Risk of Progression to Type 2 Diabetes Based on Relationship Between Postload Plasma Glucose and Fasting Plasma Glucose

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OBJECTIVE — We sought to assess the risk of progression to type 2 diabetes in normal glucose tolerance (NGT) subjects based on the relationship between the plasma glucose concentration during oral glucose tolerance tests (OGTTs) and the fasting plasma glucose (FPG) concentration.

RESEARCH DESIGN AND METHODS — Subjects with NGT ($n = 1,282$) from the San Antonio Heart Study received an OGTT with measurement of the plasma glucose concentration at 0, 30, 60, and 120 min at baseline and after 7–8 years of follow-up. Subjects were divided into four groups based on the relationship between the plasma glucose concentration during the OGTT and the FPG concentration on the same day as the OGTT. Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) and Matsuda index. Early-phase insulin secretion was calculated as the ratio between the incremental plasma insulin and glucose concentrations during the first 30 min of the OGTT ($\Delta I_{0-30}/\Delta G_{0-30}$). Total insulin secretion was calculated as the ratio between the incremental areas under the insulin and glucose curves during the OGTT [ΔG(AUC)/ΔI(AUC)].

RESULTS — In 23 subjects (group I), the plasma glucose concentration during the OGTT returned to levels below the FPG concentration at 30 min; in 111 subjects (group II) and in 313 subjects (group III), the plasma glucose concentration during the OGTT returned to levels below the FPG concentration at 60 and 120 min, respectively. In the remaining 835 subjects (group IV), the plasma glucose concentration during the OGTT never fell below the FPG concentration.

Insulin resistance, measured by HOMA-IR and the Matsuda index, increased progressively from group I through group IV, while insulin secretion measured by $\Delta I_{0-30}/\Delta G_{0-30}$ and ΔG(AUC)/ΔI(AUC) decreased progressively from group I through group IV.

The incidence of type 2 diabetes was 0% in group I and progressively increased to 0.9% in group II, 3.2% in group III, and 6.4% in group IV.

CONCLUSIONS — Subjects whose postload plasma glucose concentration returned to baseline (i.e., FPG level) more quickly had greater insulin sensitivity, a higher insulinogenic index, and a lower risk of developing type 2 diabetes after 8 years of follow-up compared with subjects whose postload glucose concentration returned to baseline more slowly.

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Abbreviations: AUC, area under the curve; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

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

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The term impaired glucose tolerance (IGT) was first introduced in 1979 and was defined as a 2-h plasma glucose concentration of 140–199 mg/dl following a 75-g oral glucose load (1). IGT was developed to replace the clinical states known at that time as borderline or chemical diabetes, which identified individuals at high risk for progression to overt diabetes (1). Subsequently, many studies confirmed that ~30–40% of individuals with a diagnosis of IGT developed diabetes over a 5- to 10-year follow-up period (2–6), and in 1997, the American Diabetes Association recognized IGT as a stage in the natural history in the deterioration of carbohydrate metabolism from normal to overt type 2 diabetes (7). Mechanistic studies confirmed that subjects with IGT manifested physiologic abnormalities that were characteristic of subjects with type 2 diabetes: insulin resistance and β-cell dysfunction (8–12). In 1997, the American Diabetes Association also defined a new category (7,13), impaired fasting glucose (IFG) (fasting plasma glucose [FPG] 100–125 mg/dl), that also identified individuals at high risk of developing type 2 diabetes (2–6).

Although subjects with normal fasting glucose (NFG) and normal glucose tolerance (NGT) have a lower relative risk for progression to diabetes than subjects with either IGT or IFG, in absolute terms, ~30–40% of all subjects who develop diabetes had NGT and NFG at baseline (2–6). Consistent with this observation, we have shown that impaired β-cell function and insulin resistance are present well before the onset of IGT and are linearly related to the log of the 2-h plasma glucose concentration over the range of 100–139 mg/dl (9,10). Thus, a substantial number of subjects with NGT and NFG are at risk for developing type 2 diabetes.

In this study, we used the relationship between the 2-h plasma glucose concentration during oral glucose tolerance tests (OGTTs) and FPG concentration to define a new risk factor that identifies NGT

subjects who are at greater risk for progression to type 2 diabetes.

RESEARCH DESIGN AND METHODS

— All subjects were participants of the San Antonio Heart Study, which is a population-based, epidemiological study of type 2 diabetes and cardiovascular disease (14–17). A total of 2,941 Mexican Americans and non-Hispanic whites, aged 25–68 years, were enrolled in phase 2 of the San Antonio Heart Study. We excluded phase 2 participants with IFG, IGT, and overt diabetes at baseline based on World Health Organization criteria (18). We also excluded all phase 1 participants, since in these participants, plasma glucose levels were not measured at 30 and 60 min. A total of 2,616 eligible participants, who had NFG and NGT at baseline, completed a 7- to 8-year follow-up examination. The study population was comprised of 1,282 of 2,616 NFG/IGT participants who had plasma glucose and insulin measurements at 0, 30, 60, and 120 min during the OGTT. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave written informed consent.

Definition of variables and outcomes

All studies were performed in a mobile clinic following a 12-h overnight fast. A fasting blood specimen was obtained for determination of plasma glucose and serum insulin and lipid concentrations. Following collection of the baseline blood sample (time 0), subjects ingested 75 g glucose (Orangedex; Custom Laboratories, Baltimore, MD), and blood was obtained at 30, 60, and 120 min for determination of plasma glucose and serum insulin concentrations. Plasma glucose and serum lipids were measured with an Abbott Bichromatic Analyzer (South Pasadena, CA). Serum insulin was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA), which has a relatively high degree of cross-reactivity with proinsulin (~70%). The diagnosis of diabetes was based on World Health Organization criteria (18): 2-h plasma glucose ≥200 mg/dl or FPG ≥126 mg/dl. Subjects on insulin or oral antihyperglycemic medications were considered to have diabetes.

Calculations

Areas under the glucose and insulin curves (AUCs) were calculated by the trapezoid rule. The homeostasis model assessment of insulin resistance (HOMA-IR) (19) and Matsuda index (20) were calculated as previously reported. The insulinogenic index was calculated by dividing the increment in serum insulin at 30 min by the increment in plasma glucose at 30 min of the OGTT. The metabolic syndrome was diagnosed using National Cholesterol Education Program-III criteria (21).

Statistical methods

Statistical analyses were performed with the SAS statistical software system (Cary, NC). Continuous variables were evaluated by one-way ANCOVA testing with overall differences with group treated as a categorical variable, testing for linear trend by treating group as an interval variable, and testing for group IV versus groups I–III as another categorical variable. Similar categorical variable comparisons were tested by χ^2 tests with Yates correction for continuity used for the analysis of dichotomous variables and by the Cochran-Armitage test for trend. Multiple logistic regression analysis was used to assess the risk of developing diabetes in individuals in two groups (those with 2-h glucose ≥ fasting and those with 2-h glucose < fasting) entered as a categorical variable, independent of the diabetes risk score, computed using age, sex, ethnicity, family history of diabetes, HDL cholesterol, triglycerides, and systolic blood pressure (17).

RESULTS

— Of 1,282 nondiabetic subjects with NFG and NGT at baseline, 64 developed type 2 diabetes after 7–8 years of follow-up. Thus, in this population, the 7- to 8-year incidence rate of type 2 diabetes among subjects with NGT was 5.0%. In subjects with IGT and IFG, the conversion rate to type 2 diabetes over the same 7- to 8-year follow-up was 19.6 and 10.0%, respectively. NFG and NGT subjects were divided into two groups according to the relationship between the 2-h plasma glucose concentration during the OGTT and the FPG concentration: 381 subjects had a 2-h plasma glucose concentration lower than fasting glucose concentration, and 901 subjects had a 2-h plasma glucose concentration higher than the FPG concentration. The 7- to 8-year diabetes incidence rates in the two groups were 2.9 and 5.9%, respectively ($P = 0.004$). After adjustment for BMI, age, sex, HDL cholesterol, triglycerides, family history, and fasting glucose, the difference in diabetes incidence between the two groups remained statistically significant ($P = 0.013$). The odds ratio (OR) for developing diabetes in subjects with a 2-h plasma glucose greater than the FPG relative to those with 2-h plasma glucose less than the FPG was 2.33 (95% CI 1.19–4.54). However, when insulin resistance (measured with Matsuda index) and insulin secretion (insulinogenic index) were added to the model as independent variables, the OR for developing diabetes in subjects with 2-h plasma glucose lower than FPG was 0.75 (0.37–1.50).

We also divided subjects into four groups, according to the time point (i.e., 30, 60, and 120 min or never) (Fig. 1) at which the plasma glucose concentration during the OGTT declined below the fasting glucose concentration. Group I included subjects whose plasma glucose concentration fell below the FPG at 30 min, group II included subjects whose plasma glucose concentration declined below the FPG at 60 min, group III included subjects whose plasma glucose concentration fell below the FPG concentration at 120 min, and group IV included subjects whose plasma glucose concentration never fell below the FPG at any time during the OGTT (Table 1). The mean plasma glucose and insulin concentrations for groups I–IV are shown in Fig. 1.

The anthropometric and metabolic characteristics of the four study groups at baseline are presented in Table 1. Age increased slightly from groups I through IV, but the difference did not reach statistical significance. BMI, waist circumference, serum triglycerides, FPG, and serum insulin concentrations increased progressively from groups I through IV, while HDL cholesterol concentration decreased progressively from groups I through IV.

The incidence rate for the development of type 2 diabetes was 0% in group I and increased progressively to 0.9, 3.2, and 6.4% in groups II, III, and IV, respectively ($P < 0.001$ for both overall χ^2 and Cochran-Armitage trend tests) (Fig. 2). The incremental areas under the insulin and glucose curves increased progressively from groups I to IV, whereas the ratio of these areas progressively decreased. Plasma glucose and serum insulin concentrations during the OGTT were used to derive indexes for insulin sensitivity and insulin secretion (Table 1). Insulin resistance, calculated by HOMA-IR, increased progressively from groups I through IV, and insulin sensitivity, calcu-

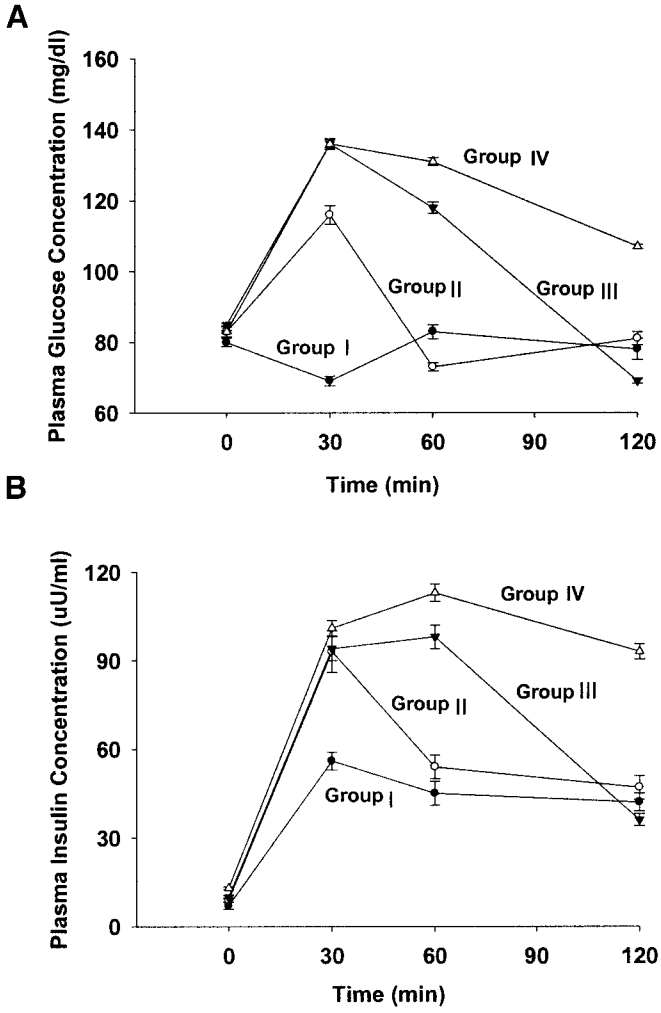

Figure 1—*Plasma glucose* (A) *and insulin* (B) *concentration at baseline based on the time (30, 60, and 120 min or never) that the plasma glucose concentration during the OGTT declined below the FPG concentration. Points are means ± SE.*

lated by the Matsuda index, declined progressively from groups I through IV.

The insulinogenic index ($\Delta I_{0-30}/\Delta G_{0-30}$), a measure of early-phase insulin secretion, declined progressively from groups I to IV. Both reduced insulin sensitivity (22) and impaired insulin secretion (23) were strong predictors of the development of diabetes at the 7- to 8-year follow-up visit.

To compare the impact of rising 2-h plasma glucose concentration on the development of diabetes, subjects were divided into four groups according to 2-h plasma glucose concentration (Table 2). As expected, the risk for future development of diabetes increased as 2-h plasma glucose concentration increased (Table 2). Each group was stratified further into high and low risk based on the relationship between FPG and 2-h plasma glucose: subjects with 2-h plasma glucose levels lower than fasting always had a lower risk than subjects with 2-h plasma glucose levels greater than the fasting.

CONCLUSIONS — In this study, we demonstrate for the first time that subjects with NFG and NGT can be stratified for risk of progression to type 2 diabetes based on the relationship between the FPG concentration and postload (OGTT) plasma glucose concentration. Moreover, stratification based on this criterion identifies physiologically distinct groups with abnormalities in insulin sensitivity and insulin secretion that are characteristic of individuals with type 2 diabetes (24–28).

The time that is required for the plasma glucose concentration to return to, or drop below, the fasting glucose level following glucose ingestion is dependent on the insulin response during the OGTT and peripheral/hepatic insulin sensitivity. The faster the postload (OGTT) glucose concentration declines to the fasting glucose concentration, the more efficient is the subject in disposing of the glucose load. Subjects in group I had the highest insulin sensitivity and the best β-cell function [low $\Delta I(AUC)/\Delta G(AUC)$]. Therefore, group I subjects were the most efficient in maintaining normal glucose homeostasis following administration of the glucose load. Thus, among subjects with NFG and NGT, group I returned their plasma glucose concentration during the OGTT below the FPG concentration within 30 min following the glucose load. Note that $\Delta I_{0-30}/\Delta G_{0-30}$ could not be calculated in this group because ΔG is negative.

Subjects in group II are also insulin sensitive. However, when compared with subjects in group I, they were more insulin resistant and required a higher $\Delta I(AUC)/\Delta G(AUC)$ to maintain normal glucose homeostatis following ingestion of the glucose load. Previous studies in this cohort (22) and others (23) reported increased insulin resistance and impaired insulin secretion to be independent predictors of future development of type 2 diabetes. The high insulin sensitivity for subjects in groups I and II, in combination with preserved β-cell function, most likely explains their very low risk for progression to type 2 diabetes (<1% in 7–8 years).

Subjects in group III had a further worsening of insulin resistance compared with subjects in groups I and II. They also had reduced insulin secretion compared with subjects in group II. The insulinogenic index, which correlates with early-phase insulin secretion following an intravenous glucose bolus, was decreased in group III compared with group II subjects. Reduced insulin sensitivity, combined with diminished insulin secretion, explains the significantly higher risk of progression to type 2 diabetes for subjects in group III. It should be noted that if only the fasting and 2-h plasma glucose concentrations in group III subjects were compared with group II subjects (Fig. 2*A*), the former would be falsely identified as having better glucose tolerance because both groups had similar FPG concentrations, while subjects in group III had a lower 2-h plasma glucose concentration.

Subjects in group IV had the most severe insulin resistance and worst β-cell function among subjects with NFG and

Table 1—*Clinical and laboratory characteristics of the four study groups based on the time that the plasma glucose concentration during the OGTT declined below the FPG concentration*

	Group I	Group II	Group III	Group IV
n	23	111	313	835
Age (years)	40.5 ± 9.6	40.1 ± 9.8	41.9 ± 10.1	42.6 ± 0.8
Sex (M/F)	78.3%	68.5%	35.5%	63.2%
BMI (kg/m^2)	24.0 ± 3.0	25.4 ± 4.1	26.6 ± 4.4	27.6 ± 5.4
Waist (cm)	78.1 ± 0.4	82.1 ± 11.6	89.3 ± 12.1	88.4 ± 13.2
Total cholesterol (mg/dl)	189 ± 35	187 ± 35	194 ± 36	195 ± 37
LDL cholesterol (mg/dl)	114 ± 33	115 ± 32	123 ± 33	123 ± 35
HDL cholesterol (mg/dl)	57 ± 12	52.7 ± 13.3	46.8 ± 13.3	47.3 ± 2.9
Triglycerides (mg/dl)	88 ± 43	97.4 ± 55.2	126.6 ± 78.5	134 ± 84
Fasting glucose (mg/dl)	79 ± 6	83 ± 8	84 ± 7	83 ± 8
2-h glucose (mg/dl)	78 ± 17	82 ± 20	69 ± 12	107 ± 17
Fasting insulin (μU/ml)	7 ± 5	9 ± 7	10 ± 8	13 ± 14
2-h insulin (μU/ml)	42 ± 38	49 ± 38	35 ± 32	95 ± 78
ΔGlucose (AUC) (mg · dl^{-1} · h^{-1})	−2.9 ± 22.9	8.9 ± 15.3	44.1 ± 27.8	75.0 ± 35.1
ΔInsulin (AUC) (μU · ml^{-1} · h^{-1})	71.1 ± 51.0	94.1 ± 61.7	120.7 ± 76.7	161.5 ± 114
[ΔI(AUC) + 60]/[ΔG(AUC) + 60]*	3.0 ± 1.6	2.3 ± 0.9	1.8 ± 0.7	1.7 ± 0.8
I_{0-30}/G_{0-30}	†	3.6 ± 3.5	2.1 ± 2.4	2.0 ± 2.3
HOMA-IR	1.4 ± 1.1	1.9 ± 1.4	2.1 ± 1.7	2.8 ± 2.9
Matsuda index	9.5 ± 5.7	7.8 ± 7.6	6.2 ± 5.9	4.6 ± 4.9
ΔI(AUC)/ΔG(AUC) ÷ IR	3.1 ± 2.6	2.0 ± 1.5	1.7 ± 1.1	1.1 ± 0.9
I_{0-30}/G_{0-30} Matsuda index		23.2 ± 28.1	9.9 ± 12.3	7.5 ± 12.9
With metabolic syndrome	4.4%	3.6%	11.8%	16.6%

Data are means ± SE unless otherwise indicated. Three tests were performed for each row: *1*) overall difference, *2*) trend, and *3*) differences between group IV and groups I–III. Each test was highly significant ($P < 0.001$) in each row except: age (each of the 3 tests was non-significant, $P > 0.05$); total cholesterol and LDL cholesterol (each $P < 0.05$); and waist, HDL cholesterol, fasting glucose, and I_{0-30}/G_{0-30} (overall and trend highly significant, $P < 0.001$) and group IV vs. groups I–III, $P < 0.05$. *Because of negative values in glucose AUC in subjects from groups I–IV, a constant number (60) was added to calculate the ΔI/ΔG. †The insulinogenic index was not calculated for subjects in group I because of negative glucose AUC.

NGT, and the combination of high insulin resistance plus low insulin secretion explains their highest risk for progression to type 2 diabetes among all subjects with NFG and NGT.

In the multiple logistic model, subjects with 2-h plasma glucose above the FPG concentration at 2 h had a 2.33-fold higher risk of developing diabetes compared with subjects with 2-h plasma glucose below fasting at 2 h. However, this risk was abolished when indexes for insulin sensitivity and insulin secretion were included as independent variables in the model, suggesting that stratifying subjects on the relationship between fasting and 2-h plasma glucose concentration is a simple method for identifying those who are highly insulin sensitive with preserved β-cell function (group I, II, and III) and, therefore, are at a very low risk for developing diabetes.

Subjects in groups I, II, and III are characterized by the ability to maintain NGT, i.e., to return the plasma glucose concentration to, or below, the starting FPG concentration within 2 h after ingestion of the glucose load. When groups I, II, and III are combined into one group, their mean fasting glucose concentration was 84 mg/dl and their mean 2-h plasma glucose concentration was 73 mg/dl. When compared with subjects in group IV (mean FPG 83 mg/dl), they had a comparable fasting glucose concentration.

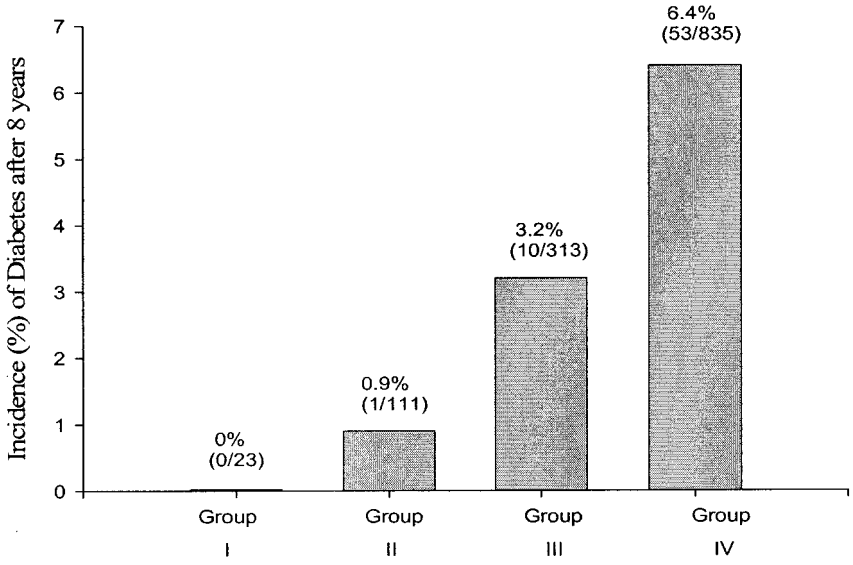

Figure 2—*Incidence of diabetes after 7–8 years based on the time (30, 60, and 120 min or never) that the plasma glucose concentration during the OGTT declined below the FPG concentration. The incidence (%) is shown at the bar for each of the four groups. The number of subjects converted to diabetes and the total number of subjects in each group is shown in parenthesis below the incidence.*

Table 2—*Incidence of type 2 diabetes based on the 2-h plasma glucose concentration during the OGTT (columns 1 and 2) and the 2-h plasma glucose minus FPG for groups I–III and IV according to the 2-h plasma glucose concentration (columns 3 and 4)*

2-h plasma glucose (mg/dl)	Incidence of diabetes	2-h plasma glucose minus FPG (group)	Incidence of diabetes
<85	13/428 (3.0%)	I–III	10/361 (2.7%)
		IV	3/47 (6.4%)
85–100	15/277 (5.4%)	I–III	1/65 (1.5%)
		IV	14/212 (6.6%)
100–125	21/388 (5.4%)	I–III	0/21 (0%)
		IV	21/367 (5.7%)
125–139	15/140 (10.7%)		

However, subjects in group IV had a significantly higher mean 2-h plasma glucose concentration (107 mg/dl, $P < 0.001$). These results indicate that, among subjects with NFG and NGT who have comparable FPG levels, an increase in 2-h plasma glucose concentration from 73 to 107 mg/dl, which is well within the normal range, is associated with a significant increase in insulin resistance, a significant decrease in insulin secretion, and a greater likelihood of progression to type 2 diabetes. This observation is consistent with earlier studies (9,10) in a completely separate group of subjects in whom we demonstrated that the insulin secretion/insulin resistance (so called "disposition") index decreased precipitously as the 2-h plasma glucose concentration increased above 100 mg/dl. In the present study, we demonstrate that these metabolic alterations (insulin resistance and impaired insulin secretion), which occur with normal plasma glucose concentrations, are clinically significant because they are associated with 2.6-fold increase (from 2.4 to 6.3%) in the risk for progression to type 2 diabetes (2–6).

In a recent cross-sectional study (30) that evaluated subjects with NGT (FPG 90 mg/dl) (i.e., similar to that in the present study) plus coronary heart disease, an increase in 2-h (OGTT) plasma glucose concentration from 110 to 130 mg/dl was associated with a significant increase in severity of coronary heart disease. Thus, subjects with a 2-h (OGTT) plasma glucose concentration within the normal range of glucose tolerance (particularly those with a 2-h plasma glucose concentration greater than the fasting glucose concentration [group IV]) are not completely "normal" with respect to glucose tolerance and risk for progression to diabetes and development of macrovascular complications (9,10,30). Taken collectively, these observations (worsening insulin resistance, high risk for progression to type 2 diabetes, and increased severity of coronary heart disease) in subjects with a 2-h (OGTT) plasma glucose concentration <140 mg/dl argue against the notion that all patients below the 2-h (OGTT) cut-off point of 140 mg/dl are safe from the risks associated with glucose intolerance. Rather, glucose intolerance, insulin resistance, and β-cell dysfunction should be considered continuous variables that increase the likelihood of developing type 2 diabetes and perhaps coronary artery disease (30).

Lastly, if we had relied only on the relationship between the 120-min plasma glucose concentration during the OGTT and the FPG concentration to categorize NFG and NGT subjects, 66 (12%) individuals from groups I and II (the low-risk groups <1%) would have been classified into group IV (the higher-risk group 6.4%), since the plasma glucose concentration had rebounded to levels above the FPG concentration at 120 min. This observation underscores the importance of obtaining additional plasma glucose samples during the OGTT, preferably at 60 min, in order to more precisely assess the risk for progression to type 2 diabetes.

In conclusion, we have demonstrated that subjects with NFG and NGT, whose plasma glucose concentration does not return to their FPG level within 2 h following an oral glucose load, have a significantly higher risk of progression to type 2 diabetes than NFG/NGT subjects whose 2-h glucose returns to the fasting level. These individuals also manifest greater insulin resistance and reduced insulin secretion compared with subjects whose plasma glucose concentration returns below the fasting glucose level.

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