Lipid and Carbohydrate Metabolism in IDDM During Moderate and Intense Exercise

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Insulin-dependent diabetes mellitus (IDDM) is characterized by a metabolic and hormonal disarray that may be more evident during exercise. However, the metabolic response to exercise of different intensities has not been evaluated in IDDM. We therefore used stable isotope techniques and indirect calorimetry to quantify substrate kinetics and oxidation during 30 min of exercise at 45 and 75% of maximal oxygen uptake ($\dot{V}O_{2max}$) in seven men with IDDM (D group) infused with insulin at a constant basal rate. Normal control subjects (C group) matched for age, weight, and $\dot{V}O_{2max}$ were also studied. During moderate exercise, glucose uptake (R_d) was lower in the D than in the C group (15.3 ± 1.0 vs. 20.8 ± 1.6 $\mu mol \cdot min^{-1} \cdot kg^{-1}$; $P < 0.05$). Carbohydrate oxidation also tended to be lower in the D group (71.0 ± 7.2 vs. 87.5 ± 10.6 $\mu mol \cdot min^{-1} \cdot kg^{-1}$; $P = 0.08$). The D group relied on fat oxidation to a greater extent than did the C group (16.9 ± 1.1 vs. 10.4 ± 1.6 $\mu mol \cdot min^{-1} \cdot kg^{-1}$; $P < 0.05$). The enhanced fat oxidation was not due to increased lipolysis because no differences occurred in glycerol release (R_a) or in plasma free fatty acid R_a or concentration, and the source of the extra lipid appeared to be intramuscular fat stores. These differences in substrate metabolism were not evident during exercise at 75% of $\dot{V}O_{2max}$. The lower glucose uptake and oxidation in the diabetic subjects during moderate, but not intense, exercise suggest that glucose metabolism is regulated differently depending on exercise intensity. During moderate exercise, glucose uptake into muscle seems to be limiting, and the higher intramuscular triglyceride oxidation observed in IDDM might be a compensatory adaptation needed to maintain energy supply. *Diabetes* 44:1066–1074, 1995

In insulin-dependent diabetes mellitus (IDDM), normal fuel homeostasis adjustments to exercise are lacking. This may present a problem in exercise because insulin concentration cannot decrease appropriately and thus hepatic glucose production may not match glucose uptake by exercising muscle. On the other hand, in IDDM patients, reduced glucose uptake has also been localized to muscle tissue (1). Both oxidative (2) and nonoxidative (3) pathways of glucose metabolism are impaired, and the rate of glucose utilization in muscle and adipose tissue appears to be limited by glucose transport (4–6). In addition, IDDM is characterized by increased lipolysis (7), and this is most apparent during exercise (8). A greater lipolytic response to catecholamines and increased plasma concentrations of these hormones may account for this higher lipolysis during exercise (9). It is therefore reasonable to expect a shift in fuel utilization, from carbohydrate to fat metabolism, during exercise in patients with IDDM. Indeed, previous studies (10,11) demonstrated a preferential utilization of free fatty acids (FFAs) in IDDM during moderate exercise, that is, at 40–60% of maximal oxygen uptake ($\dot{V}O_{2max}$). However, these experiments were performed after 24 h of insulin withdrawal, so it is not clear if the response was due to diabetes or to the absence of insulin per se. Other studies have investigated glucose metabolism (12–14). At a similar exercise intensity, a normalization of glucose uptake was observed only at an insulin level fourfold higher (~200 pmol/l) than that in control subjects (12–14). No information regarding interactions between lipid and carbohydrate metabolism was provided by these studies.

In normal volunteers, when the exercise intensity increases from moderate to severe, fat oxidation declines, as does the rate of FFA release and plasma FFA concentration (15,16). A corresponding increase occurs in plasma glucose uptake and muscle glycogenolysis, and carbohydrate becomes the most important fuel for oxidation (15,16). Consequently, in diabetic patients, because of insulin resistance and impaired glycogen storage, one might expect a further discrepancy from normal in their metabolic response to intense exercise. However, the regulation of substrate utilization in IDDM patients during high-intensity exercise has not previously been evaluated.

The aim of this study, therefore, was to evaluate substrate utilization in men with IDDM during both moderate and intense exercise. The control group consisted of nondiabetic volunteers matched for age, weight, and $\dot{V}O_{2max}$. To best compare the responses of the IDDM patients and the control subjects, the patients were studied during a constant infusion of insulin that maintained glucose concentrations near normal at rest. Stable isotope techniques and indirect calorimetry were used to quantify substrate kinetics and oxidation. Plasma levels of insulin, glucagon, epinephrine, and norepinephrine were also measured.

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FFA, free fatty acid; GCMS, gas chromatography–mass spectrometry; IDDM, insulin-dependent diabetes mellitus; m/e, mass-to-charge ratio; PDH, pyruvate dehydrogenase; R_a, rate of appearance; R_d, rate of disappearance; RIA, radioimmunoassay.

TABLE 1
Subject characteristics

	Control	IDDM
Age (years)	26.0 ± 2.0	24.0 ± 3.0
Height (cm)	177.5 ± 3.2	176.4 ± 2.1
Weight (kg)	72.7 ± 2.9	74.1 ± 3.8
Body mass index (kg/m^2)	21.3 ± 0.8	21.7 ± 1.1
Duration of diabetes (years)	—	10.1 ± 4.3
Dose of insulin (pmol/day)	—	370 ± 30
HbA_{1c} (%)	5.2 ± 0.2	8.0 ± 0.7*
Fasting plasma glucose (mmol/l)	5.1 ± 0.2	6.5 ± 0.6*
$\dot{V}o_{2max}$ (ml · min^{-1} · kg^{-1})	41.1 ± 1.5	40.5 ± 2.0

Data are means ± SE for seven subjects per group. *Significantly higher than control subjects ($P < 0.01$).

RESEARCH DESIGN AND METHODS

Subjects. Seven men with insulin-treated IDDM and seven normal men participated in the study. Characteristics of the study groups are shown in Table 1. The patients were recruited from the diabetic outpatient clinic using the following criteria: age at onset of disease <30 years; undetectable fasting C-peptide concentration; HbA_{1c} <9% (normal range 3.5–6.0%); fasting blood glucose <8 mmol/l; no clinical or chemical evidence of hepatic, renal, cardiovascular, or other endocrine diseases, proliferative retinopathy, or autonomic neuropathy; and no medication other than insulin. Patients consumed a weight-maintaining diet containing at least 250 g carbohydrates daily.

$\dot{V}o_{2max}$ was determined 1 week before the primary experiments (described below) using an incremental cycling protocol lasting 7–10 min. Normal volunteers were selected for age, weight, and $\dot{V}o_{2max}$ to closely match the diabetic subjects. The study was approved by the institutional review board of the University of Texas Medical Branch, and informed consent was obtained from each volunteer.

Experimental protocol. The subjects were studied on two occasions. On day 1, moderate exercise was performed, 47 ± 2 and 44 ± 1% of $\dot{V}o_{2max}$ for the diabetic patients and control subjects, respectively (absolute workload as $\dot{V}o_2$ was 1.41 ± 0.12 in diabetic patients and 1.36 ± 0.08 l/min in control subjects, NS). One week later, four subjects from each group repeated the study (day 2), performing intense exercise at 77 ± 3 and 78 ± 2% of $\dot{V}o_{2max}$ for diabetic patients and control subjects, respectively (absolute workload as $\dot{V}o_2$ was 2.34 ± 0.22 l/min in diabetic patients and 2.40 ± 0.21 l/min in control subjects, NS). The patients were admitted to the Clinical Research Center the day before each study. They were withdrawn from their intermediate or long-acting insulin preparations 24 h before the study. After dinner, a continuous intravenous infusion of short-acting human insulin (Humulin R, Lilly, Indianapolis, IN) was started at variable rates to achieve and maintain plasma glucose concentrations of ~6 mmol/l (plasma glucose was monitored hourly during the night). The insulin infusion rate averaged 0.66 ± 0.30 pmol · min^{-1} · kg^{-1}. Insulin was infused throughout the experimental sessions at the rate fixed at the beginning of tracer infusions, and no modifications were allowed in the insulin infusion rate until the end of the experiment. In the morning, after the patients had fasted for 12 h, indwelling catheters were placed into the antecubital vein of one arm for tracer infusions and into a contralateral dorsal hand vein for arterialized venous sampling using the heated hand technique. After a blood sample was drawn to determine background enrichment, primed constant infusions of [6,6-^{2}H]glucose (0.22 μmol · min^{-1} · kg^{-1}, prime 17.6 μmol/kg), [$^2H_5$]glycerol (0.1 μmol · min^{-1} · kg^{-1}, prime 1.5 μmol/kg), and [1-^{13}C]palmitate (0.04 μmol · min^{-1} · kg^{-1}, no prime) were started using calibrated syringe pumps (Harvard Apparatus, Natick, MA). The exact infusion rates in each experiment were determined by measuring the concentrations of the infusates. On the morning of the experiment, plasma glucose concentration was measured every 30 min in the patients, and the tracer infusions were started after three consecutive values <7 mmol/l. No further changes in insulin infusion were made after this point.

After 2 h of rest, to allow for isotopic equilibration, the subjects exercised for 30 min on an electrically controlled cycle ergometer (Monark 829E, Varberg, Sweden). Immediately after exercise, subjects reclined in bed, and tracer infusions were continued for 30 min of recovery.

Isotope infusion. At the onset of exercise and every minute thereafter, the rate of [6,6-^{2}H]glucose infusion was increased to mimic a monoexponential function, with an asymptote of 0.44 μmol · min^{-1} · kg^{-1} during moderate exercise and 0.66 μmol · min^{-1} · kg^{-1} during intense exercise. The [$^2H_5$]glycerol infusion rate was increased in a similar manner to 0.15 μmol · min^{-1} · kg^{-1} by the end of both moderate and intense exercise. After exercise, the infusion rates were decreased every minute after the same monoexponential function until the preexercise rate was reached after 30 min. The goal of these changes in tracer infusion rates was to minimize changes in isotopic enrichment during the physiological non-steady state in the transition from rest to exercise and from exercise to recovery, thus improving tracer estimates of substrate kinetics (17). Because only minimal changes in FFA kinetics were anticipated during exercise of this intensity and duration (16), the rate of [1-^{13}C]palmitate infusion was not altered during exercise.

Indirect calorimetry. Oxygen uptake and carbon dioxide release were measured using an Ametek OCM-2 metabolic cart (Thermox Instruments, Pittsburgh, PA) at rest, for at least 15 min continuously, while the subjects sat quietly on the cycle ergometer. Additional measurements were made over 5-min intervals ending at 10, 20, and 30 min of exercise and at 10, 20, and 30 min of recovery.

Blood sampling. Blood samples were obtained at 110, 115, and 120 min after the start of infusion to determine resting substrate kinetics. During exercise and recovery, blood was drawn every 5 min. All samples were placed in 10-ml evacuated tubes containing lithium heparin. Additional aliquots of blood for insulin/glucagon and norepinephrine/epinephrine determination were also obtained at rest, after 15 and 30 min of exercise, and after 15 and 30 min of recovery and placed in tubes containing EDTA/aprotinin and EGTA/reduced glutathione, respectively. All tubes were placed on ice. Samples were centrifuged shortly after drawing and frozen until further processing.

Sample analysis. Plasma glucose and lactate concentrations were measured using a YSI 2300 glucose/lactate analyzer (Yellow Springs Instruments, Yellow Springs, OH). The enrichment of [6,6-^{2}H]glucose in plasma was determined as previously described (18). Briefly, isotopic enrichment was determined on the pentaacetate derivative by gas chromatography–mass spectrometry (GCMS) (Hewlett-Packard 5985, Palo Alto, CA) using electronic impact ionization, selectively monitoring ions at mass-to-charge ratio (m/e) 202, 201, and 200. Correction was made for the contribution of singly labeled molecules (m/e 201) to the apparent enrichment m/e 202 (18).

Glycerol concentrations were measured by enzymatic colorimetric assay (Technicon RA-500, Tarrytown, NY). Isotopic enrichment of glycerol was determined by GCMS by previously described procedures (18). Ions of m/e 205, 206, 207, and 208 were monitored. Correction was made for the contribution of m/e 206 and 207 to the apparent enrichment m/e 208.

FFAs were extracted from plasma, isolated by thin-layer chromatography, and derivatized to their methyl esters. Palmitate and total FFA concentrations were determined by gas chromatography (Hewlett-Packard 5890) using heptadecanoic acid as the internal standard. Isotopic enrichment of palmitate was measured by GCMS analysis of the methyl ester derivatives. Ions of m/e 270 and 271 were selectively monitored (18).

Plasma catecholamine concentrations were measured using a radioenzymatic assay according to Hussain and Benedict (19). Plasma glucagon and free insulin concentrations were measured using commercial radioimmunoassay kits (ICN Biomedicals, Costa Mesa, CA).

Calculations. Carbohydrate and fat oxidation rates were calculated using stoichiometric equations (20). The nitrogen excretion rate was assumed to be 100 μg · min^{-1} · kg^{-1}. This average value was taken from the measured values determined in another exercise study performed in our laboratory (21). Fatty acid oxidation (in μmol · min^{-1} · kg^{-1}) was determined by converting the rate of triglyceride oxidation (in g · min^{-1} · kg^{-1}) to its molar equivalent, assuming the average molecular weight of triglyceride to be 860 g/mol and multiplying the molar rate of triglyceride oxidation by 3 because each mole of triglyceride contains 3 mol of fatty acids (20).

Rates of appearance (R_a) and disappearance (R_d) of glucose, glycerol, and palmitate were calculated using the Steele equation (22), as modified for use with stable isotopes (18). During exercise and recovery, substrate kinetics were calculated after first fitting enrichment and concentration data to curves using a spline fitting program (23). Volumes of distribution were assumed to be 100, 230, and 40 ml/kg for glucose, glycerol, and palmitate, respectively (16). Note that with this approach, even if the adjustment in tracer infusion rate is unsuccessful in completely preventing changes in isotopic enrichment during exercise and recovery, it is still possible to calculate R_a. The R_a of FFA was calculated

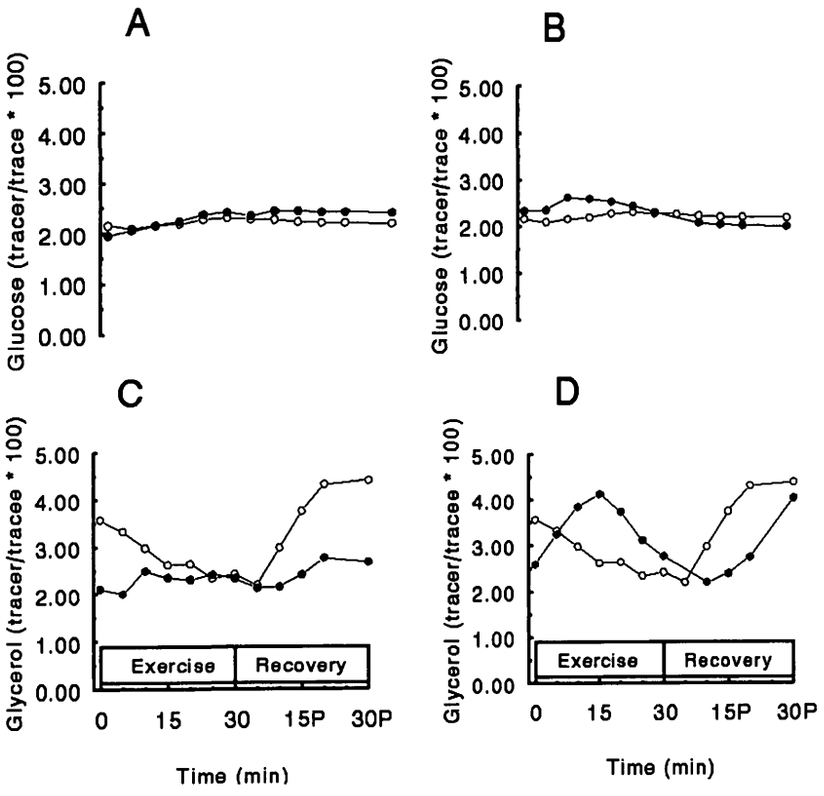

FIG 1. Plasma glucose enrichment at rest and during and after moderate-intensity exercise (*A*) and high-intensity exercise (*B*); plasma glycerol enrichment at rest and during and after moderate-intensity exercise (*C*) and high-intensity exercise (*D*) in one normal control subject (●) and in one patient with IDDM (○).

by dividing the R_a of palmitate by the fractional contribution of palmitate to the total FFA concentration, as determined by gas chromatography.

Assuming that during exercise all of the glucose taken up from plasma is oxidized, the difference between the overall rate of carbohydrate oxidation, as measured by indirect calorimetry, and glucose R_d provides a minimal estimate of the contribution of muscle glycogen stores to carbohydrate oxidation (16). With the same assumption for FFAs, the difference between the total rate of fat oxidation, obtained by indirect calorimetry, and FFA R_d reflects the minimal rate of intramuscular triglyceride oxidation (16). The validity of these assumptions and the limitations of these calculations have been discussed in detail previously (16).

Statistical analysis. Results are presented as means ± SE. The paired *t* test was used to analyze differences between rest, exercise, and recovery within each group. Analysis of variance was used in comparing the diabetic and control groups during each period.

RESULTS

The infusion rates of glucose and glycerol were increased at the start of exercise to minimize the effect of non-steady-state conditions of isotopic enrichment on the calculation of substrate kinetics (17,23). We were successful in maintaining isotopic steady state for glucose enrichment (Fig. 1*A*, moderate exercise; Fig. 1*B*, intense exercise). Glycerol enrichment was less steady (Fig. 1*C*, moderate exercise; Fig. 1*D*, intense exercise). For calculation of kinetic factors, we used data between 20 or 25 min and 30 min of exercise and the last 10 min of recovery. In addition, as explained above (see METHODS), enrichment and concentration data were smoothed using a spline fitting program.

Substrate concentrations. On study day 1, the basal plasma glucose concentration was higher in the diabetic patients compared with the control subjects (6.5 ± 0.5 vs. 5.1 ± 0.2 mmol/l; $P < 0.01$) (Fig. 2*A*).

No differences were observed between the two groups in basal glycerol or FFA concentrations (Fig. 2*B* and *C*). During moderate exercise, glucose concentration was constant in the control group and increased slightly but not significantly in the diabetic patients (Fig. 2*A*). In the diabetic patients, glycerol concentration increased from 0.09 ± 0.02 at rest to 0.13 ± 0.02 mmol/l ($P < 0.01$) and returned to basal values at the end of recovery (Fig. 2*B*). Glycerol levels at the end of exercise in the control subjects were the same as in the diabetic patients, but the increase above basal was not statistically significant ($P = 0.34$). FFA concentration decreased during moderate exercise and increased during recovery in both groups, but the exercise-induced suppression was significant ($P < 0.05$) only in the control subjects (Fig. 2*C*). Plasma lactate concentration rose ($P < 0.001$) during exercise in both groups but was lower in the diabetic patients than in the control subjects (1.9 ± 0.2 vs. 2.6 ± 0.4 mmol/l, $P < 0.01$) (Fig. 4*A*).

On study day 2, basal glucose, glycerol, and FFA concentrations were similar in both groups to the values observed on day 1. During high-intensity exercise, glucose concentration increased slightly but not significantly in the diabetic group and was constant in the control subjects (Fig. 3*A*). Plasma glycerol concentration rose ($P < 0.001$) during exercise and returned to basal during recovery, with no significant difference between the two groups (Fig. 3*B*). FFA concentration decreased from rest to the end of high-intensity exercise in both groups ($P < 0.05$) and then returned to basal during recovery (Fig. 3*C*). Plasma lactate concentration increased ($P < 0.001$) markedly during exercise in both groups, with no difference between the diabetic and control subjects (6.1 ± 0.8 vs. 6.6 ± 0.8 mmol/l; NS) (Fig. 4*B*).

Glucose kinetics. At rest, glucose R_a and R_d did not differ between groups on either day. At the lower exercise intensity, glucose R_d increased in both groups, but the increase in diabetic patients (from 10.7 ± 1.0 to 15.3 ± 1.0 $\mu mol \cdot min^{-1} \cdot kg^{-1}$) was less ($P < 0.01$) than in the control

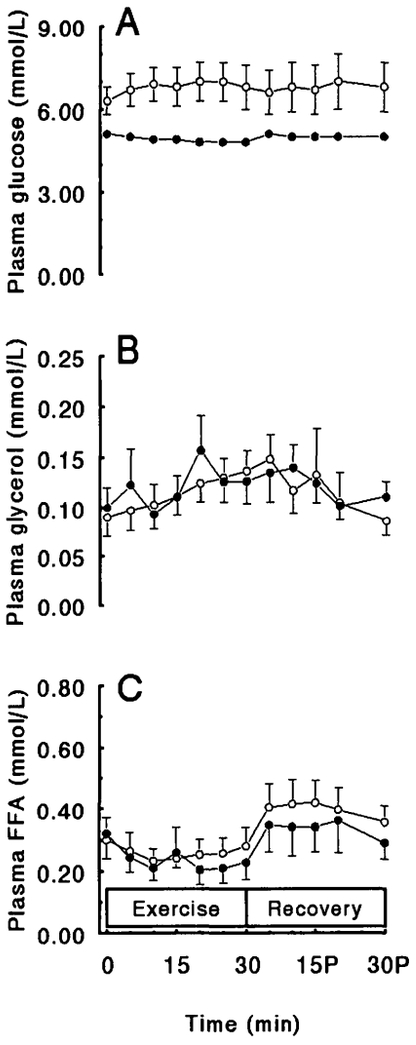

FIG 2. Plasma glucose (*A*), glycerol (*B*), and FFA (*C*) concentrations at rest and during and after moderate-intensity exercise in normal control subjects (●) and in patients with IDDM (○).

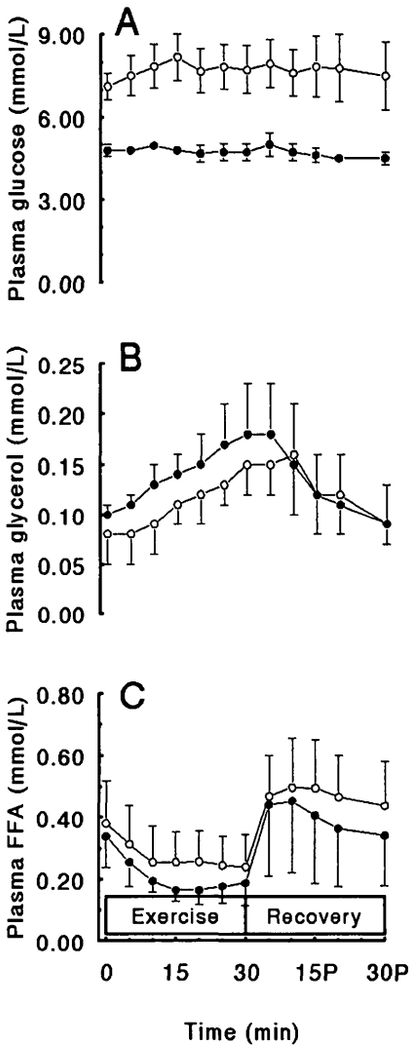

FIG 3. Plasma glucose (*A*), glycerol (*B*), and FFA (*C*) concentrations at rest and during and after high-intensity exercise in normal control subjects (●) and in patients with IDDM (○).

subjects (from 10.8 ± 0.7 to 20.8 ± 1.6 μmol · min^{-1} · kg^{-1}). During exercise at the higher intensity, this difference was no longer evident. Glucose R_a (Fig. 5) closely matched glucose R_d in both groups during both trials.

Glycerol kinetics. Glycerol R_a did not change during moderate exercise and increased during high-intensity exercise with no difference between the two groups (Fig. 6). During recovery from moderate-intensity exercise, glycerol R_a dropped in both groups but more so in the diabetic patients ($P < 0.05$). In contrast, during recovery from intense exercise, glycerol R_a was higher in the diabetic patients ($P < 0.05$).

FFA kinetics. At rest, the two groups had the same plasma appearance and disappearance rates of FFAs. During moderate-intensity exercise, FFA R_a increased slightly (but not significantly) in diabetic patients but not in control subjects. However, no significant difference occurred between the groups ($P = 0.2$) (Fig. 7*A*). Likewise, no differences were observed during high-intensity exercise (Fig. 7*B*). FFA R_d was not statistically different between the groups either at the end of moderate exercise (control subjects 4.9 ± 0.6 and diabetic subjects 6.4 ± 1.5 μmol · min^{-1} · kg^{-1}, NS) or at the end of intense exercise (control subjects 3.9 ± 0.6 and diabetic subjects 5.0 ± 1.2 μmol · min^{-1} · kg^{-1}, NS).

Substrate oxidation. During moderate exercise, the rate of carbohydrate oxidation was lower, although not statistically, in the diabetic patients than in the control subjects (Table 2). However, when expressed as percentage of total energy expenditure, carbohydrate oxidation was significantly lower in diabetic patients (52 ± 6 vs. 64 ± 6%, $P < 0.05$) (Fig. 8*A*). Fat oxidation, on the other hand, was higher in the diabetic patients (Table 2), with the main source apparently being intramuscular triglycerides (Fig. 8*A*). In contrast, during intense exercise, substrate oxidation was very similar in the two groups (Table 2 and Fig. 8*B*).

Hormone concentrations. At rest, plasma free insulin concentration did not differ between the diabetic patients and control subjects on either day, but during exercise and recovery, it was higher in the diabetic patients (Table 3). No differences were observed between groups in plasma glucagon or catecholamine concentrations.

DISCUSSION

Alterations in carbohydrate metabolism were observed in men with IDDM during 30 min of moderate exercise. Glucose production and uptake were lower in diabetic patients than in control subjects, as was the rate of carbohydrate oxida-

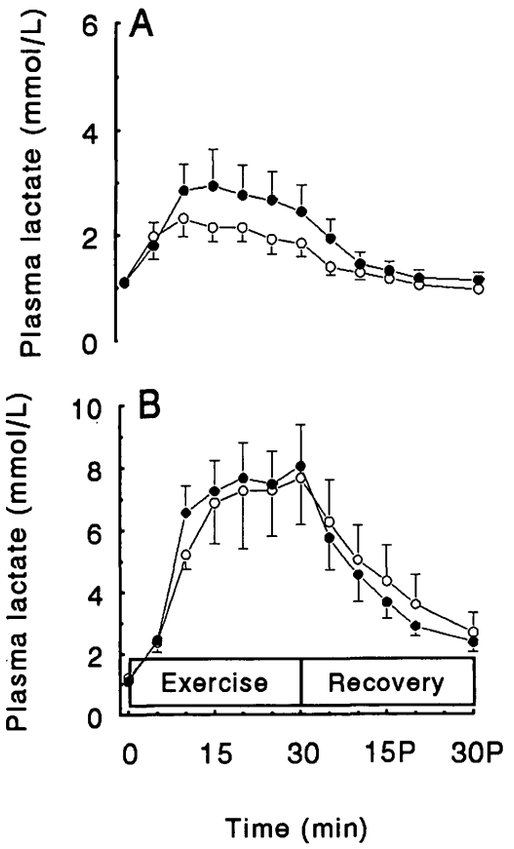

FIG 4. Plasma lactate concentration at rest and during and after moderate-intensity (*A*) and high-intensity exercise (*B*) in normal control subjects (●) and in patients with IDDM (○).

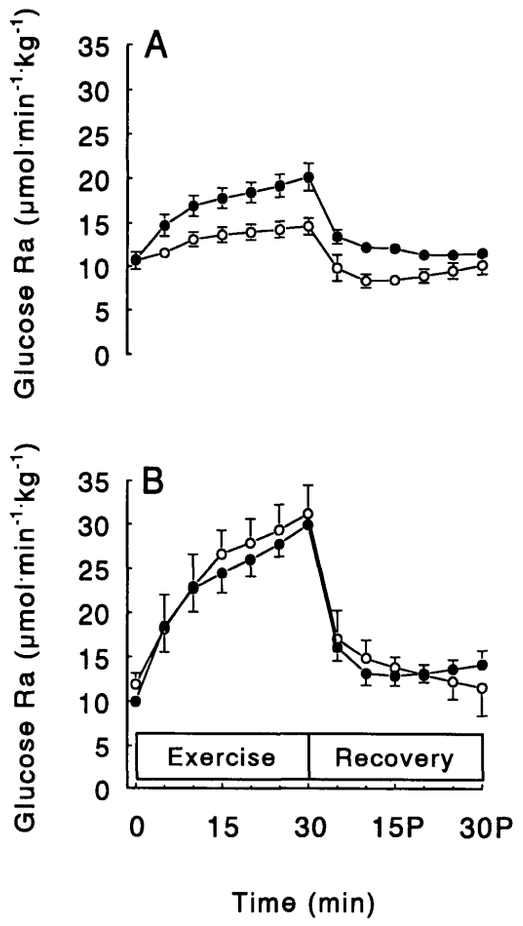

FIG 5. Glucose production (R_a) at rest and during and after moderate-intensity (*A*) and high-intensity (*B*) exercise in normal control subjects (●) and in patients with IDDM (○).

tion. Plasma lactate concentration was also lower in diabetic patients, suggesting that both the oxidative and the glycolytic pathways of glucose metabolism were impaired, probably because of a reduced intracellular availability of glucose. Although plasma lipid turnover in the patients with diabetes was not different from that in control subjects, total fat oxidation was higher and intramuscular triglycerides appeared to be the main source. During the higher exercise intensity, the impairment neither in glucose uptake nor in carbohydrate oxidation was evident. As observed previously in trained subjects (16), fat oxidation was lower than during moderate exercise in both groups and carbohydrate became the main source of energy.

There are contrasting data regarding the effect of IDDM on glucose uptake during exercise. Some studies reported that during moderate-intensity exercise, glucose uptake increases in patients with diabetes to the same extent as in normal subjects at the same insulin concentration (24) or at fourfold higher insulin concentrations (12–14). Other studies found that glucose utilization by exercising muscles is impaired by diabetes (25–29). In our study, the smaller increase in glucose uptake in the diabetic patients during moderate exercise (~60% over basal compared with ~90% in the control subjects) was unlikely to have resulted from inadequate insulin replacement. At rest, no differences occurred between the two groups in glucose production or uptake and free insulin concentrations were similar. Glucose concentration was higher in the diabetic subjects, and all but one had good glycemic control. When the hyperglycemic patient was excluded from the sample, the average glucose concentration before starting exercise was reduced from 6.5 ± 0.5 to 5.9 ± 0.3 mmol/l, but the average glucose uptake at the end of exercise did not change and was still lower than in the control subjects (15.4 ± 0.9 vs. 20.8 ± 1.6 μmol ·min^{-1} · kg^{-1}, $P < 0.05$). During exercise, the free insulin concentration dropped in the control subjects, whereas, because the insulin infusion was constant, it increased slightly in the diabetic patients. At the end of exercise, the free insulin concentration, although still in the physiological range, was almost three times higher in the diabetic patients than in the control subjects (55 ± 5 vs. 20 ± 5 pmol/l, $P < 0.01$). Moreover, no correlation was found between insulin concentration and glucose uptake in the diabetic group. Thus, it seems that the impairment in glucose uptake in the diabetic patients was not due to the immediate preexercise condition or to a relatively low insulin concentration.

A possible explanation for decreased glucose utilization by diabetic patients during moderate exercise could be an impairment in the activation of glucose transport into muscle due to a defective recruitment of glucose transporters. Muscle contraction and insulin are stimuli for glucose uptake. The glucose transport response to insulin plus exercise in muscle may be additive with respect to the response evoked by each stimulus alone (30,31). Studies in rat muscle tissue (6) have shown that chronic insulin deficiency results in a lower rate of 3-*o*-methylglucose transport in skeletal muscle after contractile activity. Although our diabetic pa-

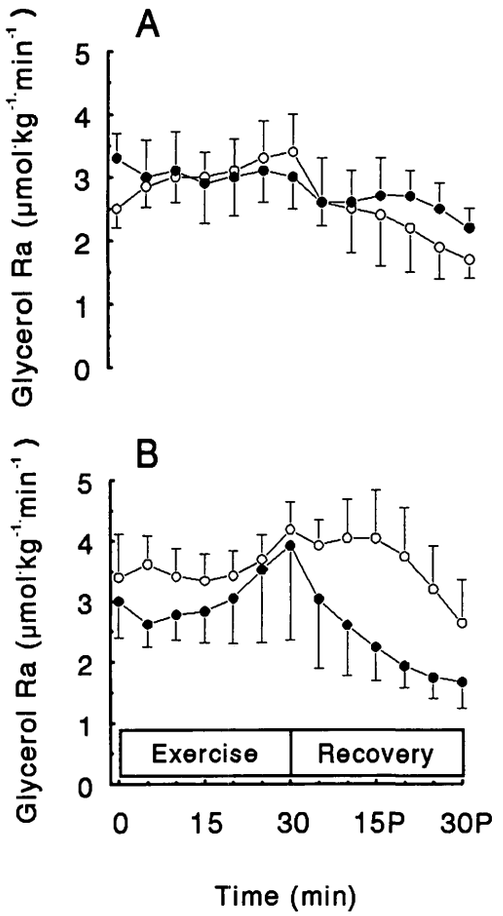

FIG 6. Glycerol release (R_a) at rest and during and after moderate-intensity (*A*) and high-intensity (*B*) exercise in normal control subjects (●) and in patients with IDDM (○).

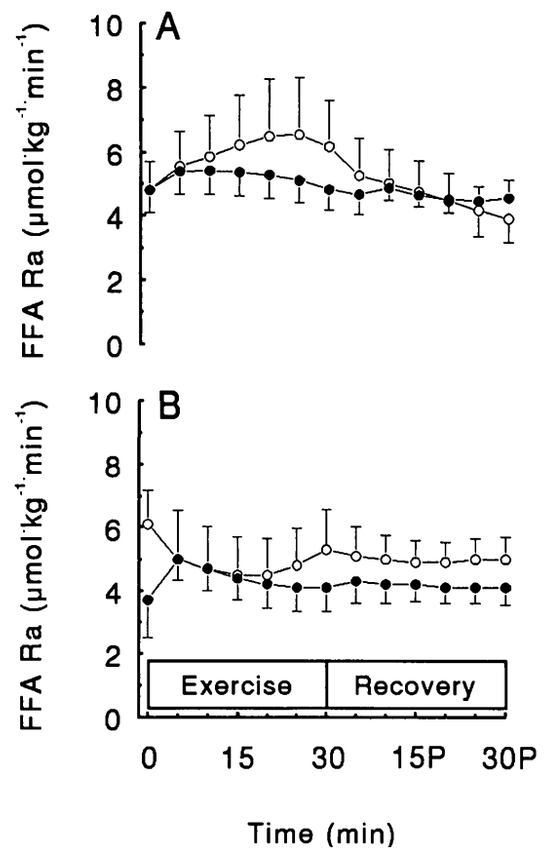

FIG 7. FFA release (R_a) at rest and during and after moderate-intensity (*A*) and high-intensity (*B*) exercise in normal control subjects (●) and in patients with IDDM (○).

tients can be considered clinically well controlled and their glucose utilization was not different from control values at rest, an impairment in glucose transport activation due to diabetes may become evident during a physiological stress such as exercise.

During intense exercise, glucose uptake increased in response to exercise to the same extent in diabetic patients and in control subjects. Thus, because the impairment in glucose uptake observed during moderate exercise was overcome during strenuous exercise at the same insulin level, this suggests that the impact of insulin in regulating glucose utilization depends on the intensity of exercise. This suggestion is consistent with evidence that there are two separate pools of glucose transporters in muscle: one sensitive to insulin and the other one to exercise (32). It is possible that during moderate-intensity exercise, glucose transporters are recruited from both pools. Because glucose transporter recruitment may be reduced in patients with IDDM, as discussed above, the impairment of glucose uptake during moderate-intensity exercise could be due to a deficiency in the insulin-sensitive pool. By increasing the exercise intensity, muscle contraction may become the predominant determinant of the stimulation of glucose uptake, and this may not be impaired in the diabetic patient.

Another interpretation of these data could be that glucose transport is the rate-limiting step for glucose uptake during moderate exercise, and this would explain why diabetic patients had a lower glucose R_d during moderate-intensity exercise. During intense exercise, however, a higher glycogenolytic rate may result in an intracellular accumulation of glucose-6-phosphate, with an inhibitory effect on hexokinase (33). Presumably, in this case glucose phosphorylation would be the rate-limiting step in both diabetic patients and control subjects.

It has been previously demonstrated that high plasma FFA concentrations can affect glucose utilization by exercising muscle (34–36), and it is known that insulin-deficient IDDM patients have an enhanced lipolytic response to catecholamines during exercise (8). However, in our study plasma FFA concentration did not differ between the two groups; also, no differences occurred in FFA or glycerol turnover. Thus, differences in plasma lipid kinetics between control subjects and diabetic patients during exercise cannot explain the differences in glucose metabolism.

Although we did not observe any differences in lipolysis, total fat oxidation was higher in diabetic patients during moderate exercise. It might be that according to the FFA-glucose cycle proposed by Randle et al. (37), increased FFA oxidation restrains glucose uptake. This could explain why during high-intensity exercise, when fat oxidation was dramatically reduced, glucose uptake was no longer different between the groups. However, studies of diabetic dogs without or with subbasal insulin replacement demonstrated that inhibition of FFA oxidation with methylpalmoxirate causes an improvement, but not a normalization, of glucose uptake during moderate exercise (27,28).

Glucose production matched glucose uptake in both groups on both days. Because hepatic glucose output is very

TABLE 2
Substrate oxidation

	Rest	10 min	20 min	30 min
Moderate exercise				
Carbohydrate oxidation ($\mu mol \cdot min^{-1} \cdot kg^{-1}$)				
Control	17.8 ± 3.8	100.6 ± 16.7	90.4 ± 11.5	87.5 ± 10.6
IDDM	12.2 ± 1.6	82.4 ± 12.8	81.6 ± 10.3	71.0 ± 7.2
Lipid oxidation ($\mu mol \cdot min^{-1} \cdot kg^{-1}$)				
Control	3.1 ± 0.7	8.4 ± 2.1	10.3 ± 1.3	10.4 ± 1.6
IDDM	5.6 ± 0.5*	12.4 ± 1.1	12.9 ± 1.2	16.9 ± 1.1*
Intense exercise				
Carbohydrate oxidation ($\mu mol \cdot min^{-1} \cdot kg^{-1}$)				
Control	14.4 ± 5.6	208.9 ± 2.2	184.6 ± 8.8	186.8 ± 3.8
IDDM	12.1 ± 3.5	224.3 ± 30.8	221.7 ± 32.7	217.1 ± 32.5
Lipid oxidation ($\mu mol \cdot min^{-1} \cdot kg^{-1}$)				
Control	5.0 ± 1.9	6.3 ± 3.6	10.1 ± 1.5	9.5 ± 2.4
IDDM	6.3 ± 1.5	6.9 ± 4.0	8.7 ± 4.8	9.9 ± 4.4

Data are means ± SE for seven subjects per group during moderate exercise and four subjects per group during intense exercise. *Significantly higher than control subjects ($P < 0.05$).

sensitive to the suppressive effect of insulin (38) and, as recently shown, systemic rather than intraportal concentrations of insulin mediate hepatic glucose output (39), it is possible that the lower R_a observed in the diabetic patients during moderate-intensity exercise was due to their higher insulin concentration.

During high-intensity exercise, glucose production reached the same values in both groups, even though the free insulin concentration in diabetic patients was higher than in control subjects and was not different from the moderate exercise trial. It is possible that the catecholamines, which were similar in control and diabetic subjects, became the predominant stimulator of glucose production during high-intensity exercise.

It previously has been proposed that the enzyme pyruvate dehydrogenase (PDH) is inhibited in diabetic patients (40). Because this enzyme catalyzes the entry of pyruvate into the tricarboxylic acid cycle, thereby linking glycolysis and glucose oxidation, the lower glucose oxidation in the diabetic patients is consistent with the notion of impaired PDH

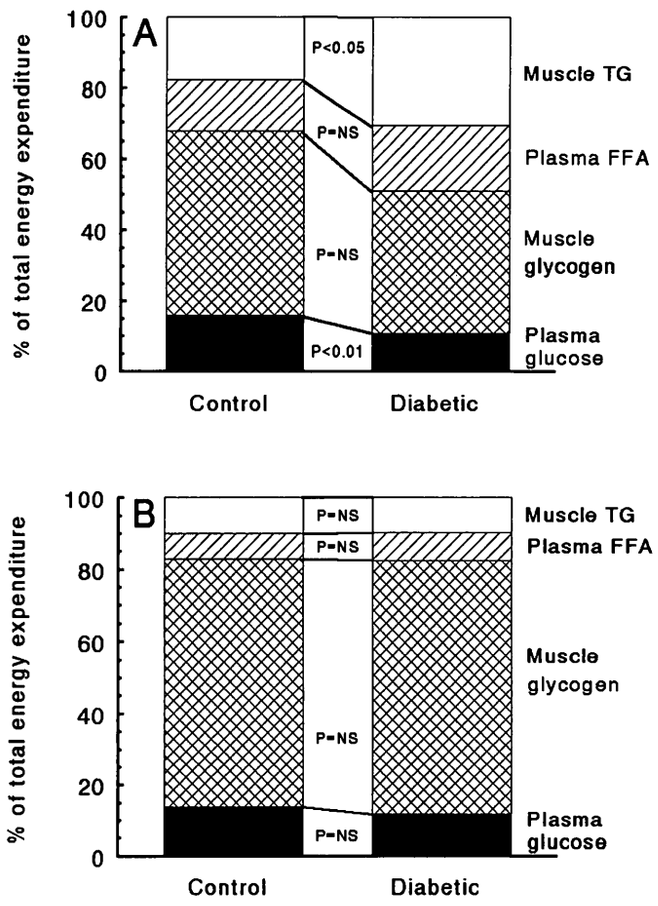

FIG 8. Estimated rates of substrate oxidation during the last 10 min of moderate-intensity (*A*) and high-intensity (*B*) exercise in normal control subjects and in patients with IDDM.

TABLE 3
Plasma hormone concentrations

	Rest	Exercise	Recovery
Moderate exercise			
Glucagon (ng/l)			
Control	230 ± 70	240 ± 60	190 ± 50
IDDM	170 ± 30	170 ± 40	140 ± 40
Insulin (pmol/l)			
Control	45 ± 15	25 ± 10	20 ± 5
IDDM	55 ± 5	65 ± 5*	65 ± 10*
Norepinephrine (nmol/l)			
Control	1.91 ± 0.39	3.40 ± 0.55	1.52 ± 0.27
IDDM	2.03 ± 0.56	3.32 ± 0.53	1.48 ± 0.28
Epinephrine (pmol/l)			
Control	280 ± 40	530 ± 30	280 ± 30
IDDM	300 ± 70	580 ± 120	350 ± 80
Intense exercise			
Glucagon (ng/l)			
Control	240 ± 50	280 ± 40	240 ± 50
IDDM	140 ± 20	170 ± 20	140 ± 30
Insulin (pmol/l)			
Control	50 ± 20	25 ± 15	15 ± 10
IDDM	75 ± 5	65 ± 20*	85 ± 15*
Norepinephrine (nmol/l)			
Control	3.09 ± 0.29	12.90 ± 2.32	2.44 ± 0.53
IDDM	2.02 ± 0.39	14.70 ± 1.32	2.09 ± 0.25
Epinephrine (pmol/l)			
Control	390 ± 60	1280 ± 400	330 ± 40
IDDM	330 ± 80	1330 ± 300	330 ± 50

Data are means ± SE for seven subjects per group during moderate exercise and four subjects per group during intense exercise. *Significantly higher than control subjects ($P < 0.05$).

activity. However, decreased PDH activity would cause a higher proportion of pyruvate to be converted to lactate, yet in the diabetic patients the lactate concentration was also lower. Thus, it seems likely that the lower carbohydrate utilization in diabetic patients was due to a reduced availability of glucose for oxidation by muscle. Consistent with this interpretation, the supply of glucose from plasma (i.e., glucose R_d) was reduced in diabetic group, as discussed above. We did not measure muscle glycogen content, but it is known that it is lower in patients with IDDM to an extent dependent on their metabolic control (3,41,42). Furthermore, during exercise, the rate of glycogenolysis correlates strongly with the resting glycogen concentration (41). Consistent with this interpretation, we found that muscle glycogen utilization, as calculated as the difference between total carbohydrate oxidation and glucose R_d, tended to be lower (although not significantly) in the diabetic group. During moderate-intensity exercise, it appeared that the diabetic patients compensated for the impairment of carbohydrate utilization by relying more on intramuscular fat oxidation.

In conclusion, glucose uptake is impaired during moderate exercise in patients with IDDM. During more intense exercise, glucose utilization in diabetic patients is not different from control values, presumably reflecting a greater importance of muscle contraction in stimulating glucose uptake. A higher rate of fat oxidation in diabetic patients compensates for the decreased availability of glucose during moderate-intensity exercise. This higher rate of fat oxidation is due to a greater reliance on intramuscular fat stores rather than to a change in the availability of plasma FFA.

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