

Prediction of Diabetes Based on Baseline Metabolic Characteristics in Individuals at High Risk

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 FOR THE ACT NOW STUDY

OBJECTIVE—Individuals with impaired glucose tolerance (IGT) are at high risk for developing type 2 diabetes mellitus (T2DM). We examined which characteristics at baseline predicted the development of T2DM versus maintenance of IGT or conversion to normal glucose tolerance.

RESEARCH DESIGN AND METHODS—We studied 228 subjects at high risk with IGT who received treatment with placebo in ACT NOW and who underwent baseline anthropometric measures and oral glucose tolerance test (OGTT) at baseline and after a mean follow-up of 2.4 years.

RESULTS—In a univariate analysis, 45 of 228 (19.7%) IGT individuals developed diabetes. After adjusting for age, sex, and center, increased fasting plasma glucose, 2-h plasma glucose, ΔG_{0-120} during OGTT, HbA_{1c}, adipocyte insulin resistance index, ln fasting plasma insulin, and ln ΔI_{0-120} , as well as family history of diabetes and presence of metabolic syndrome, were associated with increased risk of diabetes. At baseline, higher insulin secretion (ln [$\Delta I_{0-120}/\Delta G_{0-120}$]) during the OGTT was associated with decreased risk of diabetes. Higher β -cell function (insulin secretion/insulin resistance or disposition index; ln [$\Delta I_{0-120}/\Delta G_{0-120} \times$ Matsuda index of insulin sensitivity]); odds ratio 0.11; $P < 0.0001$) was the variable most closely associated with reduced risk of diabetes.

CONCLUSIONS—In a stepwise multiple-variable analysis, only HbA_{1c} and β -cell function (ln insulin secretion/insulin resistance index) predicted the development of diabetes ($r = 0.49$; $P < 0.0001$).

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Individuals with impaired glucose tolerance (IGT) are at high risk for diabetes; ~50% of all IGT subjects progress to diabetes during their lifetime, with annual diabetes conversion rates that

vary between 3 and 11% (1,2). Therefore, it is important to identify these individuals at high risk and to institute preventive therapy, be it lifestyle modification (3,4) or pharmacologic therapy, to prevent the

development of microvascular and macrovascular complications (5–11).

In ACT NOW, 602 IGT subjects at high risk were randomly assigned to receive therapy with placebo or pioglitazone, in addition to advice about diet and exercise (7,12). During a mean follow-up period of 2.4 years, subjects in the placebo and pioglitazone groups experienced conversion to diabetes at the rates of 7.6 and 2.1%, respectively (hazard ratio 0.28; $P < 0.00001$). All subjects in ACT NOW underwent baseline phenotypic, anthropometric, and clinical measurements. An oral glucose tolerance test (OGTT) measuring plasma glucose, free fatty acid (FFA), insulin, and C-peptide (CP) concentrations was performed to provide indices of glucose tolerance, insulin secretion, β -cell function, and insulin sensitivity at baseline (12–17). In the current study, we describe those variables that are independent predictors of type 2 diabetes mellitus (T2DM) in IGT subjects treated with placebo in ACT NOW, and we describe a multivariate model that is highly predictive of the eventual development of diabetes. In the predictive model, we used variables that are routinely obtained by practicing physicians, as well as physiologic variables derived from the OGTT.

RESEARCH DESIGN AND METHODS

Subjects

A total of 602 subjects at high risk (fasting plasma glucose [FPG] of 95–125 mg/dL and at least one additional risk factor for diabetes) with IGT (2-h plasma glucose 140–199 mg/dL) comprised the ACT NOW study population. Additional inclusion and exclusion criteria have been published (7,12). Demographic, anthropometric, and metabolic characteristics of the 602 subjects at baseline were similar in pioglitazone-treated and placebo-treated groups and have been published previously (7). In this study, we report 228 placebo-treated IGT subjects who completed the study and underwent an end-of-study OGTT or who experienced

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Prediction of diabetes

conversion to diabetes and underwent an end-of-study OGTT (Table 1). Subjects who were treated with pioglitazone, lost to follow-up, or who dropped out and did not undergo end-of-study OGTT were not included in the present analysis.

Study design

Detailed descriptions of the study design (12) and results have been published (1). Briefly, eight centers participated in the study, which was approved by each site's Institutional Review Board. After eligibility was determined, 602 IGT subjects were randomized by center or sex to receive pioglitazone or placebo. Subjects were recruited over the course of 2.1 years and followed up for a median of 2.4 years.

At baseline, all subjects underwent a 75-g OGTT with plasma glucose, insulin, CP, and FFA concentrations measured at -30, -15, and 0 min and every 15 min for 2 h. Additional baseline assessments included medical history, physical examination, HbA_{1c}, lipid profile, screening blood tests, urinalysis, and electrocardiogram.

Plasma glucose, FFA, insulin, CP, HbA_{1c}, and lipids were measured in a central laboratory (Texas Diabetes Institute, San Antonio, TX) (7,12). Body weight (nearest 0.1 kg on digital scale; Health-O-Meter, Bridgeview, IL) and height (nearest 0.1 cm) were recorded. Waist circumference was measured with a Gulick II Tape Measure (Gays Mills, WI) at the midpoint between the highest point at the iliac crest and the lowest part of the costal margin in the midaxillary line. Total body fat and percent body fat were measured by dual-energy X-ray absorptiometry (Hologic 4500; Hologic, Boston, MA).

Participants were randomized to pioglitazone 30 mg/day or placebo and returned at 2, 4, 6, 8, 10, and 12 months during the first year and then every 3 months thereafter. Subjects were followed-up until they reached the primary end point of diabetes, dropped out, were lost to follow-up, or reached study end. FPG was determined at each follow-up visit. HbA_{1c} was measured every 6 months, and OGTT was performed annually. Baseline

measurements were repeated at the end of the study or at the time of conversion to diabetes.

IGT conversion to diabetes. The primary outcome was development of diabetes defined as FPG \geq 126 mg/dL or 2-h glucose during OGTT \geq 200 mg/dL. The diagnosis was confirmed by a repeat OGTT (2-h glucose \geq 200 or FPG \geq 126 mg/dL).

Data analysis

Matsuda index (MI) of insulin sensitivity was calculated from plasma glucose and insulin concentrations during OGTT (18) as follows:

$$MI = \frac{10,000}{\sqrt{(FPI \cdot FPG) \times MPI \cdot MPG}}$$

MPI and MPG indicate mean plasma insulin and mean plasma glucose concentrations, respectively, during the OGTT.

The incremental area under plasma glucose, insulin, CP, and FFA curves during OGTT were determined using the trapezoidal rule. Insulin secretion rate (ISR) was calculated from deconvolution of the plasma CP concentration curve (19). ΔI , ΔISR , $\Delta I/\Delta G$, and $\Delta ISR/\Delta G$ were calculated as indices of insulin secretion during the OGTT, where Δ = increment above baseline. The β -cell function during the OGTT was calculated as the insulin secretion/insulin resistance (disposition) index using the following three different estimates of insulin secretion: $\Delta I_{0-120}/\Delta G_{0-120} \times MI$, $\Delta CP_{0-120}/\Delta G_{0-120} \times MI$, and $\Delta ISR_{0-120}/\Delta G_{0-120} \times MI$, where $_{0-120}$ represents the 0- to 120-min time point during the OGTT (3-6). The MI was calculated as described previously (18). The early insulin response was calculated as $\Delta I_{0-30}/\Delta G_{0-30} \times MI$, $\Delta CP_{0-30}/\Delta G_{0-30} \times MI$, and $\Delta ISR_{0-30}/\Delta G_{0-30} \times MI$. The adipocyte insulin resistance index was calculated as the product of fasting plasma insulin and FFA concentrations (20).

Metabolic syndrome was defined according to the American Heart Association and the Updated National Cholesterol Education Program Adult Treatment Program III definition (21) (i.e., three criteria among the following: increased waist circumference [men, >40 inches or 102 cm; women, >35 inches or 88 cm], elevated triglycerides ≥ 150 mg/dL [1.7 mmol/L], reduced HDL cholesterol [men, <40 mg/dL or 1.03 mmol/L; women, <50 mg/dL or 1.29 mmol/L], elevated blood pressure $\geq 130/85$ mmHg

Table 1—Baseline characteristics of the 228 placebo-treated IGT subjects who underwent baseline and end-of-study OGTTs

Characteristic	Placebo (n = 228)
Isolated IGT (n)	73
IGT/IFG (n)	155
Female/male ratio (%)	58/42
Race or ethnic group (n)	
Hispanic	54
White	137
Black	30
Other	7
Family history of diabetes [n (%)]	126 (55)
Mean age (years)	52.5 \pm 0.8
Mean BMI (kg/m ²)	34.4 \pm 0.4
Waist circumference (cm)	
Men	112 \pm 1
Women	103 \pm 1
HbA _{1c} (%)	5.60 \pm 0.03
FPG (mg/dL)	105 \pm 0.5
2-h plasma glucose (mg/dL)	169 \pm 1
Fasting plasma insulin (mU/L)	10.2 \pm 0.6
Lipid levels (mg/dL)	
Total cholesterol	171 \pm 2
LDL cholesterol	106 \pm 2
HDL cholesterol	41 \pm 1
Triglycerides	118 \pm 4
Fasting FFAs (μ mol/L)	547 \pm 13
Blood pressure (mmHg)	
Systolic	127 \pm 1
Diastolic	73 \pm 1

Data are mean \pm SD unless otherwise indicated.

or use of medication for hypertension, or elevated fasting glucose ≥ 100 mg/dL [5.6 mmol/L] or use of medication for hyperglycemia).

Statistical analysis addressed what metabolic, physiologic, anthropometric, or clinical parameters at baseline predict the development of T2DM in IGT subjects treated with placebo and followed up for a mean of 2.4 years. Intention-to-treat analyses were conducted using all available data for the period of follow-up. Baseline insulin concentration, insulin area under the curve, MI of insulin sensitivity, adipose tissue insulin resistance index, and insulin secretion/insulin resistance index were ln-transformed before analysis. Normality of distribution was tested by the Kolmogorov-Smirnov test. After adjusting for age, sex, and center, we examined the independent factors that predicted the development of diabetes in IGT subjects treated with placebo. We then used stepwise regression analysis including all variables that could be routinely measured in a physician's office (FPG, HbA_{1c}, blood pressure, family history of diabetes, BMI, waist circumference, and plasma lipid profile). In a second analysis, we used those variables from the previous stepwise regression analysis that were associated with development of diabetes and also added all OGTT-derived variables.

Methods for determination of HbA_{1c} and plasma glucose, insulin, CP, and lipids were published previously (7). All statistical tests were two-sided. Statistical significance was accepted for $\alpha < 0.05$. Data are presented as the mean \pm SE or median (Table 1 and Fig. 1).

RESULTS

Study cohort

The study population ($n = 228$; 58% female) had a mean age of 52.5 ± 0.8 years and mean BMI of 34.4 ± 0.4 kg/m²; 155 subjects had both IGT and impaired fasting glucose (IFG), and 73 had isolated IGT (Table 1). Baseline HbA_{1c}, FPG, and 2-h plasma glucose were $5.60 \pm 0.03\%$, 105 ± 0.5 mg/dL, and 169 ± 1 mg/dL, respectively.

Follow-up results

During a median follow-up of 2.4 years, 45 of 228 (19.7%) individuals in the placebo-treated IGT group developed diabetes. The annual average incidence rate of diabetes, calculated using person-years, was 8.2%.

Prediction of diabetes from baseline characteristics

After adjusting for age, sex, and center, increased FPG (odds ratio [OR] 1.11; $P < 0.0001$), 2-h plasma glucose (1.03; $P < 0.001$), ΔG_{0-120} (1.01; $P = 0.001$), and HbA_{1c} (8.37; $P < 0.0001$) at baseline and a positive family history (first-degree relative) of diabetes (2.46; $P = 0.02$) were associated with increased risk of diabetes. Higher adipocyte insulin resistance (1.48; $P = 0.05$), ln fasting plasma insulin (1.56; $P = 0.07$), and ln ΔI_{0-120} (0.61; $P = 0.08$) were or tended to be associated with increased risk for diabetes. At baseline, higher insulin secretion (ln $\Delta I_{0-120}/\Delta G_{0-120}$; OR 0.44; $P = 0.003$) and higher ln $\Delta ISR_{0-120}/\Delta G_{0-120}$ (0.25; $P = 0.003$) were associated with decreased risk of diabetes. Higher β -cell function (insulin secretion/insulin resistance or disposition index = $\ln [\Delta I_{0-120}/\Delta G_{0-120} \times MI]$; OR 0.11; $P < 0.0001$) at baseline was the variable most closely associated with reduced risk of diabetes.

At baseline, reduced insulin sensitivity (MI) (OR 0.92; $P = 0.22$), higher BMI (1.02; $P = 0.40$), higher percent body fat (1.02; $P = 0.40$), and higher waist circumference (0.99; $P = 0.37$) were not significantly related to future diabetes risk. Increased total cholesterol (1.02; $P < 0.05$) and reduced HDL (1.05; $P = 0.01$) at baseline were associated with increased risk for diabetes, whereas plasma triglycerides (1.01; $P = 0.78$), LDL cholesterol (0.99; $P = 0.15$), triglyceride/HDL cholesterol ratio (1.13; $P = 0.14$), and blood pressure (systolic blood pressure: OR 1.00; $P = 0.85$; diastolic blood pressure: OR 1.01; $P = 0.60$) were not associated with increased risk of T2DM.

At baseline, 63% of the subjects had the metabolic syndrome (defined according to the American Heart Association and the Updated National Cholesterol Education Program Adult Treatment Program III criteria). Metabolic syndrome was associated with increased risk of development of diabetes (OR 2.8; $P = 0.009$).

Relationship between plasma insulin response to hyperglycemia and insulin sensitivity

At baseline, the plot of insulin sensitivity (MI) versus the plasma insulin response to hyperglycemia ($\Delta I_{0-120}/\Delta G_{0-120}$) during the OGTT was curvilinear. It became linear on ln transformation (Fig. 1).

Predictive model

Using the cohort of 228 IGT subjects who received placebo treatment in the ACT

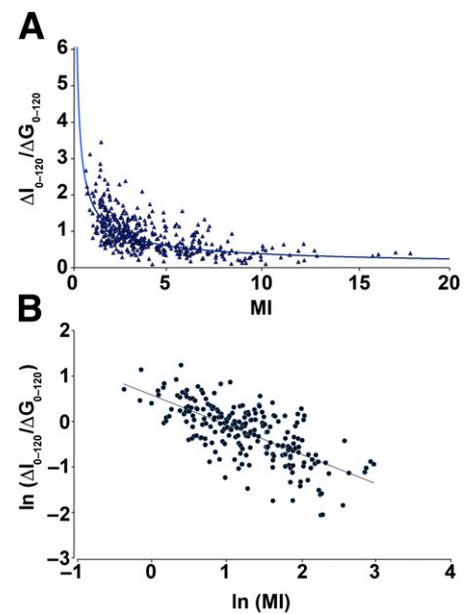


Figure 1—Relationship between the MI of insulin sensitivity and insulin secretion ($\Delta I_{0-120}/\Delta G_{0-120}$) before (A) and after ln transformation (B).

NOW study, we performed a multivariable stepwise regression analysis to examine which factors (that routinely could be measured in the physician's office) at baseline were associated with end-of-study glucose tolerance status (normal glucose tolerance [NGT] and IGT compared with T2DM). In this analysis, only HbA_{1c}, FPG, and family history of diabetes predicted the development of T2DM ($r = 0.45$; $P < 0.0001$). Of these three variables (after adjusting for age, sex, and center), HbA_{1c} had the greatest predictive power for future glucose tolerance status ($R^2 = 0.124$; $P < 0.0001$). Sequential addition of the FPG (adjusted $R^2 = 0.164$; $P < 0.0001$) and family history of diabetes (adjusted $R^2 = 0.178$; $P < 0.0001$) provided only a modest further increase. Individuals with HbA_{1c} of 5.6–5.9% ($n = 69$) and HbA_{1c} of 6.0–6.4% ($n = 20$) were at increased risk (OR 2.5 [$P = 0.01$] and OR 12.4 [$P < 0.0001$], respectively) for developing diabetes compared with those with HbA_{1c} $< 5.5\%$ ($n = 139$). Subjects with combined IGT and IFG ($n = 155$) at baseline were at increased risk (OR 3.0; $P = 0.008$) for developing diabetes compared with individuals with isolated IGT. When OGTT-derived physiologic variables were included with HbA_{1c}, FPG, and family history of diabetes in a stepwise multivariable regression analysis, only HbA_{1c} and ln insulin secretion/insulin

resistance predicted the development of diabetes ($r = 0.49$; $P < 0.0001$).

Of the easiest measured metabolic and physiologic parameters, HbA_{1c} had the greatest predictive value (adjusted $R^2 = 0.124$; $P < 0.0001$). Addition of the 2-h plasma glucose (adjusted $R^2 = 0.143$; $P < 0.0001$) or ΔG_{0-120} (adjusted $R^2 = 0.142$; $P < 0.0001$) during the OGTT increased the prediction of diabetes development only modestly. Addition of ΔI_{0-120} (adjusted $R^2 = 0.157$; $P < 0.0001$) or $\Delta I_{0-120}/\Delta G_{0-120}$ (adjusted $R^2 = 0.157$; $P < 0.0001$) to HbA_{1c} modestly increased the prediction of diabetes more than the addition of ΔG_{0-120} to HbA_{1c} did.

CONCLUSIONS—The prevalence of T2DM has increased to epidemic proportions in the United States and throughout the world (22), and this epidemic has been driven by the epidemic of obesity (23). T2DM and its associated microvascular and macrovascular complications cause considerable morbidity and mortality and represent a major burden on the health care economy (24). Therefore, in individuals at high risk, it is reasonable to consider interventions that will reduce the incidence of T2DM and its associated complications. Subjects with IGT are at high risk for development of T2DM (1), and individuals with combined IGT and IFG are at especially high risk (25,26), as substantiated by the present findings. Thiazolidinediones improve insulin secretion (17) and enhance insulin sensitivity (27–30); therefore, they represent a logical choice for treatment of individuals with IGT and IFG (5–8,31–34). In ACT NOW (7), we previously reported that pioglitazone decreased the conversion rate of IGT to T2DM by 72%, and 42% of pioglitazone-treated subjects reverted to NGT. In this study, we examined the physiologic, metabolic, and anthropometric parameters measured at baseline that predict final glucose tolerance status in ACT NOW participants treated with placebo. Indices of glycemic control (increased FPG, glucose area under the curve₀₋₁₂₀, and HbA_{1c}), increased fasting plasma insulin, higher insulin secretion, low insulin secretion or insulin resistance index, family history of diabetes, and presence of the metabolic syndrome were associated with the development of T2DM in subjects treated with placebo. IGT subjects with the best β -cell function at baseline were least likely to develop diabetes in the placebo-treated group.

These observations are consistent with results of a prospective study in which Hispanic women at high risk with history of gestational diabetes mellitus were followed up for 3.8 years (33). In the current study, low baseline insulin sensitivity, measured with the MI, was not predictive of future development of T2DM. This finding may appear to be somewhat discordant from that reported for women with gestational diabetes mellitus (31), but it should be noted that the majority of IGT subjects in the current study were moderately to severely insulin-resistant, and the narrow range of insulin resistance may have limited our ability to detect a significant relationship. At baseline, no anthropometric parameters predicted the future development of diabetes or reversion to NGT. Again, this most likely is explained by the very high BMI, waist circumference, and percent body fat with little variation among subjects. Although metabolic syndrome, increased total cholesterol, and reduced HDL cholesterol were independent predictors of the development of diabetes, they contributed no additional predictive power beyond that provided by HbA_{1c}. Blood pressure, plasma triglyceride, and LDL cholesterol were not associated with the development of diabetes in IGT individuals.

Multiple studies have documented that individuals with IGT are at high risk for future development of T2DM (1,2). The present results clearly demonstrate that IGT subjects at highest risk for development of diabetes later in life can be identified by their level of β -cell function, as quantitated by the ln insulin secretion/insulin resistance index. Although performance of the OGTT has decreased with the introduction of new diagnostic criteria for diabetes and prediabetes based on the FPG concentration and HbA_{1c} (34), neither FPG nor HbA_{1c} can provide information about β -cell function, which we demonstrate in the current study is the strongest predictor of future diabetes development in subjects with IGT. By performing the OGTT with measurement of plasma insulin concentrations, the physician can derive quantitative information about β -cell function that, when combined with an index of glycemic control (HbA_{1c}), can help to identify IGT individuals at especially high risk for development of T2DM later in life. As a screening tool to identify individuals at high risk who should be selected to undergo an OGTT, the HbA_{1c},

FPG, and family history of diabetes (i.e., variables that are readily available to the physician) can be used to select individuals for performance of the OGTT with measurement of the plasma insulin concentration. Not surprisingly, IGT subjects with HbA_{1c} >6.0% were at increased risk (OR 12.4) for developing diabetes compared with those with HbA_{1c} <5.5%. These individuals at high risk can be targeted for intensive lifestyle management, with or without pharmacologic therapy (35).

Although insulin resistance is a core pathophysiologic abnormality in the progression from NGT to IGT to T2DM (36), overt diabetes does not occur in the absence of β -cell failure (13–16,33). Therefore, it is not surprising that the insulin secretion/insulin resistance (disposition) index at baseline is the strongest predictor of future development of diabetes. However, this measure of β -cell function requires performance of the OGTT with determination of the plasma insulin and glucose concentrations. This requires patient time and adds cost. The OGTT also has some inherent variability. By using HbA_{1c} as a screening tool, individuals at high risk can be selected to undergo the OGTT. HbA_{1c}, in combination with the insulin secretion/insulin resistance index and 1-h plasma glucose during the OGTT (25,26), can be used to select the individuals at highest risk with IGT for pharmacologic intervention.

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