

## NZSSD EXPERT OPINION

### **HbA1c as a diagnostic or screening test for diabetes**

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All current guidelines recommend measurement of venous plasma glucose to diagnose diabetes. Both WHO<sup>1</sup> and the ADA<sup>2</sup> use fasting plasma glucose [FPG]  $\geq 7.0$  mmol/L to define diabetes. WHO also recommends that the standard 75g OGTT is required to diagnose diabetes in high risk subjects in whom FPG does not exceed the threshold. This approach was reiterated in a joint consensus document from WHO/IDF in 2006<sup>3</sup>. The ADA recognises the validity of the two hour cut point for glucose in the OGTT of  $\geq 11.1$  mmol/L but discourages the use of the test in clinical practice because of inconvenience, cost and large biological variability. New Zealand and Australia use the WHO/IDF criteria<sup>4</sup>.

These diagnostic thresholds are derived from large amounts of overlapping data in different populations. The main feature used to choose the thresholds has been the levels of glucose at which diabetes specific microvascular complications increase markedly, especially retinopathy. Supporting evidence has come from the bimodal distribution of plasma glucose in some populations with a high prevalence of diabetes.

The thresholds chosen are not exact, as the data used is far from perfect and the methods used to derive the cut points are not precise. However, as stated in the report from WHO/IDF 'despite the limitations with the data from which the diagnostic criteria for diabetes are derived, the current criteria distinguish a group with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications'

Over the last decade there have been many research papers suggesting that HbA1c can be used in screening for diabetes, or even for diagnosis. Various expert groups, including ADA and WHO/IDF, have considered the use as a diagnostic test but have always rejected it. The grounds have been that the test is not reproducible or standardised, it is more costly than plasma glucose, it is not available in under resourced countries and levels are affected by anaemia, uraemia, haemoglobinopathies, pregnancy and other factors. In favour are the convenience of the test, an association with retinopathy that is as strong as that for the current thresholds for FPG and the OGTT and a clear linear relationship with cardiovascular risk

NZSSD has made a strong statement, dated December 2007<sup>5</sup>, rejecting the use of HbA1c for the diagnosis of diabetes unless certain criteria are fulfilled. However, in a document currently before the membership for discussion<sup>6</sup>, HbA1c is mentioned as an option for screening for diabetes in the context of an assessment for cardiovascular risk, if fasting glucose is not able to be obtained. The New Zealand Guidelines Group [NZGG] has reviewed all the available data and this option of using HbA1c for screening has already been recognised in the update of the 2003 guideline for assessment and management of cardiovascular risk [in press]<sup>7</sup>. A level of HbA1c  $\geq 6.1$  indicates the need for at least FPG and possibly an OGTT.

This decision from NZGG recognises renewed international interest in the use of HbA1c as a screening test. In a systematic review Bennett<sup>8</sup> found that only 9 of 63 studies had adequate data but the conclusion from consideration of these was that HbA1c and FPG are equally effective in screening. A level of HbA1c  $\geq 6.1\%$  was considered to be the optimum cut point, providing sensitivity and specificity near 80%. The Health Technology Report<sup>9</sup> reached a similar conclusion about the equivalent efficacy of HbA1c and FPG in screening but suggested that a more appropriate cut point might be an HbA1c of  $\geq 5.5\%$ . This would represent above the 70<sup>th</sup> centile in some populations and the need for population specific cut points was acknowledged. A very recent paper from Saudek<sup>10</sup> has also recommended  $\geq 6.1\%$  as a suitable cut point, based on the data considered in the above reviews, as well as that from several new papers.

Diabetes Australia<sup>11</sup> issued a draft evidence based discussion document in 2008 in which measurement of HbA1c is mentioned as another option for screening for undiagnosed diabetes but, unlike the previous reviews, this document does not recommend a level, stating that the appropriate cut point is uncertain

because optimum values vary with ethnicity, gender, age and the prevalence of diabetes in the population being screened. Certainly, there is a risk that levels as high as 6.1% will have poor sensitivity and the data from AUSDIAB suggested a much lower cut point, around 5.4% for 80% sensitivity.

NZGG recognised the heterogeneity of the data but a key point in adopting a level of  $\geq 6.1\%$  as a screening threshold was local data suggesting that this level would define the same proportion of both high and low risk individuals who are currently identified by the recommended cut points for FPG of  $\geq 5.5 - 6.9\text{mmol/L}$  and  $\geq 6.1 - 6.9\text{mmol/L}$  respectively. It also was considered important to give some guidance, as there is evidence to suggest that HbA1c is already being widely used in primary care for screening for diabetes, both in New Zealand and internationally.

Much of the data regarding the potential use of HbA1c as a diagnostic test is contained in the same sources as is the information for screening. The problem of standardisation of HbA1c is now largely solved but there is a remaining difficulty in that, although clinical data relating HbA1c to retinopathy is strong, much of the data was gathered with a variety of older assays in diverse populations and there will be the same difficulty in choosing a diagnostic threshold as there has been for a screening threshold. On the positive side, it is apparent that biological variability of HbA1c is less than half that of FPG and the OGTT and quality assurance data indicates that the reproducibility of assays for HbA1c is equivalent to those for glucose, with coefficients of variation of  $< 2\%$  being readily achievable.

The expert panel convened by Saudek<sup>10</sup> considers that there are serious deficiencies in the current criteria for diagnosing diabetes and have proposed that a level of HbA1c  $\geq 6.5\%$  should be considered as being strongly suggestive of diabetes, requiring confirmation by only a single other measure of glucose over the diagnostic cut point, either FPG or OGTT. An unequivocally high level,  $\geq 7.0\%$ , would require confirmation only with a second HbA1c. They suggest that various interested societies and associations consider these recommendations. The paper is currently available on the NZSSD website.

A joint committee of the ADA, EASD and IDF are also exploring the potential use of HbA1c as a diagnostic test and should report in the near future. It would be premature to make any local decision before this information is available.

### **Recommendation:**

Fasting plasma glucose should remain the preferred screening test for diabetes but HbA1c is acceptable as an option. HbA1c is not recommended as a diagnostic test for diabetes but this is under review and it may be included as an option in the near future.

## References:

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