Commentary

The JBS-2 guidelines on prevention of cardiovascular disease in clinical practice: an opportunity missed

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Introduction

In December 2005, a Working Party for the Joint British Societies (JBS-2) published guidelines on the prevention of cardiovascular disease in clinical practice ‘to promote a consistent multi-disciplinary approach to the management of people with established atherosclerotic cardiovascular disease and those at high risk of developing symptomatic atherosclerotic disease’.1 The Working Party has produced a comprehensive document that addresses most aspects of cardiovascular risk prevention. However important issues arise from the JBS-2 guidance in relation to: (i) screening for new diabetes and (ii) the investigation of impaired glucose tolerance.

Screening for new diabetes: the role of fasting glucose measurement

In the section on risk factor assessment, JBS-2 recommends: ‘if non-fasting glucose is $\geq 6.1$ mmol/l then measure fasting glucose for evidence of impaired glucose regulation or new diabetes. If this fasting glucose measurement is normal ($\leq 6.0$ mmol/l) there is no need to repeat it’. JBS-2 is proposing that a single normal fasting glucose measurement is an adequate screening test for new diabetes. There is however a large body of evidence to refute the wisdom of this pragmatic approach, particularly in the ‘at risk’ population in question.2–8

Fasting glucose is a poor indicator of impaired glucose regulation

The DECODE study group (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) reported a normal fasting blood glucose (FBG) in $31\%$ of subjects confirmed as diabetic on oral glucose tolerance testing (OGTT).2 Evidence from the Euro Heart Survey emphasizes that without the use of OGTT, almost two-thirds of patients with impaired glucose regulation (new detected diabetes or impaired glucose tolerance, IGT) would remain undiagnosed.3 This holds true for both acute and stable presentations of cardiovascular disease (CVD) (63% and 64%, respectively). Furthermore, albeit in smaller studies,4–7 the prevalence of IGT and newly diagnosed diabetes in acute coronary syndrome is grossly underestimated if fasting glucose is used as the sole assessment. This is a consistent finding in the literature from around the world (Table 1). JBS-2 does acknowledge that their recommended approach to screening for diabetes will ‘inevitably miss some patients with impaired glucose tolerance (IGT) or even diabetes’, justifying this by suggesting that lifestyle management and other risk factor modification can also ‘reduce glycaemia’.

In practice, the use of a single normal fasting glucose measurement will miss nearly all those with impaired glucose tolerance and (more worryingly) a majority of frank diabetes will remain undiagnosed in the highest risk populations, as highlighted above.2–8 Data from the DECODE study group2 quantify this risk: the hazard ratio for death for...
those newly diagnosed diabetics with normal fasting glucose is 2.00 (95%CI 1.46–2.75). The corresponding figure for high fasting glucose is 2.36 (1.8–3.09), demonstrating the substantial risk run by the ‘normal fasting glucose group’.

Unrecognized diabetes is common in cardiovascular disease

IGT and newly diagnosed diabetes are surprisingly common in those presenting with cardiovascular events. The Euro Heart Survey reported a prevalence of IGT of 36%, and 22% for newly detected diabetes (DM) in patients presenting acutely. For those with stable disease, the figures were similar (IGT 37%; DM 14%). The same scenario is seen across the spectrum of CVD (Tables 1 and 2). In a majority of these patients, an opportunity for diagnosis and appropriate management would have been missed using the ‘single fasting glucose’ criterion recommended by JBS-2.

JBS-2 and oral glucose tolerance testing

JBS-2 recommends: ‘In people who present with an acute CVD event: fasting glucose should (also) be measured on at least one occasion, or an oral glucose tolerance test (OGTT) performed during the in-hospital stay. Fasting glucose should be measured during the acute phase of the illness and, if there is evidence of impaired fasting glucose (IFG, \(\geq 6.0\) mmol/L but <7.0 mmol/L), or an indication of diabetes (\(\geq 7.0\) mmol/L), a fasting glucose measurement should be repeated on two occasions (or an OGTT on one occasion) between 8–12 weeks following discharge from the hospital.’ While acknowledging that JBS-2 has considered OGTT as an important diagnostic test for impaired glucose regulation, there is some surprise that the OGTT has not been considered mandatory in this group. As highlighted above, the ‘fasting glucose’ approach recommended by JBS2 would miss up to 70% of patients with newly diagnosed diabetes, and will miss the majority of those with impaired glucose tolerance. \(^4-7\) The failure by JBS-2 to recommend mandatory oral glucose tolerance testing, at least at acute presentation, is disappointing.

**Impaired glucose tolerance: a ‘marker of risk’ or a ‘risk factor’ requiring modification?**

Without oral glucose tolerance testing, the vast majority of patients with impaired glucose tolerance will remain undetected. Whilst JBS-2 does acknowledge the increased risk of developing CVD in individuals with IGT versus those with normal glucose metabolism (quoting a relative risk of 1.5),

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### Table 1

Detection of unrecognized impaired glucose regulation in acute coronary syndrome: oral glucose tolerance testing vs. fasting blood glucose estimation

<table>
<thead>
<tr>
<th>Geographic population</th>
<th>(n)</th>
<th>Oral glucose tolerance testing</th>
<th>Fasting blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal glucose tolerance</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>Sweden (^4)</td>
<td>164</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>Japan (^5)</td>
<td>134</td>
<td>53%</td>
<td>37%</td>
</tr>
<tr>
<td>UK (^6)</td>
<td>22</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Korea (^7)</td>
<td>30</td>
<td>27%</td>
<td>40%</td>
</tr>
</tbody>
</table>

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### Table 2

Prevalence of impaired glucose tolerance and undiagnosed diabetes mellitus following oral glucose tolerance test in subjects with cardiovascular disease

<table>
<thead>
<tr>
<th>Author</th>
<th>(n)</th>
<th>Study population</th>
<th>Prevalence IGT (%)</th>
<th>Prevalence DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramachandran et al.(^9)</td>
<td>142</td>
<td>Acute coronary syndrome</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Stiefel et al.(^10)</td>
<td>270</td>
<td>Untreated hypertension</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Kernan et al.(^11)</td>
<td>98</td>
<td>Recent transient ischaemic attack/ischaemic stroke</td>
<td>28</td>
<td>24</td>
</tr>
</tbody>
</table>

IGT – impaired glucose tolerance; DM – diabetes mellitus.
no attempt is made in the guidelines to suggest that this risk is more vigorously explored in clinical practice. The DECODE group (discussed above) analysed data from 13 prospective European cohort studies (n=25,364 subjects, mean follow-up 7.3 years). ‘Fasting blood glucose’ as a predictor of adverse events was significantly inferior to the predictive value of the ‘two hour post glucose load blood glucose’ (2hBG). Furthermore, the same dataset indicated that the largest number of excess deaths during follow-up did not occur in the newly diagnosed diabetics, but rather in the men and women with IGT associated with a fasting glucose concentration ≤6.0 mmol/l. Further conclusive evidence of IGT as a ‘marker of risk’ comes from a 1999 meta regression analysis of data from 20 studies involving 95,783 individuals followed for 12.4 years, demonstrating a relative risk for subsequent cardiovascular events of 1.58 (CI 1.19–2.10) in those with abnormal 2hBG.12

There is some evidence to suggest that ‘managing’ IGT is of positive benefit in terms of the subsequent development of diabetes.13,14 This is perhaps unsurprising, given that the risk of developing diabetes in the year following detection of IGT is 2–12%.15,16 Clinical trials in IGT, such as the Rational for the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication study (n=5000) and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research trial (n=≈9150), are currently underway to study the effect of these newer pharmacological agents on progression of IGT to type 2 diabetes, postulating a positive effect on subsequent cardiovascular morbidity and mortality.17

Logistics of oral glucose tolerance testing

OGTT, the ‘gold standard’ for the assessment of impaired glucose regulation, can be undertaken cost-effectively in primary care,18 and can also be conveniently and cheaply performed opportunistically during any in-patient admission with a cardiovascular event. In the UK, the cost of the 75 g glucose load and biochemical testing is approximately £1.20 per test. This compares favourably with costs of measuring PSA (Prostatic Specific Antigen) for example, which costs about £1.46 per test.

Conclusion

The JBS-2 guidelines, while comprehensive, have some important shortcomings in relation to recommendations for screening for impaired glucose regulation in cardiovascular disease. There is no doubt that fasting glucose alone, as recommended by JBS-2, is a poor indicator of impaired glucose regulation, whose sole use results in a systematic under-diagnosis of new diabetes. Current evidence strongly supports oral glucose tolerance testing as the assessment tool of choice for impaired glucose regulation, especially in those at high risk, in whom diabetes is easily missed. Furthermore, JBS-2 has failed to acknowledge the growing body of evidence of the importance of impaired glucose tolerance despite its rising profile in cardiovascular medicine. Given the global health agenda, it might be considered mandatory to explore all reasonable approaches to managing the cardiovascular health of a population—particularly those at high risk. We regret an opportunity missed.

References


