Diabetes Risk Scores in 2011

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Abstract
Diabetes risk scores can be used as pre-screening tools to detect those likely to have diabetes. Scores usually include clinical characteristics such as age, sex, family history of diabetes and hypertension. However, it is disputed whether screening for diabetes is cost-effective. The recently reported Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study, in which diabetes was diagnosed following screening by a risk score, did not show that intensive treatment in such individuals was different from routine care in terms of cardiovascular outcomes. Risk scores are also used to identify those at risk of diabetes in the future, and at-risk individuals may then be encouraged to participate in diabetes prevention programmes. Risk scores from routine biology, in particular fasting glucose, have also been developed to improve prediction over clinical risk factors. Now more sophisticated approaches are being used to predict diabetes – multiple biomarkers, genetics, proteomics, lipidomics and metabolomics – with the idea that if individuals are identified a long time in advance of the onset of the disease, prevention can start much earlier when it may be more successful. Diabetes risk scores follow on from a long history of cardiovascular risk scores. Scores should be given with an uncertainly or prediction interval within which the score lies with 95% confidence.

It is now well known that the prevalence of diabetes has increased over the last few decades and is predicted to continue to increase. This is not just due to the ageing of populations.[1,2] In comparison with 2010, by 2030 it is predicted there will be a 20% increase in the number of diabetic patients in developed countries, and 69% in developing countries.[3] These estimates do not take into account possible increases in diabetes incidence, nor the likely increases in obesity and overweight, nor whether better treatment will increase the lifespan of patients with diabetes. The predictions take account of the predicted future age structure of populations.

Is Screening and Treatment of Benefit to the Individual?
The ADDITION Study Results
There is a general belief that diagnosing diabetes earlier and subsequent earlier treatment is beneficial. This has been challenged by the investigators of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study, an Anglo–Danish–Dutch general practice study of intensive treatment and complication prevention in patients with type 2 diabetes who have been identified by screening.[4] The study aimed to evaluate: whether screening for prevalent undiagnosed type 2 diabetes is feasible, whether subsequent optimised intensive treatment of the disease and associated risk factors is feasible and whether such optimised intervention is beneficial.

The first results of this five-year trial were presented at the European Association for the Study of Diabetes meeting in September 2010, and there are reports available on the Internet.[5,6] As yet, there are no published reports by the investigators on the results presented at this meeting. Over 70,000 people were screened for diabetes using the first step in the screening process: the completion of a risk questionnaire, which differed between the recruitment centres. For those deemed to be at risk of having diabetes based on their score on this risk questionnaire, capillary glucose testing and/or evaluation of fasting and/or two-hour plasma glucose with an oral glucose tolerance test were carried out. People screened as positive for diabetes were re-tested. The trial recruited 3,000 newly diagnosed patients with diabetes, who were allocated to one of two treatment arms: intensive or routine care. General practices were randomised into these two treatment arms. After five years of follow-up, the various cardiometabolic risk factors were better controlled in the intensive treatment group, but while the improvements were statistically significant, they were modest. Thus, the protocol of intensive treatment was feasible. However, there were no statistically significant differences in outcomes: cardiovascular events were reduced by 17% and cardiovascular deaths by 12% in the intensive care group compared with the routine care group. The Kaplan–Meier morbidity curves started to separate at 3.5 years; perhaps a longer follow-up would be necessary to have more events and a higher power to detect differences. It is probable that improvements in the routine care of

Table 1: Effects of More versus Less Intensive Glycaemic Control on Major Cardiovascular Events (Cardiovascular Death, Non-fatal Stroke or Non-fatal Myocardial Infarction)[11]

Trials	Number of Events (Annual Event Rate, %)		ΔHbA_{1c} (%)	Favours More Intensive	Favours Less Intensive	Hazard Ratio (95% CI)
	More Intensive	Less Intensive				
ACCORD	352 (2.11)	371 (2.29)	-1.01			0.90 (0.78–1.04)
ADVANCE	557 (2.15)	590 (2.28)	-0.72			0.94 (0.84–1.06)
UKPDS	169 (1.30)	87 (1.60)	-0.66			0.80 (0.62–1.04)
VADT	116 (2.68)	128 (2.98)	-1.16			0.90 (0.70–1.16)
Overall	1,194	1,176	-0.88			0.91 (0.84–0.99)

The diamond is the point estimate, with the 95% confidence interval (CI) of the overall effect for each study. The hazard ratios are given for more intensive compared with less intensive glucose control. ΔHbA_{1c} = mean glycated haemoglobin (HbA_{1c}) of more intensive group minus mean HbA_{1c} of less intensive group. ACCORD = Action to Control Cardiovasular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evalauation; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

Figure 1: One of the First Questionnaires to Screen for Undiagnosed Diabetes

patients with diabetes and the control of obesity and other risk factors resulted in similar levels of risk factors at follow-up in the intensive and the routine care groups. Thus, this trial showed that both screening and intervention were feasible, but the intervention was marginally beneficial for cardiovascular disease.

Reviews of Screening for and Treating Diabetes

A recent systematic review from the American Centers for Disease Control and Prevention analysed the cost-effectiveness of interventions to prevent and control diabetes.[7] For screening, only two interventions had been published in the literature, and the report concluded that "one-time opportunistic targeted screening for undiagnosed type 2 diabetes in hypertensive persons aged 45 years and older compared with no screening was cost-effective" (the only study performed on those at risk of diabetes). By contrast, 'universal' screening among the general population was not cost-effective.

For microvascular disease, in particular for retinopathy, the UK Prospective Diabetes Study (UKPDS) and other clinical trials have shown that intensive glucose treatment is effective in reducing risk.[8]

Epidemiological studies continue to show that both macrovascular events and mortality increase in line with glucose levels.[9,10] By contrast, numerous clinical trials have not been so clear in showing that intensive glycaemic control reduces macrovascular complications. A recent meta-analysis published in *Diabetologia*[11] studied intensive glucose control and macrovascular outcomes in type 2 diabetes. Data from four clinical trials with over 27,000 patients and an average follow-up of 4.4 years showed that major cardiovascular events were modestly reduced, with no one trial reaching statistical significance (see *Table 1*).

The above-mentioned systematic review[7] included 12 studies of intensive glucose control and concluded that glucose lowering was cost-effective in those under 54 years of age, but for older patients it was not cost-effective.

Risk Scores for Diabetes Using Clinical Risk Factors

Risk scores can be used for two purposes: to pre-screen those who may already have diabetes, so they can be sent for a blood test; and to screen those who have a high chance of developing diabetes in the future and who may be targeted for intervention programmes for the prevention of diabetes. The scores can be used in the general population or in a population pre-selected to be at risk of diabetes owing to, for example, their age, adiposity, hypertension or other risk factors. Often, the scores developed in cross-sectional studies or in prospective studies are used for both screening and prediction, and they seem to perform equally well for both purposes.[12–15] All of the risk scores have been developed in epidemiological studies where diabetes was defined by known diabetes, by fasting glucose or by glucose at fasting and two hours after an oral glucose tolerance test. A limitation with all studies is that they are based on just one blood sample, rather than the two required by the diagnostic criteria for diabetes.[16,17]

Diabetes Risk Scores for Screening for Diabetes

Diabetes risk scores for pre-screening have been available for a number of years. In 1995, Herman provided a simple algorithm, based on an analysis of the American National Health and Nutrition Examination Study (NHANES) survey using a 'tree function'; this algorithm was converted into a simple questionnaire,[18] and adapted as the American Diabetes Association diabetes risk test (see *Figure 1*) (http://journal.diabetes.org/clinicaldiabetes/V18N22000/pg69.htm, accessed March 26 2011).

Many other scores were subsequently created. In the ADDITION study described above,[4] diabetes risk factor questionnaires were used that had been developed from cross-sectional studies in Dutch, English and Danish populations.[19–21]

Table 2: Risk Factors Included in Multivariate Scores to Predict Incidence of Diabetes

	Number of Scores with Each Risk Factor
Fixed Factors	
Age	12
Gender	7
Family history of diabetes	11
Ethnicity	4
Immmigrant status	1
Height	3
Deprivation score	1
Education	2
Lifestyle Factors	
Consumption of vegetables	2
Fresh fruit	2
Wholegrain bread	2
Red meat	1
Coffee	1
Alcohol	1
Smoking	7
Physical activity	4
Cardiometabolic Risk Factors	
Body mass index	9
Waist circumference	5
Weight	1
Hypertension treatment, high blood pressure	10
Pulse Rate	1
History of cardiovascular disease	1
Use of corticosteroids	1
Biological Factors	
Fasting plasma glucose or impaired fasting glucose	7
Two-hour plasma glucose or impaired glucose tolerance	1
Glycated haemoglobin (HbA$_{1c}$)	1
Total cholesterol	2
High-density lipoprotein cholesterol	6
Low-density lipoprotein cholesterol	1
Triglycerides	6
Insulin or insulin resistance	1
C-reactive protein	1
Gamma-glutamyl transpeptidase	1
Uric acid	2
Glomerular filtration rate	1

Figure 2: The Finnish FINDRISC Score Sheet for the Calculation of Risk of Diabetes[12]

Test designed by Professor Jaako Tuomilehto, Department of Public Health, University of Helsinki and Jaana Lindström, MFS, National Public Health Institute.
FINDRISC = Finnish diabetes risk score.

Diabetes Risk Scores for Predicting Diabetes

More recently, risk scores have been developed to predict future diabetes. The first and the most commonly used clinical risk score in Europe comes from Finland, the Finnish Diabetes Risk Score (FINDRISC).[12] This score was based on data from a registry of diabetes treatment, and was for 10-year incident diabetes. This questionnaire is used either in its original version (see *Figure 2*) or in various adaptations in other countries to select individuals for diabetes prevention programmes.[22,23]

There are now many risk scores for predicting diabetes.[12–15,24–34] They are usually developed from logistic regression or Cox proportional hazard models, and include factors that remain significant in multivariate prediction models. *Table 2* lists the factors that have been included in such risk models. As might be expected, the factors that appear often are age, gender, family history of diabetes, smoking, blood pressure and body mass index (BMI) or waist circumference.

The question of whether glucose measurements should be added to these scores before initiating prevention programmes was studied by Chen in the Australian AusDiab study.[35] The conclusion was that the initial screening should be by questionnaire, with a second risk score evaluation, including fasting glucose, being made for those at higher risk based on their score in the first questionnaire.

How Do the Clinical Diabetes Risk Scores Perform?

The usual metric used to determine how well a risk score performs is the area under the receiver operating characteristic curve (AROC) of sensitivity and specificity. The closer to one, the better the discrimination between those who will or will not have diabetes in the future (or, in the case of screening for prevalent diabetes, the discrimination between those who have and do not have diabetes). Different risk scores have been compared on this basis in populations other than the one in which the risk scores were developed.[36,37] The sensitivity and specificity and hence the AROC are heavily dependent on the study population, that is whether it is a general population or

a population at high or low risk that has been selected for study.[38] However, it is equally important to take into account the positive predictive value: given the risk score, the probability that an individual will have incident diabetes in the next five or 10 years. This is how the score will be used in practice to predict diabetes. Sensitivity, specificity and also the positive predictive value are dependent on the prevalence of the disease in question and the population selected, so there is no reason to prefer sensitivity and specificity over judging risk scores by the positive predictive value.[38]

Biological, Genetic, Proteomic, Lipodomic, Metabolomic, MicroRNA Profiling

Scores with biological markers are not as common as scores with clinical risk markers. One of the earliest was from Stern and was based on the San Antonio Heart Study.[39] There are now a number of published studies with risk scores including routine biological markers, and some of these come from the above publications with clinical risk scores.[14,24,25,28,29,31,32,34] *Table 2* shows the biological risk factors in these risk scores. Not unexpectedly, fasting plasma glucose is the most common risk factor, with high-density lipoprotein (HDL) cholesterol and triglycerides being the next most common.

Recently, there has been a search for other biomarkers of diabetes to include in risk scores. At-risk individuals in the Inter99 Danish cohort (>40 years of age, BMI ≥25kg/m^2) were included in a study to test 58 candidate biomarkers of five-year incident diabetes.[40] Of these biomarkers, six were retained and included in a score: fasting glucose, insulin, adiponectin, C-reactive protein (CRP), ferritin and interleukin-2 receptor. The score did not include any clinical factors, and the AROC was higher than that for a model using age, BMI, waist circumference and family history of diabetes. An editorial by Meigs[41] commented that this panel of biomarkers still requires a fasting sample, and he doubted whether there is a need for a new score to identify pre-diabetes.

More recently, another group investigated 31 biomarkers for incident diabetes and arrived at a best model, that included adiponectin, apolipoprotein B (apoB), CRP and ferritin, after adjusting for age, sex, HDL cholesterol, triglycerides, BMI, systolic blood pressure, hypertensive treatment, smoking, glucose and history of cardiovascular disease (CVD).[42] However, this model did little to improve the AROC over and above the classic risk factors, which included glucose.

Genetic polymorphisms have been disappointing in their ability to predict diabetes: their predictive power is limited even in univariate analysis.[14] Scores have been created using the number of at-risk alleles, but again the phenotypic data were much stronger.[14,43,44] Proteomics, metabolomics, lipidomics and microRNAs are other possible avenues for predicting diabetes, and they will certainly provide insights into the pathophysiology of diabetes, even if their ability to predict diabetes is limited.[45–47]

Cardiovascular Risk Scores

Cardiovascular risk scores have been used since the 1970s. The early scores for coronary events came from the Framingham Study.[48] The Framingham score has been updated, but the basic risk factors remain: age, sex, systolic blood pressure, smoking, diabetes and some combination of total and HDL cholesterol.[49] Many other scores have been derived in various populations. In Europe, the SCORE project developed an algorithm to predict cardiovascular mortality from European cohorts,[50] using the same factors as the Framingham score but with adjustments for countries at high and low risk of CVD. Indeed, risk factors seem to be fairly consistent over cohorts, and it is only the absolute risk that appears to change from population to population. We have recently shown in analyses in France and Australia that while the risk factors and their effects on coronary events are the same as in the Framingham score, the absolute risk differs.[51,52]

Conclusions

Diabetes risk scores have not had the same long history as CVD risk scores, and perhaps scores using clinical factors to predict diabetes will also settle and become more consistent. As these risk scores become better known in the general population, self-identification of the factors associated with a risk of diabetes will become easier; this may help in prevention. These scores could be used by general practitioners, with self-questionnaires available in their waiting rooms. The inclusion of dietary factors and physical activity in these risk scores may be an element for the communication of prevention strategies, even if these factors are statistically not significant. For diabetes risk scores using blood sampling, glucose and glycated haemoglobin should be provided as part of the results, not just as a statement about the risk of future diabetes. Risk scores should be given with a confidence or an uncertainty interval to better quantify the risk. ■

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