Impact of Family History of Diabetes on the Assessment of β-Cell Function

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Numerous factors impinge on β-cell function, and include the genetic background and insulin sensitivity of the individual. The aim of the present study was to evaluate the impact of a family history of non–insulin-dependent diabetes mellitus (NIDDM) on β-cell function and to determine whether the relationships between β-cell function and insulin sensitivity and age are influenced by a family history of diabetes. Thirty-three healthy control subjects (CON), 20 normal glucose-tolerant first-degree relatives of known NIDDM patients (REL), and 12 nondiabetic identical twins with an identical twin with known NIDDM were studied. Insulin and C-peptide responses to an acute intravenous glucose (AIRg) and glucagon bolus (at euglycemia [$AIR_{[G.GON]}$]) were measured, as well as each individual's insulin sensitivity. Fasting insulin and C-peptide levels were similar in all groups. AIRg was significantly reduced by 65% in the nondiabetic twins compared with the CON and REL groups, with the latter group being similar to CON, whereas for the $AIR_{[G.GON]}$, the insulin responses in the twin subjects were reduced only by 35% compared with CON. Following stepwise (default) multiple regression analysis, three independent variables (insulin sensitivity, 23%; family history of NIDDM, 20%; and fasting glucose, 7%) were identified, and these combined to fit a model for prediction of acute β-cell responses to glucose that yielded an R^2 (adjusted) value of 50%. Following analysis of covariance (ANCOVA), a positive family history of NIDDM and insulin sensitivity but not the age of the subject were confirmed as separate factors affecting AIRg. In conclusion, in subjects with normal or mild glucose intolerance, the individual's genetic background and insulin sensitivity are important determinants of insulin secretion.

THE CURRENT VIEW is that in established non–insulin-dependent diabetes mellitus (NIDDM), defects of both insulin action and insulin secretion contribute to the development and persistence of the hyperglycemia.[1,2] It is generally considered that the quantitation of insulin action in vivo, ie, insulin resistance, is relatively precise[3] even using different methodologies,[4-6] although the euglycemic-hyperinsulinemic clamp remains the "gold standard."[4] In contrast, assessment of insulin secretion from the β cell is more problematic.[3] This may be due to the fact that it is uncertain which defect of insulin secretion is present in the prediabetic: Is it a problem of capacity of β-cell mass or a defect of sensitivity of the β cell to glucose, or the dynamics of insulin secretion, or a combination of all of these defects[3]? In addition, insulin resistance itself influences β-cell responses to its secretagogues,[5] as does the presence of chronic hyperglycemia, so-called glucose toxicity.[7] Genetic factors may also significantly impact β-cell secretion in normoglycemic individuals.[8-13] Thus, multiple tests of β-cell function have been used to test the β cell in studies in "prediabetic" individuals with or without normal glucose tolerance.[8-14]

For a number of years, we have been examining β-cell function and insulin action in subjects with normal[8,14] and abnormal[8] glucose tolerance and variable degrees of insulin resistance.[8,14] Of interest, the genetic background as defined by a family history for the development of NIDDM varied in the subjects studied, which included normal healthy controls without any family history of NIDDM, normoglycemic first-degree relatives of NIDDM patients (a group known to have about a 40% incidence of future diabetes[15]), and the nondiabetic twin of identical twins, one of whom had established NIDDM (a group known to have a >85% incidence of future diabetes).[16] The purpose of this report is to critically reexamine β-cell function in these previously studied subjects[8,14] to address the following question: Does the genetic background of an individual influence the measurement of β-cell function? In addition, because of the known influence of age[17] and insulin sensitivity[14,18] on β-cell function, the relationships between these parameters and the individual's genetic background were also examined. To this end, insulin secretion was measured following an acute bolus of glucose and glucagon (at euglycemia) and insulin sensitivity was determined in all subjects.

SUBJECTS AND METHODS

A total of 65 subjects were examined (Table 1): 33 healthy normal glucose-tolerant control subjects with no family history of NIDDM, 20 normal glucose-tolerant first-degree relatives of known NIDDM patients as previously reported,[14] and 12 nondiabetic identical twins, each with an identical twin with known NIDDM as detailed previously,[8] divided into two subgroups, five with normal and seven with mildly impaired glucose tolerance (2-hour post–glucose load plasma glucose between 7.8 and 10.5 mmol/L).[8] Although the age range of the control group spanned that of the other groups, the relative group was significantly younger than the other groups, and the impaired glucose tolerance twin group was significantly older than the control subjects (Table 1). All groups had a similar body mass index (BMI) and percent body fat (as measured by the bioimpedance method[19]), but there was a trend towards more adiposity in the twin groups, which was confirmed by a significantly higher waist to hip ratio (WHR) in the glucose-intolerant twins (Table 1). The two twin groups had significantly higher fasting and 2-hour post–glucose load plasma glucose levels[8] compared with both the control and relative groups, which were reflected by significantly lower Kg values for the twins (Table 1). Plasma lipid status was similar for all groups. All subjects were fasted overnight for 10 hours prior to any test and were requested to consume greater than 150 g carbohydrate daily for 3 days before each test. Subjects had at least 5

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Table 1. Clinical Characteristics of Subjects Studied (mean ± SE)

Characteristic	CON (n = 33)	REL (n = 20)	NTW (n = 5)	ITW (n = 7)	*P* (Kruskal-Wallis ANOVA)
Age (yr)	41.6 ± 2.9§ (18-71)	29.4 ± 1.7† (19-40)	58.8 ± 5.4§ (44-70)	67.3 ± 1.5*§ (63-72)	.001
Sex (M:F)	19:14	12:8	3:2	4:3	—
BMI (kg/m^2)	25.4 ± 0.7	25.1 ± 1.0	27.3 ± 1.5	27.6 ± 2.0	.511
WHR	0.89 ± 0.02	0.88 ± .02	0.93 ± 0.02	1.04 ± 0.03*§	.005
Body fat (%)	27.2 ± 1.7	26.1 ± 2.0	32.2 ± 5.4	33.9 ± 2.9	.224
TG (mmol/L)	1.11 ± 0.09	1.11 ± 0.13	1.34 ± 0.30	1.16 ± 0.14	.831
CHOL (mmol/L)	5.2 ± 0.2	5.0 ± .3	5.6 ± 0.4	5.3 ± 0.4	.813
HDL-C (mg/mL)	1.28 ± 0.05	1.31 ± 0.05	1.05 ± 0.06	1.14 ± 0.14	.217
FBG (mmol/L)	5.2 ± 0.1	5.4 ± 0.1	6.2 ± 0.1*	5.8 ± 0.2*	.001
2-h OGTT.G (mmol/L)	5.5 ± 0.2	5.5 ± 0.2	6.8 ± 0.3*	9.1 ± 0.5†‡§	.001
Kg (min^{-1} 10^{-2})	1.57 ± 0.13	1.60 ± 1.4	0.90 ± 0.7*	0.86 ± 0.08†	.001
F insulin (mU/L)	6.22 (5.54-6.99)	7.35 (6.47-8.36)	6.91 (5.12-9.32)	7.21 (5.37-9.70)	.276
F C-peptide (pmol/L)	468 (416-528)	584 (520-655)	428 (266-686)	523 (419-652)	.082
Basal-SR (pmol · kg^{-1} · min^{-1})	1.55 (1.38-1.73)	1.95* (1.66-2.30)	1.33 (0.83-2.14)	1.62 (1.36-1.92)	.028

Abbreviations: SR, insulin secretion rate (C-peptide model-derived[22]); FBG, fasting blood glucose; 2-h OGTT.G, 2-hour post–oral glucose load blood glucose; TG, fasting triglyceride; CHOL, fasting cholesterol.

*$P < .05$, †$P < .01$: *v* CON.

‡$P < .05$ *v* NGT.

§$P < .01$ *v* REL as analyzed by Mann-Whitney *U* test.

days between tests, the protocols were approved by the regional ethics committee, and investigations were performed in accordance with the principles of the Declaration of Helsinki.

Insulin Secretion Tests

Two tests of β-cell function were performed.

Intravenous glucose tolerance test. This test was performed in all 65 subjects, as previously detailed from our laboratory, using 300 mg/kg body weight glucose load injected over 60 seconds. Frequent arterialized blood samples were taken from the contralateral warmed arm for glucose, insulin, and C-peptide assay post–glucose load.[14] From this test, the acute insulin response (AIRg) and total insulin secretion (AIRg-SR) to glucose were calculated.

Intravenous glucagon test. This test was performed in 13 control and 12 twin subjects. After an overnight fast, a glucagon (1 mg glucagon) test at basal glycemia was performed for estimation of the acute insulin response to glucagon ($AIR_{[G.GON]}$) from frequent blood samples taken for insulin over 10 minutes post–glucagon bolus.

Insulin Sensitivity Measurement

Insulin sensitivity (SI) was calculated from the IVGTT in all 65 subjects by the minimal model method of Bergman[5] as implemented in our laboratory.[14,20] Frequent blood samples for glucose and insulin were collected over 180 minutes post–glucose bolus.[14]

Assays

The plasma glucose concentration was measured by the glucose oxidase method on a Glucose Analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin was assayed by a double-antibody radioimmunoassay (Kabi Pharmacia Diagnostic, Uppsala, Sweden), the within- and between-assay coefficient of variation being 5.6% and 6.2%, respectively.[14] C-peptide was assayed by the time-resolved immunofluorometric assay of Hemmila et al.[8,21] Triglyceride, cholesterol, and high-density lipoprotein (HDL)-cholesterol levels were measured by standard techniques.

Calculations

The AIRg was calculated as the mean of the incremental plasma insulin concentrations from 0 to 10 minutes above basal following the intravenous glucose load.[14,18] As noted previously, this measurement of acute insulin release correlates highly with the minimal model–derived first-phase insulin release ($r_s = .97$, $P < .001$[14]). The acute insulin response to glucagon at basal glycemia ($AIR_{[G.GON]}$) was calculated as the incremental area under the plasma insulin from 0 to 10 minutes above basal post–glucagon bolus. Prehepatic insulin secretion rates basally (basal-SR) and during the AIRg test (AIRg-SR) were calculated from the C-peptide values by deconvolution[22] using the standard kinetic parameters for C-peptide clearance adjusted for age, sex, and body surface area,[23] as implemented by the ISEC computer program of Hovorka.[24]

Insulin sensitivity (SI) was calculated from the IVGTT using the program SAAM (Simulation Analysis and Modelling) together with the conversational part of the program (CONSAM) as reported from our laboratory.[14,20] Because of the known hyperbolic relationship between β-cell secretary function and insulin sensitivity of the individual,[5,18] the product of β-cell secretory parameters and their matching insulin sensitivity were calculated.

Statistical Analysis

The mean ± SEM or geometric mean (with 95% confidence limits) are presented. Nonparametric statistical methods (Mann-Whitney test for unpaired data, Spearman rho [r_s] for simple correlation analysis, and Kruskal-Wallis test for multiple group comparisons) were used in the primary analyses of data. Logarithmic transformation of the variables (ie, fasting insulin, AIRg, and SI) was used in the multiple regression and stepwise (default) and ANCOVA analyses where linear data were not normally distributed. To examine separately the impact of the genetic background for NIDDM on the relationships between AIRg versus SI and AIRg versus age, ANCOVA was applied. All computations were performed using SPSS (Chicago, IL) software. *P* values of .05 or less were considered significant.

RESULTS

Fasting Insulin and C-Peptide and Basal Insulin Secretion Rate

Fasting insulin and C-peptide levels and basal insulin secretion rates were similar in all groups, with almost complete overlap of insulin levels for all groups. However, the calculated

basal insulin secretion rate in the relative group was significantly elevated (Table 1).

Acute Insulin Responses to Glucose and Glucagon and Insulin Secretion Rate to Glucose

The AIRg was significantly reduced by about 65% in both twin groups compared with the control and relative groups (CON 34.09 [26.80 to 43.36], REL 37.46 [26.42 to 53.13], NTW 10.26 [3.15 to 33.47], and ITW 10.39 [6.26 to 17.24] mU/L). When the control group was subdivided by age to match the older twin subjects, the AIRg remained significantly ($P < .03$) lower in NTW and ITW groups (TWIN CON, 28.37 [14.8 to 42.95] mU/L).[8] The control and relative groups appeared similar. When these data were calculated as prehepatic insulin secretion rates (AIRg-SR) using C-peptide data, identical results were seen (CON 8.27 [6.71 to 10.19], REL 9.51 [7.01 to 12.91], NTW 2.60 [1.12 to 6.04], and ITW 2.20 [1.09 to 4.42] pmol · kg^{-1} · min^{-1}), with a close correlation ($r_s = .91$, $P < .001$) between the insulin-derived AIRg and the C-peptide–derived AIRg-SR data. The insulin response to glucagon at euglycemia ($AIR_{[G.GON]}$) showed a pattern similar to that seen with AIRg in the control and twin groups, but with a mean reduction of only about 35% (CON 37.6 [27.9 to 50.6], NTW 26.1 [12.6 to 53.9], and ITW 21.4 [11.7 to 39.1] mU/L). For the glucagon tests, there was no statistical difference between groups (Fig 1).

Insulin Secretory Responses in Relationship to Insulin Sensitivity

The AIRg demonstrated the expected curvilinear hyperbolic relationship[18] to SI (data not shown[8,14]). When these data are replotted as the product of AIRg × SI, ie, the glucose assimilation index,[5,18] there is a clear separation of control subjects from both twin groups with a reduction of about 70%, with the relatives between the control and twin groups (CON 160 [130 to 197], REL 114 [80 to 162], NTW 46 [24 to 91], and ITW 67 [30 to 147] min^{-1}) (Fig 2). The same results hold true if the C-peptide–based AIRg-SR is used instead of AIRg for the calculation (CON 39 [31 to 49], REL 29 [20 to 41], NTW 13 [17 to 24], and ITW 12 [3 to 39] min^{-1}) (Fig 2). The glucose assimilation indices using the acute glucagon tests ($AIR_{[G.GON]}$) are also lower by about 35% for the twin groups compared with control subjects, but fail to reach statistical significance (CON 205 [158 to 266], NTW 140 [70 to 281], and ITW 177 [92 to 338] min^{-1}).

Relationship Between Clinical and Biochemical Variables, Insulin Sensitivity, and Genetic Impact on Insulin Secretion

Initially, simple direct correlations (Spearman rank) between the clinical and biochemical variables and insulin secretion (AIRg) and insulin sensitivity (fasting insulin and SI) were evaluated in the 65 subjects (Table 2). These multiple simple correlations were subsequently further examined in two ways. Firstly, multiple and stepwise linear regression analysis was

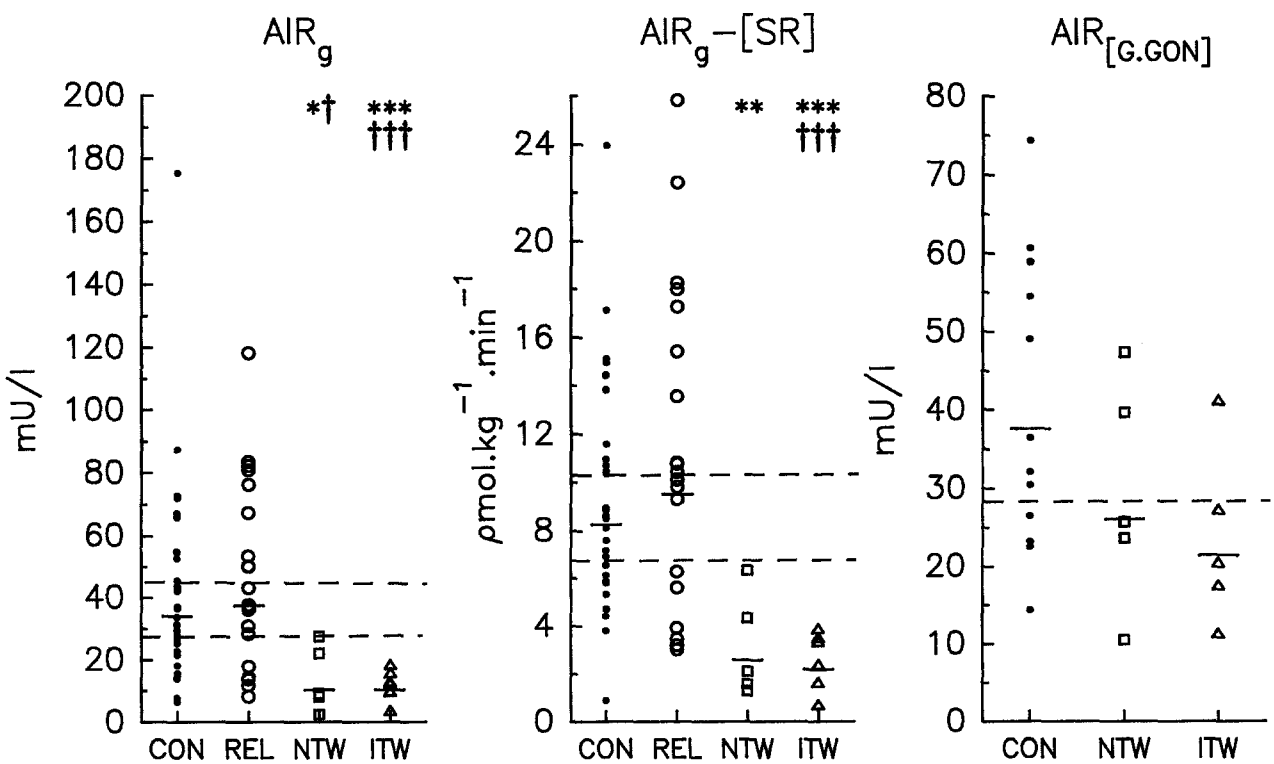

Fig 1. Acute insulin responses to intravenous glucose (AIR_g), and AIR_g calculated as the prehepatic insulin secretion rate (AIR_g-[SR]) and acute insulin response to glucagon at euglycemia ($AIR_{[G.GON]}$) for the control (CON, ●), relative (REL, ○), normal twin (NTW, □) and impaired glucose tolerant twin (ITWΔ) groups. The solid line indicates the mean and the dashed lines indicate the lower and upper 95% confidence limits for the control group. *$P < .01$, **$P < .005$ and ***$P < .001$ *v* control group; †$P < .01$ and †††$P < .001$ *v* relative group.

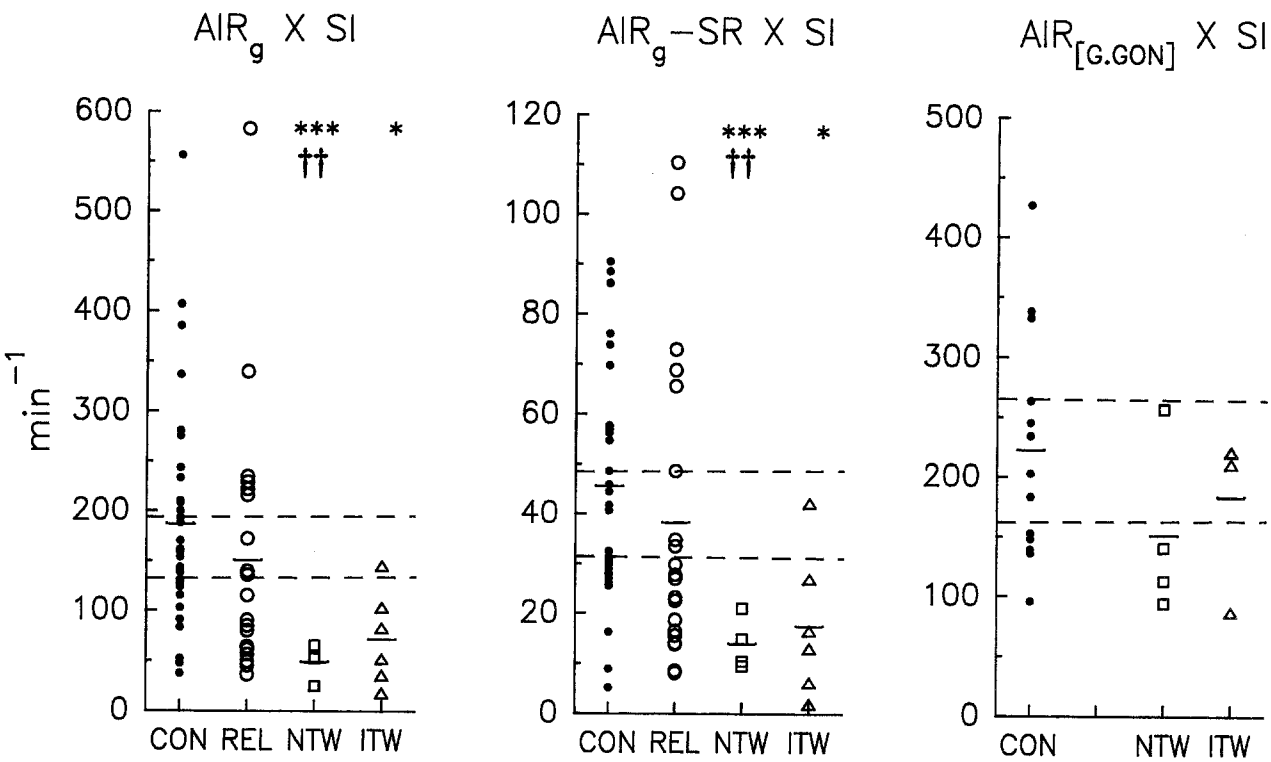

Fig 2. Product of insulin sensitivity (SI) and acute insulin response to intravenous glucose (AIR$_g$) [glucose assimilation index[5]] or the AIRg (SR), and the acute insulin response to glucagon (AIR$_{[G.GON]}$) for the control (CON ●), relative (REL, ○), normal twin (NTW, □) and impaired glucose tolerant twin (ITWΔ) groups. The solid lines indicate the mean and the dashed lines indicate the lower and upper 95% confidence limits for the control group. *$P < .05$ and ***$P < .004$ *v* control group; ††$P < .01$ *v* the relative group.

used to test their true independent effect on determining the altered insulin secretion observed in the subjects. For these latter analyses, the two twin groups with normal and abnormal (but nondiabetic) glucose tolerance were combined as one group,[8] since insulin secretion and insulin sensitivity were similar in these two subgroups (although reduced compared with the matched controls) and because both groups had similar family histories of NIDDM, (ie, one identical twin with NIDDM).[8] However, each subject's data were used individually in the multiple and stepwise regression analyses assuming a "continuous" distribution of the expression of the genetic background for diabetes, despite the separation into distinct groups, and all data were entered into the models in random order over repeated runs. Secondly, because the division into the three main groups (CON *v* REL *v* twins) was arbitrarily based on the predefined family history of NIDDM, separate analyses examining the impact of a family history of NIDDM on the continuous covariate relationships between AIRg versus insulin sensitivity and AIRg versus age were made by ANCOVA where the family history of diabetes was considered the discontinuous factor for the analyses.

Table 2. Simple Correlation Analyses (Spearman rank, r_s) of Clinical and Biochemical Variables Versus In Vivo Indices of Insulin Secretion in the Four Groups of Subjects

	Insulin Secretion	
Parameter	Fasting Insulin	AIRg
Age	.06	−.46‡
BMI	.50‡	−.11
WHR	.26*	−.22
Fasting glucose	.36†	−.36†
2-h OGTT glucose	.18	−.27*
Kg	.17	.79‡
TG	.30*	−.12
HDL-C	−.30*	.07
Fasting insulin	—	.25*
AIRg	.25*	—
SI	−.44‡	−.49‡

*$P < .05$.
†$P < .005$.
‡$P < .001$.

Thus, Table 2 shows that a strong significant negative correlation was demonstrated for age versus AIRg but not for age versus fasting insulin. Adiposity, expressed as the BMI and WHR, correlated with fasting insulin but not with AIRg. Fasting glucose correlated with fasting insulin and negatively with AIRg, whereas the 2-hour OGTT glucose level and Kg correlated with AIRg only. TG and HDL-C only correlated with fasting insulin. Finally, there was a significant decline in glucose tolerance with age expressed as Kg ($r_s = -.38$) or 2-hour OGTT glucose concentration ($r_s = .48$), but not for age versus insulin sensitivity ($r_s = .23$).

AIRg was significantly correlated with six variables using nonparametric analysis (Table 2). In subsequent multiple regression analysis, the significant variables that were not normally

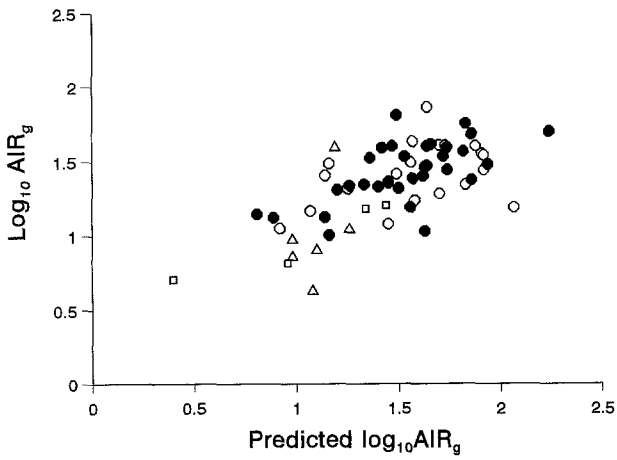

Fig 3. Correlation between the measured acute insulin response to intravenous glucose expressed as the log AIRg and the predicted log AIRg from the stepwise linear regression analysis. ● control, ○ relative, □ normal twin, and Δ impaired glucose tolerant twin subjects. For the acute insulin response to glucose: log AIRg = 3.257 − 0.716 log SI − 0.148 log STATUS − 0.211 F.Glucose [r^2(adj) = 0.50, $P < 0.001$].

distributed (AIRg, fasting insulin, and SI) were logarithmically transformed to achieve stabilization of the variance and normality of distribution. However, only the variables that were truly independent of AIRg were included in the regression analysis, as well as a measure of adiposity (either BMI and/or WHR) and either age or the genetic background of the individual, ie, no family history or a positive family history of diabetes or an identical twin with NIDDM, identified as "status" but entered as individual data as a continuous variable. For AIRg, the initial multiple regression analysis yielded an R^2 (adjusted) value of 62%, with fasting insulin and 2-hour glucose being rejected by the simple linear regression model. When stepwise (default) analysis was performed to determine the independent variables, three variables combined to fit the model, yielding an R^2 (adjusted) value of 50% (Fig 3), which is described by the regression equation, log AIRg = 3.257 − 0.716 log SI − 0.148 status − 0.211 F.glucose, where status represents the family history of the individual. That is, the actual measured $\log_{10}$ AIRg (vertical axis in Fig 3) is closely predicted ($r = .71$) by the three-variable model combining the SI, status, and fasting glucose of each individual (horizontal axis in Fig 3). For this model, SI contributed 23% and the family history of the individual a further 20%, with fasting glucose only adding 7% to the total adjusted R^2 value. The age of the subject was not accepted by the model even when the subject's status was excluded from the analysis.

When the alternate ANCOVA was used specifically to examine whether the relationships between AIRg and status were independent of age and SI, ie, age and SI entered as the covariate and status as the factor, we found that age did not significantly relate to AIRg ($F = 1.88$, $P < .20$), with the main effect being the factor status ($F = 6.33$, $P < .005$). In contrast, SI did significantly relate to AIRg ($F = 17.32$, $P < .0001$), as did the factor of status ($F = 10.80$, $P < .001$). These data are similar to the stepwise regression analysis.

DISCUSSION

In this study, we examined the potential defects of insulin secretion in a group of healthy controls (subjects without a family history of NIDDM) versus a group of nondiabetic subjects who either had at least one first-degree relative with NIDDM[14] or, alternatively, an identical twin with established NIDDM.[8] These subjects were chosen in our earlier studies because of the potential influence on their β-cell function and insulin sensitivity of their differing genetic background, as defined by their relative[15] or twin[16] status. However, it is important to recognize that the genetic differences between the relatives and twins may be due to differences in a particular gene or gene cluster, or gene interaction(s) rather than a numerical gene load, and that within a single group there is likely to be a continuum of phenotypic gene expression.[15,16] Nevertheless, regardless of the exact genetic interactions, the relatives and the twins have different risks for future NIDDM compared with each other and the control subjects.[15,16] In addition, our subjects displayed different degrees of insulin sensitivity and age varied significantly between groups, but there was a relatively narrow range of obesity and glucose tolerance between the groups. Finally, the IVGTT was used to examine first-phase insulin release to glucose (AIRg) and the relationship between the insulin response and insulin sensitivity, thereby defining the ability of the β cell to adjust to the individual's insulin sensitivity.[5,18] First-phase insulin release was tested also with a nonglucose secretagogue, glucagon, at euglycemia.

The results show that an adequate separation of β-cell function is made with the AIRg test, although a better separation occurs when corrected for the individual's insulin sensitivity (AIRg × SI product[18]). As noted previously, when subtle differences in β-cell function occur between subject groups (eg, control and relative groups), the insulin sensitivity–corrected AIRg is a more powerful discriminator of β-cell function.[14,18] Importantly, no additional information or better separation was obtained by calculating the prehepatic insulin secretion from the C-peptide level after the acute glucose load,[24] which also confirms a prior report.[25] Although the subject numbers were small for the twin groups, which may have had an impact on the analyses,[26] the glucagon stimulation test (at euglycemia) poorly separated the twin groups from the control subjects. The latter finding is similar to that reported for "early" insulin-dependent diabetes mellitus, where acute intravenous glucose stimulation, as compared with intravenous tolbutamide, arginine, and glucagon stimuli, was the most sensitive test for detecting β-cell dysfunction.[27] In addition, Byrne et al,[28,29] in a group of subjects (including relatives of NIDDM) with either normal or only mild impairments of glucose tolerance, found that when they used a number of sophisticated tests including entrainment of the β-cell response to a prolonged (42 hours) oscillatory glucose infusion, glucose priming of the β cell, and β-cell glucose sensitivity testing with small graded intravenous glucose infusions with calculation of true insulin secretion rates,[28,29] the AIRg response to the IVGTT normalized to the insulin sensitivity remained a most satisfactory test.[29]

The main aim of this study was to determine whether there

was a measurable impact of each subject's genetic background on their β-cell function when they were still normoglycemic and nondiabetic. With the multiple and stepwise (default) regression analyses, only three independent variables combined to explain 50% of the predicted acute insulin response, ie, the extent of the family history of NIDDM and the insulin sensitivity, with a small contribution from the fasting glucose. Importantly, in this model, the family history of NIDDM and the insulin sensitivity of the individual contributed approximately equally to the predicted AIRg, which reaffirms the original suggestion of Vaag et al.[8] Interestingly, although the simple correlation analyses demonstrated that age may also affect β-cell function, for both the controls and the other groups, it was the extent of the family history of NIDDM and not age that influenced the acute insulin response when the stepwise analysis was used. The importance of insulin sensitivity and "status" of the subject to AIRg was confirmed when analyzed by the ANCOVA approach. The latter approach also confirmed the lack of effect of age on AIRg, despite some previous studies that found a significant negative impact of age on β-cell function,[17,28] but certainly not uniformly.[30,31] It is also noted that obesity did not influence β-cell function in our subjects, despite the generally recognized positive impact of obesity.[2] This may have been due to the relatively narrow range of BMI and WHR in our subjects, but it could also reflect that the unique genetic background of the β cell limited the responses of the obese subjects.[18]

The impact of family history of NIDDM on β-cell function is complex. In studies in first-degree relatives, normal,[9,27] increased,[13,32,33] or reduced[11,12,14,34] acute insulin responses have been reported as summarized elsewhere.[8,14] However, in many of these studies, the insulin responses have not been related to the subject's degree of insulin sensitivity. It is also not possible from the present study to reconcile these previously published data with respect to the interaction between advancing age and the impact of family history for NIDDM on the ultimate expression of the phenotypical β-cell dysfunction and emergence of diabetes in the insulin-resistant individual. Our patients were deliberately chosen for their particular genetic background, but despite our attempts to statistically isolate age, insulin sensitivity, and genetic background as independent factors in β-cell dysfunction, our unique twin subjects still may have biased the stepwise regression analysis. However, the subsequent ANCOVA that examined the specific impact of family history of NIDDM on the relationship between AIRg versus insulin sensitivity and AIRg versus age clearly supports the notion that the extent of the family history of NIDDM has a significant and independent role in the development of β-cell dysfunction. Finally, it is recognized that the impaired β-cell function in the nondiabetic NIDDM twins may not be due to genetic factors alone. Recently, Vaag et al[35] found a significantly lower birth weight in the diabetic NIDDM twin compared with the identical nondiabetic twin, suggesting a possible role for intrauterine malnutrition in the future development of diabetes and/or an adverse response to the environment in genetically predisposed NIDDM individuals.[35] In particular, this intrauterine environment may have played a significant role in the expression of altered β-cell function in our adult subjects. Nevertheless, our analysis strongly supports the suggestion that the insulin sensitivity and positive family history of the individual has a profound impact on AIRg. This is confirmed by a recent study of normal twin subjects that also noted the importance of genetic effects on insulin levels.[36]

In conclusion, the present study establishes that the acute insulin release to an intravenous glucose load, normalized to the individual's own insulin sensitivity, obtained from an IVGTT adequately describes β-cell function in subjects with normal or mild glucose intolerance and varying insulin sensitivity. The study also highlights the unique importance of the genetic background of the individual as a determinant of β-cell function.

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