What is a Normal Glucose Value?

Differences in indexes of plasma glucose homeostasis in subjects with normal fasting glucose

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OBJECTIVE — To evaluate differences in indexes of plasma glucose/insulin homeostasis and cardiovascular disease risk factors among subjects with normal fasting glucose (NFG), impaired fasting glucose, or glucose intolerance. Although individuals with fasting plasma glucose (FPG) concentrations >5.4 mmol/l but <6.1 mmol/l have been shown to have an increased risk of developing type 2 diabetes over 5 years, little is known about glucose metabolism abnormalities in this population.

RESEARCH DESIGN AND METHODS — We compared insulin secretion and insulin sensitivity using several indexes derived from an oral glucose tolerance test (OGTT) in 668 subjects from the Quebec Family Study who had varying degrees of FPG.

RESULTS — There was a progressive decline in indexes of β-cell function and insulin sensitivity when moving from NFG to type 2 diabetes. Compared with subjects with low NFG (FPG <4.9 mmol/l), subjects with high NFG (FPG 5.3–6.1 mmol/l) were more insulin resistant ($P < 0.01$), had higher insulin and C-peptide responses during an OGTT ($P < 0.05$), and had reduced insulin secretion (corrected for insulin resistance). Subjects with high NFG were also characterized by higher plasma triglyceride levels and reduced HDL cholesterol concentrations and by a smaller LDL particle size. All these differences remained significant, even after adjustment for age, sex, BMI, and waist circumference. In addition, subjects with mid NFG (FPG 4.9–5.3 mmol/l) were characterized by impaired insulin secretion, decreased insulin sensitivity, higher triglyceride concentrations, and lower HDL cholesterol concentrations compared with subjects with low NFG.

CONCLUSIONS — Independent of age, sex, and adiposity, there are differences in indexes of plasma glucose/insulin homeostasis and in cardiovascular risk factors among subjects with low, mid, and high NFG, suggesting the presence, in the upper normal glucose range, of abnormalities in glucose homeostasis, which may predispose to type 2 diabetes.

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Abbreviations: 2hPG, 2-h plasma glucose; ADA, American Diabetes Association; CVD, cardiovascular disease; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; OGTT, oral glucose tolerance test; QFS, Quebec Family Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The 1997 American Diabetes Association (ADA) (1) revision of the diagnosis and classification criteria for diabetes and glucose intolerance recommended two important changes in the diagnosis criteria. The major revision involved lowering the diagnostic value for the fasting plasma glucose (FPG) level from 7.8 to 7.0 mmol/l because the latter level was considered to be a better predictor of the risk of microvascular complications. In addition, a new stage in glucose tolerance, impaired fasting glucose (IFG) (FPG concentration 6.1–7.0 mmol/l and 2-h plasma glucose [2hPG] <7.8 mmol/l), was introduced. Similar to the category of impaired glucose tolerance (IGT) (2hPG 7.8–11.0 mmol/l after a 75-g glucose load and FPG <6.1 mmol/l), this new diagnostic entity was meant to be indicative of an intermediate metabolic state between normal and diabetic glucose homeostasis. The justification for its introduction is evidence that high but nondiabetic FPG values are associated with cardiovascular disease (CVD) and future type 2 diabetes (2). Also, it was thought that type 2 diabetes could be categorized properly on the FPG values (1). Although some studies confirm the risk associated with this condition, the definition of a high FPG has been inconsistent, making it difficult to select appropriate limits (3–6).

Impaired insulin sensitivity and insulin secretion are both involved in the deterioration of glucose tolerance from normal to a glucose-intolerant state (7). Differences in insulin secretion and insulin sensitivity among groups with apparently normal fasting glucose (NFG) (FPG <6.1 mmol/l) are not well documented. Many studies suggest that lower degrees of hyperglycemia than those defined by IFG are associated with a higher-than-normal risk for type 2 diabetes and CVD (4,5). There is limited data on indexes of plasma glucose/insulin homeostasis and their relation to CVD risk factors in these groups with NFG. Shaw et al. (5) have reported that an FPG >5.4 and <6.1 mmol/l is associated with a deteriorated

cardiovascular risk-factor profile (increased total cholesterol and triglycerides) and with an increased risk of developing type 2 diabetes over 5 years. In the few studies that have investigated these plasma glucose ranges, most did not adjust for differences in adiposity when comparing CVD risk factors (4,8,9). Furthermore, information on insulin secretion or sensitivity within this glucose range was not available (5,8,9).

Therefore, the aim of the present study was to evaluate potential differences in measures of plasma glucose/insulin homeostasis and CVD risk factors among subjects with varying values of FPG, taking into account age, sex, and expected differences in adiposity. We hypothesized that there would be a progressive deterioration of insulin resistance and insulin secretion even within this range of glucose values, which is currently considered normal.

RESEARCH DESIGN AND METHODS

— This cross-sectional study was conducted in 668 subjects (aged 18–61 years) recruited through the media in the Quebec City metropolitan area as part of the Quebec Family Study (QFS). QFS is an investigation of French-Canadian families designed to study factors involved in the etiology of obesity and its comorbidities (10). There were three phases in QFS. Initially between 1979 and 1981, a population-based sample of members of families was evaluated. In phases two and three, a sample of families from phase one was remeasured, and additional families, ascertained through obese probands (BMI >32 kg/m^2), were recruited and incorporated into the cohort. The maximal cross-sectional sample of subjects from phases two and three was analyzed in the present study. FPG concentration was calculated as the average of two baseline samples taken on the morning of the oral glucose tolerance test (OGTT), after a 12-h overnight fast. Systolic and diastolic blood pressures were measured in the right arm of seated participants. Subjects were classified into different stages of glucose tolerance based only on their FPG concentrations (except for the type 2 diabetes category). The group of subjects with NFG was divided into tertiles of FPG in order to compare groups with low (FPG <4.9 mmol/l), mid (FPG 4.9–5.3 mmol/l), and high (FPG 5.3–6.1 mmol/l) NFG. IFG was defined as an FPG ≥6.1 and <7.0 mmol/l and 2hPG <11.1 mmol/l (included subjects with isolated IFG or combined IFG and IGT), whereas type 2 diabetes was diagnosed on the basis of an FPG ≥7.0 mmol/l and/or a 2hPG ≥11.1 mmol/l. All participants gave informed consent before entering the study, which was approved by the Laval University Medical Ethics Committee.

Anthropometric and computed tomography measurements

Body density was estimated by the hydrostatic weighing technique as previously described (11). Fat mass was obtained by multiplying the percentage of body fat by body weight. Height, body weight, and waist circumference were determined following the procedures recommended at the Airlie Conference (12). Measurements of abdominal adipose tissue areas were performed by computed tomography at the abdominal level between L4 and L5 vertebrae with a Siemens Somatom DRH scanner (Erlangen, Germany) following the procedures of Sjöström et al. (13), as previously described (14).

OGTT

A 75-g OGTT was performed in the morning after an overnight fast. Blood samples were collected in EDTA-containing tubes (Becton Dickinson, Franklin Lakes, NJ) through a venous catheter from an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min for the determination of plasma glucose, insulin, and C-peptide concentrations. Assay procedures used to measure plasma glucose, insulin, and C-peptide levels have been described in detail in a previous publication from our group (11). The interassay coefficient of variation was 1.3% for a basal glucose value set at 5.0 mmol/l. We used several indexes derived from the OGTT to evaluate insulin secretion and insulin sensitivity (15–21). These indexes, shown in Table 1, have been correlated with more precise measurements.

Plasma lipids and lipoproteins

Blood samples were collected in the morning after a 12-h fast from an antecubital vein into vacutainer tubes containing EDTA. Cholesterol and triglyceride concentrations were determined enzymatically in plasma and lipoprotein fractions with a Technicon RA-500 analyzer (Bayer, Tarrytown, NY), and enzymatic reagents were obtained from Randox Laboratories (Crumlin, U.K.). Plasma lipoprotein fractions (VLDL, LDL, and HDL) were isolated by sequential ultracentrifugations that have been previously described (22). Nondenaturing 2–16% polyacrylamide gradient gel electrophoresis was used to characterize LDL particle size as previously described (23).

Statistical analysis

Statistical analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC). Subjects on pharmacological treatment for diabetes were excluded. Subjects were classified into five groups according to FPG values. Morphological and metabolic variables were compared among the groups using ANOVA with the general linear model procedure. Group comparisons were made with adjustment for age, sex, BMI, and waist circumference. BMI was used to estimate body fat, whereas waist circumference was found to reflect body fat distribution. The absence of colinearity between these two variables was confirmed with a regression analysis using the variance inflation factor. For analysis with insulin secretion indexes, comparisons were performed after adjustment for age, sex, BMI, and waist circumference, with or without an index of insulin sensitivity (Matsuda index). Participants on antihypertensive or lipid-lowering medication were excluded from comparisons of plasma lipid lipoprotein and blood pressure variables. To determine the insulin sensitivity secretion profile in relation to FPG concentrations, subjects with NFG were divided into tertiles of insulin sensitivity and insulin secretion. Subgroups of subjects with different insulin sensitivity and secretion patterns were formed, and the corresponding FPG concentrations were determined. Groups were compared with each other in regard to FPG by using ANOVA with the general linear model procedure. Group comparisons were made after adjustment for age, sex, BMI, and waist circumference, with least square mean procedure. A factorial analysis was also performed to determine the possible interaction between insulin sensitivity and insulin secretion in modulating FPG. The critical *P* value for significance was set at 0.05. Several variables required log transformation in order to improve distribution (body fat mass, triglycerides, FPG,

Table 1—*Indexes of β-cell function and insulin sensitivity derived from fasting and OGTT measurements of glucose, insulin, and C-peptide*

Index	Formula	Reference
β-Cell function indexes		
First-phase Stumvoll index	700 + (1,283 + [1.829 × insul30]) − ([138.7 × glyc30] + [3.372 × insul0])	15
30-min insulinogenic index	insul30 − insul0/glyc30 − glyc0	16
30-min insulin/30-min glucose	insul30/glyc30	17
30-min C-peptide/30-min glucose	pepti30/glyc30	18
30-min C-peptide–to–30-min glucose ratio	pepti30 − pepti0/glyc30 − glyc0	18
Insulin sensitivity indexes		
$HOMA_{IR}$ index	$([insul0 \times glyc0]/22.5)^{-1}$	19
Cederholm index	(75,000 + [glyc0 − glyc120] × 1.15 × 180 × 0.19 × weight)/(120 × log[insulmean] × glycmean)	20
Matsuda index	10,000/sqrt (glyc0 × insul0 × [glycmean × insulmean])	21
MCR OGTT	(18.8 − [0.271 × BMI] − [0.0052 × insul120] − [0.27 × glyc90])	15
ISI OGTT	(0.226 − [0.0032 × BMI] − [0.0000645 × insul120] − [0.00375 × glyc90])	15

$HOMA_{IR}$, homeostasis model assessment for insulin resistance; ISI, insulin sensitivity index; MCR, metabolic clearance rate.

2hPG, glucose area, fasting insulin, insulin area, 30-min insulinogenic index, 30-min insulin/30-min glucose, first-phase Stumvoll index, homeostasis model assessment for insulin resistance, and Matsuda index).

RESULTS — Table 2 shows the baseline characteristics of FPG categories. Subjects with a high NFG were older than subjects in the mid- and low-NFG categories. In addition, BMI, waist circumference, and visceral and subcutaneous adipose tissue were significantly higher in subjects with mid and high NFG than in subjects with low NFG ($P < 0.05$). Although there were differences in systolic and diastolic blood pressures among NFG categories, these differences disappeared after adjustment for age, sex, BMI, and waist circumference. Also, subjects with IFG and type 2 diabetes were older and had greater adiposity than those with NFG.

As shown in Table 2, after adjustment for age, sex, BMI, and waist circumference, subjects in the mid-NFG category

Table 2—*Baseline characteristics according to FPG category*

	FPG categories (mmol/l)				
	Low NFG (<4.9)	Mid NFG (4.9–5.3)	High NFG (5.3–6.1)	IFG (6.1–7.0)	Type 2 diabetes (≥7.0)
n	187–216	174–193	172–206	25–30	15–23
Physical characteristics					
Sex (M/F)	64/152	87/106	109/97	22/8	15/8
Age (years)	38.0 ± 14.5	39.5 ± 14.7	46.5 ± 14.1*†	51.0 ± 8.7*†	57.2 ± 12.1*†‡
BMI (kg/m^2)	24.3 ± 4.3	26.5 ± 5.7*	31.0 ± 8.1*†	34.2 ± 8.0*†‡	35.3 ± 7.2*†‡
Body fat mass (kg)	16.6 ± 8.7	20.2 ± 10.5*	29.5 ± 16.2*†	34.8 ± 17.0*†‡	38.3 ± 15.6*†‡
Waist circumference (cm)	78.3 ± 11.2	85.7 ± 14.4*	98.3 ± 18.0*†	107.4 ± 14.9*†‡	114.2 ± 14.4*†‡§
Visceral adipose tissue (cm^2)	75 ± 46	97 ± 57*	145 ± 74*†	190 ± 74*†‡	260 ± 119*†‡
Subcutaneous adipose tissue (cm^2)	225 ± 128	266 ± 159*	341 ± 185*†	357 ± 168*†	368 ± 172*†‡
Blood pressure (mmHg)					
Systolic	113 ± 15	115 ± 17	121 ± 18	123 ± 14	140 ± 23*†‡§
Diastolic	69 ± 8	71 ± 10	73 ± 11	78 ± 9	79 ± 10‡
Lipoprotein lipid profile					
Total cholesterol (mmol/l)	4.71 ± 0.97	4.64 ± 0.99	4.94 ± 0.98	4.99 ± 1.10	5.02 ± 1.06*†‡
LDL cholesterol (mmol/l)	2.86 ± 0.87	2.83 ± 0.83	3.03 ± 0.85	3.02 ± 0.84	3.00 ± 0.82*†‡
HDL cholesterol (mmol/l)	1.36 ± 0.33	1.20 ± 0.31*	1.14 ± 0.30*	1.07 ± 0.31	1.02 ± 0.25
Cholesterol/HDL cholesterol	3.61 ± 1.01	4.09 ± 1.27	4.59 ± 1.40	4.87 ± 1.31	5.12 ± 1.49
Triglycerides (mmol/l)	1.10 ± 0.49	1.37 ± 0.73*	1.74 ± 0.81*	2.07 ± 1.51	2.38 ± 1.89‡
LDL peak particle size (Å)	254.3 ± 3.8	252.7 ± 4.3	250.9 ± 4.8*	251.0 ± 3.3	248.0 ± 6.1

Data are means ± SD. *Significantly different from individuals with low NFG ($P < 0.05$); †significantly different from individuals with mid NFG ($P < 0.05$); ‡significantly different from individuals with high NFG ($P < 0.05$); §significantly different from individuals with IFG ($P < 0.05$). Statistical analyses were performed after adjustment for age and sex (BMI, body fat mass, waist circumference, and visceral and subcutaneous adipose tissue variables) or age, sex, BMI, and waist circumference (all other variables) with log transformation for body fat mass, visceral adipose tissue, and triglycerides.

Table 3—*Glucose-insulin homeostasis variables according to FPG category*

	FPG categories (mmol/l)				
	Low NFG (<4.9)	Mid NFG (4.9–5.3)	High NFG (5.3–6.1)	IFG (6.1–7.0)	Type 2 diabetes (6.1–7.0)
Glucose insulin homeostasis					
Fasting glucose (mmol/l)	4.65 ± 0.20	5.07 ± 0.11*	5.57 ± 0.20*†	6.42 ± 0.28*†‡	8.70 ± 1.64*†‡§
2-h glucose (mmol/l)	5.68 ± 1.47	6.04 ± 1.61*	6.95 ± 1.76*†	7.64 ± 2.02*†	15.88 ± 3.14*†‡§
Glucose area (mmol/l)	1,083.9 ± 220.4	1,153.9 ± 214.5*	1,335.5 ± 232.5*†	1,528.8 ± 265.3*†‡	2,591.6 ± 457.3*†‡§
Fasting insulin (pmol/l)	49.2 ± 26.9	65.0 ± 42.2*	89.6 ± 53.2*†	118.5 ± 68.6*†	184.2 ± 119.9*†‡
Insulin area ($\times 10^{-3}$ pmol/l)	62.5 ± 32.5	73.4 ± 49.6	92.2 ± 55.9*	121.1 ± 83.2*†‡	94.1 ± 68.9†§
Fasting C-peptide (pmol/l)	655.0 ± 288.3	812.1 ± 350.7*	1,021.9 ± 443.8*†	1,306.1 ± 530.7*†‡	1,351.3 ± 476.8*†
C-peptide area ($\times 10^{-3}$ pmol/l)	474.4 ± 182.3	539.5 ± 219.4*	647.4 ± 242.7*	750.2 ± 274.5*†	530.5 ± 184.3*†‡§
Insulin sensitivity indexes					
HOMA	1.20 ± 3.56	0.69 ± 1.38*	0.48 ± 1.76*†	0.23 ± 0.12*†‡	0.12 ± 0.06*†‡§
Cederholm	18.48 ± 4.36	16.78 ± 4.12*	13.78 ± 3.54*†	11.42 ± 2.88*†‡	5.10 ± 1.31*†‡§
Matsuda	20.9 ± 20.0	15.9 ± 14.3*	10.5 ± 5.0*†	6.6 ± 3.1*†‡	4.2 ± 2.0*†‡
MCR OGTT	28.8 ± 2.0	27.7 ± 3.1	25.4 ± 3.8*	23.6 ± 4.4*†‡	21.7 ± 3.7*†‡
ISI OGTT	0.60 ± 0.02	0.59 ± 0.04	0.56 ± 0.05*†	0.54 ± 0.05*†‡	0.51 ± 0.05*†‡

Data are means ± SD. *Significantly different from individuals with low NFG ($P < 0.05$); †significantly different from individuals with mid NFG ($P < 0.05$); ‡significantly different from individuals with high NFG ($P < 0.05$); §significantly different from individuals with IFG ($P < 0.05$). Statistical analyses were performed on age-, sex-, BMI-, and waist circumference–adjusted values. For Cederholm index, Matsuda index, metabolic clearance rate (MCR) OGTT, and insulin sensitivity index (ISI) OGTT, analyses were performed on age, sex, and waist circumference adjusted value. Analyses were performed on log-transformed values for FPG, 2hPG, glucose area, fasting insulin, insulin area, HOMA index, and Matsuda index.

had reduced HDL cholesterol concentrations and increased plasma triglyceride concentrations compared with the low-NFG group ($P < 0.05$). In addition, triglyceride concentrations were increased and HDL cholesterol concentrations, as well as LDL particle size, were significantly reduced in subjects with high NFG compared with the low-NFG group ($P < 0.05$). Many differences in the plasma lipid lipoprotein profile were also observed among subjects with type 2 diabetes and those with NFG. However, after excluding subjects under lipid-lowering medication, group numbers ($n = 15$) became too low to produce strong conclusions.

As expected, the FPG concentrations as well as the 2hPG values differed significantly among the five categories of FPG (Table 3). Analyses performed on 2hPG revealed that 8.8% of subjects in the low-NFG group, 10.5% in the mid-NFG group, 28.9% in the high-NFG group, and 40.0% in the group with IFG had IGT ($P < 0.0001$). Significant differences in insulin and C-peptide concentrations among the groups of NFG, IFG, and type 2 diabetic subjects were observed. In fact, the mid- and high-NFG groups showed higher fasting plasma insulin and C-peptide, as well as higher C-peptide area, compared with subjects with a low NFG. In addition, fasting plasma insulin and C-peptide concentrations were significantly higher in the high-NFG group than in the mid-NFG group ($P < 0.05$). Total insulin area under the curve was higher for subjects in the high-NFG category than for subjects in the low-NFG category.

Values of various surrogate measures of insulin sensitivity from the total sample are shown in Table 3. Insulin sensitivity progressively declined from low-NFG subjects to type 2 diabetic subjects, even after adjustment for age, sex, and adiposity. NFG subjects were more insulin sensitive than those with IFG or type 2 diabetes. Insulin sensitivity was lower in both mid- and high-NFG groups than in low-NFG subjects and was significantly lower in high-NFG compared with mid-NFG subjects.

Insulin secretion progressively increased as a function of the progressive decline in insulin sensitivity without significant differences among NFG categories (data not shown). However, after taking into account differences in age, sex, adiposity, and insulin sensitivity, insulin secretion progressively decreased with increasing FPG. In fact, significant differences were observed among subjects with high NFG and those in the other NFG groups. β-Cell function (as estimated by first-phase Stumvoll index, 30-min insulinogenic index, and 30-min (C-peptide/30-min glucose) was significantly reduced in the high-NFG group compared with the low- and mid-NFG groups (Fig. 1) ($P < 0.001$). We also observed that subjects in the mid-NFG category had lower first-phase Stumvoll index and 30-min insulin–to–30-min glucose ratio (data not shown) than subjects in the low-NFG category ($P < 0.01$). Finally, insulin secretion indexes were significantly decreased in subjects with IFG and type 2 diabetes compared with subjects with NFG.

The insulin sensitivity secretion profile in relation to FPG is shown in Fig. 2. These results clearly show that subjects in the lower tertile of insulin sensitivity and insulin secretion had higher FPG. In fact, subjects in the lowest insulin sensitivity tertile and low– or mid–insulin secretion tertile had higher FPG than subjects with low insulin sensitivity but high secretion. In the mid–insulin sensitivity group, FPG was inversely related to insulin secretion, with the highest values in the low–insulin secretion group. If insulin sensitivity is high, insulin secretion plays a minor role. Thus, impairments in both insulin sensitivity and insulin secretion contribute to the increased levels of FPG found in these subjects. Factorial analyses show a significant interaction between insulin secretion and insulin sensitivity in modulating FPG ($P < 0.05$). However, this interaction was no longer significant after

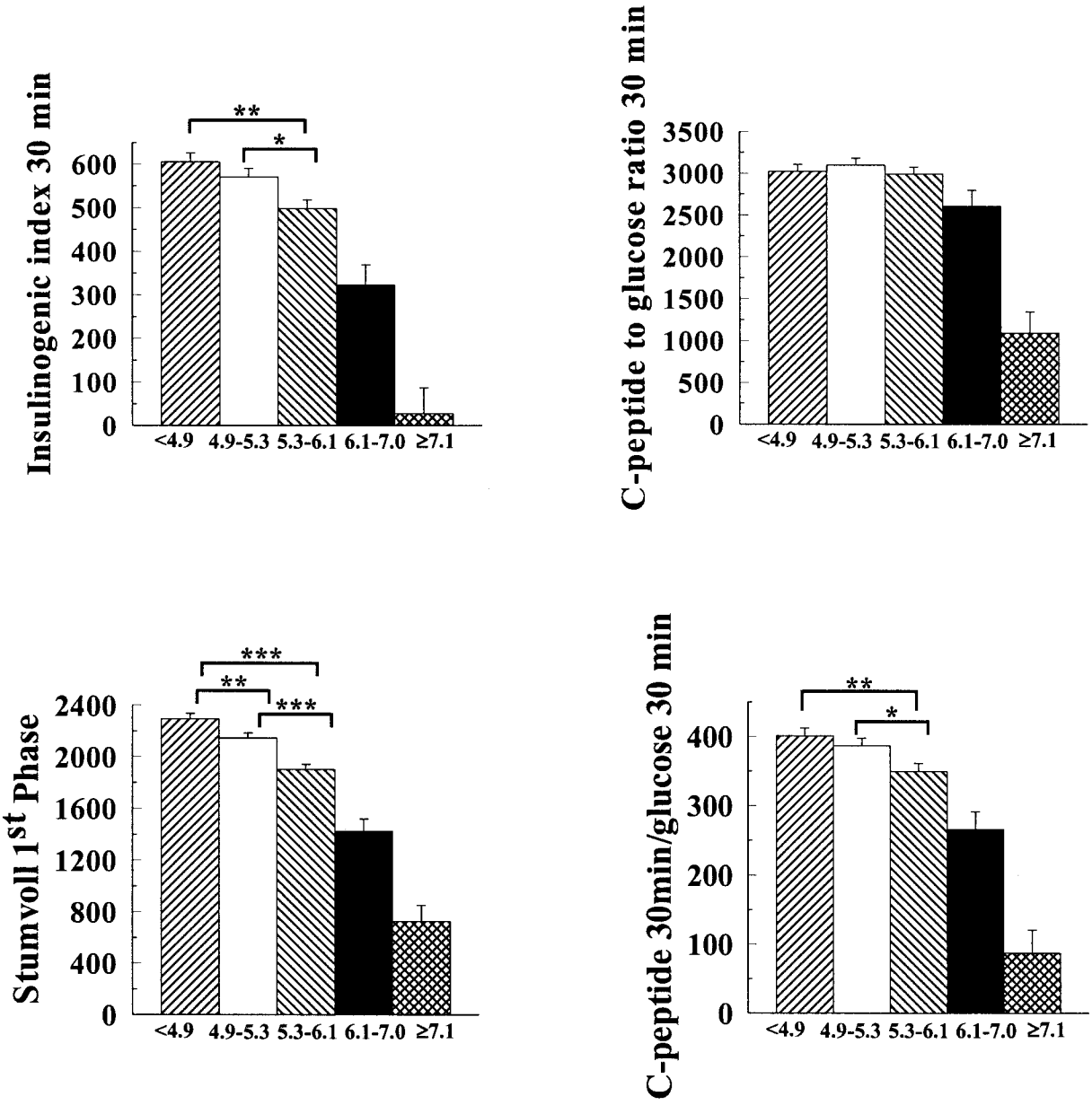

Figure 1—*Indexes of insulin secretion in 668 subjects according to their FPG categories. ▨, subjects with low NFG; □, subjects with mid NFG; ▧, subjects with high NFG; ■, subjects with IFG; ▩, subjects with type 2 diabetes. Data are presented as least square means ± SE, adjusted for age, sex, BMI, waist circumference, and insulin sensitivity (Matsuda index). All insulin secretion indexes are significantly different in IFG and type 2 diabetic groups compared with NFG groups (*$P < 0.0001$). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.0001$ for the low- vs. high-NFG groups. Values are expressed as inverse log-transformed values.*

including age, sex, BMI, and waist circumference in the model.

CONCLUSIONS — In 1997, the new diagnostic category, IFG, was introduced by the ADA to function as a category analogous to IGT (based on 2hPG concentrations). The glucose criteria for a diagnosis of diabetes are derived from data relating glucose concentration to the risk of eye and kidney disease, without regard to the risk for CVD (1). In this context, if there is as glucose threshold for CVD, it may be lower than that for the present definition of type 2 diabetes. Several reports suggest that degrees of hyperglycemia lower than those defined by IFG are associated with an increased risk of CVD and a higher risk of developing type 2 diabetes (2,4,5). In addition, data presented in a recent study demonstrate a continuous relationship between FPG and a number of CVD risk factors (24). However, the observed relationship between FPG and cardiovascular risk is often unadjusted for age, BMI, and abdominal obesity measured by waist circumference, a well-known independent risk factor for type 2 diabetes (25,26). Overweight not only affects insulin sensitivity but can also lead to compensatory increase in β-cell function (27).

In this study, we calculated several indexes of insulin sensitivity and secretion

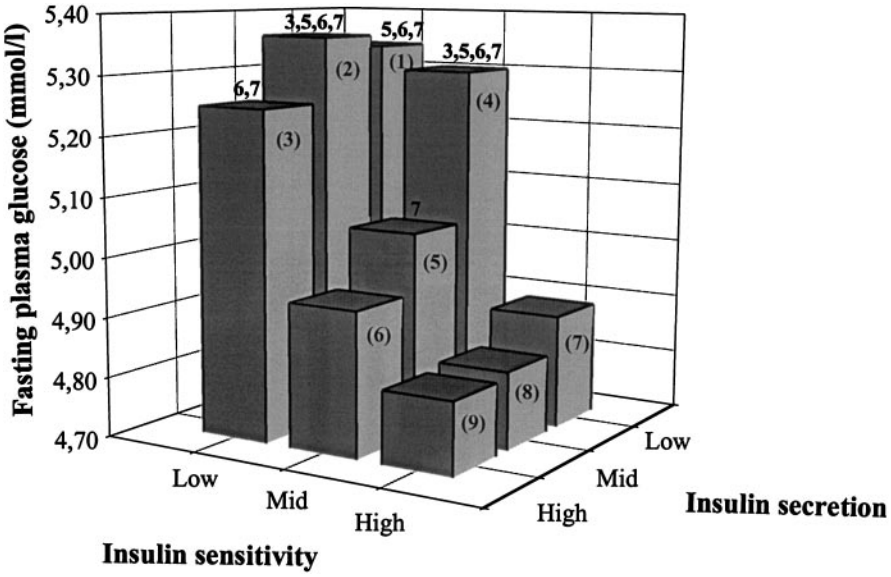

Figure 2—*NFG concentrations (FPG <6.1 mmol/l) in 615 subjects as a function of tertiles of insulin sensitivity (estimated with Matsuda index) and insulin secretion (estimated with first-phase Stumvoll index). Significant differences in FPG in the low–insulin sensitivity tertile were observed between mid– and high–insulin secretion groups (*$P < 0.01$*). In the mid–insulin sensitivity group, FPG was significantly different between insulin secretion groups (*$0.0001 > P < 0.01$*), with the highest values in the low–insulin secretion group. Differences in FPG among each subgroup with low insulin secretion were also observed (*$0.0001 > P < 0.01$*). No significant differences in FPG were observed in the high–insulin sensitivity tertile for insulin secretion categories.*

derived from the fasting state and OGTT and compared these among subjects with various degrees of FPG. We also compared the cardiovascular risk profile among different categories of FPG. To our knowledge, our study is the first to compare parameters of plasma glucose/insulin homeostasis and cardiovascular risk profile in different groups of subjects with FPG currently considered normal, after adjustment for important covariates such as age, sex, and body fat composition (measured as BMI) and distribution (measured as waist circumference). We further adjusted for insulin sensitivity in our analyses of insulin secretion indexes because insulin secretion and sensitivity are strongly linked through a hyperbolic relationship (28).

Our results show that subjects with a high NFG have significantly higher triglyceride concentrations, lower HDL cholesterol concentrations, and reduced LDL particle size than low-NFG subjects, even after adjustment for age, sex, BMI, and waist circumference. Furthermore, the high-NFG lipid lipoprotein profile was very similar to that observed in the IFG group, suggesting dyslipidemia even at this level. Subjects with mid NFG also showed higher triglyceride concentrations and reduced HDL cholesterol concentrations compared with subjects in the low-NFG category. All these lipid lipoprotein deteriorations are well-known components of the metabolic syndrome (29). These results support data from a recent metaregression analysis demonstrating a continuous positive relationship between initial FPG and cardiovascular events that extend below the current thresholds for IFG (4). Sex did not modulate these relationships, as similar results were obtained when analyses were performed on men and women separately (data not shown).

The gold-standard methods to assess insulin sensitivity and β-cell function are time consuming and difficult to use in large-scale clinical or epidemiological studies, where simpler methods are required. In recent years, several indexes of β-cell function and insulin sensitivity, which could be derived from fasting and OGTT measurements, have been described and validated with reference methods (15–21). Using these measures, our study shows that insulin sensitivity decreases with increasing FPG categories in the normal range, independent of age, sex, and body fat composition (measured as BMI), and distribution (measured as waist circumference). In fact, insulin sensitivity was lower in both the mid- and high-NFG groups than in the low-NFG group. In addition, subjects in the high-NFG category were more insulin resistant than subjects in the mid-NFG category. This reduction in insulin sensitivity found in subjects in the mid- and high-NFG categories may reflect an early defect already present in the NFG range and independent of adiposity.

To further take into account fat distribution, we adjusted for abdominal visceral adipose tissue accumulation in a subgroup of subjects ($n = 587$) who had initially undertaken a computed tomography scan, which is a direct measure of abdominal adipose tissue accumulation. After adjustment for age, sex, and visceral adipose tissue, similar results were found for all physical and metabolic variables studied (data not shown).

As a general concept, it is considered that glucose tolerance deteriorates when insulin secretion cannot compensate for insulin resistance. Insulin secretion and sensitivity follow a hyperbolic relationship, which emphasizes the importance of considering insulin sensitivity in evaluating the levels of β-cell function (28). In the present study, before any adjustment, insulin secretion indexes increased with increasing FPG level (data not shown). However, after adjustment for age, sex, adiposity, and insulin sensitivity, insulin secretion declines progressively when moving from low NFG to higher glucose levels. In fact, our results show significant decreases in relative insulin secretion between high- and low-NFG subjects and between mid- and low-NFG subjects. Thus, a relative defect in insulin secretion may already be present in high normoglycemic subjects, suggesting that impaired β-cell function is present even before the diagnostic criterion for diabetes and IFG have been met. Furthermore, our results support a study performed in Pima Indians, in whom the incidence of type 2 diabetes was highest among subjects in the lowest tertile of insulin sensitivity and insulin secretion (30). For instance, we observed that lower insulin sensitivity was strongly associated with increased FPG levels, as illustrated with the tertiles of insulin secretion and sensitivity relationship to FPG levels. Interestingly, we found that even in the normal glucose range, subjects with lower insulin sensitivity and low or mid insulin secretion

had higher FPG than subjects with low insulin sensitivity and high secretion. In addition, FPG was inversely related to insulin secretion in the mid–insulin sensitivity group. We further explored the independent contribution of insulin sensitivity and insulin secretion in FPG determination and CVD risk factors through multivariate analysis. Only FPG and insulin sensitivity were independent predictors of CVD risk factors (data not shown). Therefore, if insulin secretion plays a role in CVD risk factors, it is probably through IFG.

Insulin secretion is characterized by both an early and late response phase. The early response phase appears to play an important role in maintaining normal glucose response after a glucose challenge (31). Therefore, in this report, we used indexes based on the first 30 min of the OGTT as markers of early β-cell response. When taking insulin resistance into account, all of these indexes were lower in the high-NFG group than in the low- and mid-NFG groups. The presence of reduced early insulin secretion could explain the marginally increased FPG concentrations in this group. This would support previous evidence on the role of adequate early insulin secretion to maintain normal control of FPG (32) and could explain the differences seen in glucose tolerance among the FPG subgroups. In fact, the prevalence of IGT was found to be 10.5, 28.9, and 40.0% in subjects with mid and high NFG and IFG, respectively.

In conclusion, the results of this study indicate that individuals with FPG in the apparently normal range are heterogeneous in regard to plasma glucose/insulin homeostasis and cardiovascular risk. In fact, there are significant differences in glucose metabolism measures between low-, mid-, and high-NFG categories (independent of age, sex, and adiposity). Subjects with high NFG differed from those with low NFG with regard to decreased insulin sensitivity and impaired insulin secretion relative to this degree of insulin sensitivity. In addition, there were significant differences in CVD risk factors (HDL cholesterol, triglycerides, and LDL particle size) among NFG subcategories, even after adjustment for age, sex, and adiposity. These data show that in this population, CVD and type 2 diabetes risk factors increase continually across the presumably normal range of FPG. This would suggest possible early defects in insulin secretion as well as in insulin sensitivity, both of which contribute to the development of type 2 diabetes. Therefore, it may be of important clinical relevance to take into account the FPG value below the diabetes and IFG thresholds but in the upper NFG range, as has been recently suggested in clinical guidelines from the ADA (33). Longitudinal studies are clearly warranted to evaluate subjects with respect to glucose status and the risk of developing type 2 diabetes or CVD as a function of baseline FPG, even in the normal range.

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