Lower β-Cell Secretion in Physically Active First-Degree Relatives of Type 2 Diabetes Patients

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Regular physical activity may prevent or postpone type 2 diabetes, and is thought to be related to an increase of insulin sensitivity. We studied whether physically active, glucose-tolerant first-degree relatives of type 2 diabetes patients differ in glucose tolerance (oral glucose tolerance test [OGTT]) and insulin secretion (hyperglycemic glucose clamp) from less active first-degree relatives. A group of 37 relatives was split into 2 subgroups according to the sex-specific median of the sports index, assessed by a questionnaire, as the cutoff point. Blood glucose levels during the OGTT were lower in the highly active subgroup versus the less active counterparts (multivariate ANOVA [MANOVA], $P = .011$), but the plasma insulin levels were similar. First-phase secretion was not different in the highly active group versus the less active group, but second-phase secretion (average plasma insulin in the third hour) was significantly lower ($P = .016$). As expected, the insulin sensitivity index (ISI) was higher in the highly active subgroup ($P = .011$). Subdivision into subgroups with high or low maximal O_2 consumption ($\dot{V}O_2max$) resulted in similar differences, but these were not significant. In a group of 21 controls, the results resembled the values in the relatives but were less often statistically significant. In conclusion, regular physical activity not only is associated with increased insulin sensitivity but also downregulates the pancreatic β cell. This downregulation may provide an extra mechanism by which physical activity diminishes the development of type 2 diabetes.

THE PATHOGENESIS of type 2 diabetes (non–insulin-dependent diabetes mellitus [NIDDM]) is not fully understood, but it is clear that at least 3 factors are of importance: a genetic predisposition to the disease, a defect in pancreatic β-cell function, and a decrease in insulin sensitivity.[1] A strong genetic component is suggested by a concordance of 60% to 90% for type 2 diabetes in identical twins. In addition, about 40% of first-degree relatives of patients with type 2 diabetes will develop the disease, compared with 11% for relatives of subjects without a family history of diabetes.[2] There is still debate about the initial defect of type 2 diabetes mellitus: insulin resistance or impaired β-cell function. Both insulin sensitivity and insulin secretion are under genetic control and have been reported to be disturbed in healthy normal glucose-tolerant first-degree relatives of type 2 diabetes patients.[3-5]

Besides genetic factors, environmental factors such as obesity, and more specifically upper-body fat distribution, hypertension, and physical inactivity contribute to the development of type 2 diabetes.[2,6-10] The protective effect of physical activity on the development of type 2 diabetes is independent of gender and is reported to be strongest in persons at the highest risk for type 2 diabetes, ie, those with hypertension or obesity and possibly also first-degree relatives.[7-10] Physical activity may reduce the risk of type 2 diabetes indirectly by prevention of obesity or central body fat distribution, or directly since exercise can improve insulin sensitivity in patients with type 2 diabetes and nondiabetic subjects, an effect that can persist up to 72 hours after cessation of exercise.[6,7,11,12] Indeed, in both controls and first-degree relatives, insulin sensitivity is strongly correlated with the physical work capacity as assessed by maximal oxygen uptake ($\dot{V}O_2max$).[4]

Since decreases in insulin sensitivity are known to lead to a counterbalancing elevation in insulin release (hyperinsulinemia), we wondered whether physical activity (because of the association with enhanced insulin sensitivity) is associated with decreased insulin secretion in subjects known to have an increased risk to develop type 2 diabetes, ie, first-degree relatives of type 2 diabetics. Therefore, the aim of this study was to describe the relationship of habitual physical activity with glucose tolerance, assessed by an oral glucose tolerance test (OGTT), and with insulin secretion, assessed by a hyperglycemic glucose clamp, in 37 healthy glucose-tolerant first-degree relatives of type 2 diabetic patients. For comparison, 21 healthy control subjects without a family history of type 2 diabetes were studied.

SUBJECTS AND METHODS

Subjects

Thirty-seven healthy normal glucose-tolerant first-degree relatives of type 2 diabetes patients participated in the study (10 men and 27 women). They all had a parent who developed type 2 diabetes after 50 years of age. The control group consisted of 21 healthy subjects without a family history of type 2 diabetes (4 men and 17 women). Some of these subjects have already been described.[3] All subjects were between 25 and 60 years of age. The study was approved by the local ethics committee, and after the nature of the study was explained to each participant, written informed consent was obtained. All subjects had normal values on routine laboratory measurements for hematology, hemoglobin A_{1c} ([HbA_{1c}] upper limit of normal, 6.1%), lipids, cortisol, and kidney, liver, and thyroid function. Fat-free mass was calculated from the body mass index (BMI).[13]

Habitual Physical Activity

All subjects completed a questionnaire for habitual physical activity (the modified Baecke questionnaire).[14] This questionnaire consists of 19 questions about occupation (8 questions), sports (4), and leisure time activities excluding sports activities (7). The questions refer to physical activity during the past year. If household activities or studying are the main daily activity, they are considered occupational activities. All

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responses are precoded on 5-point scales except for the questions on occupation (3-point scale) and type of sports. When the subject indicates participation in sports, a score is calculated from a combination of the intensity of the sport and the hours per week and the proportion of the year that the sport is played regularly. When more than one type of sport is mentioned, the scores are added. The total score is then coded on a 5-point scale. By averaging the responses per category, 3 indices of physical activity were obtained: the work index, the sports index, and the leisure time index. The minimum value for each index is 1 and the maximum is 5. To distinguish physically active and less active subjects, the relatives and control groups were split into 2 subgroups (high, H, and low, L) according to the sex-specific median of the work, sports, or leisure index, respectively, as the cutoff point.

Physical Work Capacity

Physical work capacity was determined by an exhaustive multistage exercise test on a cycle ergometer (Lode Excalibur, Groningen, The Netherlands). The ventilatory parameters oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were measured breath-by-breath using an Oxycon-β (Mijnhardt, Bunnik, The Netherlands). The O_2 analysis is based on the differential paramagnetic principle, CO_2 analysis on the infrared-absorption principle, and the $\dot{V}_E$ on the bidirectional vane principle (TripleV volume transducer). The respiratory quotient and the ventilation equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) were calculated. The cardiac status and heart rate were monitored continuously during the test (Megacart, Siemens, Solna, Sweden). The test was considered maximal for a RQ of 1.1 or higher, a $\dot{V}_E/\dot{V}O_2$ of 30 or higher, a heart rate that is at least the predicted maximum heart rate, ie, 220 minus age. Exhaustion was reached when the subject was not able to maintain a pedal frequency above 65 rpm.

OGTT

After an overnight fast, an OGTT was performed (75 g glucose in 300 mL water). Blood glucose was determined immediately with a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was determined by radioimmunoassay with ^{125}I-labeled insulin (IM 166; Amersham, Buckinghamshire, UK).

Hyperglycemic Glucose Clamp

Intravenous lines were placed in both forearms. One line was used for intravenous glucose infusion, and the other was used for sampling arterialized blood with the use of a heated box (55°C). A hyperglycemic glucose clamp was performed for 180 minutes, aiming at a glucose level of 10 mmol · L^{-1}, starting with an intravenous bolus of 35 mg glucose/kg per mmol · L^{-1} intended glucose increase. Glucose was analyzed with a Yellow Springs Instruments glucose analyzer at 5-minute intervals throughout the clamp; the infusion rate was adjusted according to the change in actual blood glucose. The obtained coefficients of variation were less than 5%. Blood samples for insulin analysis were obtained at all points specified in Fig 2. The glucose infusion rate (GIR) was assessed during the clamp. The insulin sensitivity index (ISI) was assessed as the GIR of the third hour, divided by the average plasma insulin of 120, 140, and 160 minutes. Plasma insulin at the end of the hour (ie, 180 minutes) was omitted, since it does not influence insulin action in the preceding 20 minutes. First-phase secretion was assessed as the area under the curve of the increment in plasma insulin from 0 to 10 minutes, and second-phase insulin secretion was assessed as the average of incremental plasma insulin at 140, 160, and 180 minutes.

Statistical Analysis

Data are given as the mean ± SEM. Plasma insulin levels were logarithmically transformed to obtain a normal distribution. These data are presented as the geometric mean and 95% confidence interval (CI).

The frequency distribution of the sexes over the groups was tested using chi-square statistics. ANOVA was used to analyze differences between the groups in baseline characteristics, physical work capacity, physical activity indices, and first- and second-phase insulin secretion. Repeated-measures ANOVA was used to investigate between-group differences and the interaction of time and group for blood glucose and plasma insulin responses during the OGTT. When appropriate, this was followed by ANOVA on the specific time points.

Linear relationships of glucose tolerance, insulin release, and the ISI with the various activity indices and physical work capacity ($\dot{V}O_2$max) were determined with Pearson correlation coefficients.

RESULTS

Characteristics

Relatives and controls were similar according to age, body weight, BMI, and fat-free mass. The sexes were equally distributed over the 2 groups (chi-square, NS). The maximal exercise test resulted in similar values for the physical work capacity ($\dot{V}O_2$max), minute ventilation, and RQ in relatives and controls. The sports and work indices were similar in the groups. The leisure index was lower in the relatives versus the controls ($P = .003$; Table 1).

Table 1. Characteristics of 37 Healthy First-Degree Relatives of Type 2 Diabetes Patients and 21 Control Subjects With High or Low Sports Activity According to the Sports Index

Characteristic	All	High	Low
Relatives			
Gender (F/M)	27/10	15/5	12/5
Age (yr)	44.7 ± 0.9	44.6 ± 1.3	44.8 ± 1.3
Body weight (kg)	74.5 ± 1.8	71.4 ± 2.3	78.2 ± 2.5
Fat-free mass (kg)	50.5 ± 1.4	48.8 ± 1.9	52.6 ± 2.1
% Fat	32.1 ± 1.1	31.6 ± 1.5	32.6 ± 1.7
BMI (kg · m^{-2})	25.1 ± 0.4	24.6 ± 0.6	25.7 ± 0.7
HbA_{1c} (%)	5.2 ± 0.1	5.2 ± 0.1	5.3 ± 0.1
$\dot{V}O_2$max (mL · kg^{-1} · min^{-1})	30.9 ± 1.4	32.6 ± 2.2	28.8 ± 1.6
$\dot{V}_E$max (L · min^{-1})	80.6 ± 4.3	83.7 ± 7.1	77.1 ± 4.3
RQ max	1.14 ± 0.01	1.14 ± 0.02	1.14 ± 0.02
Sports index	2.6 ± 0.1	3.1 ± 0.1	2.0 ± 0.1*
Leisure index	2.9 ± 0.1†	2.9 ± 0.1	3.0 ± 0.1
Work index	2.9 ± 0.1	2.8 ± 0.2	3.0 ± 0.2
Controls			
Gender (F/M)	17/4	11/2	6/2
Age (yr)	45.8 ± 1.5	44.1 ± 2.1	48.6 ± 1.7
Body weight (kg)	75.2 ± 2.3	72.1 ± 2.5	80.2 ± 3.8
Fat-free mass (kg)	49.1 ± 1.5	47.7 ± 2.0	51.3 ± 2.0
% Fat	34.3 ± 1.5	33.7 ± 1.8	35.4 ± 2.8
BMI (kg · m^{-2})	26.0 ± 0.8	25.5 ± 0.9	27.0 ± 1.4
HbA_{1c} (%)	5.2 ± 0.1	5.1 ± 0.1	5.3 ± 0.1
$\dot{V}O_2$max (mL · kg^{-1} · min^{-1})	30.0 ± 1.7	32.2 ± 2.2	26.5 ± 2.3
$\dot{V}_E$max (L · min^{-1})	84.9 ± 5.1	88.2 ± 6.9	79.6 ± 7.3
RQ max	1.14 ± 0.01	1.12 ± 0.01	1.16 ± 0.03
Sports index	2.5 ± 0.1	2.8 ± 0.1	2.0 ± 0.1*
Leisure index	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.2
Work index	3.1 ± 0.1	3.1 ± 0.1	3.1 ± 0.1

NOTE. Data are the mean ± SEM. High, sports index higher than sex-specific median; Low, sports index lower than sex-specific median.

*$P \leq .05$ by ANOVA, high *v* low.

†$P \leq .05$ by ANOVA, relatives *v* controls.

Glucose Tolerance

The relatives tended to have a higher fasting blood glucose level than the controls ($P = .089$; Table 2). After the glucose load, blood glucose increased more and remained higher in the relatives versus the controls (MANOVA, $P = .007$). From time point $t = 45$ minutes onward, blood glucose in the relatives group was significantly higher than that in the control group (all $P < .05$). Despite higher glycemia, no differences were found in plasma insulin levels, at baseline or during the OGTT.

Insulin Release and ISI

The plasma insulin response to sustained hyperglycemia (hyperglycemic clamp) was biphasic in both groups. First-phase insulin secretion was lower in the relatives ($P = .004$). Plasma insulin increased to 41.0 (34.4 to 48.9) and 60.3 (51.0 to 71.2) mU · L^{-1} at $t = 4$ minutes in relatives and controls, respectively ($P = .007$), and declined thereafter. Second-phase secretion and the GIR during the third hour were also lower in the relatives than in the control group ($P = .012$ and $P = .011$, respectively). Consequently, the ISI was similar in the groups (Table 2).

Glucose Tolerance and Insulin Release in High Versus Low Sports Index Groups

If a physically active life-style is related to glucose tolerance and insulin release, differences should exist between active and less active subjects. Therefore, the relatives and control groups were split into 2 subgroups with the sex-specific median of the work, sport, or leisure index, respectively, as the cutoff point. Only with the sport index were such differences found.

Figure 1A and B shows the results of the OGTT for relatives with a high sports index (HSI-R) and those with a low sports index (LSI-R). The HSI-R had slightly but not significantly lower glucose levels during the OGTT than the LSI-R. Glucose returned faster to the baseline level in the HSI-R versus LSI-R group (MANOVA, sport index × time effect, $P = .019$). Dur-

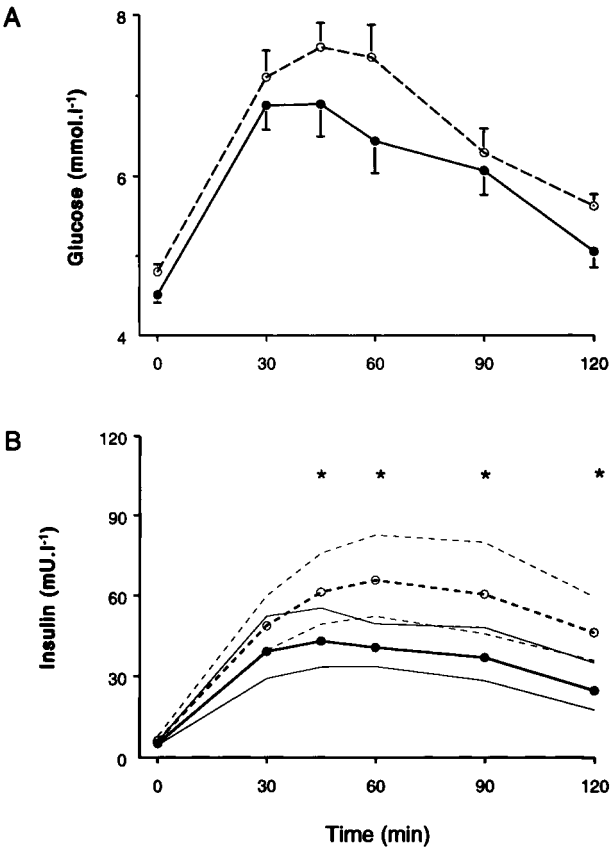

Fig 1. Mean ± SEM blood glucose (A) and geometric mean (95% CI) plasma insulin (B) during an OGTT in 18 first-degree relatives of type 2 diabetes patients with a high sports index (HSI-R, ●) and 19 with a low sports index (LSI-R, ○). Blood glucose levels during the OGTT were similar in the groups, but the values returned to baseline faster in the HSI-R (MANOVA, sport × time effect, $P = .019$) and plasma insulin was lower in the HSI-R group (MANOVA, $P = .011$). *Significant difference at specific time point.

Table 2. Fasting Blood Glucose and Plasma Insulin, Insulin Secretion Parameters, and Parameters of Insulin Action as Determined With a Hyperglycemic Glucose Clamp in 37 Healthy First-Degree Relatives of Type 2 Diabetes Patients and 21 Control Subjects

Parameter	All	High	Low
Relatives			
Fasting blood glucose (mmol · L^{-1})	4.6 ± 0.1	4.5 ± 0.1	4.8 ± 0.1
Fasting plasma insulin (mU · L^{-1})‡	5.6 (4.9-6.4)	5.1 (4.5-5.8)	6.2 (5.0-7.8)
GIR (mg · kg^{-1} · min^{-1})	9.2 ± 0.6†	9.6 ± 0.9	8.7 ± 0.8
Insulin secretion			
First-phase (mU · L^{-1} · 10 min^{-1})‡	222 (179-275)†	227 (159-325)	215 (167-277)
Second-phase (mU · L^{-1})‡	49 (42-57)†	42 (35-49)	59 (46-76)*
ISI (mg · kg^{-1} · min^{-1} · mU^{-1} · mL^{-1})	0.22 ± 0.02	0.26 ± 0.03	0.16 ± 0.02*
Controls			
Fasting blood glucose (mmol · L^{-1})	4.4 ± 0.1	4.5 ± 0.1	4.4 ± 0.1
Fasting plasma insulin (mU · L^{-1})‡	5.9 (5.0-6.9)	5.8 (4.6-7.2)	6.0 (4.3-8.2)
GIR (mg · kg^{-1} · min^{-1})	11.9 ± 0.9	12.6 ± 1.1	10.8 ± 1.4
Insulin secretion			
First-phase (mU · L^{-1} · 10 min^{-1})‡	354 (291-432)	320 (240-425)	419 (318-553)
Second-phase (mU · L^{-1})‡	70 (53-92)	60 (39-92)	89 (64-122)
ISI (mg · kg^{-1} · min^{-1} · mU^{-1} · L^{-1})	0.20 ± 0.03	0.24 ± 0.04	0.14 ± 0.03*

NOTE. Data are the mean ± SEM. High, sports index higher than sex-specific median; Low, sports index lower than sex-specific median.
*$P \leq .05$ by ANOVA, high *v* low.
†$P \leq .05$ by ANOVA, relatives *v* controls.
‡Geometric mean (95% CI).

ing the OGTT, insulin levels in HSI-R did not increase as much as insulin levels in LSI-R, and the difference between the groups was significant (MANOVA, $P = .011$). Plasma insulin levels from $t = 45$ minutes onward were significantly lower in the HSI-R (all $P < .05$).

Interestingly, during the hyperglycemic clamp, plasma insulin levels were also lower in the HSI-R group versus the LSI-R group, particularly second-phase secretion ($P = .016$). It is of note that the GIR was not different and, as expected, the ISI was clearly higher in the HSI-R versus the LSI-R ($P = .011$; Fig 3A and Table 2).

In the control group, OGTT results were not significantly different for subjects with a high sports index (high sports index-controls [HSI-C]) and those with a low sports index (LSI-C) (Fig 2A and B). In addition, first-phase and second-phase secretion during the clamp were similar in HSI-C and LSI-C. The ISI was higher in HSI-C versus LSI-C ($P = .029$; Fig 3B and Table 2).

Glucose Tolerance and Insulin Release Related to Physical Work Capacity ($\dot{V}O_2$max)

The sports index, but not the leisure or work index, was positively correlated with $\dot{V}O_2$max in the relatives and controls

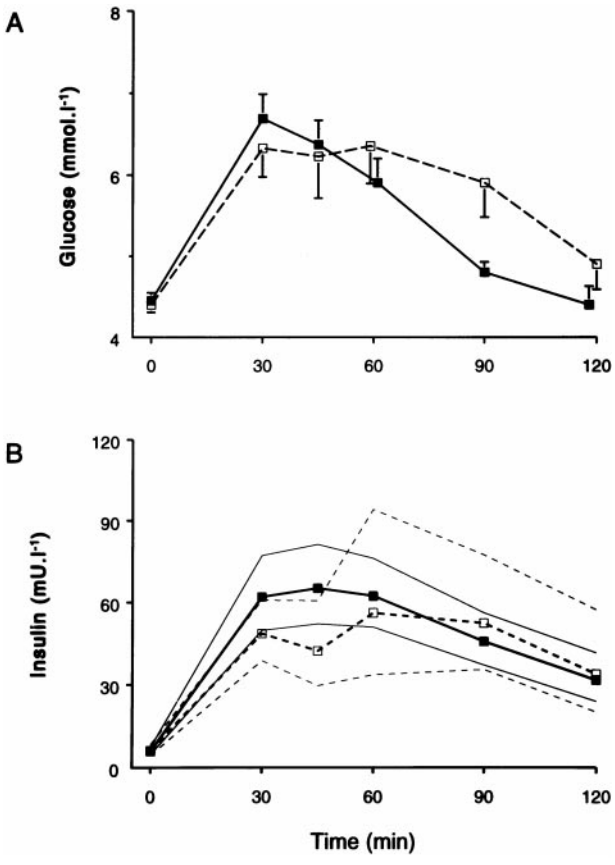

Fig 2. Mean ± SEM blood glucose (A) and geometric mean (95% CI) plasma insulin (B) during an OGTT in 13 healthy controls with a high sports index (HSI-C, ■) and 8 with a low sports index (LSI-C, □). Both blood glucose and plasma insulin during the OGTT were similar in the groups. In the HSI-C group, the insulin levels at $t = 45$ min was lower and the interaction effect was significant (MANOVA, group × time, $P = .035$).

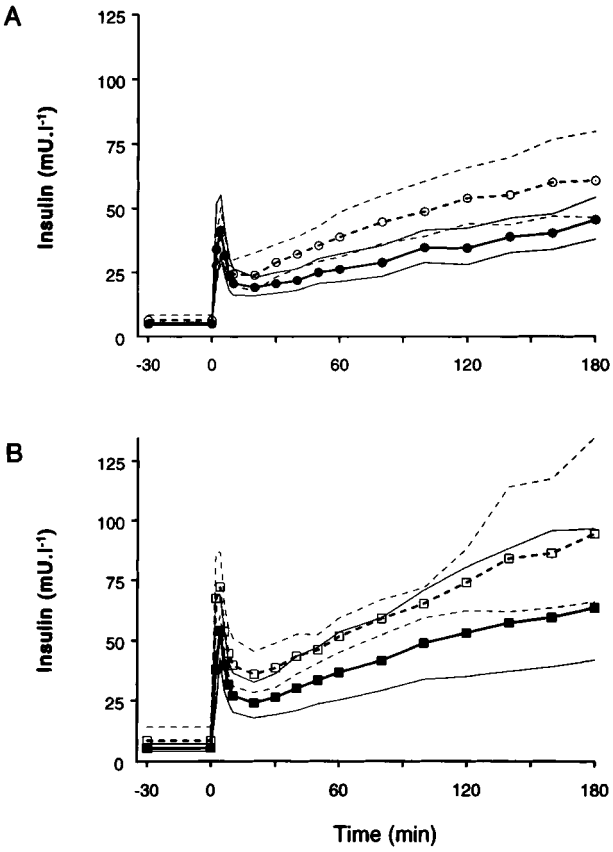

Fig 3. Plasma insulin (geometric mean) during the hyperglycemic glucose clamp in first-degree relatives of type 2 diabetes patients (A) with a high (●) or low (○) sports index and healthy controls (B) with a high (■) or low (□) sports index. The heavy lines are the geometric mean and the thin lines the 95% CI. In relatives, second-phase secretion was lower in the high *v* low sports index group ($P = .016$). In controls, differences in first-phase and second-phase secretion between the high and low sports index groups were not statistically significant.

($r = .35$, $P = .034$, and $r = .49$, $P = .024$, respectively). $\dot{V}O_2$max correlated inversely with fasting plasma insulin and the insulin level at 120 minutes during the OGTT in the relatives (both $r = -.35$, $P = .036$). In the controls, the correlation between $\dot{V}O_2$max and fasting plasma insulin was borderline significant ($r = -.41$, $P = .067$), whereas the correlation between the $\dot{V}O_2$max and the insulin level at 120 minutes was significant ($r = -.44$, $P = .044$). First-phase insulin secretion was inversely correlated with $\dot{V}O_2$max in the relatives only ($r = -.40$, $P = .015$). Second-phase insulin secretion was not correlated with $\dot{V}O_2$max in either group. $\dot{V}O_2$max correlated positively with the GIR in the relatives only ($r = .34$, $P = .042$) and with the ISI in both groups (relatives, $r = .38$, $P = .021$; controls, $r = .44$, $P = .045$). When the relatives or controls were subdivided according to a higher or lower $\dot{V}O_2$max, the differences in glucose tolerance and insulin secretion resembled those found between the high and low activity subgroups, but the differences were not statistically significant (not shown).

DISCUSSION

These studies were undertaken to address the question of whether regular physical activity influences insulin secretion in

normal glucose-tolerant first-degree relatives of type 2 diabetes patients. They show that these relatives have a diminished insulin secretion as measured with a hyperglycemic glucose clamp compared with the controls. Moreover, the relatives who engage regularly in physical activity secrete less insulin than their less active counterparts during the clamp, whereas no difference in the GIR was observed. As expected, these relatives had a higher ISI, as measured during the last hour of the clamp, than the less active relatives.

From this study, it appears that particularly the measure of sports participation, as assessed by the sports index, is associated with insulin secretion and insulin sensitivity, and not the other indices of physical activity or the $\dot{V}O_2$max per se.

It might be argued that the conditions during the hyperglycemic clamp (ie, hyperglycemia) are not physiological. However, it has been shown that there is no difference between insulin sensitivity indices measured by hyperglycemic and euglycemic glucose clamps and there is a strong correlation between the indices.[5,15] In addition, we believe that the differences in insulin secretion and the ISI are of clear physiological importance, since the insulin response to an oral glucose load was also reduced. These results extend to the reports from other groups who found reduced insulin responses to an OGTT and lower insulin secretion during hyperglycemic glucose clamps in trained versus untrained subjects, as well as cross-sectional and longitudinal studies.[11,16]

The GIR was lower in the relatives versus the controls, in line with the results from Nyholm et al.[4] However, we do not agree with their conclusion that the lower GIR could be due to a lower physical work capacity of the relatives, since in our studies this capacity is the same in relatives and controls. The discrepancy between their study and ours might be due to the different methods used for determination of physical capacity. Nyholm et al.[4] estimated aerobic power using the submaximal Åstrand exercise test. It is known that this test can be applied as a screening test for evaluation of the functional capacity of the oxygen transport system. The standard error of the prediction in highly trained athletes is about 10%, but in moderately trained individuals, it is up to 15%.[17] In our opinion, it is therefore not accurate enough. We have used an exhaustive exercise test instead, which has a standard error of 5%.[17]

The higher ISI in relation to a physically active life-style was to be expected, since this life-style is associated with an increase in $\dot{V}O_2$max. This parameter is a major determinant of insulin sensitivity in various populations, eg, healthy individuals, type 2 diabetics, and healthy first-degree relatives of type 2 diabetes patients.[4,18] In our studies, in both groups, $\dot{V}O_2$max was positively related to the ISI. The difference in $\dot{V}O_2$max between high and low activity groups was not pronounced. This is due to the fact that $\dot{V}O_2$max is largely genetically determined and can be increased by training only 20% to 30%.[17] When the relatives or controls with a higher than median $\dot{V}O_2$max were compared with the counterparts with a lower $\dot{V}O_2$max, the differences in glucose tolerance or insulin secretion were not significant. This indicates that the protective effect of physical activity against developing type 2 diabetes may only be partly explained by $\dot{V}O_2$max and that other factors are involved. To obtain an effect of physical activity on glucose tolerance and insulin sensitivity, moderate- or high-intensity exercise is needed, and it is not likely that these intensities are reached during occupational or leisure time activities, in contrast to sports activities. This probably explains why the sports index relates to glucose tolerance, insulin secretion, and insulin sensitivity while the leisure and work indices do not.

The beneficial effects of regular physical exercise on glucose metabolism appear to be explained by multiple factors including increased muscle mass, augmented muscle blood flow and capillary area, enhanced mitochondrial oxidative enzyme capacity, and activation of the glucose transport system.[11] This latter phenomenon is due to upregulation of GLUT4 (the main glucose transporter in muscle), which enhances both insulin-mediated and non–insulin-mediated glucose uptake, in combination with enhanced glucose phosphorylation and/or glycogen synthase activity.[18,19] Insulin action is improved not only in muscle but also in liver and adipocytes.[20] Physical activity is known to enhance insulin action, especially in an acute fashion.[20] However, the effect of physical training on insulin sensitivity is larger than the effect elicited by a single bout of exercise and therefore represents an adaptive change in trained subjects.[21]

Despite the increase in insulin sensitivity, the GIR in the group of highly active relatives was not different from that in the less active group. A lower GIR in first-degree relatives has been related to abnormal activities of glycogen synthase[22] and tyrosine kinase.[23] Because of the stimulatory effect of regular physical activity on glycogen synthase activity, an increase at least to the level of the control group would have seemed more plausible.

It may seem that an active life-style deteriorates the insulin secretory capacity of the relatives, since the differences in insulin secretion between highly active and less active relatives are similar to the differences between the relatives and controls. The absence of hyperglycemia in the highly active relatives indicates the opposite. The lower insulin secretion in the active relatives clearly points to a downregulation of the pancreatic β cell. Obviously, just as chronic resistance to insulin (obesity) leads to an upregulation of insulin secretion (higher setpoint) with elevations in fasting plasma insulin and the insulin secretory response after meals[24] and elevations in insulin secretion as assessed by hyperglycemic glucose clamp,[25] it may well be that a tendency for a decrease in blood glucose, as occurs after exercise, leads to a decrease in insulin secretion (lower setpoint). The latter supposition is supported by the recent finding that otherwise healthy underweight subjects have lower insulin secretion than healthy normal-weight controls during an intravenous glucose tolerance test.[26] It also agrees with the results of a study on the effects of moderate exercise on postprandial glucose homeostasis in NIDDM patients, in which glucose disappearance and glucose oxidation were decreased to normal levels within a few hours after exercise, occuring at lower plasma insulin levels.[27] This also points to a change in the setpoint of the pancreatic β cell for insulin secretion in response to a certain plasma glucose level, for which the authors invoked the inhibitory effect of catecholamines on insulin release.

Abnormalities in β-cell function, sometimes referred to as ''exhaustion'' of the cell, can lead to the development of impaired glucose tolerance and finally type 2 diabetes. The lower insulin secretion as found in our studies in the highly

active subjects may reduce the risk for developing type 2 diabetes, for example, by diminishing β-cell exhaustion.

In conclusion, in first-degree relatives of type 2 diabetes patients, regular physical activity is associated not only with an increase of insulin sensitivity but also with a downregulation of the pancreatic β cell. This downregulation may provide an extra mechanism by which physical activity inhibits the development of type 2 diabetes in these subjects with increased risk, since it may postpone the ''exhaustion'' of the pancreas that is found in type 2 diabetes.

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