

Plasma Glucose Concentration and Prediction of Future Risk of Type 2 Diabetes

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The prevalence of type 2 diabetes has increased in recent decades to epidemic proportions. About 150 million individuals worldwide had type 2 diabetes in 2000, and this number is expected to increase to ~300 million by the year 2025 (1). Because of the chronic course of type 2 diabetes and the significant morbidity and mortality associated with the vascular complications of the disease, type 2 diabetes has become not only a serious public health threat, but also a heavy economic burden on the health care system. The total annual cost of diabetes care in the U.S. was estimated to be \$175 billion in the year 2007, and this number is expected to increase further with the increasing incidence of the disease (2).

Recent clinical trials have reported a reduction in the incidence of type 2 diabetes with lifestyle intervention (3,4) and pharmacotherapy (4,5) in subjects with IGT. These results suggest that primary prevention of type 2 diabetes could be an effective strategy to restrain the epidemic increase in the disease prevalence and reduce the economic burden it poses on the health care system.

Accurate identification of subjects at increased risk for future type 2 diabetes is essential for an early prevention program. It minimizes the number of subjects in the intervention program while improving the efficacy and the cost-effectiveness of the intervention. An impaired glucose tolerance (IGT) test was introduced in 1979 as an intermediate state in the transition in glucose homeostasis from normal to overt diabetes (6). Subjects with IGT have increased risk for future type 2 diabetes (7). Thus, all previous intervention trials

that have tested the efficacy of prevention strategies have recruited subjects with IGT (3–5). Although, in general, subjects with IGT have an increased risk for future type 2 diabetes, only about half of IGT subjects ultimately convert to diabetes (7). On the other hand, the majority of subjects who develop type 2 diabetes do not have IGT at baseline (8). Therefore, if one relies solely on IGT to identify subjects at risk for future type 2 diabetes, a large fraction of high-risk individuals who do not have IGT and could have benefited from an intervention program would be missed.

In this review, we will examine prediction models for future risk of type 2 diabetes and demonstrate that models based on the pathophysiology of the disease have greater prediction value for the future development of type 2 diabetes.

WHO IS AT RISK FOR FUTURE TYPE 2 DIABETES? —

Subjects with IGT have an increased risk for future type 2 diabetes, with a conversion rate of ~5–10% per year (7). Although, in general, subjects with IGT have increased risk for future type 2 diabetes, only 35–50% of individuals with IGT convert to type 2 diabetes after 10–20 years of follow-up (7–9).

Prospective epidemiological studies have reported that subjects with isolated impaired fasting glucose (IFG) (fasting plasma glucose [FPG] 100–125 mg/dl and 2-h plasma glucose <140 mg/dl) also have an increased risk for future type 2 diabetes despite having a 2-h plasma glucose concentration in the normal range (10–13). The future risk for type 2 diabe-

tes in subjects with isolated IFG is similar to that of subjects with isolated IGT (~5% per year) (7,10–13). Most importantly, prospective epidemiological studies have demonstrated that ~40 subjects who develop type 2 diabetes at follow-up have normal glucose tolerance (NGT) at baseline (7–13). These observations suggest that 1) the future risk for type 2 diabetes is not similar among all subjects in any glucose tolerance category and 2) a group of subjects with 2-h plasma glucose <140 mg/dl have an increased risk for future type 2 diabetes. Thus, using IGT for the prediction of future type 2 diabetes would miss this group of subjects with 2-h plasma glucose concentrations in the normal range (<140 mg/dl), yet are at increased risk for type 2 diabetes and could benefit from an intervention program.

Pathogenesis of type 2 diabetes

Subjects with type 2 diabetes have two major defects: 1) increased insulin resistance in skeletal muscle and liver and 2) impaired β -cell function (14). Both increased insulin resistance and impaired β -cell function are present long before overt hyperglycemia becomes evident. Increased insulin resistance occurs early in the natural history of type 2 diabetes but is compensated by increased β -cell secretion of insulin. When β -cell failure ensues, the hyperinsulinemia no longer can compensate for the insulin resistance and glucose homeostasis deteriorates. Initially, this is manifest as impaired glucose tolerance (IGT), which eventually progresses to overt diabetes (14). Most obese individuals are characterized by moderate-to-severe insulin resistance. However, the majority (~70%) maintain NGT throughout life because increased insulin secretion by a healthy β -cell is able to compensate for the insulin resistance. Thus, insulin resistance alone is not sufficient for the development of type 2 diabetes, and progressive β -cell failure is required for the deterioration in glucose homeostasis and the development of hyperglycemia.

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The publication of this supplement was made possible in part by unrestricted educational grants from Eli Lilly, Ethicon Endo-Surgery, Genex Biotechnology, Hoffmann-La Roche, Johnson & Johnson, LifeScan, Medtronic, MSD, Novo Nordisk, Pfizer, sanofi-aventis, and WorldWIDE.

DOI: 10.2337/dc09-S309

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Predictors of future type 2 diabetes

Insulin resistance is prerequisite for the development of type 2 diabetes and becomes manifest long before hyperglycemia is evident. Thus, models that quantitate the severity of insulin resistance would be useful for predicting the future risk of type 2 diabetes. The euglycemic-hyperinsulinemic clamp is the gold standard for quantitation of whole-body insulin sensitivity (15). However, this technique is complicated and difficult to perform in clinical practice. Elevated fasting insulin levels, which represent the physiological response to insulin resistance, and insulin resistance indexes derived from fasting and plasma glucose and insulin concentrations during the oral glucose tolerance test (OGTT) have been used to predict the future risk for type 2 diabetes (16). Subjects with insulin resistance have a cluster of metabolic abnormalities known as the insulin resistance (metabolic) syndrome (17), and a number of epidemiological studies have reported that the metabolic syndrome is a significant predictor of future type 2 diabetes (18). Linear regression models comprised of individual metabolic abnormalities associated with the insulin resistance syndrome (obesity, IFG/IGT, hypertension, and dyslipidemia), in addition to age and sex, also have been used to predict the future risk of type 2 diabetes (19–24). The predictive power of these multivariate models is comparable to that of IGT. Furthermore, addition of glucose tolerance status to the multivariate model did not improve its predictive power (19). Because all metabolic components of the multivariate model are obtained during the fasting state, these models have been proposed to replace the diagnosis of IGT in identifying subjects at increased risk for future type 2 diabetes, thereby obviating the need to perform an OGTT.

As discussed earlier, insulin-resistant individuals develop type 2 diabetes only if β -cell failure ensues. Thus, measures of β -cell function might be expected to be a key predictor for future type 2 diabetes. The hyperglycemic clamp is the gold standard method for the measurement of both first- and second-phase insulin secretion (15). Decreased first-phase insulin secretion consistently has been reported to predict the future development of type 2 diabetes (25–28). However, the hyperglycemic clamp is complicated and cannot easily be performed in clinical practice or in large-scale epidemiological studies.

Surrogate measures of β -cell function

obtained from plasma glucose and insulin concentrations during the OGTT correlate well with β -cell function measured with the gold standard hyperglycemic clamp method and have been shown to be good predictors for the future risk of type 2 diabetes (29,30). A decrease in early-phase insulin secretion ($\Delta I_{0-30}/\Delta G_{0-30}$) during the OGTT has been shown to be a strong predictor of the future development of type 2 diabetes (16,31–33). Because of the dynamic interaction between insulin secretion and insulin resistance (34), the insulin secretion/insulin resistance index (insulin secretion rate related to the prevailing level of insulin resistance) ($\Delta I/\Delta G \div IR$) is a better index of β -cell function. We previously have shown that this index performs superiorly to other models in predicting the risk of future type 2 diabetes (35). Furthermore, addition of the insulin secretion/insulin resistance index to a multivariate prediction model (the San Antonio Prediction Model), which is based on measurements taken during the fasting state (e.g., FPG, HDL, blood pressure, and waist), significantly increased the predictive power of the model (35). Models based on measurements taken during the fasting state cannot incorporate any measure of β -cell function (35,36). Thus, measures of β -cell function obtained from plasma glucose and insulin concentration obtained during post-glucose load have additive information for the future risk of type 2 diabetes compared with measurements taking during the fasting state.

Insulin resistance, insulin secretion, and glucose intolerance

Subjects with IGT have impaired early- and late-phase insulin secretion and increased insulin resistance in skeletal muscle (37–41). These metabolic abnormalities contribute to the increased risk for future type 2 diabetes. In contrast, subjects with IFG have impaired early-phase (first-phase) insulin secretion (with normal late-phase insulin secretion) and increased hepatic insulin resistance (with normal/near-normal muscle insulin sensitivity) (37–44). It is noteworthy that the decline in β -cell function begins at 2-h plasma glucose concentrations considered to be well within the normal range (<140 mg/dl) and continuously declines as the 2-h plasma glucose rises into the impaired glucose tolerance range (45,46). Thus, subjects with a 2-h plasma glucose of 120–140 mg/dl manifest an ~40–50% decrease in β -cell function compared

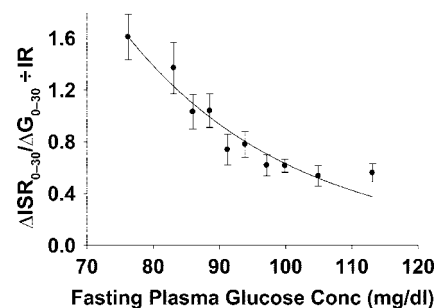


Figure 1—Relationship between β -cell function and FPG concentration in subjects with NGT. Subjects were divided in deciles based on FPG concentration. Each data point is the mean of 29 subjects. The line is the least-square fit for the data points and is best described by exponential decay function [$ISIR \text{ index} = 32 \exp(0.04FPG)$] and has a correlation coefficient of $r = 0.96$ ($P < 0.0001$). Conc, concentration; G, glucose; IR, insulin resistance measured with the Matsuda index; ISR, insulin secretory rate.

with subjects with 2-h plasma glucose <100 mg/dl, yet both groups are considered to have “normal” glucose tolerance. Similarly, the decline in first-phase insulin secretion begins with FPG concentrations well within the normal range (Fig. 1) (44,47). The impairment in β -cell function associated with the deterioration in glucose tolerance represents a continuum and clearly begins at a much earlier stage than previously appreciated. By the time the plasma glucose reaches the level of IGT (2-h plasma glucose 140 mg/dl) or IFG (FPG 100 mg/dl), ~40–50% of β -cell function has been lost (44–47). The decrease in β -cell function in subjects considered to have “normal” glucose tolerance most likely contributes to the large number of NGT subjects who convert to type 2 diabetes in prospective epidemiological studies (8). Therefore, by relying only on IFG and IGT to identify subjects at increased risk for future type 2 diabetes, those high-risk NGT subjects would not be identified. Thus, more accurate methods to predict the future risk of type 2 diabetes are required to identify this group of high-risk “normal” glucose tolerant individuals.

Fasting versus postload plasma glucose and risk of type 2 diabetes

Both the fasting and 2-h plasma glucose concentration during the OGTT are used to establish the diagnosis of type 2 diabetes. An increase in FPG concentration in the nondiabetic range has been shown to be associated with increased risk for future type 2 diabetes (7,8,11). Subjects

with isolated IFG (FPG 100–125 mg/dl and 2-h PG <140 mg/dl) have a 7.5% annual relative risk for future type 2 diabetes compared with NGT subjects (7). Moreover, the increase in future risk for type 2 diabetes associated with the increase in FPG concentration is a continuum and begins at a level below the cut point for impaired fasting glucose (100 mg/dl) (48). Similarly, an increase in 2-h plasma glucose concentration in the non-diabetic range (e.g., in subjects with IGT) also is associated with increased risk for type 2 diabetes with greater sensitivity and lower specificity compared with the increase observed with the FPG (7,8,11). However, as discussed above, both fasting and 2-h plasma glucose concentrations correlate closely with β -cell function, the principal factor responsible for the development of type 2 diabetes (35,36). First-phase insulin secretion and hepatic insulin sensitivity are important determinants of the initial rate of rise in plasma glucose concentration after glucose ingestion (49). The rate of decline in plasma glucose concentration back toward the fasting level depends on late-phase insulin secretion and insulin sensitivity in skeletal muscle (49). Thus, changes in β -cell function and insulin sensitivity will influence not only the absolute plasma glucose concentration during the fasting state and at 2 h after a glucose load, but also the shape of plasma glucose concentration curve during the OGTT: rate of plasma glucose increase, peak plasma glucose concentration, rate of plasma glucose decrease, and the time required for the plasma glucose concentration to return to the fasting level (50). Thus, the shape of the plasma glucose concentration during the OGTT provides a surrogate measure of β -cell function and whole-body insulin resistance and is a good predictor of the future risk of type 2 diabetes, above and beyond the fasting and 2-h plasma glucose concentration (50). Consistent with this concept, we have shown that the incremental area under the glucose curve during the OGTT (ΔG_{0-120}) strongly correlates with β -cell function (35,36), and it is a strong predictor for future risk of type 2 diabetes, independent of the glucose tolerance status (35,36). Addition of ΔG_{0-120} to prediction models based on measurements taken during the fasting state significantly improves their predictive power (35,36).

The time it takes for plasma glucose concentration to return to or below the FPG concentration during the OGTT also

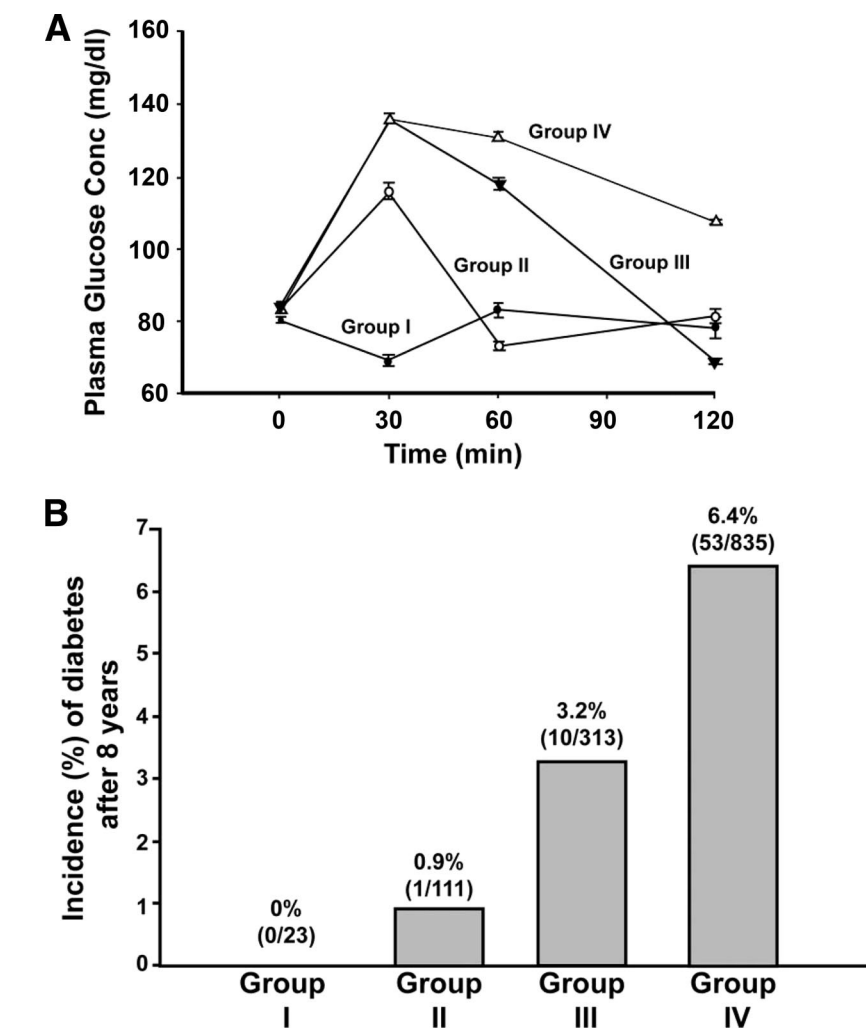


Figure 2—Plasma glucose concentration during the OGTT in NGT subjects. Subjects were divided into four groups (A) based on the time it takes to return their plasma glucose concentration below the fasting level. B: The 8-year conversion rate to type 2 diabetes in the four groups of subjects. See text for more details.

is an important predictor for the future development of type 2 diabetes. Normal glucose tolerant subjects who return their plasma glucose concentration back to the fasting level in <60 min during the OGTT have a significantly lower risk for future type 2 diabetes compared with subjects who require >60 min to return their plasma glucose concentration back to the fasting level (51) (Fig. 2).

ONE-HOUR PLASMA GLUCOSE AND FUTURE RISK OF TYPE 2 DIABETES

As discussed earlier, models that include a measure of β -cell function would be expected to have a better predictor value for the future risk of type 2 diabetes. Consistent with this, we have shown that the 1-h plasma glucose concentration during the OGTT correlates better than the 2-h

plasma glucose and FPG concentrations with indices of insulin secretion and insulin resistance (35,36) and with ΔG_{0-120} , which is a strong predictor of future risk for type 2 diabetes. Thus, the 1-h plasma glucose should be a good predictor for future risk of type 2 diabetes. To our surprise, no previous epidemiological studies have assessed the predictive power of the 1-h plasma glucose concentration for future risk of type 2 diabetes. Moreover, to the best of our knowledge, the only large epidemiological studies to measure the 1-h plasma glucose concentration at baseline are the San Antonio Heart Study (35) and the Botnia Study (36). In the San Antonio Heart Study and the Botnia Study, we measured the predictive power of 1-h plasma glucose concentration using the area under the receiver-operating curve (ROC) and compared the result to

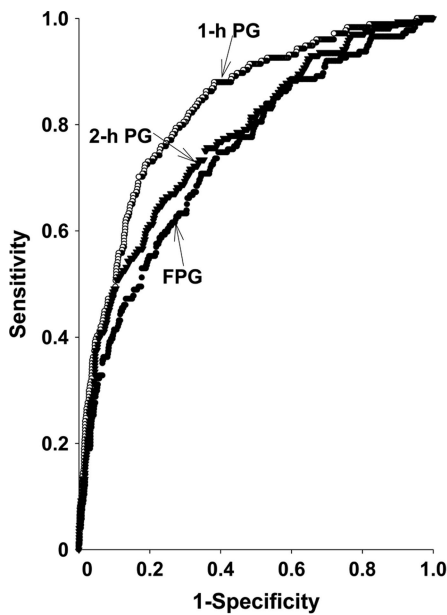


Figure 3—Area under the ROC for FPG, 1-h plasma glucose (1-h PG), during OGTT, and 2-h plasma glucose concentration during the OGTT for the prediction of future type 2 diabetes in the San Antonio Heart Study (reproduced from Abdul-Ghani et al. [35]).

area under the ROC of fasting and 2-h plasma glucose concentrations. The area under ROC for 1-h plasma glucose concentration is significantly greater compared with both the fasting and 2-h plasma glucose concentrations (Fig. 3) and to a variety of predictive models based only on measurements taken during the fasting state (Table 1) (35,36). Furthermore, addition of the 1-h plasma glucose concentration to prediction models based on measurements taken during the fasting state significantly strengthened their predictive power (35,36). A cutoff point of 155 mg/dl for 1-h

Table 1—Area under the ROC for plasma glucose concentration during the OGTT and the San Antonio Diabetes Prediction Model in the San Antonio Heart Study and the Botnia Study

Prediction model	aROC	aROC
	Botnia Study	SAHS
FPG	0.66	0.75
SADPM	0.75	0.8
Plasma glucose 60 min	0.80	0.84
Plasma glucose 120 min	0.69	0.79
ΔG_{0-120}	0.78	0.83
SADPM + plasma glucose 60 min	0.82	0.88

SADPM, San Antonio Diabetes Prediction Model. Reproduced from Abdul-Ghani et al. (37).

plasma glucose concentration stratifies subjects into high- and low-risk groups, independent of their glucose tolerance status (36,52). Subjects with a 1-h plasma glucose ≥ 155 mg/dl have high risk for future diabetes, whereas subjects with a 1-h plasma glucose < 155 mg/dl have low risk for future type 2 diabetes.

SUMMARY— Models that identify subjects at increased risk for future type 2 diabetes are essential for the development effective prevention programs. Progressive β -cell failure is the principal factor responsible for the development of type 2 diabetes. Although subjects with IGT are at increased risk for future type 2 diabetes, the limitations of IGT have provoked the search for more effective predictive models. A variety of multivariate models, based on measurements taken during the fasting state, have been developed. Although, in general, these models are useful tools for identifying subjects at increased risk for future type 2 diabetes, they correlate poorly with β -cell failure, the principal factor responsible for the progressive deterioration of glucose tolerance, and subsequent development of type 2 diabetes. The 1-h plasma glucose concentration during the OGTT strongly correlates with β -cell function and, as expected, performs superiorly to other models/indexes in predicting the future risk for type 2 diabetes. A 1-h cutoff point of 155 mg/dl during the OGTT stratifies individuals into high and low risk for future development of type 2 diabetes.

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

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