Reduced Skeletal Muscle Oxygen Uptake and Reduced β-Cell Function

Two early abnormalities in normal glucose-tolerant offspring of patients with type 2 diabetes

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OBJECTIVE — Studies on insulin sensitivity and insulin secretion in subjects with a familial predisposition for type 2 diabetes mellitus (T2DM) traditionally produce inconsistent results. This may be due to small sample size, subject selection, matching procedures, and perhaps lack of a measure of physical fitness.

RESEARCH DESIGN AND METHODS — In the present study, we specifically tested the hypothesis that a family history of T2DM is associated with reduced $V_{O_{2max}}$, measured by incremental bicycle ergometry, independent of insulin sensitivity estimated from an oral glucose tolerance test (OGTT; $n = 424$) and measured by a euglycemic-hyperinsulinemic clamp ($n = 185$). Subjects included in the study were young (34 ± 10 years), healthy, and normal glucose tolerant with either a first-degree relative (FDR) with T2DM ($n = 183$), a second-degree relative with T2DM ($n = 94$), or no family history of T2DM (control subjects, $n = 147$). BMI, percent body fat, waist-to-hip ratio (WHR), and habitual physical activity (HPA; standard questionnaire) were comparable among groups. FDRs had significantly lower $V_{O_{2max}}$ than control subjects: 40.5 ± 0.6 vs. 45.2 ± 0.9 ml O_2/kg lean body mass, $P = 0.01$ after adjusting for sex, age, BMI, HPA, and insulin sensitivity (euglycemic-hyperinsulinemic clamp).

RESULTS — BMI, percent body fat, waist-to-hip ratio (WHR), and habitual physical activity (HPA; standard questionnaire) were comparable among groups. FDRs had significantly lower $V_{O_{2max}}$ than control subjects: 40.5 ± 0.6 vs. 45.2 ± 0.9 ml O_2/kg lean body mass, $P = 0.01$ after adjusting for sex, age, BMI, HPA, and insulin sensitivity (euglycemic-hyperinsulinemic clamp). Insulin sensitivity per se was not affected by family history of T2DM after adjusting for age, sex, BMI, and percent body fat ($P = 0.76$). The appropriateness of β-cell function for the individual insulin sensitivity (disposition index: product of a validated secretion parameter [OGTT] and sensitivity [clamp]) was significantly lower in FDRs (87 ± 4 units) versus control subjects (104 ± 6 units, $P = 0.02$ after adjusting for sex, age, and BMI). Analyses of the larger OGTT group produced essentially the same results.

CONCLUSIONS — In conclusion, these data are compatible with the hypothesis that familial predisposition for T2DM impairs maximal oxygen consumption in skeletal muscle. Because habitual physical activity was not different, genetic factors may be involved. Conceivably, reduced $V_{O_{2max}}$ precedes skeletal muscle insulin resistance, providing a partial explanation for discrepancies in the literature.

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Familial predisposition is an important risk factor for type 2 diabetes mellitus (T2DM). Studies performed to identify the underlying mechanisms have produced conflicting results. Whereas some primarily demonstrated impaired insulin secretion in subjects with a family history of T2DM, others reported reduced insulin sensitivity as the main finding. To date, no consensus has been reached (1,2). Issues such as differences in experimental techniques, recruitment mechanisms (inclusion and exclusion criteria), matching procedures, adjustments for covariates, and personal bias of investigators are probably involved.

In addition, few of the available studies have controlled for physical fitness, which is a strong independent determinant of insulin sensitivity (3). Conceivably, familial clustering of insulin resistance may be the corollary of a sedentary lifestyle prevailing in a particular family and have nothing to do with a primary (i.e., genetic) defect in insulin-stimulated glucose disposal. The existence of familial aggregation of behavioral traits such as television viewing, depression, or reduced physical activity is well documented (4–11).

On the other hand, it is possible that genetic factors primarily affect the ability of skeletal muscle to maximize its oxidative capacity in response to endurance training. In this scenario, reduced glucose disposal would be a consequence of impaired skeletal muscle substrate oxidation rather than impaired insulin signaling. Consistent with this hypothesis, in insulin resistant offspring of patients with T2DM, maximal oxygen consumption

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Abbreviations: FDR, first-degree relative; FHD, family history of diabetes; GIR, glucose infusion rate; HPA, habitual physical activity; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

was reduced compared with insulin sensitive control subjects without family history of diabetes (FHD) (12). Moreover, muscle of offspring of patients with T2DM was found to be enriched with type II fibers (13), whereas maximal oxygen consumption is predominantly a function of the type 1 fiber content (14,15).

Therefore, the aim of the present study was to test the hypothesis that family history of T2DM is associated with reduced maximal oxidative capacity independent of alterations in insulin sensitivity. For this purpose, we studied a large group of healthy, normal glucose tolerant subjects with family history of T2DM ($n = 279$) and without family history of T2DM ($n = 147$). To provide a comprehensive picture of metabolic traits controlling glycemia, we included validated estimates for insulin secretion and calculated a disposition index. The size of the study group permitted mathematical adjustments for relevant covariates using general estimating equation procedures.

RESEARCH DESIGN AND METHODS

— Subjects were recruited from the ongoing Tübingen Family Study for Type 2 Diabetes (TÜF). The Tübingen Family Study recruits family members of subjects with type 2 diabetes. Over the years, subjects without any family history were asked to undergo metabolic checkup. This group was used as a control group in the present study. A total of 424 healthy subjects with normal glucose tolerance according to World Health Organization criteria were selected for analyses. In a total of 185 subjects (77 control subjects and 75 first-degree relatives [FDRs]), insulin sensitivity data from euglycemic-hyperinsulinemic clamp were available for analyses.

After the nature of the study was explained, all subjects gave informed written consent and underwent the standard procedures of the protocol, including medical history, physical examination, routine blood test, and oral glucose tolerance test (OGTT). The local ethics committee approved all protocols.

Analytical procedures and measurements

Blood glucose was measured using a bedside glucose analyzer (glucose oxidase method; Yellow Springs Instruments, Yellow Springs, CO). Serum insulin was determined with a micro particle enzyme immunoassay (Abbott, Wiesbaden, Germany). Serum C-peptide concentrations were determined by radioimmunoassay (Byk-Sangtec Diagnostika, Dietzenbach, Germany).

Body composition

Lean body mass (kg) and total body fat (%) was determined by bioimpedance analysis (BIA-101; RJL Systems) following the guidelines of the user's manual and the National Institutes of Health Consensus Conference on Bioelectric Impedance (16).

Family history status

Family history status was inquired during medical history. Only subjects with profound knowledge of their family history status were included in this study.

Habitual physical activity

All subjects completed a standardized self-administered and validated questionnaire to measure physical activity (17). Points are assigned for physical activity at work (work index), at sport during leisure time (sport index), and during leisure time excluding sport (leisure time index). The habitual physical activity (HPA) score was calculated as mean points of the three indexes.

Maximal oxygen consumption

All subjects underwent a continuous, incremental exercise test to volitional exhaustion using a cycle ergometer. The cycle ergometer test was performed on an electromagnetically braked cycle ergometer (Ergometrics 800 S; Ergoline, Bitz, Germany). Oxygen consumption was measured using a spiroergometer (MedGraphics System Breese Ex 3.02 A; MedGraphics). Subjects were asked to choose a pedaling rate of 60 rpm and to maintain that rate throughout the test. After a 2-min warm-up period at 0 W, the test was initiated at an initial power output of 20 W. Stepwise increments of 40 W were made every minute until exhaustion. $V_{O_{2max}}$ is expressed as V_{O_2} (ml/min) per kg lean body mass.

Euglycemic-hyperinsulinemic clamp

At approximately 7:00 A.M., after a 12-h overnight fast, an antecubital vein was cannulated for infusion of insulin and glucose. A dorsal hand vein of the contralateral arm was cannulated and placed under a heating device to allow sampling of arterialized blood. After basal blood was drawn, subjects received a primed insulin infusion at a rate of 1.0 mU $\cdot$ kg^{-1} $\cdot$ min^{-1} for 2 h. Blood was drawn every 5 min for determination of blood glucose, and a glucose infusion was adjusted appropriately to maintain the fasting glucose level. An insulin sensitivity index (ISI) (in μmol $\cdot$ kg^{-1} $\cdot$ min^{-1} $\cdot$ pmol^{-1}) for systemic glucose uptake was calculated as the mean infusion rate of glucose (GIR; in μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) necessary to maintain euglycemia during the last 60 min of the euglycemic-hyperinsulinemic clamp divided by the steady-state serum insulin concentration.

Calculations

Insulin sensitivity. Insulin sensitivity during OGTT was calculated by the formula of Matsuda and DeFronzo (18), as previously described.

First phase insulin secretion. First-phase insulin release during OGTT was calculated using the formula of Stumvoll et al. (19).

Disposition index. A disposition index was calculated by multiplying insulin sensitivity with insulin secretion. The importance of this index in assessing β-cell function was recently reviewed by Bergman et al. (20).

Statistical analyses

All data are given as mean ± SE unless otherwise stated. The statistical software package JMP (SAS Institute, Cary, NC) was used for statistical analyses. A P value <0.05 was considered statistically significant. Non-normally distributed parameters were log-transformed before statistical analyses. FDRs were compared with the control group using Student's t test. Comparisons between all groups were performed by one-way ANOVA.

RESULTS

Subject characteristics (all subjects)

FDRs of type 2 diabetic patients were significantly older than the control group without FHD or second-degree relatives. The groups were comparable with respect to BMI, percent body fat, and WHR. Fasting and 2-h blood glucose levels during OGTT were significantly higher in the FDR group compared with the control group (Table 1). This effect was still significant after adjusting for age and percent body fat ($P = 0.0045$ for fasting and $P =$

Table 1—*Subject characteristics*

	No FHD	FHD in the grandparents' generation	FHD in the parents' generation	FHD in two generations (parents, grandparents, or brothers and sisters)	*P* (ANOVA)	*P* (Student's *t* test)*
n (men/women)	147 (60/87)	94 (28/66)	79 (28/51)	104 (39/65)		
Age (years)	33 ±10	31 ±8	40 ±10	35 ±10	<0.001	<0.001
BMI (kg/m^2)	25 ±5	24 ±5	25 ±4	25 ±6	0.58	0.41
Weight (kg)	73.4 ±14.4	72.3 ±16.0	74.0 ±15.7	75.0 ±16.7	0.68	0.51
Percent body fat (%)	25 ±10	27 ±9	27 ±8	26 ±10	0.26	0.19
Lean body mass (kg)	54 ±10	53 ±10	54 ±12	54 ±10	0.50	0.79
WHR	0.84 ±0.08	0.83 ±0.08	0.85 ±0.08	0.84 ±0.08	0.29	0.44
Fasting glucose level (mmol, OGTT)	4.76 ±0.50	4.88 ±0.45	5.0 ±0.47	4.95 ±0.44	<0.001	<0.0001
2-h glucose level (mmol, OGTT)	5.17 ±1.17	5.31 ±1.07	5.68 ±1.01	5.56 ±1.16	0.003	<0.001
Fasting insulin level (pmol, OGTT)	44 ±28	45 ±31	43 ±23	46 ±36	0.97	0.80
2-h insulin level (pmol, OGTT)	253 ±17	255 ±22	244 ±24	251 ±21	0.29	0.82
HPA	8.2 ±1.0	8.3 ±1.0	8.2 ±1.0	8.0 ±1.1	0.27	0.17
$V_{O_{2max}}$ (ml · kg lean body mass^{-1} · min^{-1})	45.2 ±11.2	42.7 ±9.2	39.7 ±7.6	41.1 ±9.4	<0.001	<0.0001
$V_{O_{2max}}$ (ml · kg body weight^{-1} · min^{-1})	34.4 ±11.3	31.7 ±9.1	29.3 ±7.0	30.5 ±9.8	<0.001	<0.0001
ISI (clamp) (μmol · kg^{-1} · min^{-1} · pmol^{-1})	0.119 ±0.062	0.106 ±0.067	0.103 ±0.053	0.099 ±0.049	0.23	0.051
Disposition index	22,469 ±10,664	21,704 ±7,858	17,842 ±7,858	18,639 ±7,548	<0.001	<0.0001

Data are means ± SD. *Comparison between the control group and FDRs using Student's *t* test.

0.0047 for 2-h glucose). Characteristics of the subjects who also underwent a euglycemic-hyperinsulinemic clamp were similar to those of the OGTT group.

Relationships among maximal oxygen consumption, physical activity, and insulin sensitivity

Maximal oxygen consumption during incremental exercise on a bicycle ergometer was higher in men than in women (48.5 ± 0.9 vs. 39.3 ± 0.4 ml · kg lean body mass^{-1} · min^{-1}, $P < 0.001$). Habitual physical activity was positively correlated to maximal oxygen consumption ($r = 0.24$, $P < 0.001$) and insulin sensitivity (clamp) ($r = 0.23$, $P < 0.001$). Furthermore, maximal oxygen consumption was correlated to insulin sensitivity (clamp) ($r = 0.42$, $P < 0.001$). Age ($r = -0.29$, $P < 0.001$), body fat content ($r = -0.41$, $P < 0.001$) and 2-h glucose ($r = -0.18$, $P < 0.0001$) were negatively correlated with maximal oxygen consumption (Fig. 1).

Family history of T2DM and maximal oxygen consumption

Maximal oxygen consumption was highest in the control group without family history of T2DM (45.2 ± 0.9 ml · kg lean body mass^{-1} · min^{-1}) and significantly lower in second- and first-degree relatives of type 2 diabetic patients (42.7 ± 0.9 and 40.5 ± 0.6, $P < 0.001$, ANOVA). In contrast, habitual physical activity was comparable in all groups (8.2 ± 0.1 in control subjects versus 8.3 ± 0.1 in second-degree relatives versus 8.1 ± 0.1 in first-degree relatives, $P = 0.27$, ANOVA) (Fig. 2). In a multivariate regression analysis with maximal oxygen consumption as a dependent variable, the effect of family history status remained significant ($P = 0.04$) after adjusting for the effects of sex ($P < 0.001$), age ($P = 0.11$), BMI ($P = 0.06$), HPA ($P < 0.001$), and insulin sensitivity (clamp) ($P = 0.01$) (see Table 2). The results were similar using an insulin sensitivity estimate from the OGTT ($P = 0.05$ for the effect of family history status).

Family history status and its relationship with insulin sensitivity (euglycemic-hyperinsulinemic clamp) and insulin secretion

Insulin sensitivity (clamp) tended to be lower in FDRs compared with the control group (0.119 ± 0.107 vs. 0.100 ± 0.087 μmol · kg^{-1} · min^{-1} · pmol^{-1}, $P = 0.051$). This marginal effect of family history on insulin sensitivity disappeared completely after adjusting for sex, age, BMI, and HPA in a multivariate analysis ($P = 0.87$) (see Table 2). Similarly, family history status had no significant effect on insulin sensitivity estimated in the larger OGTT group after adjusting for the same covariates ($P = 0.14$). Moreover, no differences in first-phase insulin secretion between the control group and FDRs were observed (1,051 ± 43 vs. 992 ± 35, $P = 0.28$ and $P = 0.30$ after adjusting for sex, age, and BMI).

The calculated disposition index ($ISI_{clamp} \times Secretion_{OGTT}$), however, was significantly higher in control subjects compared with FDRs (104 ± 6 vs. 87 ± 4 units, $P = 0.02$), indicating reduced insulin secretion relative to insulin sensitivity in FDR subjects. This relationship remained significant ($P = 0.046$) after adjusting for the effects of sex, age, and BMI (see Table 2).

The disposition index purely derived from OGTT was also significantly higher in control subjects than in FDRs (22,468 ± 883 vs. 18,291 ± 874, $P < 0.001$). This relationship remained significant ($P = 0.02$) after adjusting for sex, age, and BMI (Fig. 3).

CONCLUSIONS — The aim of the present study was to identify early metabolically relevant abnormalities predisposing to type 2 diabetes in FDRs of patients with the disease. There was a trend for lower insulin sensitivity in FDRs who also tended to be somewhat more obese and older. After adjusting, however, insulin sensitivity became comparable between the groups, indicating that

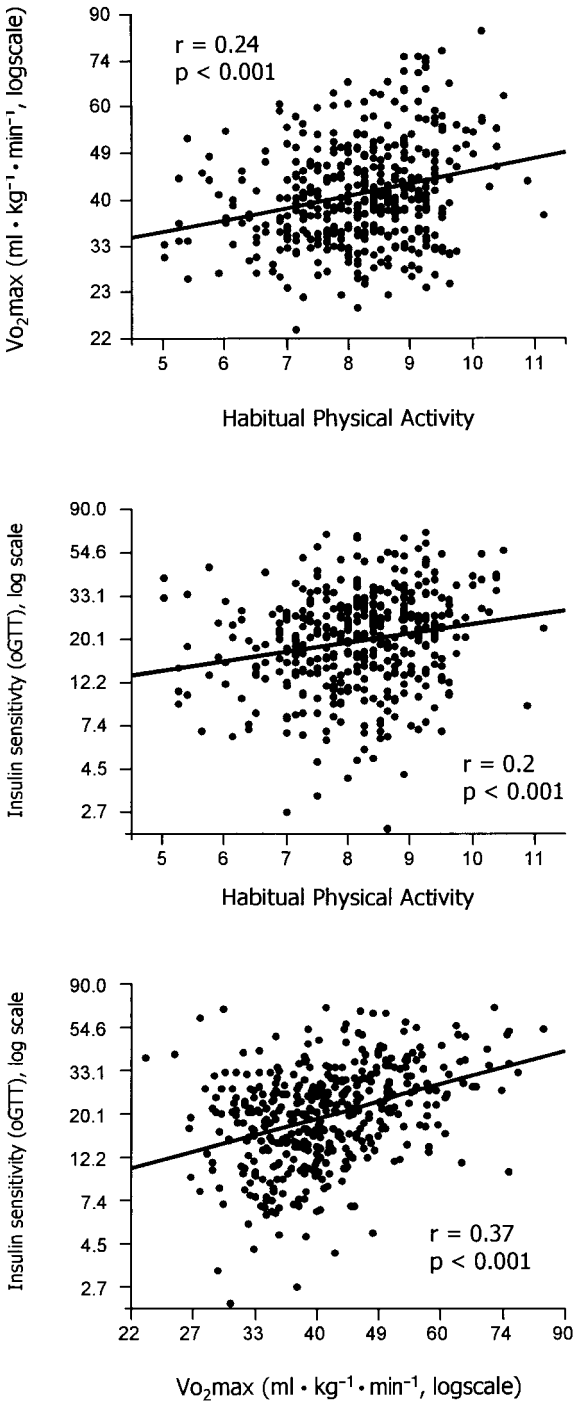

Figure 1—*Relationships between HPA and maximal oxygen consumption (top), HPA and insulin sensitivity (estimated from OGTT, middle), and $V_{O_{2max}}$ and insulin sensitivity (estimated from OGTT, bottom).*

most of the original trend was secondary to differences in fatness. Insulin secretion assessed by a validated index based on fasting and 30-min insulin and glucose concentrations during an OGTT was also comparable among the patients with FHD. However, insulin secretion relative to insulin sensitivity (expressed as the so-called disposition index) was significantly lower in FDR subjects. This is in line with results of previous studies identifying reduced β-cell compensation to insulin resistance in individuals with FHD (21–24).

An important finding of the present study is that maximal oxygen consumption was reduced in FDRs despite essentially identical physical activity scores (derived from a questionnaire). The fact that this difference was observed in the absence of any detectable difference in insulin sensitivity is the most interesting aspect but represents somewhat of a pathophysiological quandary. That is, how would an abnormality in oxidative muscle metabolism during exercise ultimately affect glucose metabolism if not via peripheral (i.e., muscle in the insulin-stimulated state) glucose uptake? There are two possible conjectures: first, our measurement of peripheral insulin sensitivity is too unphysiologic (steady-state insulin concentration during the clamp ~400 pmol/l) to detect subtle abnormalities that translate into fasting or 2-h glucose concentrations manifest only at physiologic insulin levels. Second, our measurement of insulin sensitivity may be too crude and not sufficiently specific for skeletal muscle. Variability in insulin-suppression of endogenous glucose production, which is also measured by the glucose infusion rate during the clamp, may offset an isolated muscle abnormality on the whole-body level.

It is important to emphasize that although the study population had normal glucose tolerance, the abnormal subphenotypes somehow impacted fasting and 2-h glucose levels, which were significantly higher in FDRs. The lower disposition is probably the most relevant factor responsible for the differences in glycemia. Nevertheless, mechanism secondary to maximal oxygen consumption but outside the diagnostic scope of the euglycemic-hyperinsulinemic clamp may also be involved.

Previously, reduced maximal oxygen uptake was demonstrated in insulin-resistant relatives of patients with T2DM (12). In our study, maximal oxygen uptake was a strong determinant of insulin sensitivity but, in contrast to oxygen uptake, insulin sensitivity was not different between the patients with FHD. These findings are difficult to reconcile, but the observation that in patients with overt type 2 diabetes, resistance training improves insulin sensitivity without altering $V_{O_{2max}}$ (25) in principle supports the possibility of a dissociation between effects of exercise and insulin sensitivity on skeletal muscle. Conceivably, reduced maximal oxygen consumption of skeletal muscle represents a primary defect predisposing skeletal muscle to insulin resistance when other confounding factors (e.g., physical inactivity) come into play.

The relative content of type 1 fibers in skeletal muscle was identified as a main

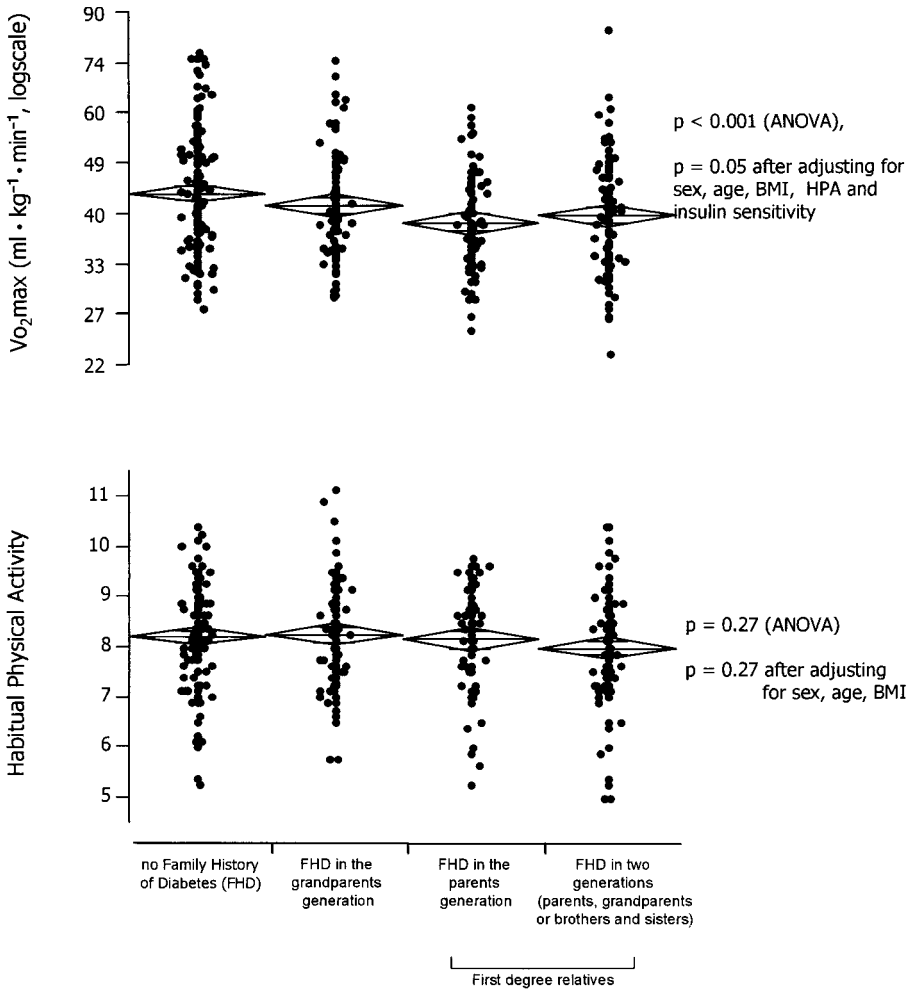

Figure 2—VO_{2max} *(top) and HPA (bottom) in the different groups of patients with FHD.*

determinant of skeletal muscle oxygen uptake during exercise (14,15). Type 1 muscle fibers are slow-twitch muscle fibers with preferentially oxidative metabolism rich in myoglobin, mitochondria, oxidative enzymes, and lipids (26). Therefore, the mechanism underlying our observation is likely to involve altered fiber composition of skeletal muscle, specifically a reduced number of type 1 fibers, which was found to be associated with adiposity and insulin resistance (27). Additionally, a high proportion of type 1 muscle fibers has been shown to protect against weight gain in response to a long-term positive energy balance (28). Moreover, fiber type proportions of skeletal muscle have been demonstrated to be genetically determined (29). In accordance with all these findings, the number of type 2 muscle fibers were found to be reduced in FDRs of patients with T2DM (13).

It is also necessary to point out that use of questionnaires in assessing habitual physical activity cannot be without problems. The same quantity or quality of physical exercise may seem more or less strenuous to different individuals. However, it is unlikely that the degree of underreporting is influenced by family history status. Therefore, and in view of the large number of subjects reported herein, our overall conclusions should remain valid.

Finally, this study is not merely another report of prediabetic subphenotypes in subjects with and without FHD. Instead, this study presents novel aspects that complement previously published work. First, by including every subject in the database and performing ANCOVA rather than matching and excluding "unmatchable" individuals, we largely avoided any selection bias. Second, we present VO_{2max} data in addition to insulin sensitivity and demonstrate that there may be dissociation between skeletal muscle glucose and exercise metabolism, which implies the possibility that only in subgroups does skeletal muscle have a primary role in the pathogenesis of T2DM. Third, we found abnormalities in both β-cells and insulin sensitivity tissue but only conditionally, i.e., using the disposition index or measuring skeletal muscle oxidative capacity. This clearly demonstrates the subtlety of the influence of FHD on diabetes-relevant traits and

Table 2—*Effect of family history in multivariate regression models*

Independent variable	Estimate	SE	*P*	Model *P*	Model r^2
Dependent Variable VO_{2max}					
Sex	−0.09	0.01	<0.001	<0.0001	0.51
Age (log)	−0.08	0.05	0.11		
BMI (log)	−0.19	0.10	0.06		
HPA	0.07	0.01	<0.001		
ISI (log)	0.07	0.03	0.01		
FHD			0.04		
Dependent Variable ISI					
Sex	−0.06	0.03	0.07	<0.0001	0.47
Age (log)	0.31	0.12	0.01		
BMI (log)	−2.21	0.19	<0.001		
HPA	0.1	0.03	<0.001		
FHD			0.87		
Dependent Variable Disposition Index					
Sex	0.05	0.87	0.18	<0.001	0.13
Age (log)	−0.003	0.04	0.98		
BMI (log)	−0.93	0.25	<0.001		
FHD			0.046		

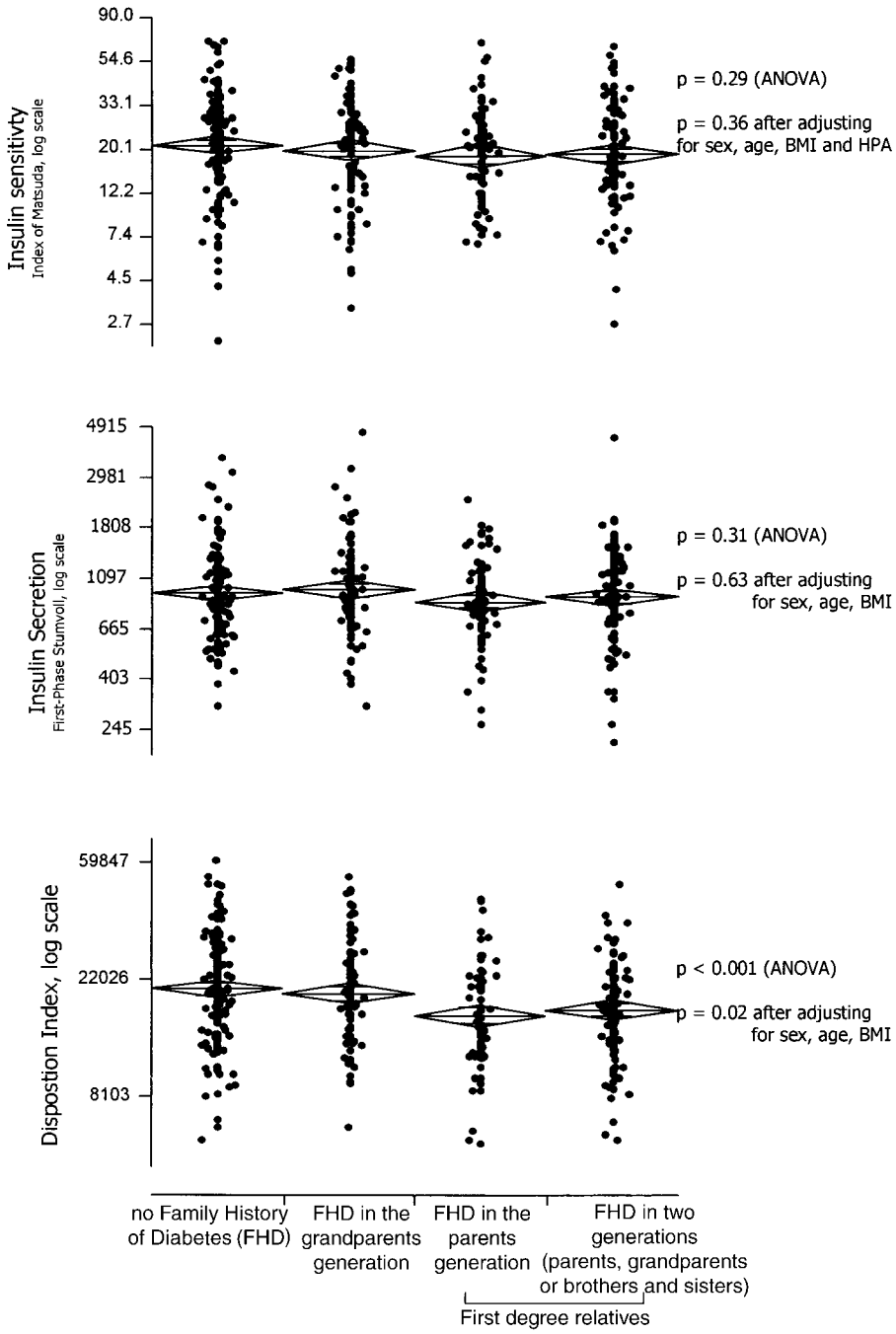

Figure 3—*Insulin sensitivity (estimated from OGTT), insulin secretion (estimated from OGTT), and the calculated disposition index (OGTT data) in the different groups of patients with FHD.*

may help to reconcile conflicting data and some ongoing debates.

In summary, we have demonstrated two metabolic abnormalities in a young and healthy group of subjects with a familial predisposition of type 2 diabetes: reduced insulin secretion relative to insulin sensitivity and reduced maximal oxygen consumption during exercise, which was not the result of lack of exercise.

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