Predicting type 2 diabetes: a role for novel parameters or simple prediction models?

by Prof. N. Sattar

Since type 2 diabetes can be prevented by lifestyle changes or pharmacotherapy, it is important to identify subjects who are at high risk of developing the disease. Screening programmes have previously relied on oral glucose tolerance tests, but such tests are time-consuming, inconvenient and expensive. This article discusses the role of novel parameters, including adipose, liver- and endothelial-derived markers, and the use of prediction models in assessing risk. However, more studies are needed to examine the clinical value of these strategies.

Type 2 diabetes, which accounts for 90% of all cases of diabetes worldwide, is a chronic, complex and life-threatening condition. At the time of diagnosis, around half of all patients already have some evidence of tissue damage, commonly related to cardiovascular disease (CVD). Indeed, individuals with diabetes have around a 2-4 fold increase in risk of coronary heart disease compared to those without diabetes (the relative risk being higher in women), and 75% of all patients with diabetes die from CVD-related events. Insulin resistance - a reduced response to circulating insulin in its target tissues, which include skeletal muscle, adipose tissue and liver - is likely to be the major common link between type 2 diabetes and CVD and is present in around 90% of such patients. It is important to appreciate that insulin resistance precedes the clinical development of type 2 diabetes by between 10-20 years. In addition to the increased risk of CVD, chronically elevated glucose levels impair the structure and function of small arteries and capillaries such as those supplying the eyes, kidneys and nerves and, as a result, diabetes is a major cause of blindness, kidney failure and peripheral neuropathy.

Rising prevalence and cost of diabetes

The rising prevalence of obesity worldwide is contributing to the substantially increasing rates of type 2 diabetes. Indeed, the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030, an increase to which both higher obesity rates and an aging population contribute [1]. At the other end of the age spectrum, numerous recent reports of type 2 diabetes in children have caused alarm in the United Kingdom and elsewhere. The rising prevalence of diabetes allied to its multiple health consequences, mean that health care expenditure on diabetes in all countries will rise in future years. Type 2 diabetes is more common amongst some ethnic groups, particularly those of South Asian and African Caribbean origin, thus specific countries already suffer significant economic and health consequences from the effects of type 2 diabetes.

Current methods for diagnosing diabetes and the need for screening

Type 2 diabetes is often asymptomatic in the early stages and diagnosis commonly occurs 5 to 12 years after hyperglycaemia first develops. Patients usually present to their doctors with hyperglycaemia-related symptoms such as thirst, polyuria, weight loss or fatigue. Subsequently, either a very high random blood glucose level (≥11.1 mmol/L) or elevated fasting blood glucose level (≥7 mmol/L) confirm the diagnosis. In cases where the fasting blood glucose level is raised but not diagnostic (e.g. between 5.5 to 6.9 mmol/L) an oral glucose tolerance test (OGTT) can be conducted if clinical suspicion of Type 2 diabetes is high; a 2-hour reading ≥11.1 mmol/L is diagnostic.

Given the rising prevalence of diabetes, the associated morbidity and mortality, and the associated costs for health care systems, recent studies demonstrating prevention of this condition in subjects at risk (those with OGTT-determined impaired glucose tolerance - 2-hr glucose 7.8 to 11.0 mmol/L) by lifestyle changes or pharmacotherapy, are timely and encouraging [2]. Such studies would also appear to pave the way for screening programmes to detect subjects at elevated risk. Yet presently such programmes are the exception rather than the rule. This is partly because most preventative trials have recruited patients with OGTT-determined impaired glucose tolerance. However, the OGTT is time consuming, costly and inconvenient and thus has been met with considerable resistance. It is now less frequently used in ordinary clinical practice. Investigators have therefore begun proposing ‘simple’ prediction models to identify subjects at high risk of type 2 diabetes that do not require an OGTT and examples of these are described more fully in Table 1. In addition to the fasting glucose concentration...
level, these models [3-6] have combined factors such as age and family history of type 2 diabetes with commonly measured clinical parameters including elevated body mass index (BMI), blood pressure, and abnormal lipids (high triglyceride and low HDL-cholesterol). All such factors are linked to insulin resistance, albeit to variable extents, and as a result their levels are often perturbed well in advance of type 2 diabetes [Figure 1A]. Many such parameters also predict vascular disease (lipids, blood pressure, obesity) and, as a result, they form the basis criteria for diagnosis of the metabolic syndrome. The data from a few recent relevant studies [Table 1] suggest that simple prediction models can be as effective as the more cumbersome 2 hour OGTT and superior to current metabolic syndrome diagnostic criteria for the prediction of individuals at elevated risk of type 2 diabetes. However, much more data are needed from different ethnic groups before such prediction models can be widely incorporated. In addition, the cost-benefit ratio of screening for type 2 diabetes on the basis of simple models needs to be determined. In addition to such markers, many recent papers, including several from our own group [5, 7, 8] have examined novel diabetes risk factors, and a brief overview of these follows.

### Multiple roles of insulin

To understand the link between many novel parameters and the elevated risk of type 2 diabetes, it is important to appreciate that insulin imparts its effects on many tissues, not just on skeletal muscle tissue. Adipose tissue, the liver, the endothelium and immune cells respond to insulin. Thus insulin is relevant not simply to glucose uptake and metabolism, but also:

With increasing obesity, fat cells become enlarged and less responsive to insulin i.e. insulin resistant. The subsequent excess release of FFAs into the portal circulation in part drives excess hepatic fat accumulation and synthesis (hence elevated circulating triglyceride and associated lipid changes) and muscle fat accumulation. Excess fat in the latter two organs renders them insulin resistant; specifically, too much fat in the liver limits glucose storage (in the form of glycogen) but enhances glucose synthesis via gluconeogenesis, whereas too much fat in muscle lessens glucose uptake. The combined effects thus promote hyperglycaemia. This hyperglycaemia can be offset for many years by an increase in pancreatic insulin secretion, and hence hyperinsulinaemia accompanies insulin resistance. In people who go on to develop type 2 diabetes, the pancreas eventually becomes ‘exhausted’ - it can no longer produce sufficient insulin to counteract the hyperglycaemic drive - and glucose concentrations rise into the diabetic range.

#### Table 1. Recent studies deriving and testing 'simple' prediction models for type 2 diabetes versus oral glucose tolerance test-derived data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population tested</th>
<th>Duration and no. of incident type 2 diabetes cases</th>
<th>Parameters included</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Stem et al [6]</td>
<td>San Antonio Heart Study (1791 Mexican Americans and 1112 non-Hispanic whites)</td>
<td>7.5 years 275 new cases</td>
<td>Age, sex, ethnic group, fasting glucose, SBP, HDL, BMI and family history</td>
<td>Simple prediction model as near as good as OGTT-2-hour result</td>
</tr>
<tr>
<td>Lysenkov et al [6]</td>
<td>Botnia Study (2115 from western Finland)</td>
<td>6 years 127 new cases</td>
<td>Fasting glucose, BMI, family history of diabetes</td>
<td>Parameters predicted type 2 diabetes with no significant improvement with 2 hour glucose &gt; 7.8 mmol/l</td>
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<tr>
<td>Kanaga et al [3]</td>
<td>Rancho Bernardo Study (7154 and Health ABC study 2003 participants 70-79 years old)</td>
<td>5 years 143 new cases</td>
<td>Age, sex, fasting glucose, triglycerides</td>
<td>Simple prediction rate as good as a 2-hour OGTT-derived glucose</td>
</tr>
<tr>
<td>Metabolic syndrome criteria</td>
<td>Various (e.g. Sattar et al [5])</td>
<td>4.3 years 127 new cases</td>
<td>Waist, triglyceride, HDL-C, SBP/DBP, fasting glucose</td>
<td>Not directly compared to OGTT but inferior to other simple models (e.g. Stem et al [6])</td>
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</table>

#### Figure 1B. This figure demonstrates the relevance of insulin action not simply to skeletal muscle glucose uptake, but also to adipose tissue, liver, endothelium and immune cell function. As fat cells enlarge with greater obesity and become more insulin resistant, they enhance (e.g. IL-6) or suppress (e.g. adiponectin) the release of many agents into the circulation. Similarly, a sub-clinical ‘fatty liver’, dysfunctional endothelium and irritated immune cells in insulin resistance release an array of molecules into the circulation. As a result, the circulating concentrations of such parameters give indications of the degree of insulin resistance and predict the risk for type 2 diabetes.

- Suppresses free fatty acid (FFA) release from adipose tissue.
- Limits hepatic triglyceride synthesis.
- Helps maintain endothelial homeostasis.
- Is involved in regulating thrombotic cascades.
- May have a role in regulating inflammatory cascades [Figure 1b].

#### Adipocyte-derived parameters as risk markers for type 2 diabetes

Although around a decade ago adipose tissue was considered to be largely an ‘inert’ depot for fat storage and release, it is now known that fat cells synthesise and release not only excess FFAs but also many other factors including cytokines (e.g. IL-6 and TNF-α), haemostatic factors such as plasminogen activator inhibitor (PAI-1), and adipokines such as leptin and adiponectin [9]. When fat cells are enlarged and insulin resistant, as they are in obese subjects, they release more cytokines and PAI-1, and less adiponectin, into the circulation. The latter protein is potently insulin sensitising and hence lower levels with rising obesity may contribute to the risk of type 2 diabetes. Similarly it has been proposed that elevated levels of cytokines or PAI-1 may contribute to the risk of type 2 diabetes and several studies have independently linked the circulating concentrations of such parameters to subsequent diabetes [10] [Table 2].
counts currently fulfil such standards, but even then additional studies of all the novel parameters in Table 2, only liver function tests and white cell should be automatable, internationally standardised and universally available.

Although novel parameters yield potentially pathogenic insights into new ways of preventing or treating type 2 diabetes (e.g. anti-inflammatory agents), it is too early to consider them in terms of prediction models for clinical use. If novel parameters are to be used, tests for their measurement should be automatable, internationally standardised and universally available. Of all the novel parameters in Table 2, only liver function tests and white cell counts currently fulfil such standards, but even then additional studies employing rigorous statistical techniques, such as receiver operator characteristic curves, are required to examine their potential clinical value.

Conclusion
The rising incidence of type 2 diabetes combined with knowledge that we can prevent this common, chronic and life-threatening condition has stimulated intense research on simple diabetes prediction models that do not require the OGTT. Although emerging data are encouraging, future prospective studies testing both classical and novel predictors of type 2 diabetes, as well as cost-benefit considerations, are urgently required to move this important area of research towards the clinical setting.

References

Liver-derived parameters as risk markers for type 2 diabetes
As explained above, insulin resistance and obesity are associated with enhanced liver fat accumulation. Serum concentrations of alanine aminotransferase (ALT) are indirectly correlated to the amount of liver fat, and elevated levels of ALT predict greater hepatic insulin resistance. In line with such observations, we recently demonstrated that an elevated ALT level within the ‘normal’ range predicts diabetes independently of classical predictors (fasting glucose, BMI, lipids and blood pressure), C-reactive protein (CRP) level and metabolic syndrome in middle-aged Caucasian men of average BMI [8]. Men with baseline ALT levels above 29 U/L had more than twice the risk of diabetes compared to men with ALT levels below 17 U/L after adjustment for other predictors and alcohol intake. Other workers have previously demonstrated that elevated level of gamma-glutamyltransferase (GGT), another liver enzyme that rises with hepatic fat accumulation, also predicts diabetes. Similarly, in addition to adipocyte-derived factors, excess fat in the liver may also help to explain why elevated CRP and plasminogen activator inhibitor (PAI-1) levels predict type 2 diabetes in respective studies.

Endothelial-derived parameters as risk markers for type 2 diabetes
There is a wealth of data suggesting a potential role for endothelial dysfunction in insulin resistance. Although the direction of causality remains hotly debated, circulating elevated levels of some endothelial-derived factors, cell adhesion molecules and tissue plasminogen activator (t-PA), have been shown to predict the risk of type 2 diabetes, independently of other predictors.

Barriers to clinical utility of novel parameters
Although novel parameters yield potentially pathogenic insights into new ways of preventing or treating type 2 diabetes (e.g. anti-inflammatory agents), it is too early to consider them in terms of prediction models for clinical use. If novel parameters are to be used, tests for their measurement should be automatable, internationally standardised and universally available. Of all the novel parameters in Table 2, only liver function tests and white cell counts currently fulfil such standards, but even then additional studies

<table>
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<tr>
<th>Parameters commonly used in type 2 diabetes prediction models</th>
<th>Potential novel predictors of type 2 diabetes (source)</th>
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<tr>
<td>Age (diabetes risk increases with age)</td>
<td>Adhesion molecules e.g. ICAM-1 (endothelial)</td>
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<tr>
<td>Blood pressure</td>
<td>Adiponectin (adipose tissue)</td>
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<tr>
<td>BMI (BMI &gt;30 versus &lt;25 gives around a 10-fold increased risk)</td>
<td>ALT, GGT (liver)</td>
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<tr>
<td>Ethnic group (e.g. South Asians have significant higher risk)</td>
<td>High sensitivity C-reactive protein (liver)</td>
</tr>
<tr>
<td>Family history of type 2 diabetes</td>
<td>Cytokines, e.g. IL-6, TNF-α (adipose tissue, immune cells or endothelium)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>PAI-1 (adipose tissue or liver)</td>
</tr>
<tr>
<td>Fasting triglyceride</td>
<td>SHBG (liver)</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1-PA (endothelium)</td>
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<tr>
<td>Waist circumference</td>
<td>White cell count</td>
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Table 2. Commonly used and novel predictors of type 2 diabetes.

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