Impact of Physical Fitness and Glycemic Control on In Vivo Insulin Action in Adolescents With IDDM

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The relationship of in vivo insulin-mediated glucose utilization to the state of physical fitness and the degree of glycemic control was examined in 27 adolescents with insulin-dependent diabetes mellitus (IDDM) compared with 10 nondiabetic adolescent control subjects. In vivo total-body insulin-mediated glucose metabolism was evaluated by the hyperinsulinemic-euglycemic clamp. Physical fitness was assessed by maximal oxygen consumption ($Vo_{2\ max}$) during cycle ergometry. Patients and control subjects had similar levels of $Vo_{2\ max}$ (34.9 ± 8.6 vs. 38.6 ± 9.9 ml · kg^{-1} · min^{-1}, $P = 0.3$). Patients had lower total-body insulin-mediated glucose metabolism compared with control subjects (33.9 ± 14.3 vs. 63.8 ± 17.2 μmol · kg^{-1} · min^{-1}, $P = 0.0002$). Among the patients, females had lower total-body insulin-mediated glucose metabolism compared with males (24.2 ± 2.8 vs. 40.7 ± 3.4 μmol · kg^{-1} · min^{-1}, $P < 0.001$); however, this difference disappeared after correcting for sex differences in fitness levels. Insulin-mediated glucose metabolism correlated with $Vo_{2\ max}$ in patients and control subjects ($r = 0.83$, $r = 0.81$, $P < 0.05$). The regression of total-body insulin-mediated glucose metabolism on $Vo_{2\ max}$ for patients was −2.84 ± 0.255 $Vo_{2\ max}$ and for control subjects was 7.12 ± 0.143 $Vo_{2\ max}$, indicating that for similar degrees of physical fitness patients have lower total body insulin-mediated glucose metabolism levels than control subjects. In patients, total-body insulin-mediated glucose metabolism correlated with the degree of glycemic control as assessed by the level of glycosylated hemoglobin ($r = -0.63$, $P < 0.001$). In a multiple regression analysis including $Vo_{2\ max}$ and glycosylated hemoglobin, the coefficient of determination explaining the variation in total-body insulin-mediated glucose metabolism was 73%. It is concluded that adolescents with IDDM are insulin resistant compared with healthy control subjects, and this resistance is attributable to the state of diabetes control. However, the level of physical fitness explains a major part of interindividual variation in insulin action in both control subjects and adolescents with IDDM. *Diabetes Care* **13:9–15, 1990**

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Insulin-dependent diabetes mellitus (IDDM) is generally regarded as a disease of insulin deficiency, whereas non-insulin-dependent diabetes mellitus is predominantly the result of insulin resistance. However, there is now considerable evidence that insulin resistance is also a feature of IDDM (1,2). In 1982 DeFronzo et al. (3,4), with the insulin-clamp technique, demonstrated that insulin-mediated glucose disposal was significantly diminished in adult patients with long-standing IDDM. Subsequent studies indicated that this diminished insulin-mediated glucose metabolism could be improved or normalized with institution of insulin therapy (5–9). Recently, it has been shown that insulin resistance is also present in adolescents with IDDM and is more pronounced during puberty (10). Whether the insulin resistance of IDDM in adolescents is the result of diabetes and puberty or is related to other factors is unclear.

Inactivity has long been shown to be a cause of glucose intolerance and insulin resistance in humans (11). Thus, our studies were undertaken to examine the relationship of in vivo insulin-mediated glucose utilization to physical fitness in adolescents with IDDM compared with healthy nondiabetic adolescent control subjects. In

addition, the roles of glycemic control and obesity were evaluated, each of these being factors we thought might have an influence on body sensitivity to insulin.

RESEARCH DESIGN AND METHODS

Twenty-seven patients (16 males, 11 females) with IDDM were recruited from patients who regularly attended the diabetes clinic at Children's Hospital of Pittsburgh. Mean age was 16.6 yr (range 12–19 yr), and mean duration of diabetes was 7.7 yr (range 3–18 yr). With the exception of 1 patient, all were beyond Tanner 1 pubertal stage. All patients were on once or twice daily intermediate-acting (lente or NPH) plus short-acting (regular) subcutaneous insulin injections, with a mean daily insulin dose of 1 U · kg^{-1} · day^{-1} (range 0.68–1.35 U · kg^{-1} · day^{-1}). Mean glycosylated hemoglobin (HbA_1) at the time of evaluation was 9.6% (range 7.2–12.6%). None of the patients had clinical or laboratory evidence of diabetic complications or other systemic diseases. Two patients had been on synthroid for autoimmune hypothyroidism and were euthyroid at the time of evaluation. Body mass index (BMI; calculated as weight (kg)/height (m^2) was 22.4 kg/m^2 (range 18–27 kg/m^2). Patients were compared with 10 healthy volunteers (6 females, 4 males) with a mean age of 14.3 yr (range 11–17 yr) and a mean BMI of 21.9 kg/m^2 (range 17–28 kg/m^2). Informed consent was obtained from participating subjects and their parents after a thorough explanation of all proposed procedures. The study protocol was approved by the Human Rights Committee of Children's Hospital of Pittsburgh. All subjects were admitted to the Clinical Research Center of Children's Hospital of Pittsburgh. During this time, patients and control subjects consumed a weight-maintaining diet containing 55% carbohydrate, 30% fat, and 15% protein. The following studies were performed during hospitalization.

In vivo glucose metabolism and insulin sensitivity were evaluated by the hyperinsulinemic-euglycemic clamp technique after an overnight fast (10–12 h) (12). Twenty-four hours before the clamp, all intermediate-acting insulins were discontinued. Patients received regular insulin subcutaneously before meals. The night before the clamp, overnight normoglycemia was achieved by a variable rate intravenous infusion of regular insulin with a Harvard pump, depending on frequent plasma glucose determinations. Overnight insulin infusion was discontinued 0.5 h before the clamp study was begun. For the clamp study, two intravenous catheters were inserted. One was placed in a vein on the forearm for administration of insulin and glucose. The second was placed into a vein on the dorsum of the contralateral hand for blood sampling. This hand was placed in a warmer box to arterialize the venous blood (13). A continuous infusion of Humulin regular insulin (Lilly, Indianapolis, IN) was infused at a constant rate of 1.7 mU · kg^{-1} · min^{-1} for 180 min to obtain plasma free insulin levels of ~718 pM. Plasma glucose was clamped at 5.6 mM by concomitant intravenous infusion of 10% glucose. The rate of glucose infusion was adjusted on the basis of plasma glucose determinations every 5 min at the bedside. In addition, blood was sampled every 15 min for determination of plasma free insulin.

Physical fitness was assessed by determining maximal oxygen consumption ($V_{O_2\ max}$) during progressive bicycle ergometry to exhaustion in the Cardiopulmonary Physiology Laboratory at Children's Hospital of Pittsburgh. The test was conducted 42 h before the clamp while patients received their usual daily insulin. Progressive exercise followed Godfrey's protocol (14) and consisted of cycle ergometry, beginning with unloaded pedaling and increasing the resistance each minute by increments based on body size (10 W for patients <125 cm, 15 W for patients between 125 and 150 cm, and 20 W for patients >150 cm in height). Minute ventilation, O_2 consumption, CO_2 production, and respiratory exchange ratio were determined each minute via a Medical Graphics 2001 metabolic cart. ECG was monitored continuously, and heart rate was determined each minute. Fitness was defined by the highest O_2 consumption attained with a respiratory exchange ratio >1.10 and a heart rate that approached 100% of age-predicted maximal heart rate (14). In two subjects, the test was inadequate.

Biochemical measurements. Plasma glucose was measured by the glucose oxidase method with a YSI glucose analyzer (Yellow Springs, OH). Plasma samples were treated with polyethylene glycol within minutes of withdrawal to precipitate antibody-bound insulin. The resultant supernatant was assayed for free immunoreactive insulin (15). The presence of insulin antibodies in patients' serum was determined as reported previously (16). HbA_1 was measured by column chromatography (Isolab, Akron, OH) after saline incubation at a temperature of 22 ± 0.5°C, the normal range being 4.4–7.3% (17).

During the hyperinsulinemic-euglycemic clamp under steady-state plasma glucose conditions, the amount of glucose infused was assumed to be equal to the amount of insulin-mediated glucose metabolism by the total body, because insulin at this dose level has been shown to inhibit hepatic glucose production by 95% in diabetic patients (3). The rate of glucose metabolism in milligrams per kilogram per minute was computed over the last 100 min of each clamp. To be precise in estimating the body's sensitivity to insulin, the ratio of insulin-mediated glucose metabolism to free immunoreactive insulin was computed to take into account slight variations in the plasma free-insulin levels that result from individual patient variation. This ratio is a measure of the quantity of glucose metabolized per unit plasma free-insulin concentration and thus a reasonable index of tissue sensitivity to insulin (12). For convenience of data expression, we multiplied the ratio of insulin-mediated glucose metabolism to free immunoreactive insulin by 100.

Statistical analyses. Standard statistical methods were used with Student's *t* test where applicable. Linear

regression and correlation coefficients were used to express bivariate relationships. Multiple regression analysis and partial correlation coefficients were applied to express multivariate relationships. Data are expressed as means ± SD except where otherwise indicated. Statistical significance was implied by $P \leq 0.05$.

RESULTS

During the hyperinsulinemic-euglycemic clamp, patients' mean steady-state plasma glucose concentration was 5.5 ± 0.1 mM with a coefficient of variation of 0.3 ± 0.1 mM mg/dl; their steady-state plasma free-insulin levels were 606 ± 134 pM. In control subjects, steady-state plasma glucose was 5.6 ± 0.1 mM with a coefficient of variation of 0.3 ± 0.1 mM, and plasma free-insulin was 736 ± 118 pM (Table 1). The steady-state plasma free-insulin level was significantly lower in patients than control subjects ($P = 0.01$). The plasma free-insulin level of patients correlated inversely with insulin-antibody levels ($r = -0.64$, $P < 0.001$), suggesting that some of the infused insulin became bound to insulin antibodies.

Total-body insulin-mediated glucose utilization rate was significantly lower in patients than control subjects (33.9 ± 14.3 vs. 63.8 ± 17.2 μmol · kg^{-1} · min^{-1}, $P = 0.0002$; Table 1; Fig. 1). Similarly, insulin sensitivity index was significantly lower in IDDM compared with control subjects (5.54 ± 2.30 vs 9.18 ± 3.64 μmol · kg^{-1} · min^{-1} per pM, $P = 0.01$; Table 1, Fig. 2). Both glucose utilization and insulin sensitivity index were significantly lower in female than male patients (24.2 ± 2.8 vs. 40.7 ± 3.4 μmol · kg^{-1} · min^{-1} and 4.55 ± 0.54 vs. 6.28 ± 0.62 μmol · kg^{-1} · min^{-1} per pM, $P = 0.001$; Figs. 1 and 2). However, this sex difference disappeared after adjusting for differences in fitness levels between males and females. There was no sex-related difference in glucose disposal among control subjects (Figs. 1 and 2).

Physical fitness was similar in patients and control subjects as assessed by $VO_{2\ max}$ (34.9 ± 8.6 vs. 38.6 ± 9.9 ml · kg^{-1} · min^{-1}; Fig. 3). Among patients, females had significantly lower $VO_{2\ max}$ compared with males (27.1 ± 5.1 vs. 39.8 ± 6.4 ml · kg^{-1} · min^{-1}, $P < 0.00001$; Fig. 3). However, there was no sex difference in $VO_{2\ max}$ among control subjects (Fig. 3).

TABLE 1
Biochemical data from euglycemic clamp studies

	Patients (n = 27)	Control subjects (n = 10)	P
Insulin-mediated glucose metabolism (μmol · kg^{-1} · min^{-1})	33.9 ± 14.3	63.8 ± 17.2	0.0002
Steady-state plasma glucose (mM)	5.5 ± 0.1	5.6 ± 0.1	NS
Steady-state plasma free insulin (pM)	606 ± 134	736 ± 118	0.01
Insulin sensitivity index (μmol · kg^{-1} · min^{-1} per pM^{-1})	5.54 ± 2.30	9.18 ± 3.64	0.01

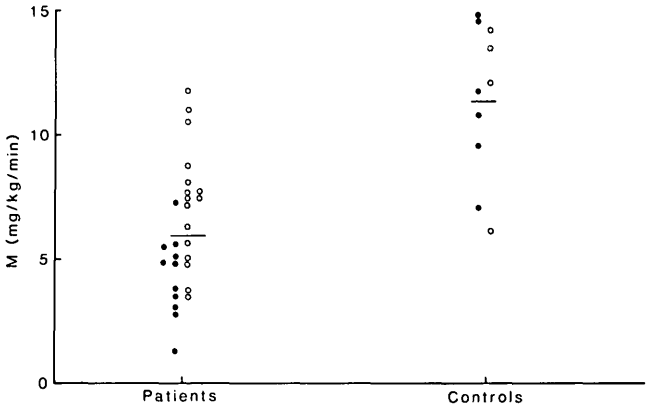

FIG. 1. Individual data and means of insulin-mediated glucose metabolism (M) in insulin-dependent diabetes mellitus patients and healthy control subjects. ●, Female; ○, male. $P = 0.0002$.

The relationship between glucose metabolism and physical fitness is shown in Fig. 4. There was a strong direct correlation between glucose metabolism and physical fitness in both diabetic ($r = 0.83$, $P < 0.001$) and control subjects ($r = 0.81$, $P < 0.05$). In addition, there was an inverse correlation ($r = -0.63$, $P < 0.001$) between glucose metabolism and HbA_1 level in diabetic subjects (Fig. 5). To evaluate more precisely the contribution of each of the two factors ($VO_{2\ max}$ and HbA_1) on insulin-mediated glucose metabolism, we used partial correlation coefficient analysis. When insulin-mediated glucose metabolism was plotted against $VO_{2\ max}$, the partial correlation was 0.76 ($P < 0.0001$) and against HbA_1

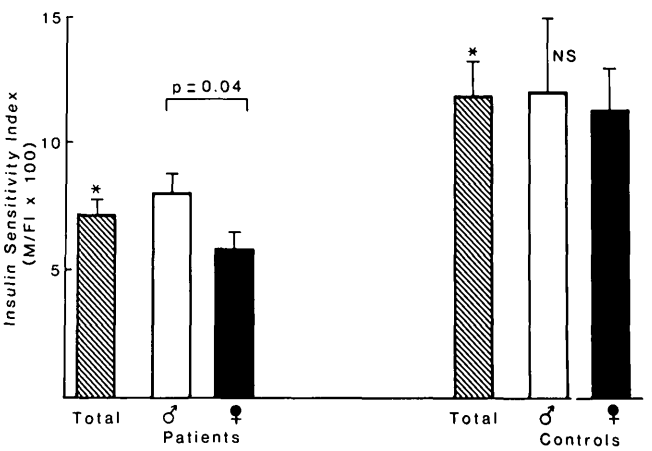

FIG. 2. Insulin-sensitivity index according to sex in insulin-dependent diabetic patients and control subjects. Values are means ± SE. *$P = 0.01$.

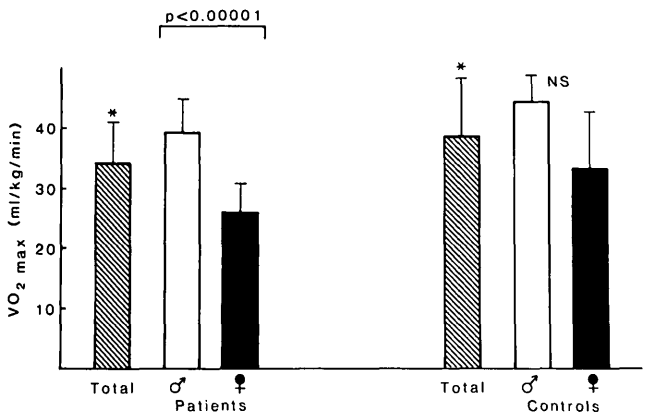

FIG. 3. Physical fitness according to sex in insulin-dependent diabetic patients and control subjects. *NS.

was -0.40 ($P < 0.05$). The combined effect of $VO_{2\ max}$ and HbA_1 on insulin-mediated glucose metabolism was calculated with multiple regression analysis. The multivariate correlation coefficient between insulin-mediated glucose metabolism versus $VO_{2\ max}$ and HbA_1 was 0.85 ($P < 0.0001$). The regression equation obtained for the predicted insulin-mediated glucose metabolism was $0.203\ VO_{2\ max} - 0.351\ HbA_1 + 2.27$. There was no relationship between total-body insulin-mediated glucose metabolism and BMI ($r = -0.18$), age, and duration of diabetes. However, in control subjects, there was a significant inverse relationship between insulin-mediated glucose metabolism and BMI ($r = -0.85$, $P < 0.001$).

DISCUSSION

The objectives of this study were to evaluate the relationship of in vivo insulin action to physical fitness in adolescents with IDDM and to assess additional factors known to alter insulin sensitivity. Our data demonstrated that insulin-mediated glucose disposal was positively related to the state of physical fitness as assessed by $VO_{2\ max}$ and negatively related to diabetes control as assessed by HbA_1.

The amount of glucose metabolized during the hyperinsulinemic-euglycemic clamp is the sum of infused plus endogenously (by the liver) produced glucose. Although we did not measure hepatic glucose production, preliminary data from our laboratory that used stable isotope [6,6-$^2H_2$]glucose indicated complete suppression of hepatic glucose production at this level of hyperinsulinemia.

The fact that in vivo insulin-stimulated glucose disposal is greater in physically trained individuals during hyperinsulinemia has been previously demonstrated in cross-sectional studies of healthy adults and elderly subjects (11,18). In diabetic subjects, such a relationship has been shown in intervention studies. In these studies, physical training programs as short as 6 wk resulted in improved physical fitness and improved insulin action in adults (19,20). In diabetic adolescents, the only reported study demonstrated that short-term exercise training alone, although it improves physical fitness and insulin sensitivity, does not improve glycemic control (21).

The physical fitness of an individual is dependent on age, sex, genetics, physical activity, muscle mass, and the capacity of the respiratory and circulatory organs (22–23). In our study, which was limited to adolescents with no clinical evidence of cardiorespiratory disease, physical fitness was 32% lower in female patients than male patients. This sex difference in the level of physical fitness has been described previously in diabetic and nondiabetic children and has been attributed to lower muscle mass in females (24,25). The insulin sensitivity index was 28% lower in female diabetic subjects, however, this observed sex difference in insulin sensitivity disappeared after adjusting for differences in the level of physical fitness. Thus, female patients appeared to have lower insulin sensitivity secondary to decreased levels of physical fitness. In control subjects, however, we found no sex difference in either insulin sensitivity or physical fitness. The lack of a sex difference in physical fitness among control subjects was probably due to the small number of subjects studied (because of difficulties of studying control subjects in a childhood population) and because two of the female control subjects were extremely athletic (Fig. 1; the 2 points representing the highest insulin-mediated glucose metabolism level).

Because physical fitness is an important determinant of insulin sensitivity, and because previous studies have demonstrated decreased fitness levels in diabetic patients compared with healthy control subjects (24,26), we initially hypothesized that the observed insulin re-

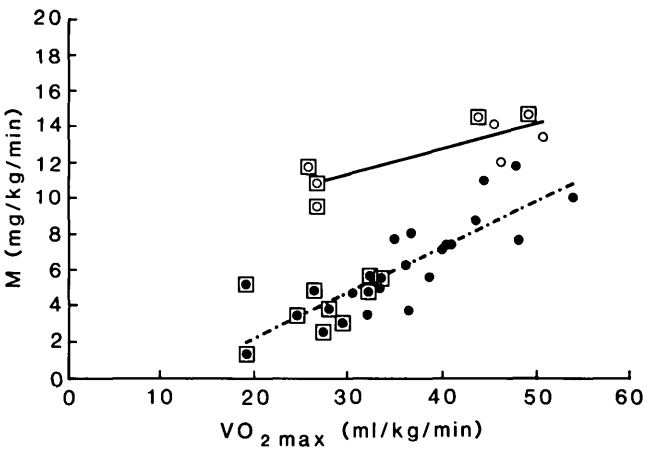

FIG. 4. Relationship between physical fitness ($VO_{2\ max}$) and insulin-stimulated glucose metabolism (M) in insulin-dependent diabetic patients and control subjects (n = 34 observations). □, Female; ○, control subjects ($y = 7.12 + 0.143x$, $r = 0.81$); ●, patients ($y = -2.84 \pm 0.255x$, $r = 0.83$).

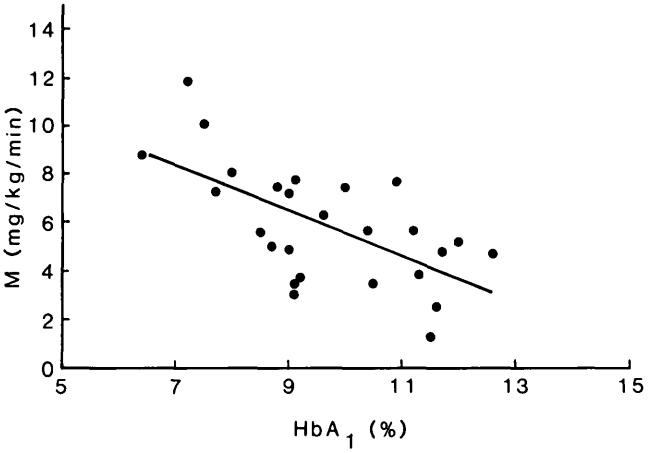

FIG. 5. Relationship between glycosylated hemoglobin (HbA_1) and insulin-mediated glucose metabolism (M) in insulin-dependent diabetes mellitus. $P < 0.001$, $r = -0.63$.

sistance in diabetic adolescents would be secondary to decreased levels of physical fitness. In our study, although insulin sensitivity in IDDM was only 60% of that in healthy control subjects, we found no difference between control and diabetic subjects in the level of $VO_{2\ max}$. This was in agreement with the findings of Larson et al. (27). Furthermore, for the same degree of physical fitness, patients with IDDM have lower levels of insulin-mediated glucose disposal with the difference in insulin-mediated glucose metabolism becoming exaggerated at the lower levels of fitness, indicating that some other factor must be involved (Fig. 4). A major factor appeared to be the state of diabetes control, because we found a significant inverse relationship between the level of HbA_1 and insulin-mediated glucose metabolism. Although this relationship can be secondary to the simple inverse relationship of HbA_1 to $VO_{2\ max}$ ($r = -0.56$, $P < 0.01$) such that the more fit patients have the better glycemic control, in multiple regression analysis physical fitness and glycemic control independently contributed to the outcome in insulin-mediated glucose metabolism (insulin-mediated glucose metabolism = $0.203\ VO_{2\ max} - 0.351\ HbA_1 + 2.27$). Thus, we conclude that diabetes and/or glycemic control independently influences insulin sensitivity in adolescents with IDDM. In agreement with such a conclusion are previous studies that have demonstrated that peripheral insulin senstivity increases after improvement of the diabetic state with constant subcutaneous insulin-infusion devices (28–31). In these studies, it is still questionable whether the improvement of insulin action is specifically due to improvement of hyperglycemia or due to the improvement in the general metabolic milieu (e.g., lower plasma free–fatty acid levels). In support of hyperglycemia playing an important role is the recent observation by Yki-Järvinen et al. (32) that short-term hyperglycemia for 24 h compared with normoglycemia, without change in insulin delivery and plasma free insulin levels, reduced insulin-mediated glucose uptake in IDDM subjects. In addition, the findings of Rossetti et al. (33) provide strong evidence for a glucotoxic phenomenon involved in glucose utilization. They demonstrated that in partially pancreatectomized rats who became hyperglycemic insulin-mediated glucose utilization was decreased compared with sham-operated rats; however, achieving normoglycemia with phlorizin, a glycosuric agent, normalized glucose disposal.

The effect of obesity, which is a known cause of insulin resistance (34), was assessed by studying the relationship between insulin-mediated glucose metabolism and BMI. In healthy subjects we found a strong negative correlation between BMI and insulin-mediated glucose metabolism ($r = -0.85$, $P < 0.001$), however, there was no association in diabetic patients. A similar association between insulin-mediated glucose metabolism and BMI, although of lesser magnitude, has been shown previously in healthy children (35). The lack of an association between BMI and insulin-mediated glucose metabolism in diabetic subjects was intriguing and could have resulted for many reasons. First, BMI is a crude way of expressing adiposity, and knowledge of the different proportions of muscle and fat tissue is of importance in interpreting in vivo insulin sensitivity. For this reason, we use additional techniques for assessing body composition, including impedance plethysmography (36). Second, the lack of association between insulin-mediated glucose metabolism and BMI might be due to the narrow range of BMI (19–26 kg/m^2) in our group of patients; however, with a similar narrow range of BMI in control subjects, we were able to find a strong relationship between insulin-mediated glucose metabolism and BMI. Third, other factors related to the diabetic state (e.g., degree of glycemic control) may overshadow the relationship of BMI to insulin-mediated glucose metabolism; however, there was still no relationship between BMI and insulin-mediated glucose metabolism after adjusting for HbA_1 levels.

In conclusion, our results demonstrated that adolescents with IDDM have in vivo insulin resistance, but more important, we provide evidence that physical fitness and glycemic control together explain 73% of the variation in insulin-mediated glucose metabolism. It remains to be shown if modifying aerobic fitness via physical training simultaneous with improving glycemic control would normalize insulin action in adolescents with IDDM.

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