Relative Contributions of β-Cell Function and Tissue Insulin Sensitivity to Fasting and Postglucose-Load Glycemia

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We performed hyperglycemic clamps in 283 nondiabetic Caucasians and, with multiple linear regression, determined the contribution of β-cell function and tissue insulin sensitivity to variations in glycemia and insulinemia during oral glucose tolerance tests (OGTTs). Impaired glucose tolerance (IGT) subjects had reduced insulin sensitivity ($P < .02$) and β-cell function ($P < .0001$). Normal glucose tolerance (NGT) subjects with first-degree type 2 diabetic relatives had reduced first and second phase insulin secretion (both, $P < .05$), but normal insulin sensitivity ($P = .37$). β-Cell function and insulin sensitivity accounted for one fourth of the variability in glucose tolerance. Fasting plasma glucose in subjects with NGT (n = 185) was a function of both phases of insulin secretion and of insulin sensitivity (all, $P < .05$), whereas, in IGT subjects (n = 98), it was a function of first phase insulin secretion and insulin sensitivity ($P < .01$). Two-hour glycemia was a function of second phase secretion and insulin sensitivity ($P < .01$). Fasting and 2-hour plasma insulin levels were determined by insulin sensitivity (and glycemia) in NGT subjects ($P < .001$), but by second phase secretion in IGT ($P < .001$). We conclude that β-cell function is reduced in subjects with IGT; glycemia and insulinemia are not regulated by the same mechanisms in IGT and NGT; insulin sensitivity does not contribute to insulinemia in IGT; family history of diabetes influences β-cell function, but not insulin sensitivity in Caucasians.

MAINTENANCE OF normal glucose tolerance is dependent on the integrity of both insulin-dependent and insulin independent mechanisms.[1] However, most attention has been focused on insulin-dependent processes, such as suppression of glucose production and stimulation of glucose utilization.[2] Their regulation by insulin may be considered to be a function of the insulin available to tissues (ie, islet β-cell function) and the responses of tissues to insulin (ie, tissue insulin sensitivity). It is of note that insulin availability to major target tissues (muscle, adipose tissue) is also partly determined by the removal of insulin by the liver and kidney. Abnormalities in both insulin secretion and insulin sensitivity have been shown to be risk factors for type 2 diabetes.[3,4] It is unclear, however, to what extent each of these contributes to maintenance of normal glucose tolerance and to the development of type 2 diabetes. Numerous studies have attempted to address this issue by comparing insulin secretion and insulin sensitivity in individuals with and without diabetes.[5] Some studies have used the euglycemic hyperinsulinemic clamp to evaluate insulin sensitivity,[4,6-9] but none to date has directly examined both β-cell function and insulin sensitivity in a large number of nondiabetic individuals using clamp techniques to assess their contribution to maintenance of normal glucose tolerance. The hyperglycemic clamp is the generally accepted method to assess β-cell function under standard conditions. In previous studies, Mitrakou et al[10] compared the insulin sensitivity index determined using a hyperglycemic glucose clamp with the insulin sensitivity index determined using a euglycemic hyperinsulinemic glucose clamp (the ''gold standard'') in the same subjects. They found a good correlation and a good agreement between the 2 methods with almost the same numerical values and proposed the use of the hyperglycemic glucose clamp for both β-cell function and for the assessment of the insulin sensitivity index.

Accordingly, we used this approach to compare pancreatic β-cell function in 98 subjects with impaired glucose tolerance (IGT) with 185 subjects with normal glucose tolerance (NGT). Moreover, with multiple linear regression, the contribution of variations in β-cell function and insulin sensitivity to variation in glucose tolerance (fasting and 2-hour postglucose challenge plasma glucose levels) were determined. In addition, we assessed the influence of various demographic characteristics including a family history of type 2 diabetes on β-cell function and insulin sensitivity.

MATERIALS AND METHODS

Subjects

A total of 283 healthy subjects took part in this ongoing multicenter study; 159 with and 124 without a first-degree relative with type 2 diabetes mellitus (a parent who had developed type 2 diabetes after the age of 50 years); maturity onset diabetes of the young (MODY) was excluded on the basis of the late onset of diabetes. Subjects were recruited by advertisement. All individuals were nondiabetic according to the 1997 revised American Diabetes Association criteria.[11] Of these, 98 subjects had IGT according to the World Health Organization (WHO) criteria (a 2-hour plasma glucose level between 7.8 and 11.1 mmol/L[12] with a fasting plasma glucose level <7.0 mmol/L). The study had been approved by the local ethical committees, and after the nature of the study had been explained to each participant, informed written

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consent was obtained. Data from some of these subjects has been previously reported.[10,13-15]

All subjects had normal values for routine laboratory measurements for hematology, lipids, and kidney, liver, and thyroid function. Lean body mass (LBM) was calculated according to Hume's formula[16]; fat mass (FM) was calculated as body weight minus LBM.

Oral Glucose Tolerance Test

An oral glucose tolerance test (OGTT) was performed using 75 g glucose (in 300 mL water). Blood samples for glucose and insulin determinations were taken at 0, 30, 60, 90, and 120 minutes.

Hyperglycemic Glucose Clamp

On a separate day, this test was performed as previously described[14,15]; arterialized venous blood glucose was maintained at 10 mmol/L (coefficient of variation [CV], ≃3%) with variable infusion with 20% glucose. Blood samples for insulin determination were taken at points specified (see Fig 2). During the clamp, the glucose infusion rate (GIR) was assessed.

Laboratory Measurements

Plasma insulin was determined by radioimmunoassay as previously described.[13,14]

Calculations

Subjects were divided into the categories NGT or IGT and into categories of positive or negative family history of type 2 diabetes mellitus.

OGTT. Logarithmic transformation for plasma insulin was used because plasma insulin levels showed a log-normal distribution.

Hyperglycemic clamp. The consistency and the variability of the clamp were assessed as mean and as CV of plasma glucose levels, respectively. First phase insulin secretion was taken as the sum of increments of plasma insulin levels from 2.5 to 10 minutes during the hyperglycemic clamp; second phase insulin secretion was taken as the average increment plasma insulin from 140 to 180 minutes.

Insulin sensitivity was assessed as an insulin sensitivity index (ISI), defined as GIR necessary to maintain the hyperglycemic clamp from 120 to 180 minutes (as μmol/kg LBM^{-1}/$minute^{-1}$) divided by the mean plasma insulin level of the third hour.

Statistical Analysis

Data are presented as mean ± SEM. Plasma insulin levels were log-transformed for analyses because they had a log-normal distribution and are presented as geometric mean with 95% confidence intervals (CI).[17]

Analysis of variance (ANOVA) was used for all assessments. First, multiple (M)ANOVA was assessed for all 4 groups of subjects together; separate analyses were performed only if the overall MANOVA showed statistically significant differences. For OGTT data, first MANOVA for repeated measures was performed; separate ANOVA were performed only if MANOVA for repeated measures showed statistically significant differences.

ANOVA was performed with use of age, gender, body mass index (BMI), and waist-to-hip ratio (WHR) as covariates because they affect insulin secretion and insulin sensitivity.

Multiple linear regression was used for the assessment of the influence of (first and second phase) insulin secretion and of ISI on fasting (average of both study days) and 120-minute plasma glucose and plasma insulin levels of the OGTT, and for the assessment of the influence of baseline characteristics on β-cell function and the ISI.

The contribution of each parameter to the variance in fasting and 120-minute postglucose-load plasma glucose and insulin levels was assessed with the multiple linear regression by the use of the squares of the partial correlation coefficients; this was expressed as percentage.

RESULTS

Demographic and Metabolic Characteristics

As shown in Table 1, subjects with IGT differed from those with NGT in age, BMI, WHR, fat mass (FM), glycated hemoglobin ($HbA1_c$), fasting plasma glucose (FPG), and fasting plasma insulin (FPI) (all, $P < .01$). During OGGTs, plasma glucose values were greater at all times ($P < .001$) in the IGT group (Fig 1). The 30-minute increment in their plasma insulin was significantly lower than in the NGT group (207 [179 to 238]

Table 1. Clinical and Metabolic Characteristics of Subjects

	NGT			IGT		
	All	FH^-	FH^+	All	FH^-	FH^+
No.	185	85	100	98	39	59
Gender	63M/122F	33M/52F	30M/70F	38M/60F	19M/20F	19M/40F‖
Age (yr)	42.9 ± 0.8	44.7 ± 1.2	41.4 ± 1.0*	49.3 ± 1.1†	51.0 ± 1.7‡	48.1 ± 1.5¶
Weight (kg)	75.5 ± 1.0	74.4 ± 1.4	76.5 ± 1.5	78.7 ± 1.6	81.3 ± 2.3	76.9 ± 2.2
Height (m)	1.70 ± 0.01	1.69 ± 0.01	1.70 ± 0.01	1.68 ± 0.01	1.68 ± 0.01	1.67 ± 0.01
BMI (kg/m^2)	26.1 ± 0.3	25.9 ± 0.4	26.3 ± 0.4	28.0 ± 0.5†	28.7 ± 0.8‡	27.6 ± 0.7
WHR	0.82 ± 0.01	0.83 ± 0.01	0.82 ± 0.01	0.88 ± 0.01†	0.90 ± 0.01§	0.86 ± 0.01¶‖
LBM (kg)	51.1 ± 0.5	50.6 ± 0.7	51.3 ± 0.8	51.2 ± 0.8	52.6 ± 1.1	50.2 ± 1.1
FM (kg)	24.5 ± 0.6	23.8 ± 0.9	25.2 ± 0.9	27.5 ± 1.0†	28.6 ± 1.6‡	26.7 ± 1.3
$HbA1_c$ (%)	5.11 ± 0.04	5.03 ± 0.06	5.18 ± 0.05*	5.56 ± 0.06†	5.59 ± 0.07§	5.54 ± 0.07#
FPG (mmol/L)	5.04 ± 0.04	4.97 ± 0.04	5.16 ± 0.05*	5.49 ± 0.05†	5.62 ± 0.09§	5.40 ± 0.06¶‖
FPI (pmol/L)	38 (35-40)	38 (35-42)	37 (34-41)	53 (47-61)†	59 (50-70)§	49 (40-61)¶

NOTE. Data are mean ± SEM; FPI is geometric mean (95% CI).

*$P < .05$, NGT FH^+ *v* NGT FH^-.

†$P < .01$, All IGT *v* all NGT.

‡$P < .02$, IGT FH^- *v* NGT FH^-.

§$P < .0001$, IGT FH^- *v* NGT FH^-.

‖$P < .05$, IGT FH^- *v* IGT FH^+.

¶$P < .01$, IGT FH^+ *v* NGT FH^+.

#$P < .0001$, IGT FH^+ *v* NGT FH^+.

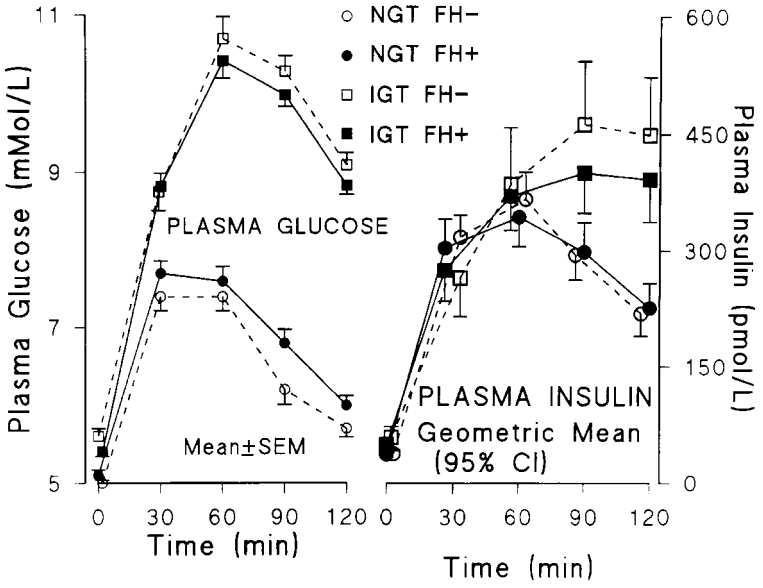

Fig 1. Mean (±SEM) plasma glucose and geometric mean (95% CI) plasma insulin levels after oral glucose tolerance tests in 283 subjects. Circles depict mean values for NGT subjects and squares depict IGT subjects; closed symbols depict subjects with a first-degree relative with type 2 diabetes (FH^+), while open symbols depict subjects without a family history of diabetes (FH^-).

v 265 [244 to 289] pmol/L, $P = .012$), whereas the plasma insulin values were greater in this group at 90 and 120 minutes ($P < .001$) (Fig 1).

During the hyperglycemic clamps, plasma glucose concentrations were nearly identical in both groups (9.99 ± 0.02 *v* 10.1 ± 0.02 mmol/L). Beta-cell function, ie, first phase ($P = .000001$) and second phase ($P = .00007$) insulin secretion, was significantly reduced in the subjects with IGT (Fig 2, Table 2). The differences in β-cell function remained statistically significant (all, $P < .0001$) when gender, age, BMI, and WHR were included as covariates. Insulin sensitivity was significantly lower for IGT than for NGT subjects ($P = .018$, Table 2); however, the differences disappeared when gender, age, BMI, and WHR were taken into account ($P = .91$).

CONTRIBUTIONS OF β-CELL FUNCTION AND INSULIN SENSITIVITY TO GLUCOSE TOLERANCE

FPG

All subjects. First phase insulin secretion and insulin sensitivity index were significant contributors to the variance in FPG level ($r = .48$, $P < .00001$) (Table 3). Based on partial correlation coefficients, first phase insulin secretion and insulin

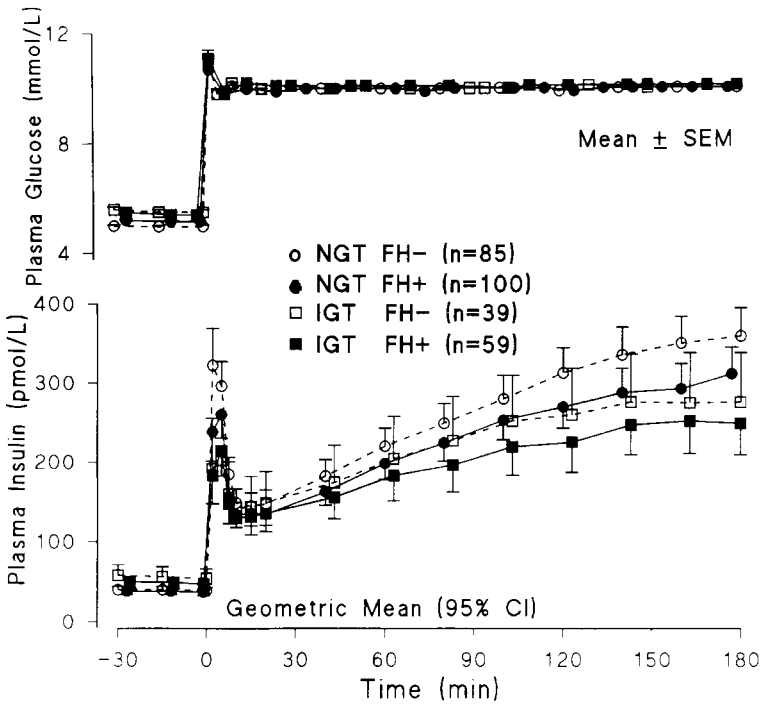

Fig 2. Mean (±SEM) plasma glucose levels (top) and geometric mean (95% CI) plasma insulin levels (bottom) during 180-minute hyperglycemic glucose clamps (10 mmol/L). Symbols depict same groups of subjects as in Fig 1.

Table 2. Indices of Insulin Secretion and Insulin Sensitivity in Subjects With NGT and IGT

	NGT			IGT		
	All	FH⁻	FH⁺	All	FH⁻	FH⁺
Insulin secretion						
First phase (pmol/L⁻¹)	711 (651-777)	796 (718-883)	647* (562-745)	467‡ (398-548)	449§ (359-562)	480¶ (378-609)
Second phase (pmol/L⁻¹)	281 (261-304)	301 (272-334)	266† (239-297)	203‡ (178-233)	209§ (176-249)	199¶ (160-248)
Insulin sensitivity						
M (μmol/kg LBM⁻¹ min⁻¹)	74.1 ± 2.0	77.5 ± 3.1	71.2 ± 2.5	46.7 ± 1.6‡	44.0 ± 2.7§	48.4 ± 2.0¶
ISI (μmol/kg LBM⁻¹ min⁻¹/pmol⁻¹/L⁻¹)	0.236 ± 0.008	0.228 ± 0.011	0.242 ± 0.012	0.202 ± 0.012‡	0.179 ± 0.019‖	0.217 ± 0.016

NOTE. Data for insulin secretion is geometric mean (with 95% CI). Data for insulin sensitivity is mean ± SEM.

Abbreviations: M, glucose infusion rate during third hour of hyperglycemic clamp divided by lean body mass; ISI, insulin sensitivity index (M divided by mean plasma insulin level during third hour of hyperglycemic clamp).

*$P < .01$, †$P < .05$, NGT FH⁺ *v* NGT FH⁻.

‡$P < .001$, all IGT *v* all NGT.

§$P < .0001$, ‖$P < .02$, IGT FH⁻ *v* NGT FH⁻.

¶$P < .01$, IGT FH⁺ *v* NGT FH⁺.

sensitivity index explained 14% and 10% of the variance in FPG.

NGT. First and second phase secretion and the ISI contributed significantly to FPG ($r = .37$, $P < .0001$), explaining 11%, 4%, and 2% of the variance.

IGT. First phase secretion and the ISI contributed significantly to FPG ($r = .50$, $P < .0001$), explaining 16% and 10% of the variances.

Plasma Glucose at 120 Minutes

All subjects. Insulin sensitivity index, first and second phase insulin secretion all contributed significantly ($r = .56$, $P < .00001$) and explained 21%, 2%, and 11% of the variance, respectively.

NGT. Only second phase secretion and insulin sensitivity contributed significantly ($r = .36$, $P < .001$), explaining 4% and 10% of the variance, respectively.

Table 3. Multiple and Partial Correlation Coefficients of the Relationships of Fasting and 120-Minute Postload Plasma Glucose and Parameters of Insulin Secretion and Insulin Sensitivity as Estimated During Hyperglycemic Clamps in All 283 Subjects, Those With NGT (n = 185), and Those With IGT (n = 98), Separately

		Partial Correlation Coefficient		
	Multiple *R*	First Phase	Second Phase	Insulin Sensitivity
Fasting plasma glucose				
NGT	0.37*	−0.33*	0.19†	−0.15‡
IGT	0.50*	−0.40‡	0.12	−0.28†
All	0.48*	−0.38*	0.09	−0.32*
120-min plasma glucose				
NGT	0.36§	0.02	−0.20†	−0.32§
IGT	0.32†	−0.09	−0.27†	−0.31†
All	0.56*	−0.13‡	−0.33*	−0.48*

*$P < .00001$.

†$P < .01$.

‡$P < .05$.

§$P < .001$.

IGT. Only second phase secretion and ISI contributed significantly to 120-minute plasma glucose ($r = .32$, $P < .01$), explaining 7% and 10% of the variances, respectively.

DETERMINANTS OF FASTING AND 2-HOUR PLASMA INSULIN CONCENTRATIONS

Fasting Plasma Insulin

All subjects. Only insulin sensitivity and plasma glucose contributed significantly ($r = 0.72$, $P < .00001$), explaining 18% and 14% of the variances, respectively (Table 4).

NGT. Insulin sensitivity and plasma glucose contributed significantly to plasma insulin ($r = .62$, $P < .00001$), explaining 16% and 4% of the variances, respectively.

IGT. In sharp contrast to the NGT group, in the IGT group, second phase insulin secretion and plasma glucose contributed significantly ($r = .85$, $P < .00001$), explaining 19% and 22% of the variances, respectively.

Plasma Insulin at 120 minutes

All subjects. Second phase secretion, insulin sensitivity index, and plasma glucose contributed significantly to the plasma insulin level ($r = .72$, $P < .00001$) and explained 4%, 7%, and 30% of the variances, respectively.

NGT. Only insulin sensitivity and 120-minute plasma glucose contributed significantly ($r = .69$, $P < .00001$), explaining 12% and 25% of the variances, respectively.

IGT. Again, in sharp contrast to the NGT group, only second phase insulin secretion contributed significantly to plasma insulin ($r = .64$, $P < .00001$), explaining 40% of the variance, while insulin sensitivity did not contribute significantly.

Relationship Between β-Cell Function and ISI

The relationship between first and second phase insulin secretion and insulin sensitivity index is depicted in Fig 3. Curvilinear relationships were found both for NGT and for IGT subjects, but for a given insulin sensitivity, insulin secretion was reduced in IGT subjects.

Table 4. Multiple and Partial Correlation Coefficients of Mean Fasting and 120-Minute Postload Plasma Insulin Levels and Parameters of Insulin Secretion and Insulin Sensitivity as Estimated During Hyperglycemic Clamps in All 283 Subjects, Those With NGT (n = 185), and Those With IGT (n = 98) Separately

	Fasting Plasma Insulin Level				
		Partial Correlation Coefficient			
	Multiple *R*	First Phase	Second Phase	Insulin Sensitivity	Fasting Glucose
NGT	0.62*	0.10	0.09	−0.40*	0.20‡
IGT	0.85*	0.14	0.43†	−0.19	0.47*
All	0.72*	0.11	0.12	−0.42*	0.38*
	120-Minute Plasma Insulin Level				
		Partial Correlation Coefficient			
	Multiple *R*	First Phase	Second Phase	Insulin Sensitivity	120-Minute Glucose
NGT	0.69*	−0.05	0.09	−0.35*	0.50*
IGT	0.64*	0.08	0.63*	−0.07	0.18
All	0.72*	0.03	0.19§	−0.26*	0.55*

*$P < .00001$.
†$P < .001$.
‡$P < .05$.
§$P < .01$.

DETERMINANTS OF β-CELL FUNCTION AND ISI

First Phase Secretion

All subjects. Multiple linear regression indicated that BMI and family history contributed significantly to first phase insulin secretion ($r = .34$, $P < .00001$), explaining 8% and 2% of the variances, respectively (Table 5).

NGT. BMI, family history, and body weight contributed significantly, explaining 10%, 4%, and 3% of the variances, respectively.

IGT. BMI and gender contributed significantly ($r = .50$, $P < .00001$), explaining 9% and 5% of the variances, respectively.

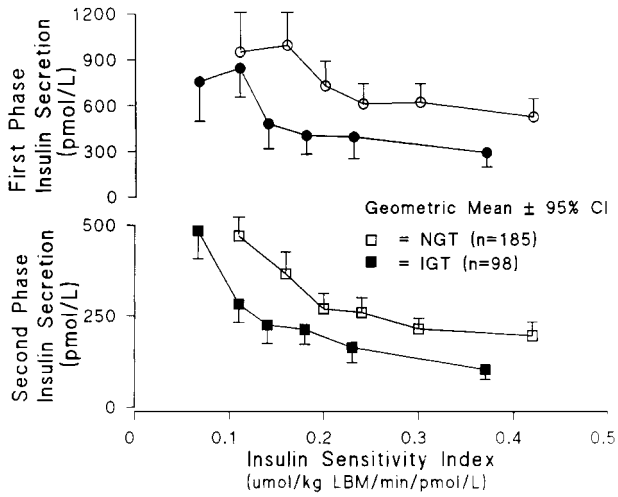

Fig 3. Relationship between first phase secretion (upper panel) and second phase (lower panel) (geometric mean, 95% CI) and insulin sensitivity index in NGT (open symbols) and IGT subjects (closed symbols); the subjects were subdivided into sextiles of insulin sensitivity.

Second Phase Secretion

All subjects. BMI, family history, and age contributed significantly ($r = .43$, $P < .00001$), explaining 17%, 2%, and 2% of the variances, respectively.

NGT. BMI, WHR, age, and family history contributed significantly ($r = .43$, $P < .00001$, explaining 9%, 3%, 3%, and 3% of the variances, respectively.

IGT. Only BMI contributed significantly to second phase secretion ($r = .57$, $P < .00001$) explaining 27% of the variance.

Insulin Sensitivity Index

All subjects. BMI and WHR contributed significantly ($r = .51$, $P < .000001$), explaining 19% and 2% of the variances, respectively.

NGT. Only BMI contributed significantly ($r = .40$, $P < .00001$), explaining 14% of the variance.

IGT. Only BMI contributed significantly to insulin sensitivity ($r = .67$, $P < .00001$), explaining 34% of the variance.

INFLUENCE OF FAMILY HISTORY OF TYPE 2 DIABETES

NGT Subjects

Clinical characteristics. NGT subjects with a family history of type 2 diabetes differed from those with no family history of type 2 diabetes only in $HbA1_c$ ($P = .041$), FPG ($P = .006$), and age ($P = .039$) (Table 1).

Metabolic characteristics. MANOVA for repeated measures showed that plasma glucose, as well as plasma insulin levels, were different between the 4 groups during OGTTs (both, $P < .01$) (Figs 1 and 2, Table 2). NGT subjects with a family history of type 2 diabetes had higher plasma glucose values at 90 minutes ($P = .015$) and at 120 minutes ($P = .039$) than NGT subjects without a family history, but plasma insulin concentrations did not differ.

During hyperglycemic clamp experiments, plasma glucose concentrations were comparable in the groups with (9.97 ± 0.01

Table 5. Partial Correlation Coefficients Determined With Multiple Linear Regression of Baseline Characteristics and Parameters of Insulin Secretion and ISI as Estimated During Hyperglycemic Clamps in All 283 Subjects, Those With NGT (n = 185), and Those With IGT (n = 98), Separately

	All Subjects			NGT Subjects			IGT Subjects		
	First Phase	Second Phase	ISI	First Phase	Second Phase	ISI	First Phase	Second Phase	ISI
Family history	−0.13*	−0.14*	0.08	−0.19†	−0.16*	0.08	0.09	0.06	0.06
Gender	−0.11	−0.02	−0.002	0.05	−0.03	0.01	−0.22*	−0.09	−0.03
Age	−0.11	−0.15*	−0.03	−0.07	−0.16*	−0.03	0.05	0.05	−0.15
Body weight	−0.01	0.02	0.02	−0.16*	−0.11	0.02	−0.02	0.03	0.03
Height	−0.02	0.02	0.02	0.03	−0.01	0.03	0.11	0.03	−0.11
BMI	0.28‡	0.41‡	−0.44‡	0.31§	0.30§	−0.38‡	0.30†	0.52‡	−0.58‡
WHR	−0.02	0.03	−0.14*	0.05	0.15*	−0.07	0.12	0.16	−0.17
Multiple *R*	0.34‡	0.43‡	0.51‡	0.39‡	0.43‡	0.40‡	0.50‡	0.57‡	0.67‡

*$P < .05$.
†$P < .01$.
‡$P < .00001$.
§$P < .001$.

mmol/L; CV, 3.3% ± 0.2%) and without (10.01 ± 0.03 mmol/L; CV, 4.4% ± 0.4%) a family history of type 2 diabetes. First phase and second phase plasma insulin responses ($P = .006$ and $P = .040$, respectively) were significantly reduced in those with a family history of type 2 diabetes, when gender, age, BMI, and WHR were used as covariates (Table 2). The ISIs were not significantly different ($P = .37$).

IGT Subjects

Clinical characteristics. IGT subjects with a family history of type 2 diabetes differed from those without such a history only in gender ($P = .04$), WHR ($P = .016$), and FPG ($P = 0.04$) (Table 1).

Metabolic characteristics. During OGTTs, there were no differences in plasma glucose and insulin concentrations between the IGT groups (Figs 1 and 2, Table 2).

During hyperglycemic clamp experiments, plasma glucose concentrations were comparable in the groups with (10.09 ± 0.03 mmol/L; CV, 2.7% ± 0.2%) and without a family history of type 2 diabetes (10.11 ± 0.03 mmol/L; CV, 3.1% ± 0.3%). First phase ($P = .46$) and second phase ($P = .57$) plasma insulin responses nor the ISIs differed between the 2 IGT groups ($P = .13$) with age, gender, BMI, and WHR as covariates (Table 2).

DISCUSSION

The present studies were undertaken primarily to compare β-cell function in IGT subjects with NGT subjects; moreover, we wanted to determine the relative contributions of variations in β-cell function and insulin sensitivity to maintenance of NGT. As a secondary goal, we sought to assess the influence of various commonly measured demographic characteristics including family history of type 2 diabetes on β-cell function and insulin sensitivity.

We had previously reported that NGT first-degree relatives of type 2 diabetes subjects have a lower β-cell function, but a normal insulin sensitivity index as compared with NGT controls.[13,14]

In the present studies, we find that individuals with IGT not only have diminished insulin sensitivity as has been previously reported by others,[18-20] but also have diminished β-cell function. Previously, various investigators have concluded that IGT subjects have an increased,[20] normal,[19] or disturbed[21,22] insulin secretion on the basis of plasma insulin levels after an intravenous (IV) GTT, or during 28-hour glucose infusions[23]; however, these approaches do not take into account that plasma glucose levels are different between controls and IGT subjects.

It is important to draw a distinction between insulin secretion and β-cell function. The latter represents the appropriateness of the β-cell response for the stimulus, while the secretion is merely the amount of insulin secreted per unit of time. The use of the standardized stimulus with the clamp technique evaluates β-cell function, because the stimulus (glucose) is kept constant.

We find that variations in β-cell function and insulin sensitivity, as measured in the present study, were able to account for less than a third of the variance in fasting and 2-hour plasma glucose concentrations after an OGTT. Taken at face value, these observations suggest that the majority of the variation in fasting and 2-hour plasma glucose may be determined by non–insulin-mediated mechanisms. With respect to fasting plasma glucose, this is not too surprising, because in the postabsorptive state, most of glucose disposal occurs in insulin independent tissues (ie, brain).[2] However, it was unexpected that only about a third of the variation in the 120-minute plasma glucose is apparently accounted for by insulin-mediated mechanisms, because insulin-induced suppression of hepatic glucose release and insulin-stimulated muscle glucose uptake are thought to be major factors regulating postprandial glucose metabolisme.[2,5,24,25] It could well be that other factors, such as insulin stimulation by incretins, first pass hepatic extraction of insulin, insulin clearance by other tissues, influence of insulin on glucagon, and insulin regulation of its own receptor number after 2 hours of hyperinsulinemia all play their role. Indeed, the 120-minute plasma glucose value can vary considerably from day to day in a given individual. The finding that the 120-minute plasma glucose values on 2 consecutive OGTTs only 10 days apart correlated with a R^2 of only 0.544,[26] suggests that roughly half of the variation of the 120-minute plasma glucose is due to these factors.

Regarding the individual contributions of components of

insulin-mediated pathways, we found roughly comparable contributions of insulin secretion and insulin sensitivity to fasting and 120 minutes plasma glucose; this is consistent with the inverse correlation of β-cell function and insulin sensitivity noted by Bergman et al[1] using minimal model analysis (Fig 3).

Both fasting and the 120-minute postglucose-load plasma insulin were correlated independently with insulin sensitivity. However, the ambient plasma glucose concentration was at least as important an explanation of the variances.

The practical consequence of these findings is that fasting and 120-minute plasma insulin levels must be used with caution as surrogate markers for insulin resistance (see below).

Influence of IGT

In IGT subjects, the fasting plasma glucose concentrations were a function of first phase insulin release and insulin sensitivity, whereas, in both groups, the 120-minute plasma glucose was a function of second phase insulin release and insulin sensitivity (but not first phase insulin release). Although the physiologic rationale behind this relationship of fasting plasma glucose and first phase release (which is seen both in IGT and NGT) may not be immediately clear, it might be that first phase release limits glucose excursions, which would then lead to lower (fasting) plasma glucose levels. Alternatively, it cannot be excluded that even a slightly raised fasting plasma glucose itself continuously induces release of the same β-cell pool of releasable insulin that is used for IV glucose-induced first phase release, thereby leading to finding a low ''first phase release'' during hyperglycemic glucose clamping. It is of note in this respect that the low (or absent) first phase release in type 2 diabetes subjects can return after 20 hours of euglycemia.[27] NGT and IGT individuals differed in the factors involved in the variation of fasting and 120-minute insulin levels. In NGT, insulin sensitivity and ambient plasma glucose were the main determinants, whereas in IGT, second phase insulin release and ambient glucose were involved. There is evidence for the existence of long-term adaptation of β-cell function to tissue insulin sensitivity; for example, very lean (presumably insulin-sensitive) NGT subjects have lower β-cell function than normal-weight controls[28]; conversely, insulin-resistant subjects show higher insulin secretion during glucose infusions than subjects with a normal insulin sensitivity.[29] Our finding that BMI and WHR contribute to insulin secretion points to the same phenomenon. Thus, it becomes plausible that insulin sensitivity (and plasma glucose) determine 120-minute plasma insulin in the NGT subjects. In IGT subjects, β-cell function (and ambient glycemia) mainly determine insulinemia. It therefore appears that the capacity to secrete insulin becomes rate-limiting for the fasting and 120-minute plasma insulin. Our finding that insulin sensitivity does not contribute to the plasma insulin level may point to a disturbance in the adaptation-process of the beta-cells to insulin (in)sensitivity in IGT, or may indicate that maximal adaptation/upregulation of β-cell function is generally already achieved when a person has become impaired glucose-tolerant. The relationship between insulin sensitivity and first phase secretion is depicted in Fig 3, which has a plateau for the lowest insulin sensitivity; this figure therefore points to a maximal upregulation in the most insulin-resistant individuals, even in NGT subjects. However, such a plateau was not found for second phase. Although it is not clear what is the cause of the fact that we could not find a plateau for second phase in this figure, it is conceivable that a number of insulin-resistant individuals who happened to have a slightly lower insulin release than the ones represented in that figure fell out of the scope of the present studies because they would have developed type 2 diabetes.

Determinants of Insulin Secretion and Insulin Sensitivity

Multiple linear regression indicated that BMI, which reflects percent body fat,[30] and family history of type 2 diabetes affected both first and second phases of insulin release; as noted above, because insulin release was determined during glucose clamping, this pertains to β-cell function. The correlation of family history with both parameters of islet β-cell function is consistent with there being a genetic influence on insulin secretion.[31-33] Regarding insulin sensitivity, BMI and WHR contributed significantly to its variance. These factors are known to be associated with insulin resistance.[34-36] In contrast, neither family history, gender, age, body weight, nor height independently contributed to the variation in insulin sensitivity. Previously, insulin resistance has been reported to occur in familial clusters.[37,38] Because the present analysis adjusted for BMI and WHR, which are thought to be under genetic control, it is possible that familial clustering of these variables may explain the lack of association with family history. In conclusion, our studies indicate that subjects with IGT not only have insulin resistance, mainly explained by obesity, but that their β-cell function is diminished, and not increased as has often been assumed. Furthermore, they indicate that β-cell function and tissue insulin sensitivity explain only one third of the variation in fasting and 2-hour postglucose load glycemia suggesting that non–insulin-mediated mechanisms may be more important than previously thought. Both fasting and 120-minute plasma insulin levels were determined by different factors in NGT and in IGT. Therefore, neither fasting nor postload plasma insulin levels can be used as a marker of insulin resistance in IGT; similarly, they cannot be used as markers of insulin secretion in NGT.

Finally, NGT first-degree relatives of subjects with type 2 diabetes have a lower insulin secretion than controls without a change in insulin sensitivity; first-degree relatives with IGT have similarly diminished insulin secretion as IGT subjects without a family history of type 2 diabetes; insulin sensitivity was lower in IGT subjects without a family history of diabetes than in NGT subjects without a family history, while such a difference in insulin sensitivity was not found in IGT subjects with a positive family history of diabetes.

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