Athletes With IDDM Exhibit Impaired Metabolic Control and Increased Lipid Utilization With No Increase in Insulin Sensitivity

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Physical exercise is traditionally recommended to diabetic patients as part of their treatment. Although healthy athletes exhibit enhanced skeletal muscle insulin sensitivity, the metabolic effects of vigorous training in patients with insulin-dependent diabetes mellitus (IDDM) are not known. This study was designed to examine the effects of competitive sports on fuel homeostasis and insulin sensitivity in athletes with IDDM. We studied 11 athletes and 12 matched sedentary men with IDDM. In each subject, we measured glycemic control, insulin-stimulated glucose uptake in the whole body and forearm, rates of glucose and lipid oxidation, and muscle glycogen, glycogen synthase, and glucose transport protein (GLUT4) concentrations. The athletes had higher Vo_{2max} (52 ± 1 vs. 42 ± 1 ml · kg^{-1} · min^{-1}, $P < 0.001$) and HbA_{1c} levels (8.4 ± 0.4 vs. $7.2 \pm 0.2\%$, $P < 0.05$) than sedentary patients, but took smaller insulin doses (41 ± 3 vs. 53 ± 3 U/day, $P < 0.05$). The insulin-stimulated rates of whole-body and forearm glucose uptake and glucose oxidation were similar in the two groups, whereas both energy expenditure and lipid oxidation were increased in the athletes. Lipid oxidation correlated inversely with glycogen synthase activity. The mean glucose arterialized venous blood–deep venous blood (A-V) difference during the insulin infusion (60–240 min) correlated with the whole-body glucose disposal throughout the insulin infusion (after 60 min, $r > 0.73$, $P < 0.001$ for all 30-min periods). This association is accounted for by the relationship between glucose A-V difference and nonoxidative glucose disposal. Muscle glycogen and GLUT4 protein contents were not different in the two groups. In conclusion, in athletes with IDDM: *1*) competitive exercise performed at variable schedules and intensities leads to a decrease in required insulin dose, impairment of metabolic control, and increase in lipid utilization; *2*) insulin sensitivity is not enhanced; and *3*) glucose A-V difference, not blood flow, is the major determinant of body sensitivity to insulin. Thus, more intense glucose monitoring and education may be required for the maintenance of good control in patients with IDDM involved in competitive sports. *Diabetes* 44:471–477, 1995

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A-V, arterialized venous blood–deep venous blood; FFA, free fatty acid; G-6-P, glucose-6-phosphate; HDL, high-density lipoprotein; IDDM, insulin-dependent diabetes mellitus; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; SDS, sodium dodecyl sulfate; SSC, sodium chloride–sodium citrate; SSPE, saline–sodium phosphate–EDTA buffer; UDP, uridine diphosphate.

Regular exercise is recommended to diabetic patients as one of the cornerstones in their treatment in addition to diet and insulin or oral antidiabetic drugs (1). A physical training program, performed in a controlled manner, enhances body sensitivity to insulin in patients with insulin-dependent diabetes mellitus (IDDM) who have not previously engaged in physical training (2) and in those with non-insulin-dependent diabetes mellitus (NIDDM) (3) as it does in healthy subjects (4). Cross-sectional studies in healthy athletes have found that insulin sensitivity is increased and is proportional to their physical fitness (5,6). The improvement in insulin action in healthy athletes can be mediated by several factors such as enhanced muscle blood flow (5), increased concentrations of muscle glucose transport protein (GLUT4) (5,6), elevated activity of muscle glycogen synthase (7), or shift in the body composition from an adipose to a muscular type (8).

We are not aware of any cross-sectional studies of insulin sensitivity or metabolic control in athletes with IDDM. Because moderate physical training performed in a controlled experimental setting by patients with IDDM has not improved glycemic control in patients with IDDM (9), though it has in patients with NIDDM (10), it is possible that irregular and strenuous exercise such as that associated with competitive sports may even worsen the control in insulin-treated patients. In addition, competitive elite-class sports require a lot of traveling, which may further complicate the maintenance of good control (11). Since poor control decreases insulin sensitivity (12), this may counterbalance the possible beneficial effects of physical training on insulin sensitivity.

Our present study was performed to compare metabolic control and body sensitivity to insulin in athletes and sedentary patients with IDDM. In addition, we examined various factors such as blood flow, rates of glucose and lipid oxidation, glucose storage, and muscle glucose transport protein concentration, all involved in the regulation of glucose and lipid homeostasis in the resting state and during physical exercise.

RESEARCH DESIGN AND METHODS

Eleven athletes and 12 sedentary patients with IDDM participated in the study. The characteristics of the two groups are given in Table 1. Of the athletes, three were cross-country skiers, two were runners, one was a cyclist, one played ice hockey, one played tennis, two were badminton players, and one was an ice surfer. Some of the athletes were competitive at the international level. They performed both aerobic and

anaerobic training three to five times per week, 1–2 h at a time. Patients in the sedentary control group did not participate in regular physical training. Fifteen of the patients (seven athletes and eight sedentary patients) were C-peptide–negative and the remaining eight (four athletes and four sedentary patients) had detectable, but low, C-peptide concentrations (mean 0.14 ± 0.02, range 0.06–0.21 nmol/l). None of them had clinical or other signs of neuropathy, proliferative retinopathy, or microalbuminuria, and none of the patients was using any medication except insulin. Home blood glucose monitoring was done by all of the patients on an irregular basis, with an average of two to four determinations per week. The purpose, nature, and possible risks of the study were explained to all subjects before informed consent was obtained. The study protocol was approved by the Ethical Committee of the Helsinki University Hospital.

We performed a 240-min euglycemic insulin clamp in each subject. Indirect calorimetry, forearm blood flow, and glucose disposal were determined throughout the study, and muscle biopsies were performed before and at the end of the clamp. The following measurements were made: whole-body total, oxidative, and nonoxidative glucose disposal, rate of lipid oxidation and basal metabolism, and muscle blood flow and glucose disposal in the forearm. In biopsy specimens from musculus quadriceps femoralis lateralis, we determined glycogen and glycogen synthase and its mRNA. From the baseline samples only, we measured glucose transport protein (GLUT4) and its mRNA concentration. In addition, we determined maximal aerobic power in each subject 1–2 weeks after the clamp study.

Maximal aerobic power. Maximal aerobic power (Vo_{2max}) of the patients was determined using a work-conducted upright exercise test with an electrically braked cycle ergometer (Bosch ERG 220, Berlin, Germany) combined with continuous analysis of expiratory gases and minute ventilation (EOS-Sprint, Jaeger, Wuertzburg, Germany). After a 10-min rest, the exercise was started with a work load of 50 W. The work load was then increased stepwise by 50 W every 3 min until the subject reached exhaustion (grade 19–20/20 according to the Borg scale of perceived exertion) (5,13).

Whole-body glucose disposal. Whole-body insulin-stimulated glucose disposal, or insulin sensitivity, was determined using the euglycemic insulin clamp technique, as previously described (4,5,14). The subjects were asked not to perform any training for 2 days or any heavy exercise for 4 days before the study and to ingest 250–300 g carbohydrate per day for at least 3 days. On the evening before the study, the patients adjusted their insulin dose to avoid hypoglycemia during the night and to achieve a fasting glucose concentration between 8 and 10 mmol/l. None of the patients had hypoglycemic symptoms during the 2 days before the study. At 8:00 A.M. after the patients had undergone an overnight fast, three catheters were inserted: one in an antecubital vein for the infusion of insulin and glucose, one in an ipsilateral antecubital deep vein for blood sampling and blood flow determinations, and the third into a heated (60°C) hand vein for the sampling of arterialized blood. Insulin (Actrapid Human, Novo Nordisk, Copenhagen, Denmark) was infused in a primed continuous rate (9 nmol[1.5 mU] · kg^{-1} · min^{-1}) for 240 min. Although insulin action is determined only at a single insulin concentration, the rate of glucose uptake is called insulin sensitivity. Plasma glucose was adjusted to and maintained at a euglycemic level with 20% glucose infused at a variable rate based on plasma glucose determinations from the arterialized blood at 5- to 10-min intervals. Because the fasting glucose concentration was elevated in the athletic and sedentary patients (see RESULTS), it was allowed to decrease to the normal level (5 mmol/l) before the glucose infusion was started. The period of infusion of insulin alone was 48 ± 12 min in the athletes and 48 ± 7 min in the sedentary patients. The rate of glucose disposal is calculated during the last hour of the insulin infusion in both groups. Since hepatic glucose production is totally suppressed with even lower insulin infusion rates than used here (15), the glucose infusion rate corrected for changes in plasma glucose concentration equals the rate of glucose disposal.

Rates of glucose and lipid oxidation and basal metabolism. Glucose and lipid oxidation and energy expenditure were determined with indirect calorimetry (Deltatrac Metabolic Monitor, Datex, Helsinki) in the basal state and three times during the insulin clamp study (Fig. 1), as previously described from our laboratory (5,16). The constants to calculate glucose and lipid oxidation from respiratory exchange data have been given previously (17). The rates of glucose and lipid oxidation are calculated during the last hour of the insulin infusion in both groups. Nonoxidative glucose disposal (storage) is defined as the difference between total and oxidative glucose disposal.

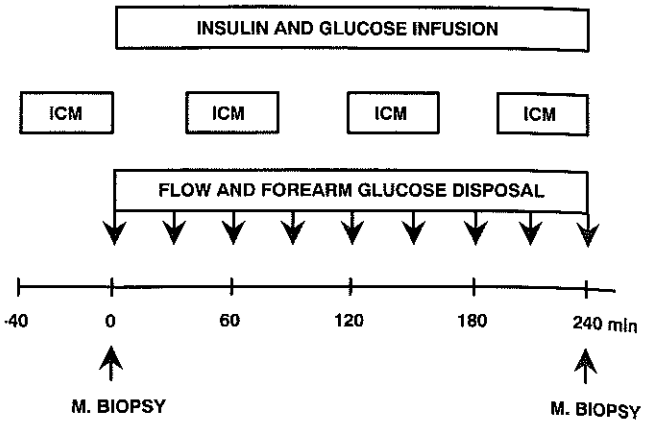

FIG. 1. Design of the study. In each subject, we performed a 240-min euglycemic insulin clamp with indirect calorimetry (ICM) and determined forearm blood flow and glucose uptake (arrows). A muscle sample (musculus quadriceps femoralis lateralis) was taken before and at the end of insulin infusion.

Forearm blood flow. Forearm blood flow was determined by capacitance plethysmography (model 2560, UFI, Morro Bay, CA) as previously described (16). Briefly, hand blood flow was first excluded with high (250 mmHg) pressure. Thereafter, forearm venous flow was excluded, and at the start of a rise in voltage on the recorder chart, blood was drawn into the syringe through a catheter inserted retrogradely into a deep vein. Blood was drawn at a rate that prevented any further change in voltage. Thus, the rate at which blood was drawn into the syringe equaled the rate of arterial blood flow into the arm. After ~10 ml of blood was drawn, the determination was discontinued and both the hand flow and forearm venous flow were released. Forearm volume was determined by water displacement. Because of problems with small veins in 1 sedentary patient, flow was determined only in 11.

Forearm glucose disposal. Forearm glucose uptake (μmol · 100 ml forearm^{-1} · min^{-1}) was determined by multiplying total forearm blood flow (ml · 100 ml forearm^{-1} · min^{-1}) by the arterialized venous blood–deep venous blood (A-V) difference (mmol/l) for glucose as determined from a single pair of blood samples taken at 30-min intervals as previously described (5,16). Hand blood flow was excluded before the blood sample from the deep vein was obtained.

Muscle biopsies. Fifteen minutes before and at the end of the 240-min insulin clamp study, a percutaneous muscle biopsy (100–150 mg) was performed with a Bergström needle under local anesthesia (1% lidocaine). The samples were obtained from musculus quadriceps femoralis lateralis from opposite sites before and after the study. The specimen was removed from the muscle with suction by a syringe attached to the needle, and the needle was immediately emptied into liquid N_2. The specimens were stored in liquid N_2 until analyzed. Muscle biopsies were taken from seven athletes and eight control patients.

Quantitation of mRNAs. Total tissue RNA was extracted from frozen muscle samples by standard methods (5,18). After the integrity of the RNA preparation was determined on minigels (5), aliquots of total RNA (5.0 and 10.0 μg) were dotted onto two nylon membranes and prehybridized. One was hybridized with freshly synthesized human glycogen synthase ^{32}P-cRNA (19), the other with human GLUT4 ^{32}P-cRNA probes (5×10^6 cpm/ml) for 18 h at 60°C in 50% formamide, 5 × saline–sodium phosphate–EDTA buffer (SSPE = 0.75 mol/l NaCl, 50 mmol/l Na_2PO_4, and 5 mmol/l EDTA), 3 × Denhardt's solution, and 0.1% sodium dodecyl sulfate (SDS). After the blots were washed in 0.1 × sodium chloride–sodium citrate (SSC = 0.15 mol/l sodium chloride, 0.015 mol/l sodium citrate, pH 7.0) and 0.1% SDS at 65°C, the dots were visualized by autoradiography with Fuji Rx film. The amount of glycogen synthase and GLUT4 mRNA present in each sample dot was measured by densitometric analysis (20).

Immunoblotting. The GLUT4 protein content was determined by quantitative Western blotting as previously reported (5). Briefly, muscle was homogenized, and aliquots containing 50 μg of protein were subjected to SDS-polyacrylamide gel electrophoresis. Protein was then electrophoretically transferred to nitrocellulose paper. It was subsequently blocked with 5% powdered milk and incubated with a polyclonal antibody specific for the COOH terminus of the GLUT4 protein (F349) and, after washing, with ^{125}I-labeled donkey anti-rabbit IgG antibody (Amersham, Arlington Heights, IL). Quantitation was performed by

TABLE 1
Clinical characteristics of athletes and sedentary patients with IDDM

	Athletes	Sedentary patients
Age (years)	28 ± 2	30 ± 2
Body weight (kg)	71 ± 3	74 ± 2
Body mass index (kg/m^2)	22 ± 1	24 ± 1
Vo_{2max} (ml · kg^{-1} · min^{-1})	52 ± 1*	42 ± 1
Body fat (%)	7.7 ± 0.4†	11.3 ± 1.2
Duration of diabetes (years)	11 ± 1	16 ± 2
Insulin dose (U/day)	41 ± 3†	53 ± 3
HbA_{1c} (%)	8.4 ± 0.4†	7.2 ± 0.2

Data are means ± SE. *$P < 0.001$. †$P < 0.05$.

generation of autoradiographs and performance of densitometry against a gray-scale standard using standard software (Image 1.32f, National Technical Information Service, Springfield, VA).

Muscle glycogen and glycogen synthase. Muscle glycogen and glycogen synthase assays were done as previously described (5,16). The samples were freeze-dried and dissected free from connective tissue and blood. Approximately 10 mg of muscle was powdered, weighed, and used for glycogen determination. Muscle powder was extracted with KOH and neutralized, glycogen was hydrolyzed with amyloglucosidase, and the liberated glucose was analyzed with the glucose oxidase method. Glycogen concentration is expressed as millimoles per kilogram of dry muscle (16). Glycogen synthase activity was measured by a fluorometric method as described previously (21). This method determines the production of uridine diphosphate (UDP) from the incorporation of UDP-glucose into glycogen. Samples and blanks were incubated for 15 min at 37°C with 0, 0.1, and 10 mmol/l glucose-6-phosphate (G-6-P). The assay was linear for the homogenate protein concentration, which was determined according to Lowry et al. (22). The enzyme activity determined at 0.1 mmol/l G-6-P is called glycogen synthase activity, the concentration at 10 mmol/l G-6-P is called total glycogen synthase activity, and the ratio of the two (0.1:10 mmol/l G-6-P) is called glycogen synthase fractional activity.

Other determinations. Glucose in the plasma and glycogen assays was determined with a glucose oxidase method using a Beckman glucose analyzer (Fullerton, CA). Free fatty acid (FFA) concentrations in serum were determined by using the fluorometric method of Miles et al. (23). Serum insulin was measured by a double-antibody radioimmunoassay (Pharmacia, Uppsala, Sweden) (24). Serum C-peptide concentration was determined with a radioimmunoassay (25). Total serum cholesterol, serum high-density lipoprotein (HDL) cholesterol, and serum triglyceride concentrations were measured before the insulin infusion. Serum cholesterol concentration was determined enzymatically (26) after very low-density lipoprotein and low-density lipoprotein (LDL) were precipitated (27). Serum LDL cholesterol was calculated using the Friedewald formula (28), and serum triglyceride concentration was measured enzymatically (29). The estimation of body fat was calculated by summing up six skinfold measurements from triceps, subscapular, pectoral, umbilical, suprailiac, and thigh regions, and 8 mm was subtracted to correct for the nonadipose content of the skinfolds. The fat percentage was calculated from the equation: percentage fat = 11.5453 × corrected skinfold/total body wt − 0.2838 (30).

Statistical analysis. Comparison between the groups was done with Mann-Whitney's two-sample rank sum test. Wilcoxon-Pratt's test was used in the calculations between paired items. The correlation analysis was done with Spearman's test. P values <0.05 were considered significant. The results are given as means ± SE.

RESULTS

Vo_{2max} body composition, glycemic control, and insulin requirements. In the athletic patients, Vo_{2max} was greater and body fat percentage was lower than in the sedentary patients (Table 1). In addition, glycemic control, as estimated by HbA_{1c} level, was worse and insulin dose requirements were smaller for the athletes than for the sedentary patients (Table 1).

Whole-body glucose disposal. In the fasting state, plasma glucose (9.8 ± 1.1 vs. 9.5 ± 0.7 mmol/l), serum insulin (37.0 ± 4.8 vs. 38.7 ± 2.7 pmol/l), and glucose oxidation rate (6.4 ± 0.9 vs. 5.4 ± 0.7 μmol · kg^{-1} · min^{-1}) were not different in the athletes and control patients (respectively). During hyperinsulinemia, steady-state plasma glucose (5.6 ± 0.3 vs. 5.4 ± 0.1 mmol/l) and insulin concentrations (578.0 ± 29.8 vs. 642.3 ± 40.5 pmol/l) were not different in the athletes and the control subjects. The total glucose disposal rate was nearly identical in the athletes (44.1 ± 3.3 μmol · kg^{-1} · min^{-1}) and the control patients (45.2 ± 2.2 μmol · kg^{-1} · min^{-1}) because of similar rates of nonoxidative (28.2 ± 3.2 vs. 27.7 ± 2.4 μmol · kg^{-1} · min^{-1}) and oxidative glucose disposal (15.9 ± 1.0 vs. 17.6 ± 0.9 μmol · kg^{-1} · min^{-1}) in the two groups. Also, when calculated per lean body mass, the values were similar in the athletes and control subjects (data not shown). Whole-body glucose disposal was inversely related to the daily insulin dosage (U/kg) ($r = -0.53$, $P < 0.01$). This is accounted for by the association between insulin dose and nonoxidative glucose disposal ($r = -0.47$, $P < 0.05$). There was no correlation between glucose disposal rate and HbA_{1c} ($r = 0.08$).

Lipid oxidation. In the fasting state, the lipid oxidation rate was similar in the athletes and control patients (1.21 ± 0.06 vs. 1.14 ± 0.06 mg · kg^{-1} · min^{-1}, respectively). During insulin infusion, lipid oxidation rate fell in both groups. Between 130 and 160 min of insulin infusion, it was 30% higher in the athletes than in the sedentary patients (0.87 ± 0.07 vs. 0.61 ± 0.07 mg · kg^{-1} · min^{-1}, $P < 0.05$), and at the end of the study, the difference (0.63 ± 0.08 vs. 0.37 ± 0.07 mg · kg^{-1} · min^{-1}) was of borderline significance ($P = 0.06$).

Energy expenditure. The basal metabolic rate tended to be higher in the athletes than in the sedentary patients (26.5 ± 0.6 vs. 24.7 ± 0.5 kcal · kg^{-1} · 24 h^{-1}). This difference was not statistically significant, however. During insulin infusion, the energy expenditure was higher in the athletes than in the sedentary patients both between 50 and 80 min (28.3 ± 0.7 vs. 25.4 ± 0.6 kcal · kg^{-1} · 24 h^{-1}, $P < 0.02$) and between 130 and 160 min (27.9 ± 0.6 vs. 25.8 ± 0.6 kcal · kg^{-1} · 24 h^{-1}, $P < 0.05$). At the end of insulin infusion, the metabolic rate had increased significantly in the control patients to 26.1 ± 0.5 kcal · kg^{-1} · 24 h^{-1} ($P < 0.01$ vs. basal), but remained unchanged in the athletes. The basal metabolic rate was positively associated with basal lipid oxidation ($r = 0.58$, $P < 0.01$).

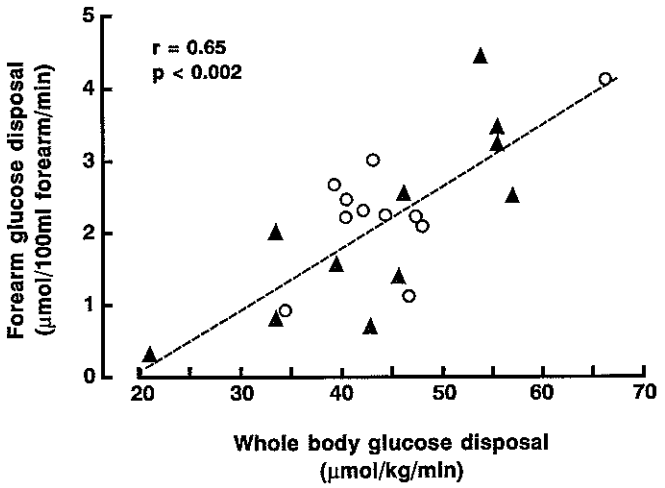

FIG. 2. Correlation between whole-body glucose disposal and forearm glucose disposal during the last hour of the study in athletes (▲) and sedentary patients (○) with IDDM.

TABLE 2
Glycogen synthase activity and its mRNA as determined in musculus quadriceps femoris in the athletes and control subjects in the basal state and after 240 min of hyperinsulinemia

	Basal		Hyperinsulinemia	
	Control subjects	Athletes	Control subjects	Athletes
Glycogen synthase activity (nmol · min^{-1} · mg protein^{-1})				
G-6-P				
0.0 mmol/l	9.4 ± 0.8	13.8 ± 1.1*	16.6 ± 1.8	17.0 ± 1.3
0.1	18.6 ± 1.6	26.2 ± 1.3†	29.9 ± 2.3‡	26.0 ± 2.7
10.0	31.4 ± 1.7	39.7 ± 2.6†	39.1 ± 3.2	38.9 ± 1.8
Fractional activity	0.59 ± 0.03	0.68 ± 0.06	0.77 ± 0.03	0.66 ± 0.06
Glycogen synthase mRNA (pg/μg RNA)	0.68 ± 0.31	0.49 ± 0.06	0.54 ± 0.12	0.57 ± 0.04

Data are means ± SE. *$P < 0.01$ vs. control subjects. †$P < 0.05$ vs. control subjects. ‡$P < 0.05$ vs. basal.

Forearm blood flow and glucose disposal. The forearm blood flow was similar in the athletes and the control subjects both in the basal state (2.5 ± 0.3 vs. 2.6 ± 0.3 ml · 100 ml forearm^{-1} · min^{-1}, respectively) and at the end of the insulin infusion (2.9 ± 0.3 vs. 3.2 ± 0.3 ml · 100 ml forearm^{-1} · min^{-1}, respectively). The insulin infusion did not significantly change the flow in either group alone, but when the two groups were combined, the 20% increase in the blood flow (0.5 ± 0.2 ml·100 ml forearm^{-1} · min^{-1}) was significant ($P < 0.05$).

Plasma glucose A-V difference in the basal state was similar in the athletes (0.35 ± 0.04 mmol/l) and sedentary patients (0.29 ± 0.06 mmol/l). During insulin infusion, the mean glucose A-V difference increased by 2.6-fold in the athletes and by 3.2-fold in the sedentary patients ($P < 0.01$ in both) with no difference between the two groups (0.91 ± 0.16 vs. 0.94 ± 0.14 mmol/l). Thus, the mean forearm glucose uptake (flow × glucose A-V difference) during insulin infusion (60–240 min) was equal in the athletes (2.5 ± 0.5 μmol^{-1} · 100 ml forearm^{-1} · min^{-1}) and sedentary patients (2.5 ± 0.3 μmol · 100 ml forearm^{-1} · min^{-1}). Forearm and whole-body glucose disposal rates were closely related (Fig. 2). Forearm blood flow and glucose A-V difference were inversely related during insulin infusion in the whole group ($r = -0.33$, $P < 0.001$) when calculated at 30-min periods from 60 to 240 min.

The mean A-V difference during the insulin infusion (60–240 min) correlated with the whole-body glucose disposal throughout the insulin infusion (after 60 min, $r > 0.73$, $P < 0.001$ for all 30-min periods) and at the end of the clamp study ($r = 0.76$, $P < 0.001$) (Fig. 3). This correlation was accounted for by the relationship between mean A-V difference and nonoxidative glucose disposal ($r = 0.63$–0.68, $P < 0.01$ for all) as determined during the three measurements with indirect calorimetry. The mean A-V difference was inversely related to daily insulin dose (U/kg) ($r = -0.54$, $P < 0.01$).

Muscle glycogen. In the basal state, muscle glycogen concentrations were virtually identical in the athletes and sedentary patients (340 ± 33 vs. 343 ± 20 mmol/kg dry wt, respectively). During the insulin infusion, glycogen content remained unchanged in the two groups (354 ± 29 vs. 343 ± 37 mmol/kg dry muscle).

Glycogen synthase. In the basal state, glycogen synthase activity was higher in the athletes than in the sedentary patients at all three G-6-P concentrations (Table 2). This difference disappeared during insulin infusion. The glycogen synthase activity in the basal state correlated with Vo_{2max} at both the 0.0 mmol/l ($r = 0.57$, $P < 0.05$) and 0.1 mmol/l G-6-P concentrations ($r = 0.54$, $P < 0.05$). Basal glycogen synthase fractional activity correlated with glucose storage as determined from 50 to 80 min of insulin infusion ($r = 0.53$, $P < 0.05$). In the muscle sample taken after the insulin infusion, the glycogen synthase fractional activity correlated with nonoxidative glucose disposal as measured from 130 to 160 min ($r = 0.56$, $P < 0.05$) and from 210 to 240 min ($r = 0.55$, $P < 0.05$) (Fig. 4) and also with the whole-body glucose disposal ($r = 0.54$, $P < 0.05$). The activity of glycogen synthase after insulin stimulus with or without different G-6-P concentrations correlated inversely with the preceding lipid oxidation rate during (130–160 min) insulin infusion (Fig. 5). The insulin-induced rise in glycogen synthase activity at 0.1 mmol/l G-6-P was significantly higher in sedentary control subjects compared with the athletes ($P < 0.05$). The HbA_{1c} level was inversely related to the change in glycogen synthase activity at 0.1 mmol/l G-6-P during insulin infusion ($r = -0.56$, $P < 0.05$).

Glycogen synthase mRNA. The glycogen synthase mRNA concentration was similar in the athletes and control patients in the basal state and remained unchanged during insulin infusion in both groups (Table 2).

GLUT4 protein and mRNA. Basal muscle GLUT4 protein concentration was 21% greater in the athletes than in control subjects (638 ± 27 vs. 528 ± 34 densitometric units/mg protein). This difference was not significant ($P = 0.07$).

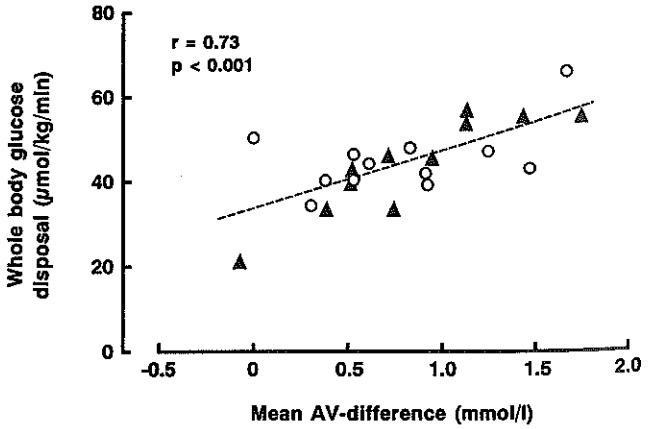

FIG. 3. Correlation between whole-body glucose disposal and the mean A-V glucose difference in the athletes (▲) and sedentary patients (○) with IDDM.

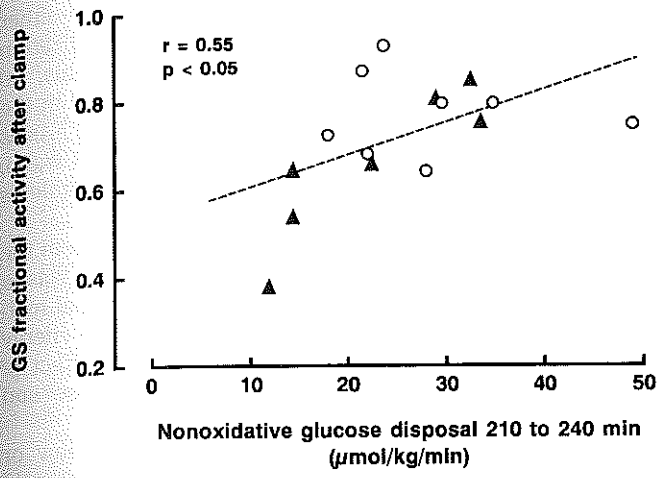

FIG. 4. Correlation between nonoxidative glucose disposal rate (210–240 min of insulin infusion) and muscle glycogen synthase (GS) fractional activity as determined at the end of insulin infusion. ▲, athletes; ○, sedentary patients.

GLUT4 mRNA concentration was similar in the athletes (113 ± 7 densitometric units/dot) and the control subjects (159 ± 20 densitometric units/dot).

FFAs. There were no differences in the FFA concentrations in the basal state between the athletes and control subjects (706 ± 131 vs. 753 ± 61 μmol/l, respectively). The values decreased rapidly after the initiation of insulin infusion and reached the nadir at the end of the study with no difference between the athletes and control subjects (104 ± 20 vs. 71 ± 7.4 μmol/l, respectively). The FFA level in the fasting state was related directly to the fasting glucose level ($r = 0.51$, $P < 0.05$). In addition, there were inverse relationships between the average (30–240 min) FFA concentration and whole-body glucose disposal ($r = -0.46$, $P < 0.05$), nonoxidative glucose disposal ($r = -0.44$, $P < 0.05$), and the mean (60–240 min) glucose A-V difference ($r = -0.57$, $P < 0.01$).

Lipids and lipoproteins. The mean fasting concentrations of total cholesterol (4.2 ± 0.2 vs. 3.7 ± 0.2 mmol/l), HDL cholesterol (1.2 ± 0.1 vs. 1.2 ± 0.1 mmol/l), LDL cholesterol (2.6 ± 0.2 vs. 2.2 ± 0.2 mmol/l), and triglycerides (0.68 ± 0.06 vs. 0.67 ± 0.05 mmol/l) were similar in the athletes and sedentary patients. The HDL cholesterol concentration was directly related to whole-body ($r = 0.48$, $P < 0.05$) and nonoxidative glucose disposal ($r = 0.43$, $P < 0.05$) and mean A-V difference ($r = 0.58$, $P < 0.01$).

DISCUSSION

The patients with IDDM examined in the current study were involved in competitive sports, some at the international level, and their high Vo_{2max} and low body fat percentage reflected their good physical fitness (8). However, the athletes had worse glycemic control and took a smaller insulin dose than did the sedentary patients. Some, but not all (31), previous studies have reported either a small decrease in insulin requirements during programmed daily physical training (2) or an inverse relationship between insulin dose and Vo_{2max} (32). The smaller insulin dose requirement in the athletes may be partly due to repeated acute exercise periods, but it may also be intentional to avoid hypoglycemia during the periods of training and competition. Consequently, the athletes had higher HbA_{1c} levels than the sedentary patients. The worse glycemic control may also be due

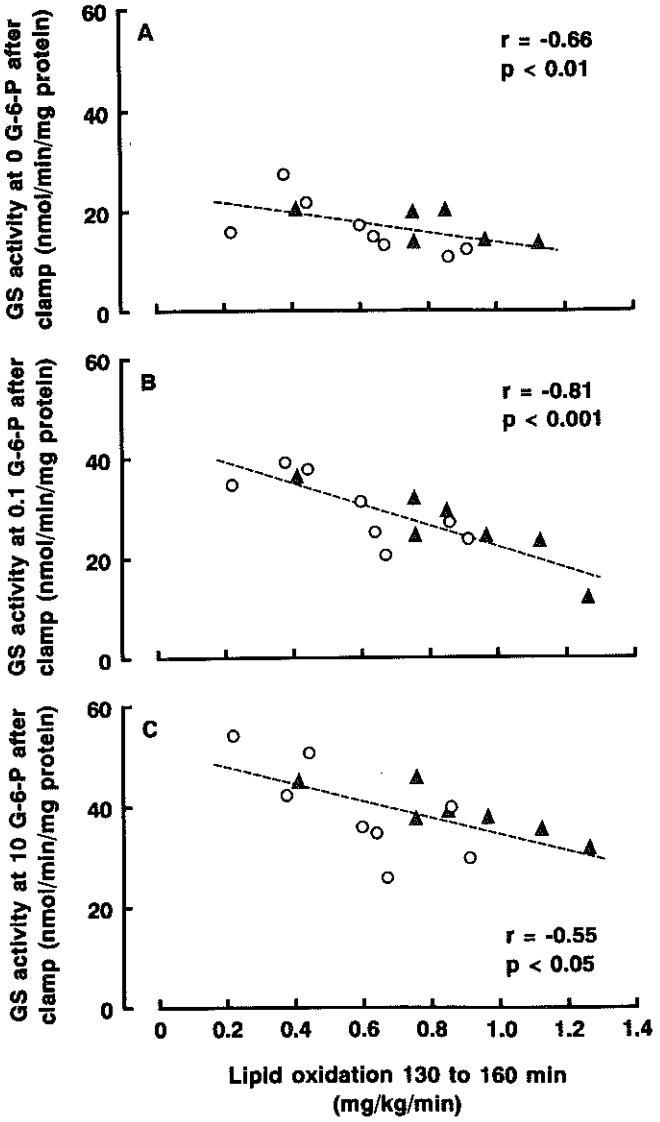

FIG. 5. Correlation between the rate of lipid oxidation and muscle glycogen synthase (GS) activity as determined after insulin stimulus in the absence (*A*) or presence of G-6-P at 0.1 mmol/l (*B*) or 1.0 mmol/l (*C*) concentrations. ▲, athletes; ○, sedentary patients.

partly to difficulties in maintaining a regular dietary schedule under conditions of irregular and vigorous sporting activities and frequent traveling (11) without intensive glucose monitoring. Thus, regarding the recommendations for physical exercise as a part of the treatment of IDDM (1), one should bear in mind that competitive sports may worsen rather than improve glycemic control. Intensive glucose monitoring and education, such as in the Diabetes Control and Complications Trial (33), should perhaps be used to help patients involved in competitive sports avoid impairment of metabolic control.

In contrast to the findings of several cross-sectional studies in healthy subjects (5) and longitudinal studies in both healthy individuals (4) and patients with IDDM (2,9), good physical fitness in our diabetic athletes was not associated with increased body sensitivity to insulin. Regarding the lack of increased insulin sensitivity in athletes with IDDM, at least four factors should be considered. First, in the current study we did not measure hepatic glucose production. However, the insulin infusion rate used has previously completely

suppressed hepatic glucose production (15). Furthermore the A-V difference, which is dependent on both infused and endogenously derived glucose, was closely correlated with the amount of glucose infused. These data support the view that hepatic glucose production was totally suppressed in our patients and that no difference in hepatic glucose production contributed to the results.

Second, hyperglycemia causes insulin resistance in patients with IDDM (12). However, the fasting blood glucose concentrations were similar in the athletes and sedentary subjects on the day of the study, and there was no correlation between glycosylated hemoglobin level and glucose disposal rate. Previous hypoglycemia may also lead to insulin resistance (34). None of our patients had hypoglycemic episodes within at least 2 days before the study. Thus, neither hyperglycemia nor preceding hypoglycemia can explain the lack of increased insulin sensitivity in the athletes.

Third, several studies in subjects with increased (5), normal (35), or decreased insulin sensitivity (36) have shown the importance of blood flow as a determinant of body sensitivity to insulin. In our current study, there was no difference in the blood flow between diabetic athletes and sedentary subjects in the basal state or during insulin infusion. The equal rate of forearm blood flow in the two groups is in keeping with similar insulin sensitivity in the two groups.

Fourth, in healthy athletes, we (5) and others (6) have demonstrated increased muscle GLUT4 protein to be a contributing mechanism for enhanced insulin sensitivity. In our diabetic patients, neither GLUT4 protein nor the mRNA concentration was significantly higher in the athletes than in the sedentary patients. Thus, not only glucose uptake rate but also the two local mechanisms of glucose disposal at the muscle site (blood flow and GLUT4 protein) were similar in the athletes and sedentary subjects with IDDM, in contrast to the observations in healthy subjects.

The only difference between the athletes and sedentary patients regarding cellular mechanisms of glucose metabolism was increased muscle glycogen synthase activity in the diabetic athletes in the basal state, as has been similarly reported in healthy athletes (5,7). Because muscle glycogen concentrations were similar in the two groups, the higher enzyme activity in the athletes was not caused by glycogen deficiency. The synthase activity correlated with Vo_{2max}, suggesting that it was a consequence of physical training. In healthy athletes, the nonoxidative glucose disposal rate was greater than in the sedentary subjects (5), whereas this difference was not observed between diabetic athletes and sedentary patients. It is thus possible that factors in diabetic athletes reduced the stimulatory effect of insulin on glucose utilization.

One such factor could be the use of lipids as an alternative fuel. The lipid oxidation rate was greater during hyperinsulinemia in the athletes and was inversely related to the glucose A-V difference, the rate of glucose storage, and the glycogen synthase activity. Although correlations do not prove causal relationships, these associations suggest that participation in competitive exercise increases the lipid oxidation rate in patients with IDDM. Augmented lipid oxidation may reduce glycogen synthase activity and glucose storage and thus decrease glucose utilization and worsen hyperglycemia. Since increased fat oxidation during hyperinsulinemia in our current study occurs in the face of normal serum FFA concentrations, the observation suggests either increased sensitivity to FFA oxidation, enhanced utilization of intracellular lipids, or both. In keeping with this, an increased capacity to oxidize fatty acids is observed in the muscle of exercise-trained rats (37). A greater use of FFAs as a fuel may prevent an increase in insulin sensitivity (38,39), which is observed after physical training in healthy athletes (5,6).

Energy expenditure was higher in the athletes than in the sedentary patients during insulin infusion. There was a positive correlation between lipid oxidation and basal metabolic rate in the basal state. Whether increased energy expenditure in athletes with IDDM is a long-term effect of training or a consequence of reduced insulin dose and associated metabolic changes is not known.

Although there was no difference in the blood flow or glucose A-V difference between athletic and sedentary patients, a close association was observed between the mean glucose A-V difference and the whole-body glucose disposal or glucose storage during insulin infusion. These data thus suggest that the A-V difference rather than blood flow closely reflects the rate of glucose uptake in patients with IDDM. It is not clear, however, whether the glucose A-V difference is a primary factor for glucose disposal, a consequence of concentration gradient between vascular and interstitial space, or a result of other intracellular factors. Regarding factors influencing glucose A-V difference itself, basal serum HDL cholesterol was directly related and the average (30–240 min) FFA concentration and daily insulin dose were inversely related. The relationship between serum HDL cholesterol and the glucose A-V difference is in accordance with the known relationship of low HDL levels and insulin resistance in healthy subjects (40).

Taken together, our data indicate that competitive exercise in athletes with IDDM leads to a decrease in required insulin dose, possibly to avoid hypoglycemic reactions. Relative insulin deficiency increases use of FFAs as a fuel, worsens hyperglycemia, and may prevent an improvement in insulin sensitivity. Our results also indicate that glucose A-V difference, not blood flow, is a major factor determining body sensitivity to insulin in patients with IDDM. Thus, our data suggest a need for more intensive therapy for the maintenance of good glycemic control in patients with IDDM involved in competitive sports. However, every effort should be made to facilitate the participation of IDDM patients in various types of sports, since regular exercise may even enhance the longevity of these patients (41).

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