Insulin Sensitivity, Glucose Effectiveness, and Insulin Secretion in Nondiabetic Offspring of Patients With Non–Insulin-Dependent Diabetes Mellitus: A Cross-Sectional Study

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To evaluate the factors that determine the worsening of intravenous glucose tolerance in subjects at high risk for developing non–insulin-dependent diabetes mellitus (NIDDM), 15 glucose-tolerant offspring of NIDDM patients and 21 control subjects were studied. Each subject underwent a frequently sampled intravenous glucose tolerance (FSIGT) test. The intravenous glucose tolerance index (K_G index) was calculated between minutes 10 and 40 of a FSIGT test. Insulin sensitivity (S_I), glucose effectiveness at zero insulin (GEZI), and first- and second-phase insulin responsiveness (Φ_1 and Φ_2) were estimated using glucose and insulin kinetic minimal models. The acute insulin response to glucose (AIRg) was calculated as the area under the insulin curve above the basal level between 0 and 10 minutes, and the suprabasal insulin effect was determined by the product of S_I times AIRg. Offspring had a lower S_I than control subjects (14.1 ± 7.5 *v* $9.25 \pm 4.20 \times 10^{-5} \cdot min^{-1}(pmol \cdot L^{-1})^{-1}$, $P < .01$), and their AIRg was similar ($3,284 \pm 2,280$ *v* $3,105 \pm 1,499$ pmol $\cdot L^{-1}$, NS). Sample division according to the median K_G value showed that control subjects with low tolerance had a lower AIRg ($4,417 \pm 2,531$ *v* $2,043 \pm 1,068$ pmol $\cdot L^{-1}$, $P < .05$) and a lower suprabasal insulin effect (0.057 ± 0.03 *v* 0.023 ± 0.009 min^{-1}, $P < .05$) than control subjects with high tolerance. Offspring with low tolerance had a lower AIRg ($2,574 \pm 1,197$ *v* $3,707 \pm 1,656$ pmol $\cdot L^{-1}$, $P < .05$) and a lower GEZI (0.101 ± 0.05 *v* $0.212 \pm 0.08 \cdot 10^{-1} \cdot min^{-1}$, $P < .05$) than offspring with high tolerance. Offspring with high and low tolerance showed lower Φ_1 (375 ± 155 *v* 272 ± 181 *v* 698 ± 336 (pmol $\cdot L^{-1}$)min(mmol $\cdot L^{-1}$), NS) than control subjects with high tolerance. In conclusion, our data suggest that decreases in GEZI and AIRg are the main factors responsible for the worsening of intravenous glucose tolerance in the offspring of NIDDM patients.

DESPITE THE LARGE NUMBER of publications on the subject, a controversy still continues as to what is the first metabolic defect to appear in the genesis of non–insulin-dependent diabetes mellitus (NIDDM).[1-7] There are two possible ways of approaching this problem: longitudinal study of initially normotolerant subjects[6-9] who subsequently become diabetic, and cross-sectional study of subjects at high risk for developing the disease.[2-4,10-12] In the second case, first-degree relatives of subjects with NIDDM,[2-4,13,14] women with a gestational diabetes history,[10] identical twins discordant for NIDDM,[12] and certain ethnic populations with a high prevalence of NIDDM (Pima Indians and Mexican-Americans)[11,15] have been studied. Although the most generally accepted idea[2-4,8,9,15] is that the first defect to appear in the genesis of NIDDM is lower insulin sensitivity, specifically, an impairment of nonoxidative glucose metabolism,[2,4] other studies[6,7,13,14] indicate that an alteration of insulin secretion is also present in the very early stages of this metabolic disorder, even if it is not the primary defect.[6] Studies have been reported in which normal or increased insulin secretion in subjects at high risk for developing NIDDM has been demonstrated, and these compel us to take into account the fact that insulin precursors (intact and split proinsulins) cross-react in standard radioimmunoassays.[16] Another factor we must consider is the concept of adequate insulin secretion for the degree of insulin resistance.[17] Finally, the importance of another factor that influences glucose tolerance has recently been reported, ie, the ability of glucose to promote its own disposal (glucose effectiveness),[18,19] which may become altered in certain subjects who later develop NIDDM.[20]

The objective of the current study was to evaluate insulin sensitivity, glucose effectiveness, and insulin secretion in a group of glucose-tolerant offspring of subjects with NIDDM, and to ascertain which factors determine the worsening of intravenous glucose tolerance in this population.

SUBJECTS AND METHODS

Subjects

The offspring group consisted of 20 non-obese subjects with normal glucose tolerance and no family history of hypertension, but with one parent with NIDDM. Probands were selected only if diabetes was diagnosed in one of the parents after age 40 years and they were treated with diet alone or oral hypoglycemic agents for at least 2 years. The offspring were matched according to age, sex, and body mass index (BMI) to a group of 25 normotolerant healthy subjects without any family history of NIDDM or essential hypertension who were not taking medications that could affect glucose metabolism. No subjects had known cardiac, renal, or hepatic disease. Normal glucose tolerance was defined in all cases per World Health Organization criteria.[21] The family history of hypertension and NIDDM for control subjects was determined by personal interview and measurement of blood pressure and basal glycemia in the parents and siblings of the subjects studied. All subjects were aged 18 to 55 years, since insulin resistance is relatively frequent at puberty and in those over age 55. The study protocol was approved by the Santiago University Hospital research ethics committee, and informed consent was obtained from each participant.

Study Protocol

The subjects consumed a diet containing at least 300 g carbohydrate per day for 3 days before the study, and they were instructed not to perform extra exercise for 1 week before the study. Each subject came

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to the Hospital at 8:30 in the morning after a 10- to 12-hour overnight fast. With the subject recumbent, an antecubital vein in each arm was cannulated with a 20-gauge catheter. One of the catheters was used for blood sampling and the other for glucose injection. The patency of the catheters was maintained with isotonic saline infusion. Basal glucose and insulin values were obtained from blood samples taken 20, 15, 10, 5, and 1 minutes prior to injection of glucose. At time 0, injection of 0.3 g/kg 50% (wt/vol) dextrose was initiated; injection was completed in less than 2 minutes, and further blood samples were taken 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, and 180 minutes after injection. Blood samples were collected in precooled glass tubes containing lithium heparin and 4 mg NaF. All samples were kept on ice until centrifugation. Later, the aliquots were centrifuged and stored at −20°C pending determination of glucose and insulin.

Minimal Model of Glucose Kinetics

Bergman's minimal model was used to calculate both insulin sensitivity (S_I) and glucose effectiveness at basal insulin (S_G) indices.[22] Briefly, the minimal model is a mathematical representation of the kinetics of glucose during a frequently sampled intravenous glucose tolerance (FSIGT) test. The model is represented by two nonlinear, first-degree differential equations. The parameters of the model were estimated with a nonlinear least-squares technique using a personal computer program (STELLUM-MMg).[23,24] Once the model parameters have been estimated, it is possible to calculate both S_I and S_G indices. The basal insulin component of S_G is BIE, calculated as the product of basal insulin (Ib) and the S_I index. Glucose effectiveness at zero insulin (GEZI) is the difference between S_G and BIE: GEZI = $S_G - (S_I \cdot Ib)$.[25] To ensure the accuracy of minimal-model indices, the fractional standard deviation (FSD) was calculated[26]: when the FSD of S_I was higher than 6% or the FSD of S_G was higher than 15%, the coefficient of variation (CV) of these indices was calculated using the Monte Carlo technique, and only CVs less than 34% were accepted as valid.[27]

Minimal Model of Insulin Kinetics

This model is the mathematical representation of plasma insulin when plasma glucose is provided during a FSIGT test.[28] The estimation of minimal-model insulin kinetics parameters was performed in the same way as for glucose, using another personal computer program (STELLUM-MMi). The parameters enable calculation of both Φ_1 and Φ_2 indices. First-phase insulin responsiveness (Φ_1) is the amount of insulin that enters the plasma insulin compartment per unit of change in plasma glucose in response to the intravenous glucose load. Second-phase insulin responsiveness (Φ_2) is the proportionality factor between the increase in the glucose concentration above a threshold glucose level and the increase in second-phase insulin secretion.

Calculations

An intravenous glucose tolerance index, K_G, was calculated as the slope of the least-squares regression line relating to the natural logarithm of glucose concentration to time between 10 and 40 minutes.

The acute insulin response to glucose (AIRg) was expressed as the area under the insulin curve above the basal level between 0 and 10 minutes. This variable was calculated using the trapezoidal method.

The product of $S_I \times$ AIRg represents insulin-mediated glucose uptake due to the hyperbolic relationship that exists between insulin sensitivity and β-cell function [17] To maintain the same units in this calculation, the value of AIRg was divided by 10.

Assays

The plasma glucose level was measured in triplicate using a Hitachi (Barcelona, Spain) 737 autoanalyzer with a glucose oxidase method (intraassay CV, 0.5%; interassay CV, 1.6%) The immunoreactive plasma insulin level was measured by radioimmunoassay using a commercial kit (ICN Pharmaceuticals, Horsham, PA). Intraassay and interassay CVs were 7% and 11%, respectively.

Table 1. General Characteristics of the Subjects

Characteristic	Control (n = 21)	Offspring (n = 15)
Age (yr)	32 ± 10	26 ± 12
Sex ratio (M/F)	9/12	7/8
Height (cm)	158 ± 9	161 ± 8
Weight (kg)	57.5 ± 5.8	57.2 ± 6.9
BMI ($kg \cdot m^{-2}$)	22.8 ± 2.3	22.1 ± 1.9
SBP (mm Hg)	119.2 ± 8.6	120.0 ± 9.1
DBP (mm Hg)	72.6 ± 7.7	70.5 ± 8.1
Basal glucose ($mmol \cdot L^{-1}$)	4.8 ± 0.3	5.2 ± 0.6*
Basal insulin (pmol L^{-1})	48 ± 22	100 ± 57*
2-h plasma glucose ($mmol \cdot L^{-1}$)†	4.6 ± 0.5	5.1 ± 0.4*

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*$P < .01$.

†120 minutes after 75-g oral glucose tolerance test.

Statistical Analysis

Data are reported as the mean ± SD. Normality was checked using the Shapiro-Wilk test For comparisons, the nonpaired Student *t* test or the Mann-Whitney test were used as appropriate. For comparisons among subgroups, ANOVA or Kruskal-Wallis tests were used. The post hoc Bonferroni test was used for pair comparisons. A *P* value less than .05 was taken to indicate statistical significance. Statistical analysis was performed with the SPSS (Chicago, IL) software package.

RESULTS

Only 21 control subjects and 15 probands were finally included in the study. The other nine subjects were excluded because their minimal-model parameters did not meet the previously established accuracy criteria. General characteristics of the subjects are shown in Table 1. Plasma glucose and insulin levels during the FSIGT are illustrated in Fig 1. The offspring of NIDDM subjects had significantly higher basal glucose and insulin than the control subjects, with the insulin sensitivity being significantly lower (34.4%). No significant differences were observed between the two groups with regard to intravenous glucose tolerance and the other parameters studied (Table 2).

Subsequently, the subjects were divided into four subgroups according to the K_G index, with the dividing line being the median K_G for the whole sample of subjects studied. The results are shown in Table 3 and Fig 2. The two subgroups of control subjects (with high and low K_G) had significantly lower basal glucose and insulin levels than the subgroup of offspring with a low K_G, as well as greater insulin sensitivity. On the other hand, the subgroups of subjects with a low K_G (control subjects and offspring) had a lower GEZI, suprabasal insulin effect, and AIRg than the subjects with high intravenous glucose tolerance. Within the control group, worse intravenous glucose tolerance was explained by a smaller suprabasal insulin effect and lower insulin secretion. Glucose effectiveness was also lower but did not attain statistical significance, and there were no differences in insulin sensitivity. In the offspring of NIDDM subjects, the lower intravenous glucose tolerance was a consequence of less insulin secretion, less GEZI, and a smaller suprabasal insulin effect. First-phase insulin responsiveness was significantly reduced in the control group with low tolerance and in the

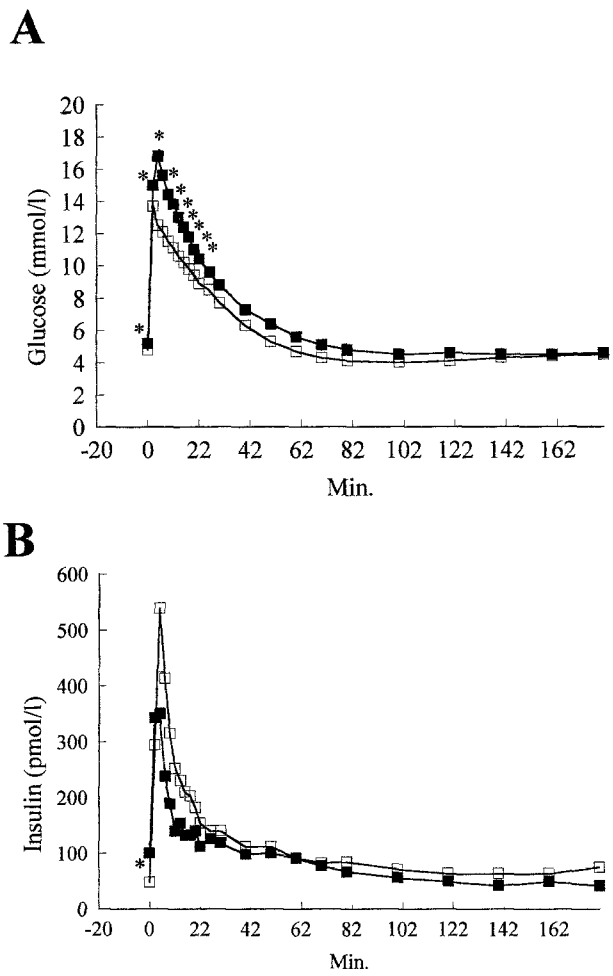

Fig 1. Mean plasma concentration profiles for glucose (A) and insulin (B) during an intravenous glucose tolerance test in 21 control subjects (□) and 15 offspring of patients with NIDDM (■). The glucose load was administered at time 0 (0.3 g/kg body weight). *$P < .05$.

offspring subgroups regardless of whether the K_G was high or low.

DISCUSSION

The present study demonstrates that the main metabolic alteration in the offspring of NIDDM patients is insulin resistance, with no change in insulin secretion or glucose effectiveness. Compensatory hyperinsulinemia and higher basal glucose levels were observed in the proband group. On the other hand, the control subjects with decreased intravenous glucose tolerance have less first-phase insulin secretion and a smaller suprabasal insulin effect. In contrast to control subjects, the probands with lower glucose tolerance have lower glucose effectiveness and less insulin secretion than the probands with good tolerance. Lastly, our study demonstrates that control subjects with low tolerance, as well as the two subgroups of probands, display significantly lower first-phase insulin responsiveness than the control subjects with high tolerance.

Table 2. Comparison Between Control Subjects and NIDDM Relatives

Variable	Control	Offspring
K_G index (min^{-1})	1.93 ± 0.65	1.74 ± 0.50
S_I index ($\times 10^{-5} \cdot min^{-1}$ ($pmol \cdot L^{-1}$)$^{-1}$]	14.1 ± 7.5	9.25 ± 4.20*
S_G index ($\times 10^{-1} \cdot min^{-1}$)	0.213 ± 0.07	0.220 ± 0.08
GEZI ($\times 10^{-1}$ min^{-1})	0.159 ± 0.08	0.153 ± 0.09
AIRg ($pmol \cdot L^{-1} \cdot min$)	3,284 ± 2,280	3,105 ± 1,499
$S_I \times$ AIRg (min^{-1})	0.041 ± 0.03	0.027 ± 0.01
Φ_1 index [($pmol \cdot L^{-1}$)min(mmol · L^{-1}]	438 ± 322	315 ± 221
Φ_2 index [($pmol \cdot L^{-1}$)min^{-2}(mmol · L^{-1})]	2,457 ± 1,161	2,102 ± 1,290

*$P < .001$.

NIDDM is a disorder characterized by insulin resistance and impaired insulin secretion. For decades, research teams have tried to establish which of these defects appears first, by studying subjects with a greater risk for the disease.[2-6,8-15,29] The presence of insulin resistance and basal hyperinsulinemia in a group of subjects at high risk for NIDDM, as in the offspring of diabetic subjects, coincides with the findings of other groups.[3,4] The most generally accepted idea is that the initial disorder in the genesis of NIDDM is insulin resistance[2-4,8,15] and that this is a genetic disorder.[12,30] Furthermore, studies in normotolerant subjects of ethnic groups with a high prevalence of NIDDM (Pima Indians,[8,15] Nauruans,[31] and Mexican-Americans[4,11]) concur with this hypothesis. Based on some of the studies, a development model of NIDDM has been established in which insulin resistance is responsible for the change from normotolerance to glucose intolerance, and in which altered insulin secretion would then be responsible for the onset of NIDDM.[8] However, data exist that make it difficult to believe that insulin resistance is the only factor responsible for the impairment of glucose tolerance. Thus, for example, not all obese subjects who have marked insulin resistance become glucose-intolerant, and neither do all of the relatives of NIDDM patients, who as a group have insulin resistance, develop NIDDM.[9] Recently, it has been reported that there is a hyperbolic relationship between insulin sensitivity and insulin secretion such that a subject with insulin resistance will maintain normal glucose tolerance at the expense of compensatory hyperinsulinemia.[17] It follows that although the offspring of NIDDM patients in our study have insulin secretion comparable to that of the control subjects, this would be inadequate for the degree of insulin resistance, although, probably due to the sample size, it is not sufficient to produce a meaningful deterioration in glucose tolerance. These results differ from other studies that found increased insulin secretion in relatives of NIDDM patients,[3,4,9,32] but coincide with studies that found comparable[2,13] or reduced[6,12,14] (with respect to the control subjects) insulin secretion. Our study demonstrates that subjects with worse intravenous glucose tolerance, irrespective of the degree of insulin resistance, have a smaller AIRg. In the case of offspring of NIDDM patients, they have both lower glucose effectiveness and first-phase insulin responsiveness. These results are similar to the findings from Doi et al.[33] Moreover, Henriksen et al[13] found that the Φ_1 index was reduced for the given insulin sensitivity in the relatives group, and Johnston et al[14] found that the acute insulin response to arginine was not increased in relatives of NIDDM patients.

The trajectory of our results is similar to that of recent investigations that studied the progression of groups at risk of developing diabetes, finding that an impairment in insulin secretion was the first defect involved in the development of

Table 3. Metabolic Variables of the Subjects Divided According to the K_G Index

Variable	Control		Offspring	
	$K_G \leq 1.72$	$K_G > 1.72$	$K_G \leq 1.72$	$K_G > 1.72$
No. of subjects	10	11	8	7
Age (yr)	33 ± 10	31 ± 11	26 ± 12	25 ± 8
BMI ($kg \cdot m^{-2}$)	22.6 ± 2.3	23.0 ± 2.4	22.4 ± 1.8	21.7 ± 2.0
Basal glucose ($mmol \cdot L^{-1}$)	4.8 ± 0.3	4.7 ± 0.3	5.3 ± 0.4*†	5.0 ± 0.7
Basal insulin ($pmol \cdot L^{-1}$)	56 ± 16	41 ± 27	108 ± 76*†	86 ± 34
K_G index (min^{-1})	1.44 ± 0.2	2.37 ± 0.5*‡	1.39 ± 0.3	2 14 ± 0.4*‡
S_I index [$\times 10^{-5} \cdot min^{-1}(pmol \cdot L^{-1})^{-1}$]	13.8 ± 9.3	14.4 ± 5.8	9.4 ± 4.8*†	9.1 ± 3.6*†
S_G index ($\times 10^{-1} \cdot min^{-1}$)	0.185 ± 0.04	0.239 ± 0.08	0.171 ± 0.04	0.276 ± 0.07*‡
GEZI ($\times 10^{-1} \cdot min^{-1}$)	0.126 ± 0.06	0.189 ± 0.09	0.101 ± 0.05†	0.212 ± 0.08‡
AIRg ($pmol \cdot L^{-1} \cdot min$)	2,043 ± 1,068	4,417 ± 2,531*	2,574 ± 1,197†	3,707 ± 1,656‡
$S_I \times$ AIRg (min^{-1})	0.023 ± 0 009†	0.057 ± 0.03	0.024 ± 0.01†	0.031 ± 0.01†
Φ_1 index [$(pmol \cdot L^{-1})min(mmol \cdot L^{-1})$]	234 ± 65†	698 ± 336	272 ± 181†	375 ± 155†
Φ_2 index [$(pmol \cdot L^{-1})min^{-2}(mmol \cdot L^{-1})$]	1,989 ± 1,005	2,259 ± 1,362	1,823 ± 1,233	2,121 ± 1,226

*$P < .05$ *v* control $K_G \leq 1.72$.
†$P < .05$ *v* control $K_G > 1.72$.
‡$P < .05$ *v* relative $K_G \leq 1.72$.

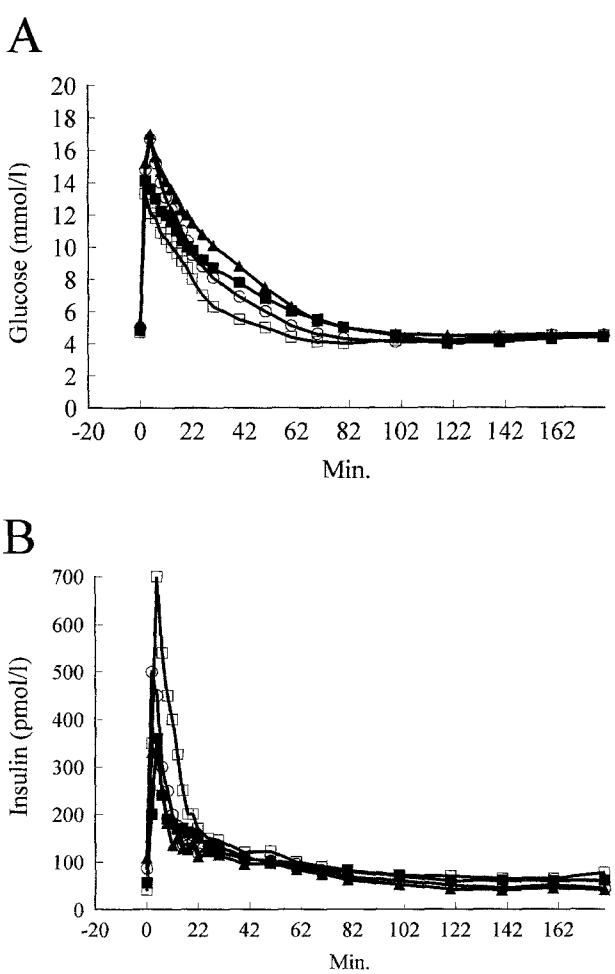

Fig 2. Mean plasma concentration profiles for glucose (A) and insulin (B) during an intravenous glucose tolerance test in 4 subgroups of subjects divided according to the KG median: 10 control subjects with a low KG (■), 11 control subjects with a high KG (□), 8 offspring subjects with a low KG (▲), and 7 offspring subjects with a high KG (○).

diabetes.[6,7] In a very recent study, Haffner et al[7] found that the main factors predicting the progression to impaired glucose tolerance are a decrease in insulin secretion and an increase in insulin resistance. Pimenta et al[6] also recently demonstrated with hyperglycemic clamps that between 36% and 54% of first-degree relatives of NIDDM patients had impaired β-cell function and only 15% had insulin resistance. Whether an impairment in insulin secretory capacity is a primary inherited defect[6,12] or is secondary to insulin resistance or glucose toxicity[34] is unclear. However, Vaag et al[12] have reported that identical twins discordant for NIDDM showed defects in insulin secretion and insulin action, and these subjects possess the necessary NIDDM susceptibility genes.

Another of the factors that must be taken into account when assessing glucose tolerance is glucose effectiveness.[18,19,35] The results obtained in different studies are disparate. Neither we nor Osei et al[3] found any differences when comparing relatives of NIDDM patients with control subjects; however, Henriksen et al[13] found an increase in GEZI in relatives of NIDDM patients, and Martin et al[20] found that the decrease in glucose effectiveness was linked to the evolution of diabetes in a certain subgroup of subjects. Despite the different results in the above-mentioned studies, these differences may be more apparent than real. Thus, Henriksen et al[13] suggested that the increment in GEZI in relatives of NIDDM patients was a compensating mechanism to maintain normal glucose tolerance, and in our study, the offspring with a high K_G had an increased GEZI in comparison to the offspring with worse glucose tolerance, and even higher levels, although not significant, versus controls with a high K_G. Also, the control subjects with low tolerance had a reduced GEZI, although this was not statistically significant.

Recently, it has been reported that the AIRg conditions glucose effectiveness values in such a way that the minimal model overestimates S_G in normal dogs.[36] However, although caution must be exercised in the interpretation of differences in minimal-model estimates of glucose effectiveness between groups of subjects with significantly different levels of insulin secretory function, other studies in dogs[37] and in humans[38]

found similar values for directly measured and minimal model–derived S_G. Moreover, we have observed that during physical exercise, GEZI increased significantly despite a significant reduction of the AIRg.[39]

Given the heterogeneity of NIDDM and its polygenic form of inheritance, and in light of the existing literature on the subject, it does not seem probable that there is a single defect responsible for the deterioration of glucose tolerance.[1,29] The presence of an initial impairment in the secretory capacity of the β cell accelerated by the insulin resistance present in certain groups at risk or secondary to obesity, and associated in some instances with reduced glucose effectiveness, will lead to the onset of NIDDM. Other factors such as ethnic differences,[15] body fat distribution,[40] age,[41] diet,[42] and physical activity[39] will accelerate or slow the process.

To summarize, our data suggest that as a group, the offspring of subjects with NIDDM are insulin-resistant and have insulin secretion comparable to that of control subjects. However, the factors responsible for the impairment of intravenous glucose tolerance in these subjects are a lower insulin secretion and lower GEZI, irrespective of the degree of insulin resistance.

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