New and Standard Methods for the Prediction of Type 2 Diabetes Mellitus

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There is strong evidence that type 2 diabetes mellitus (T2DM) can be prevented by lifestyle modification in high-risk individuals. Efficient identification of at-risk individuals using prediction models is an important component of diabetes treatment, since it can allow for early intervention and permit resources to be focused on those with higher risk.

There are a few prediction models that are based on questionnaire data or routinely collected clinical data (eg, Cambridge Type 2 Diabetes Risk Score, German Diabetes Risk Score, Finnish Diabetes Risk Score, and Framingham Offspring Type 2 Diabetes Risk Score), and over the last 10 years, a number of novel biomarkers have been identified that can help with prediction. However, few studies have systematically compared the accuracy of multiple alternative predictive models. Alexandros Heraclides, MD, Steno Diabetes Center, Gentofte, Denmark, discussed the results of a study that assessed the predictive capability of five screening models (in incremental stages of accessibility and cost) for incident T2DM. Subjects were participants in the Whitehall II Study, an occupational cohort of 10,308 British civil servants who were first recruited in 1985 and are still being followed.

The study population consisted of 4352 men and women aged 39 to 64 years who were not diabetic, based on their 1991 oral glucose tolerance test (OGTT). The following prediction models were tested:

A. Questionnaire only (age; gender; body mass index [BMI]; family history of diabetes; use of antihypertensive/lipid-lowering medication; physical activity)

B. Noninvasive Clinical (A + blood pressure + waist circumference)

C. Low-cost biomarker (B + fasting glucose + fasting triglycerides + total cholesterol + HDL-cholesterol)

D. Medium-cost biomarker (C + fasting insulin)

E. High-cost biomarker (D + C-reactive protein [CRP] + Interlukin-6 [IL-6] + fibrinogen + von Willebrand factor + factor VII + ApoA1/B + lipoprotein [a])

Diabetes status was determined using the results of the OGTT (WHO criteria) in 1997, 2002, and 2008 and supplemented by self-reported diabetes or diabetic medication use at any time during the study.

Multivariate Cox regression analysis was performed to estimate predictive models for 20-year incident T2DM. A 2-step approach was used: receiver operating characteristics (ROC) analysis was employed to assess the improvement in the prediction of each subsequent model, followed by backwards elimination analysis to derive a parsimonious model without reducing predictive performance based on the ROC results.

There were 574 cases of diabetes during the study. Those who developed diabetes were more likely to be women, older, and less physically active than those who did not develop diabetes. In addition, they had higher BMI, waist circumference, blood pressure, triglycerides, and total cholesterol. HDL levels were lower, but CRP, IL-6, and fibrinogen were higher.

The area under the ROC curve (AUC) was higher in all three screening models that required a blood sample (Models C-E) compared with the questionnaire/clinical screening models (Models A and B; Table 1). Compared with Model A, the clinical model (B) was not better at predicting incident T2DM (p for AUC difference=0.72). The "low-cost biomarker model" (C) was significantly better than Model B (p for AUC difference<0.001). Beyond Model C, there

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was improvement that was observed with the addition of fasting insulin (p for AUC difference=0.001), but the addition of lipid/inflammatory markers was not associated with incident T2DM prediction (p for AUC=0.015).

Table 1. Area Under the ROC Curve for Additive Screening Models.

Predictive Models for Incident T2DM	AUC (95% CI)	p for Model Improvement
Questionnaire only - model A (gender + age + family history of diabetes + use of antihypertensive or lipid lowering medication + BMI)	0.71 (0.68, 0.74)	n/a
Clinical - model B (questionnaire + blood pressure + waist circumference)	0.72 (0.69, 0.75)	0.72
Low-cost biomarker - model C (clinical model + fasting glucose + triglycerides + total cholesterol + HDL-cholesterol)	0.78 (0.75, 0.81)	<0.001
Medium-cost biomarker - model D (low-cost biomarker + fasting insulin)	0.79 (0.76, 0.82)	0.001
High-cost biomarker - model E (medium-cost biomarker + ApoA1/B + Lp(a) + CRP + IL-6 + fibrinogen + vWf + factor VII)	0.79 (0.76, 0.82)	0.015

AUC=area under curve; BMI=body mass index; HDL-cholesterol=high density lipoprotein-cholesterol; ApoA1/B=apolipoprotein A1/B; Lp(a)=lipoprotein(a); CRP=C-reactive protein; IL-6=interlukin-6; vWf=von Willebrand Factor.

The investigators concluded that biomarker-based models are better than noninvasive models in predicting incident T2DM. Although there was statistical improvement in predictive ability with the addition of fasting insulin, it was not clinically significant. Further, addition of more detailed lipid and inflammatory biomarkers did not improve the predictive capability of the model. A low-cost model that contains questionnaire data on demographics, family history, medication use, physical activity, and BMI, as well as standard cardiometabolic risk factors is the most efficient model in predicting incident T2DM.

Andrea Natali, MD, University of Pisa, Pisa, Italy, returned the discussion to what he referred to as the "most usual suspect" in diabetes, noting that we still do not understand how glucose tolerance deteriorates in diabetes and why.

There are several potential answers to this question. Insulin sensitivity and/or insulin secretion may be responsible, but there are few prospective studies. Those prospective studies that have been done are small (few cases), and the results, particularly with respect to insulin secretion, are inconsistent (ie, in some, insulin secretion is increased in those who developed diabetes, while in others it is decreased). The nonlinear progression of diabetes is another potential factor. When individuals with diabetes are studied over time, some remain stable, some improve, and some deteriorate. When Alvarsson and colleagues examined the factors that determined normalization of glucose intolerance in a population of Swedish diabetics, they found that the factors that predicted reversal to normal glucose tolerance (NGT) were measures that correlated not only with low insulin resistance but also lower insulin secretion, perhaps indicating a lower pancreatic β-cell workload in those who reverted [Alvarsson M et al. *Diab Med* 2009].

The Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) study was undertaken to systematically analyze the relationship between insulin sensitivity/secretion and spontaneous changes in glucose tolerance in nondiabetic subjects. The study comprised 1028 subjects (561 women and 467 men; mean age 44 years) from 19 centers in 13 European countries who were followed for 3 years. Insulin sensitivity (by a 240-pmol/min/m^2 insulin clamp) and β-cell function (ie, fasting insulin secretion rate, total insulin output, and ß-cell glucose sensitivity) were measured by mathematical modeling of the C-peptide response to a standard OGTT. Subjects were categorized as having NGT, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or T2DM and then grouped into stable NGT (NGT both at baseline and follow-up; n=809), stable non-NGT (IFG or IGT on both occasions; n=49), progressors (glucose tolerance deteriorated; n=129), or regressors (glucose tolerance improved; n=61).

In comparison with individuals with stable NGT, both progressors and regressors had a metabolic phenotype that was similar to that of stable non-NGT subjects (lower insulin sensitivity and reduced β-cell glucose sensitivity with increased fasting secretion rate and total insulin output). In a multivariate logistic model, both insulin sensitivity and glucose sensitivity were independent negative predictors of progression (OR, 0.70; 95% CI, 0.52 to 0.93 and OR, 0.42; 95% CI, 0.28 to 0.65, respectively), while waist-to-hip ratio (WHR) and fasting glucose levels were positively associated with progression. The same set of baseline variables also predicted regression. At follow-up, insulin sensitivity and β-cell glucose sensitivity were unchanged in the stable NGTs and non-NGTs, declined in the progressors, and improved in the regressors.

Deterioration of glucose regulation is predicted by insulin resistance, functionally impaired insulin secretion, and excessive insulin secretion (in addition to WHR, weight gain, and fasting glucose). Improvement of glucose regulation is predicted by negative family history of diabetes and higher insulin sensitivity and is associated with a simultaneous improvement in β-cell function (glucose sensitivity and potentiation) and insulin sensitivity.