Glucose Metabolism in Lean Patients With Mild Type 2 Diabetes Mellitus: Evidence for Insulin-Sensitive and Insulin-Resistant Variants

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Obesity and type 2 diabetes mellitus (DM2) are 2 closely related syndromes, with obesity occurring in 70% to 80% of DM2 patients. Both syndromes are characterized by insulin resistance (IR). However, the metabolic characteristics of lean DM2 patients are not clearly defined, a fact attributed to the heterogeneity of the diabetes syndrome. Our objective was to study glucose metabolism in lean DM2 patients, in terms both of the basal and the insulin-stimulated states, and particularly, to investigate whether 2 subpopulations of diabetic patients are identifiable on the basis of degree of IR. Sixteen nonobese (body mass index [BMI] less than 27 kg · m^{-2}) DM2 subjects with light to moderate fasting hyperglycemia were studied. Ten healthy subjects were used as a control group, with no family history of DM2 and matched by age, sex, and BMI in the diabetic group. All participants underwent an intravenous glucose tolerance test with frequent sampling over 180 minutes. Insulin sensitivity (IS) and glucose effectiveness at zero insulin (GEZI) were calculated using Bergman's minimal model. Non–insulin-mediated glucose uptakes (NIMGU) and insulin-mediated glucose uptakes (IMGU) were calculated for the basal (F) and insulin-stimulated states at 11.1 mmol/L of glucose (11.1). The β-cell function was calculated via the acute insulin response to glucose (AIRg). Clustering techniques were used to identify subpopulations of DM2 patients on the basis of insulin sensitivity. The group of DM2 patients was characterized by both IR (IS index, 6.23 ± 4.68 *v* 12.75 ± 7.74 × 10^{-5} · min^{-1} · (pmol · L^{-1})$^{-1}$, $P < .01$) and insulin secretion abnormalities (AIRg, 336 ± 456 *v* 1,912 ± 1,293 pmol/L · min, $P < .0001$), but showed similar values for GEZI (0.011 ± 0.005 *v* 0.011 ± 0.007 min^{-1}, not significant [NS]) in comparison to the control group. For the basal state, no differences were found between the DM2 patients and control subjects for NIMGU$_F$ (0.13 ± 0.07 *v* 0.08 ± 0.05 mmol/kg · min, NS) or for IMGU$_F$ (0.05 ± 0.04 *v* 0.05 ± 0.02 mmol/kg · min, NS). For the insulin-stimulated state, the DM2 patients showed a reduction of approximately 50% in the IMGU$_{11.1}$ value (0.20 ± 0.17 *v* 0.38 ± 0.24 mmol/kg · min, $P < .05$), but no significant differences were found for NIMGU$_{11.1}$ (0.19 ± 0.09 *v* 0.20 ± 0.12 mmol/kg · min, NS) in relation to the control group. Using the clustering technique, it was possible to identify 2 subpopulations of DM2 patients, a DM-IS group (n = 6) that was insulin sensitive (IS index, 11.70 ± 2.40 × 10^{-5} · min^{-1} · (pmol · L^{-1})$^{-1}$) and a DM-IR group (n = 10) that was insulin resistant (IS index, 3.02 ± 1.60 × 10^{-5} · min^{-1} · (pmol · L^{-1})$^{-1}$). The DM-IS group was characterized by an absence of IR, diminished GEZI, and a reduction in AIRg; whereas the DM-IR group was characterized by IR and a reduction in AIRg, but normal GEZI. We conclude that (1) as a group, DM2 patients are characterized by IR and β-cell dysfunction, but normal NIMGU; (2) two subpopulations of DM2 patients can be identified on the basis of insulin sensitivity, with the DM-IS group further characterized by diminished GEZI; and finally, (3) deterioration in the pancreatic response to glucose stimulus is a *sine qua non* condition for a profound alteration in glucose metabolism in DM2 patients.

OBESITY AND TYPE 2 diabetes mellitus (DM2) are metabolic syndromes that are reaching epidemic proportions in developed societies, and epidemiologic studies indicate that obesity is present in 70% to 80% of diabetic patients. DM2 is metabolically characterized by insulin resistance (IR) and by pancreatic β-cell dysfunction.[1,2] Nevertheless, studying insulin-mediated glucose uptake (IMGU), several groups have failed to find significant differences between lean DM2 patients and healthy control groups.[3-9] This finding has been attributed to the obesity of the majority of patients with DM2, and from this perspective, it is observed that IMGU is similar for obese cases and for lean DM2 subjects[1] and also that obesity increases IR at both the hepatic and the skeletal muscle levels, as found in DM2.[10] Although it has been suggested that transmembrane transport of glucose via the skeletal muscle is reduced in DM2 patients,[11] it is a well-known fact that a combination of hyperglycemia and hyperinsulinemia normalize peripheral IMGU, and this could account for the contradictory results obtained for peripheral glucose uptake in diabetic patients. Nevertheless, despite the increase in glucose uptake, intracellular glucose metabolism continues to be affected, suggesting that the IR is located in a subsequent level to the glucose transport system.[12]

Several investigators have drawn attention to the presence of a small proportion of lean DM2 patients with an IR value similar to that observed in healthy control individuals.[3-8] DM2 is a heterogeneous metabolic abnormality with a polygenic multifactorial inheritance.[13] Whether the primary etiopathogenic defect in DM2 is in fact due to a reduced sensitivity to insulin[14-16] or to a pancreatic β-cell dysfunction[17-19] is a subject of controversy, and both hypotheses are physiologically equally plausible,[1] although it is widely recognized that the development of hyperglycemia is always accompanied by a relative or absolute defect in insulin secretion. Moreover, a weight reduction in obese patients with DM2 normalizes the IR, but not the insulin secretion defect, and metabolic deterioration persists.[9]

Using the minimal model of glucose kinetics, it was possible

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to determine the metabolic parameters that regulate glucose tolerance, ie, insulin sensitivity (IS), glucose effectiveness, and pancreatic response to a glucose stimulus.[20,21] It is currently considered that glucose effectiveness is a regulator of glucose disposition, at least as important as IMGU,[22] and it has been suggested that this is reduced in DM2 patients.[23]

The objective of our research, applying the minimal model approach, has been to study glucose uptake in DM2 and, particularly, to investigate if 2 subpopulations of diabetic patients are identifiable on the basis of peripheral IS.

SUBJECTS AND METHODS

Subjects

Sixteen patients with DM2 (8 men, 8 women) as classified according to the Expert Committee of the American Diabetes Association criteria,[24] nonobese (defined by a body mass index [BMI] less than 27 kg · m^{-2} for males and a BMI less than 25 kg · m^{-2} for females) and with moderate fasting hyperglycemia were studied. These DM2 patients were selected from our IR database and had been used for previous studies by our team.[25,26] All of the patients manifested normal renal and hepatic functions and blood pressure was less than 140/90 mm Hg. Six patients were being treated with low doses of sulfonylureas, suspended during the week previous to the metabolic study; the remaining patients were receiving only dietary treatment; none had received insulin treatment. A DM2 family history was identified for 14 of the 16 patients studied.

The control group consisted of 10 apparently healthy nonsmoking subjects (5 men, 5 women), nonsufferers of dyslipemia, with normal oral glucose tolerance,[24] with an absence of abnormalities in the hepatic or renal functions verified in a routine analysis, with no family history of DM2 or essential hypertension, matched by age, sex, and BMI with the group of patients with DM2. All of the control individuals showed arterial tension values less than 140/90 mm Hg. The control group was also taken from our IR database. None of the subjects in either the control group or the diabetic group performed any strenuous physical exercise in the week prior to the study and were instructed to eat a diet rich in carbohydrates (at least 300 g/d) during the 3 days prior to the study. The purpose, nature, and potential risk of the study were explained before obtaining written consent from the subjects. This study was performed according to the ethical guidelines of the Declaration of Helsinki.[27]

Protocol

Each subject came to the hospital at 8:30 AM after having fasted for 12 hours overnight. With the subject recumbent, the antecubital veins in both arms were cannulated with a 20-gauge catheter (Abbocath-T 20G; Abbott, Dublin, Ireland). One of the catheters was used for blood sampling and the other for the glucose bolus infusion and for intravenous administration of the antidiabetic drug when the tolbutamide-modified protocol was used. The patency of the catheters was maintained with an isotonic saline 0.9% NaCl infusion. Basal glucose and insulin levels were obtained from blood samples taken 20, 15, 10, 5, and 1 minute before glucose injection. At time zero, injection of 0.3 g/kg 50% (wt/vol) dextrose (Glucosmon R/50; Leo, Madrid, Spain) was started and 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, 100, 120, 140, 160, and 180 minutes after starting the injection. When used, tolbutamide 4.3 mg/kg body weight (Dolipol; Hoechst, Barcelona, Spain) was injected at time 20 minutes; and additional blood samples were taken at 23, 24, and 27 minutes. 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.

IS and Glucose Effectiveness Calculations

Bergman's minimal model was used to calculate both IS and glucose effectiveness at basal insulin (S_G) indices.[20] Briefly, the minimal model of glucose kinetics (MMg) is a mathematical representation of the kinetics of glucose during a frequently sampled intravenous glucose tolerance (FSIGT) test. The parameters of the model were estimated using a nonlinear least-squares technique with a personal program (STELLUM-MMg, © 1997).[26,28,29] Once the model parameters were estimated, it was possible to calculate both the IS and S_G indices. Glucose effectiveness at zero time (GEZI) is calculated as: GEZI = S_G – (IS × FPI), FPI being fasting plasma insulin. For the accuracy of the minimal model indices, the fractional standard deviation (FSD) was calculated. When the FSD of S_I was greater than 6% or the FSD of S_G was greater than 15%, the coefficient of variation (CV) of these indices was calculated using the Monte Carlo technique. Only coefficients less than 34% were accepted as valid.[30]

Calculations

Conrad's coefficient of glucose assimilation (the K_G index) was calculated as the slope of the least-squares regression line relating to the natural logarithm of glucose concentration to time between 10 and 19 minutes.

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

The product IS × AIRg (called the disposition factor) represents IMGU, given the hyperbolic relationship that exists between IS and the β-cell function.[31]

Non–insulin-mediated glucose uptake (NIMGU), IMGU, and total glucose uptake (TGU) were calculated during the postabsorptive period (fasting) and during the FSIGT test, at a value for glycemia of 11.1 mmol/L and in accordance with the following equations[23,26]:

$$NIMGU_F = GEZI \times FPG \times V_D;\ IMGU_F = IS \times FPI \times FPG \times V_D$$

$$NIMGU_{11.1} = GEZI \times (11.1\ mmol/L\ of\ glucose) \times V_D$$

$IMGU_{11.1}$ = IS × (11.1 mmol/L of glucose) × (insulin at 11.1 mmol/L of glucose) × V_D where FPG is the fasting plasma glucose and V_D is the volume of glucose distribution (dL/kg body weight) estimated as 0.65 × 26% of body weight.

Assays

The plasma glucose level was measured in triplicate using a Hitachi (Barcelona, Spain) 737 auto-analyzer with a glucose oxidase method (intra-assay and interassay CVs, 0.5% and 1.6%, respectively). The plasma immunoreactive insulin level was measured by radioimmunoassay using a commercial kit (ICN Pharmaceuticals, Costa Mesa, CA). Intra-assay and interassay CVs were 7% and 11%, respectively.

Statistical Analysis

Data are shown as the mean ± SD. Normality was checked using the Shapiro-Wilk test. For comparisons among groups, analysis of variance (ANOVA) or Kruskal-Wallis tests were used. Comparisons between subgroups were performed *a posteriori* using the Newman-Keuls test. Hierarchical cluster analysis is a procedure that endeavors to identify groups of cases that are relatively homogenous on the basis of selected characteristics. This is done via an algorithm that starts with each case located in a different cluster to be combined successively until only one cluster remains. Statistical significance was indicated by a *P* value of

Table 1. Metabolic Parameters for Control and DM2 Subjects

	Control (n = 10)	Type 2 DM (n = 16)	*P* Value
FPG (mmol/L)	4.8 ± 0.3	7.2 ± 1.1	<.0001
FPI (pmol/L)	54 ± 19	96 ± 78	NS
K_G (min^{-1})	1.72 ± 0.45	0.98 ± 0.25	<.0001
GEZI (min^{-1})	0.0109 ± 0.0068	0.0105 ± 0.0054	NS
IS index ($10^{-5} \cdot min^{-1} \cdot [pmol \cdot L^{-1}]^{-1}$)	12.75 ± 7.74	6.23 ± 4.68	<.01
AIR_g (pmol/L · min)	1,912 ± 1,293	336 ± 456	<.0001
IS × AIRg (min^{-1})	0.2125 ± 0.1384	0.0138 ± 0.0143	<.0001

Abbreviation: NS, not significant.

less than .05. The statistical analysis was performed with the SPSS (SPSS, Chicago, IL) software package.

RESULTS

In 4 of the control subjects and in 7 of the DM2 patients, the tolbutamide-modified test was applied. The remaining control subjects and patients received the standard test. There were no significant differences, however, in the metabolic parameters between tests, and they were consequently grouped into a single sample. The DM2 patients were similar in age (47 ± 9 *v* 48 ± 6 years, not significant [NS]) and in BMI (25.3 ± 2.6 *v* 24.9 ± 1.2 kg · m^{-2}, NS) to the control group.

Table 1 shows the metabolic variables that regulate glucose tolerance in both the DM2 patients and the healthy control subjects. It can be observed that DM2 was metabolically characterized by IR (approximately 51%), and reductions both in AIRg and in the glucose disposition factor (IS × AIRg). The GEZI value for the DM2 patients, however, was similar to that for the controls.

Table 2 shows the values for IMGU during the postabsorptive state and the insulin-stimulated state (after the glucose bolus). For the basal state, no differences were found in the diabetic patients for total glucose uptake, TGU_F, (TGU = NIMGU + IMGU), $NIMGU_F$ and $IMGU_F$ compared with the control group. For both groups, almost two thirds of the glucose uptake was non–insulin-mediated. During the insulin-stimulated state, there was a quantitative and qualitative change in the glucose uptake in relation to the basal state. The DM2 patients showed a reduction in TGU that was entirely explained by a parallel reduction in $IMGU_{11.1}$ (approximately 50%) in relation to the control group, whereas the $NIMGU_{11.1}$ contribution to glucose uptake was similar for both groups. This represented half of $TGU_{11.1}$ in the DM2 patients.

Using clustering techniques, 2 subgroups were identified within the DM2 population on the basis of their IS values: an insulin-sensitive group, DM-IS (IS index = 11.70 ± 2.40 (range, 9.33 to 15.53) × $10^{-5} \cdot min^{-1} \cdot (pmol \cdot L^{-1})^{-1}$) and an insulin-resistant group, DM-IR (IS index = 3.02 ± 1.60 (range, 1.35 to 6.32) × $10^{-5} \cdot min^{-1} \cdot (pmol \cdot L^{-1})^{-1}$). The physical and metabolic characteristics are described in Table 3. Neither subgroup differed significantly in terms of age (50 ± 9 *v* 45 ± 8 years, NS) or BMI (25.4 ± 2.4 *v* 25.2 ± 3.0 kg · m^{-2}, NS), whether from each other or from the control group. The 2 subgroups showed a marked reduction in AIRg and in the glucose disposition factor. The DM-IS subgroup showed a reduction in the GEZI value in relation to the DM-IR group. In relation to the control group, the values for $IMGU_{11.1}$ and $NIMGU_{11.1}$ did not differ significantly (0.33 ± 0.17 *v* 0.38 ± 0.24 mmol/kg · min, NS and 0.10 ± 0.06 *v* 0.20 ± 0.12 mmol/kg · min, NS).

Given that the IS index calculated with the minimal model is the quotient of 2 parameters (IS = P_3/P_2), each of these was compared for the 2 DM2 patient subgroups. No differences were found in P_2 between the DM-IS and the DM-IR groups (0.0332 ± 0.0288 *v* 0.0235 ± 0.0095 min^{-1}, NS), but P_3 was significantly greater for the DM-IS group (1.630 ± 0.857 *v* 0.682 ± 0.779, $10^{-4} \cdot min^{-2} \cdot (pmol/L)^{-1}$, $P < .05$). The CVs in the IS index did not differ between the 2 subgroups (5.89 ± 4.25 *v* 9.15% ± 5.74%, NS).

DISCUSSION

Our study shows that DM2 is characterized by a diminished total body glucose uptake and that an abnormal insulin secretory capacity is a common finding in all of the patients with DM2. Glucose-mediated glucose uptake was, however, similar to that for the control group. Glucose uptake methods, on the other hand, differed both qualitatively and quantitatively in the postabsorptive and postprandial (after glucose injection) states. In the postabsorptive state, glucose disposition takes place

Table 2. Glucose Uptakes During Fasting and Insulin-Stimulated States

	Control (n = 10)	DM2 (n = 16)	*P* Value
Fasting state			
TGU_F (mmol/kg · min)	0.13 ± 0.05	0.17 ± 0.06	NS
$IMGU_F$ (mmol/kg · min)	0.05 ± 0.02	0.05 ± 0.04	NS
$NIMGU_F$ (mmol/kg · min)	0.08 ± 0.05	0.13 ± 0.07	NS
At 11.1 mmol/L glucose			
$TGU_{11.1}$ (mmol/kg · min)	0.58 ± 0.26	0.38 ± 0.14	<.05
$IMGU_{11.1}$ (mmol/kg · min)	0.38 ± 0.24	0.20 ± 0.17	<.05
$NIMGU_{11.1}$ (mmol/kg · min)	0.20 ± 0.12	0.19 ± 0.09	NS

Table 3. Metabolic Parameters for IS and IR DM2 Patients

	Control (n = 10)	DM-IS (n = 6)	DM-IR (n = 10)
FPG (mmol/L)	4.8 ± 0.3	6.6 ± 0.7*	7.5 ± 1.2*
FPI (pmol/L)	54 ± 19	65 ± 38	118 ± 86
K_G (min^{-1})	1.72 ± 0.45	0.87 ± 0.23*	1.05 ± 0.24*
IS index ($10^{-5} \cdot min^{-1} \cdot [pmol \cdot L^{-1}]^{-1}$)	12.75 ± 7.74	11.70 ± 2.40	3.02 ± 1.60†
GEZI (min^{-1})	0.011 ± 0.007	0.007 ± 0.002	0.013 ± 0.004‡
AIRg (pmol/L · min)	1,912 ± 1,293	117 ± 96§	468 ± 540§
IS × AIRg (min^{-1})	0.213 ± 0.138	0.014 ± 0.014*	0.015 ± 0.019*

*$P < .001$ *v* control; †$P < .01$ *v* control and DM-IS; ‡$P < .05$ *v* DM-IS; §$P < .01$ *v* control.

principally via NIMGU, both in healthy individuals (64%) and in DM2 patients (74%), and we observed that the IMGU does not differ significantly from the control subjects. Although it has been pointed out that in fasting TGU and NIMGU are both augmented in DM2 patients,[32,33] in our research, the absence of statistical significance may be due to the fact that our patients showed a level of basal hyperglycemia that was considerably lower than in previous studies (> 11.1 mmol/L). In the stimulated-insulin state (after glucose bolus and/or tolbutamide), both $TGU_{11.1}$ and $IMGU_{11.1}$ were reduced in the DM2 patients, but we were unable to detect any significant differences in $NIMGU_{11.1}$ between control subjects and diabetic patients. This aspect of our research differs from the work of Welch et al,[23] in which $NIMGU_{11.1}$ was shown to be reduced in diabetic patients, but is supported by the work of Baron et al,[32] which shows that for similar levels of hyperglycemia, the glucose uptake is similar in control and diabetic subjects. The discrepancies with the former work may be due to the fact that the control group was significantly younger (32 ± 3 *v* 45 ± 3 years, $P < .02$) and had a lower BMI (24.1 ± 0.7 *v* 30.7 ± 2.3 $kg \cdot m^{-2}$, $P < .02$) than the diabetic group. Although age appears to have no direct influence on glucose-mediated glucose disposal,[34,35] it may affect glucose tolerance via indirect mechanisms, such as a reduction in physical activity, changes in regional fat distribution, or changes in diet composition, among others. On the other hand, it has been suggested that the duration in time of obesity increases the incidence of DM2.[36,37] To clarify this point, we compared the glucose effectiveness value (S_G) for our present groups with a new group of young and lean control subjects of an age and BMI similar to those used in previous research (age, 23 ± 2 years; BMI, 21.6 ± 1.6 $kg \cdot m^{-2}$). In this case, the S_G value was significantly lower ($P < .01$) in both the DM2 patient group (0.0145 ± 0.0046 min^{-1}) and the age-BMI-matched control group (0.0172 ± 0.0063 min^{-1}) in relation to the younger control group (0.0232 ± 0.0073 min^{-1}). Moreover, no differences were found between the first 2 groups. Therefore, and although the mechanism by which age influences NIMGU deterioration is not clear, this should be considered a confusion variable, and so a covariance analysis should be applied when the study groups are dissimilar in age.

Nearly 2 decades ago, Rizza et al[38] suggested that in nonobese DM2 patients the principal metabolic anomaly was the insulin secretion defect rather than IR. Since then, several groups have indicated that DM2 was heterogeneous from the point of view of IR, with subgroups of insulin-sensitive DM2 patients identified in at least the African-American,[3,7] Scandinavian,[4] and Japanese[5] populations. This heterogeneity is evident in the offspring and first-degree relatives of DM2 patients[14-19,39,40] and also in normal individuals, since it is known that at least 25% of these individuals show a glucose uptake similar to that observed in DM2 patients.[41] Applying the clustering technique to our Caucasian population of DM2 patients, we identified a subgroup of insulin-sensitive patients whose IS value was similar to the control group and another insulin-resistant subgroup. Both the DM-IS and DM-IR groups were characterized by a serious deterioration in insulin secretion under glucose stimulus and an important reduction in the glucose disposition factor (IS × AIRg). It is widely known that the loss of insulin secretion during the initial phase (AIRg) is translated into a delayed inhibition of hepatic glucose production[42] and is responsible for the postprandial hyperglycemia that characterizes DM2 patients.[43] The IS index calculated using the minimal model is the quotient of 2 parameters, ie, $IS = P_3/P_2$, in which P_2 is identified with the degradation/internalization of the insulin receptor, and P_3 represents insulin action from the interstitial compartment that suppress hepatic glucose production and stimulates glucose uptake at the level of the liver and peripheral tissues (skeletal muscle and fat). Comparing both subgroups of DM2 patients, we found no differences in P_2, whereas P_3 was significantly greater in the DM-IS group. Since it has recently been suggested that the liver of lean DM2 patients with moderate fasting hyperglycemia does not show IR,[8] our data suggest that the greatest IS in DM-IS patients occurs at the peripheral level (principally skeletal muscle). This translates into an $IMGU_{11.1}$ value similar to the control group (0.33 ± 0.17 *v* 0.38 ± 0.24 mmol/kg · min, NS), a value that is consistent with those obtained for Arner et al[4] (0.38 ± 0.02 mmol/kg · min) and Banerji and Lebovitz[3] (0.42 ± 0.05 mmol/kg · min) studies using the euglycemic-hyperinsulinemic clamp technique.

We cannot elucidate, in this study, what are the etiologic factors responsible for such differences between lean diabetic subjects. Changes in both lifestyle or physical activity do not seem to be the cause, but it is not possible to rule out that other factors, such as fat distribution or lipid metabolism, could explain these differences.

In our cross-study based on the IS index, it was possible to identify 2 kinds of DM2 patients, both, however, showing a severe alteration in the pancreatic β-cell function. Therefore, although the lean DM2 patients may be heterogeneous as far as IR is concerned, it can be deduced that at the physiopathologic level, it is the β-cell defect, whether primary (inherited) or secondary to the underlying IR, which marks the clinical dete-

rioration in glucose tolerance. This hypothesis is consistent with the knowledge derived from metabolic studies of identical twins discordant for DM2.[44,45] These studies highlight 2 aspects: (1) that a defect in insulin action and in the secretion of insulin are both present in nondiabetic twins[44]; and (2) that both defects are inherited, and in such a way that the offspring of DM2 patients with a hyposecretory phenotype have a defect in the β-cell function but normal sensitivity to insulin, whereas the offspring of DM2 patients with an insulin-resistant phenotype are characterized by IR, but with a normal β-cell secretory capacity.[45] A recent study performed on a Japanese population showed that the offspring of DM2 patients with a normal range of IS are characterized by increased IS and a deterioration in AIRg.[46]

Finally, the group of DM-IS patients showed a reduced GEZI value in relation to the DM-IR group. This metabolic characteristic is consistent with previous studies: (1) our group has demonstrated that the deterioration in intravenous glucose tolerance, both for healthy individuals[35] and the offspring of DM2 patients,[16] is caused by a simultaneous decrease in insulin secretion and glucose-mediated glucose uptake, independently of the degree of obesity and IS; and (2) a previous study of lean DM2 patients with normal IS showed these to be characterized by abnormal insulin secretion and a reduced glucose effectiveness value.[5] Nevertheless, from our cross-study, we were unable to conclude whether this is a question of a primary metabolic trait in the DM-IS patients, or whether it represents a metabolic state of more intense deterioration in intravenous glucose tolerance.

In conclusion, our results would suggest that among lean patients with DM2, it is possible to identify 2 subgroups with different physiopathologic mechanisms, namely, an insulin-sensitive group characterized by both a primary β-cell defect and a deteriorated glucose-mediated glucose uptake and another insulin-resistant group with a poor pancreatic function and normal glucose effectiveness. These findings emphasize the fact that patients with DM2 must receive individualized treatment, and that, although IR is a common feature of this disease, we should bear in mind that, at least in lean diabetic subjects, insulin deficiency can be the main problem.

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