), the respiratory exchange ratio (respiratory quotient, RQ), and the heart rates at rest and during exercise. The values in diabetics with and without sulfonylurea therapy were not different and are therefore pooled. The $\dot{V}O_2$ was similar at rest in the nondiabetic and diabetic subjects and increased fourfold with exercise ($P < 0.001$) in both groups. Similarly $\dot{V}CO_2$ was identical in the two groups at rest, and fourfold increases occurred with exercise ($P < 0.001$). The RQ values rose from similar rest values to peak at 5 min in both groups ($P < 0.05$) and then declined progressively with continuation of exercise and during recovery. The heart rates at rest were similar, and with exercise a 75% increase ($P < 0.001$) occurred in both groups.

*Glycemia and glucose turnover.* Figure 1 demonstrates the changes in glycemia. At rest glycemia was 86 ± 4 mg/dl in the nondiabetic control subjects, and during exercise and recovery no change was observed. Glycemia was elevated to similar levels at rest in the diabetics on diet and those on sulfonylureas (226 ± 36 and 192 ± 24 mg/dl, respectively). During exercise equivalent decreases occurred in diabetics on diets and on sulfonylureas, respectively.

Analysis of variance was performed at each time point to compare glucose concentrations among seven obese controls (*group I*), five diabetics treated with sulfonylureas (*group II*), and 4 diabetics treated by diet alone (*group III*). The values of *F* varied between 27 ($P < 0.001$) and 14 ($P < 0.005$), showing that differences between the three groups were present at each point. The Duncan's new multiple-range test was applied and demonstrated that at each point *group I* differed from the other two groups ($P < 0.05$). Duncan's test also showed

TABLE 2. *Respiratory and heart rate response to exercise*

| | | Rest | Exercise, min | | | | Recovery, min | |
|---|---|---|---|---|---|---|---|---|
| | | | 5 | 15 | 30 | 45 | 15 | 30 |
| RQ | D | 0.80 | 0.93 | 0.90 | 0.88 | 0.87 | 0.75 | 0.72 |
| | | ±0.04 | ±0.01 | ±0.02 | ±0.02 | ±0.02 | ±0.03 | ±0.03 |
| | N | 0.78 | 0.89 | 0.87 | 0.85 | 0.83 | 0.76 | 0.73 |
| | | ±0.04 | ±0.04 | ±0.03 | ±0.03 | ±0.03 | ±0.04 | ±0.06 |
| $\dot{V}O_2$, ml·kg$^{-1}$·min$^{-1}$ | D | 3.26 | 12.21 | 12.47 | 12.72 | 12.87 | 31.7 | 2.93 |
| | | ±0.21 | ±0.71 | ±0.60 | ±0.56 | ±0.59 | ±0.18 | ±0.18 |
| | N | 2.94 | 11.80 | 11.92 | 12.05 | 12.87 | 3.05 | 2.76 |
| | | ±0.22 | ±0.57 | ±0.63 | ±0.61 | ±0.71 | ±0.37 | ±0.29 |
| $\dot{V}CO_2$, ml·kg$^{-1}$·min$^{-1}$ | D | 2.66 | 11.36 | 11.19 | 11.09 | 11.09 | 2.38 | 2.12 |
| | | ±0.32 | ±0.59 | ±0.48 | ±0.39 | ±0.37 | ±0.19 | ±0.17 |
| | N | 2.45 | 10.48 | 10.41 | 10.36 | 10.84 | 2.47 | 2.23 |
| | | ±0.25 | ±0.67 | ±0.57 | ±0.61 | ±0.69 | ±0.42 | ±0.42 |
| Heart rate, beats/min | D | 75 | 117 | 125 | 132 | 135 | 98 | 91 |
| | | ±9 | ±5 | ±5 | ±5 | ±5 | ±4 | ±3 |
| | N | 81 | 123 | 134 | 141 | 141 | 95 | 87 |
| | | ±5 | ±7 | ±3 | ±4 | ±8 | ±7 | ±7 |

Values are means ± SE. $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production; RQ, respiratory exchange ratio (expiratory quotient); D, diabetic, $n = 10$; N, nondiabetic, $n = 7$.

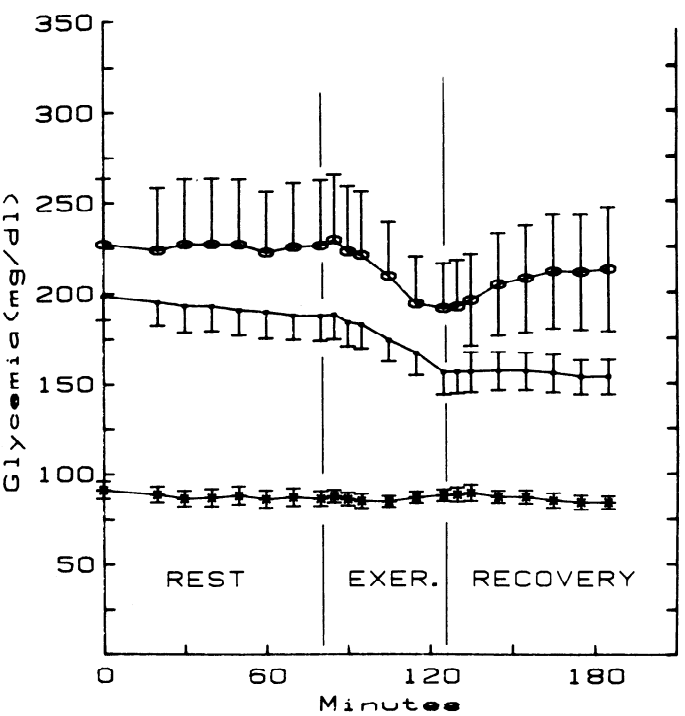


FIG. 1. Glycemia during moderate exercise in 7 obese controls (x), 4 obese diabetics treated by diet (○), and 5 diabetics treated with sulfonylureas (•). EXER signifies the 45-min exercise period. Mean and SE are shown.

that the effect of exercise was the same in *groups II* and *III*; because of the 13 time points analyzed there were no differences among 11 points. The decrease of plasma glucose in both diabetic groups during exercise was the same 37 ± 5 and 35 ± 12 mg/dl, respectively, and these decreases were significant when the paired $t$ test was applied ($P < 0.05$). Because the effect of exercise on glycemia did not differ among the diabetic groups, they were combined and subsequent analysis between diabetic and controls was analyzed by the Student's $t$ test.

Glucose turnover is shown in Fig. 2. At rest, in the control subjects glucose utilization and production were similar (140 ± 12 mg/min). During exercise, glucose disappearance and production increased twofold ($P < 0.005$) and rapidly returned to resting levels during recovery. In the diabetic subjects at rest, glucose utilization and production were elevated: 220 ± 25 mg/min ($P < 0.001$ vs. control). Because the diabetics showed greater elevations in glycemia than glucose utilization as compared to the controls, the metabolic clearance of glucose, calculated as the ratio of glucose utilization to glucose concentration, was significantly reduced (107 ± 10 vs. 178 ± 21 ml/min, $P < 0.001$). During exercise, glucose utilization increased by 159.6 ± 20.7 mg/dl ($P < 0.005$), an increase similar to that observed in the controls (120.8 ± 18.8 mg/min), and returned promptly after exercise to basal values. However, the glucose production response to exercise was variable, and the small mean increase in glucose production observed was not statistically significant.

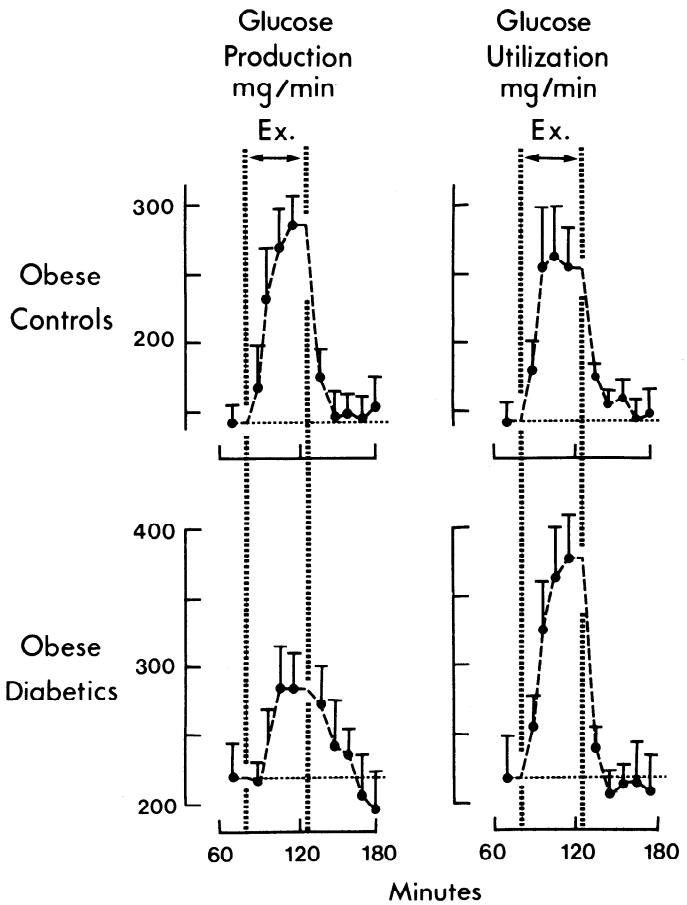


FIG. 2. Glucose production and utilization in 7 obese controls (upper panel) and 10 obese noninsulin-dependent diabetics (*lower panel*) during rest, exercise (60% $\dot{V}O_{2\,max}$) and recovery. Mean and SE are shown.

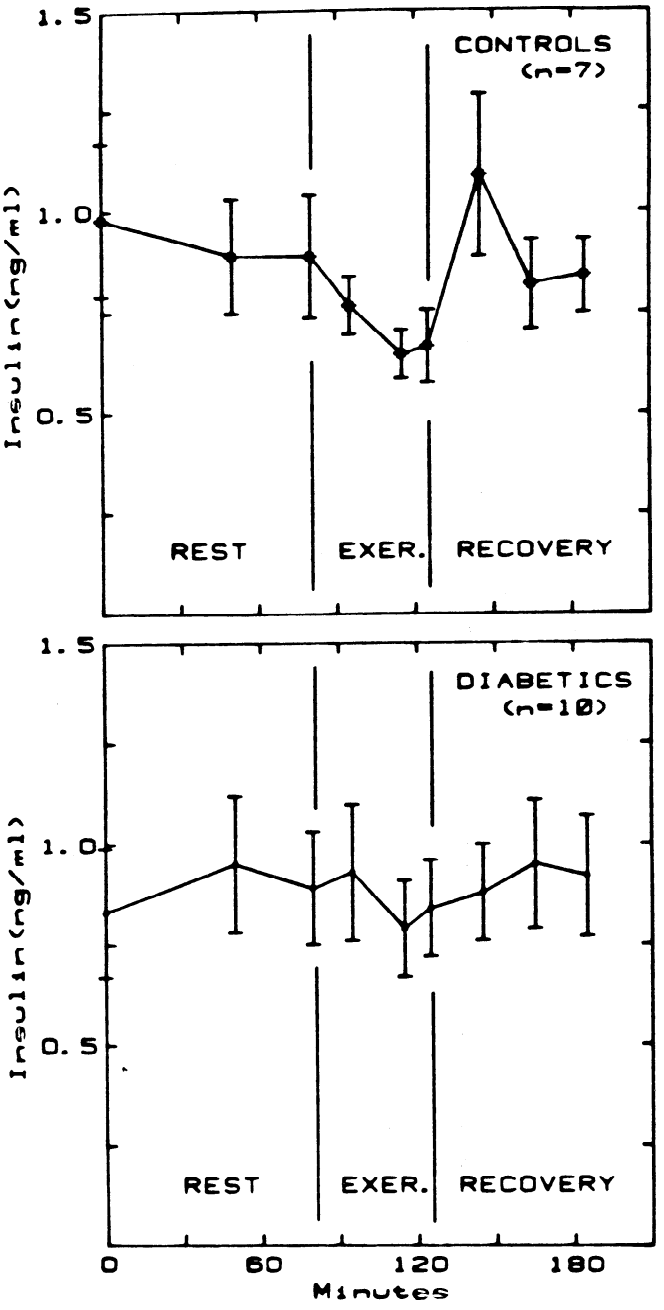


FIG. 3. Plasma immunoreactive insulin during exercise (EXER) in obese controls (*upper panel*) and diabetics (*lower panel*). Mean and SE are shown.

The remainder of the metabolic and hormonal responses observed for the diabetic subjects treated with diet alone or diet and sulfonylureas were also identical, and their results have been pooled.

*Insulin and glucagon.* IRI responses are shown in Fig. 3. In the obese control subjects at rest, IRI was 0.90 ± 0.15 ng/ml, decreased to a nadir of 0.65 ± 0.09 ng/ml by 35 min of exercise ($P < 0.025$), and then returned to rest values during recovery. IRI in the diabetic subjects was 0.89 ± 0.14 ng/ml, but no significant change occurred during exercise or recovery. At 15 and 35 min of exercise,

IRI in the diabetic subjects were significantly higher ($P < 0.02$ and $P < 0.04$) than in controls. IRG concentrations were similar at rest in normal and diabetic subjects (170 ± 16 and 175 ± 15 pg/ml, respectively), and with exercise no significant changes occurred in either. Thus the insulin/glucagon molar ratio declined in control subjects, but was unchanged in the diabetics.

*Other metabolites.* The blood pyruvate, lactate, and alanine concentrations at rest, and peak values with exercise and at 60 min recovery are shown in Table 3. Although pyruvate and lactate were slightly higher in the diabetics at rest, a similar significant increase of two- and threefold, respectively, with exercise ($P < 0.001$) was observed in both diabetic and normal control subjects. Alanine concentrations were similar at rest. The small mean increase in alanine was not statistically significant. At 60 min of recovery, all values returned to resting levels. The FFA and 3-hydroxybutyrate response are shown in Fig. 4. Plasma FFA showed similar rest values, did not change during exercise, but peaked at 15 min during recovery. In contrast, blood 3-hydroxybutyrate, equal during rest and exercise in the two groups, showed a markedly attenuated rise during recovery in the diabetics.

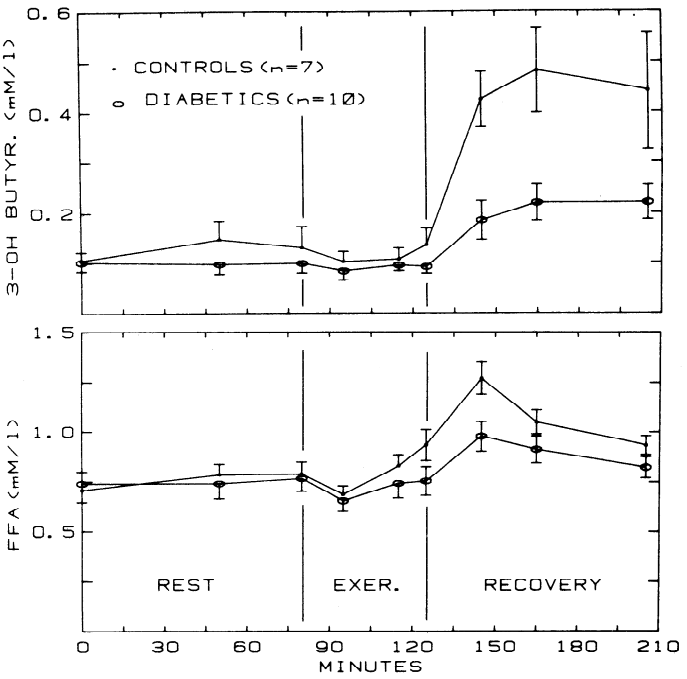


FIG. 4. Plasma free fatty acids (FFA, *upper panel*) and blood 3-hydroxybutyrate (*lower panel*) during exercise (EXER) in obese controls and diabetics. Mean and SE are shown.

## DISCUSSION

This study has demonstrated differences in both glucoregulation and metabolic responses during exercise between the obese controls and obese noninsulin-dependent diabetics. Because glucoregulation during exercise may be affected by the intensity, duration, and type of exercise, physical fitness, prior nutritional state, and drug intake, attempts were made to control these variables (19, 20, 36). Mean relative intensities of work were similar to the control and diabetic subjects (60.9% vs. 58.4%), all subjects performed similar exercise for the same time period, and lactate, pyruvate, and heart rate responses were comparable. The subjects did not participate in regular exercise programs or sports; work loads in both groups required to maintain 55–65% maximum $\dot{V}O_2$ confirm the lack of physical fitness. Although the diabetic subjects as a group were older than the controls, their ages ranged from 34 to 58 yr and no specific age-related differences in their response was apparent.

It is noteworthy that the nondiabetic control subjects, although obese, showed metabolic responses to exercise generally comparable to those of lean subjects previously studied using the same protocol (21, 39). Similarities include *a*) absence of change in glycemia; *b*) similar increments in glucose turnover during exercise, fall in IRI with no change in IRG; *c*) similar lactate, pyruvate, and alanine responses; and *d*) similar postexercise rise in 3-hydroxybutyrate. However, the FFA levels of the lean subjects were lower at rest and rose rapidly with exercise, whereas the elevated FFA levels of the obese subjects rose only after exercise, peaking at 15 min during the recovery period. The resting IRI levels were double those of lean subjects, the typical finding in obese subjects, and related to the well-documented insulin resistance of obesity (23, 24, 35). Thus with exception of IRI and FFA levels, the response of the obese and lean subjects were remarkably similar for this work load and duration of exercise. Basal turnover rates in the obese when expressed per body surface area (71 ± 9 $mg \cdot m^{-2} \cdot min^{-1}$) were comparable to those reported previously and calculated from single tracer injections (69 ± 5 $mg \cdot m^{-2} \cdot min^{-2}$) (32) or from the tracer infusion technique (75 ± 4 $mg \cdot m^{-2} \cdot min^{-1}$) (35). These values were not different from those reported in lean normal subjects (79 ± 4 mg/$m^2$-min) (35).

In the diabetic subjects at rest, glucose production and utilization were increased by 57%, whereas metabolic clearance of glucose was decreased by 40%. Because insulin concentrations were the same in both groups, insulin insensitivity of a greater degree than that seen in obesity alone must have been present in the diabetic subjects to explain the observed abnormalities in glucose flux. Such an increase in glucose turnover in the diabetics has been reported by others; its magnitude is possibly related to the severity of the metabolic derangement. In insulin-dependent diabetic subjects 24 h after their last insulin injection, an increase of glucose production of 26–

TABLE 3. *Pyruvate, lactate, and alanine response to exercise*

| | | Rest | Exercise | Recovery |
|---|---|---|---|---|
| Pyruvate | D | 79 ± 11 | 139 ± 20* | 84 ± 11 |
| | N | 61 ± 5 | 120 ± 19* | 61 ± 12 |
| Lactate | D | 883 ± 140 | 2,559 ± 446* | 1,008 ± 125 |
| | N | 770 ± 36 | 2,220 ± 491* | 924 ± 82 |
| Alanine | D | 337 ± 55 | 454 ± 55 | 355 ± 51 |
| | N | 376 ± 40 | 471 ± 56 | 387 ± 43 |

Values are means ± SE, given in micromoles per liter. D, diabetic; N, normal. Samples were drawn at the end of the rest, exercise, and recovery periods. * $P < 0.01$ when values during exercise are compared to those during rest.

75% and a decrease of clearance of 50–100% have been reported (12, 28). In lean noninsulin-dependent diabetic subjects, glucose production has been shown to be increased by 110% and clearance decreased by 20% (9).

In contrast to the precise matching of glucose production and utilization during exercise in the control subjects, the diabetic subjects showed that production failed to increase adequately with exercise, and as a result the glycemia declined. The increase in glucose utilization was comparable in the two groups, demonstrating that an adequate insulin effect on enhancing muscle glucose uptake with exercise was present (33, 40). Thus the decline in plasma glucose with exercise is entirely attributed to an inadequate response in hepatic glucose production. Several factors may be implicated in this abnormal response, including hyperglycemia itself, initially elevated glucose production, and the sustained elevated IRI during exercise. Previous observations in diabetic man (39) and depancreatized dogs (14) have demonstrated that hyperinsulinemia can impair hepatic glucose production responses to exercise and that in dogs the inhibition of glucose production is directly proportional to the preexercise plasma glucose concentrations and production rates (14). It has been suggested that in the resting state hyperglycemia per se can limit hepatic glucose production (5, 30). However, when exercise was performed and insulin levels were not elevated, hyperglycemia did not inhibit glucose production in insulin-infused diabetics (39). Thus it would appear that the observed changes in glucose production result from a combined effect of the variables discussed on the hepatic response to exercise.

With respect to glucagon, the sustained levels of IRI might not allow for expression of a glucagon effect in the diabetics, whereas the fall in IRI in controls with constant IRG suggests the possibility that glucagon in part mediates the increased hepatic glucose output (10, 27, 33). The insulin/glucagon molar ratio decreased only in controls. In exercising dogs a direct correlation between this ratio and the response of glucose production could be demonstrated (13).

Further evidence of an excessive hepatic effect of insulin during exercise may be adduced from the lesser rise in 3-hydroxybutyrate levels in the diabetic subjects despite identical FFA levels, possibly reflecting inhibition of hepatic ketogenesis.

It is generally accepted that the normal inhibition of IRI secretion during exercise is mediated by $\alpha$-adrenergic receptor activation on pancreatic $\beta$-cells, from the increase in sympathetic activity. The present observations on IRI levels during exercise suggest that such sympathetic control of insulin secretion may be abnormal in obese diabetic subjects. An alternate explanation might be that the hyperglycemia was causing excessive stimulation of $\beta$-cells, not suppressible by the adrenergic activation.

In light of the long half-life (36 h) of chlorpropamide taken by five of the six subjects, it is probable that effective plasma levels were present at the time of study. The sulfonylurea tolbutamide has been reported to attenuate the increase in hepatic glucose production in response to hypoglycemia when administered acutely to dogs (1). However, in the context of the present study, the similar responses in our subjects, whether receiving sulfonylureas or not, indicates that these drugs were neither responsible for the sustained IRI nor did they influence the overall response to exercise. In addition the two subjects studied both off and on chlorpropamide therapy demonstrated the same glycemic and metabolic effects even though (as expected) resting glycemia was lower with chlorpropamide.

In conclusion, these studies demonstrate that, as in insulin-treated diabetic subjects, exercise in noninsulin-dependent diabetic subjects results in lowering of plasma glucose, which is related to an inadequate exercise-associated increase in glucose production. This study is concerned only with an acute effect of exercise. Long-term studies will be required to clarify whether or not exercise is an important adjuvant in therapy of such patients, who form the majority of the diabetic population.

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