When to use fasting glucose to diagnose type II diabetes
Until recently, fasting plasma glucose, and in some situations, oral glucose tolerance testing, have been the investigations of choice for diagnosing people with type II diabetes. Recently, recommendations in New Zealand have changed and HbA1c has become the primary assay for diagnosing type II diabetes, along with its continued role in monitoring glycaemic control. Other countries, such as the UK, USA and Australia, have also recently placed more importance on the use of HbA1c in diagnosing type II diabetes. However, there are some clinical scenarios where HbA1c is unreliable, and fasting plasma glucose should be used in preference.

**HbA1c is the recommended test for diagnosing type II diabetes in most situations**

In September, 2011, the New Zealand Society for the Study of Diabetes (NZSSD) changed its recommendation regarding choice of test for diagnosing type II diabetes, stating that glycated haemoglobin (HbA1c) was the preferred test over fasting glucose.1 In addition, it is now recommended that HbA1c is the test of choice for population screening programmes.2 However, there are some scenarios where measuring HbA1c for diagnostic purposes may give misleading or inaccurate results (see bullet list and Table 1 over page), and therefore a fasting plasma glucose is recommended.1 Oral glucose tolerance testing (OGTT) is no longer recommended for most people as a test for type II diabetes.2 N.B. OGTT is still used for diagnosis of women with gestational diabetes.

For further information on the change in guidance and the use of HbA1c, see: “The new role of HbA1c in diagnosing type 2 diabetes”, BPJ 42 (Feb, 2012), and “Understanding the new HbA1c units for the diagnosis of Type 2 diabetes” Braatvedt G et al, NZMJ 2012;125(1362).

**Fasting plasma glucose should only be used to test for type II diabetes in situations when the use of HbA1c is inappropriate.**1 The two primary situations where HbA1c may be inaccurate are when serum glucose levels have risen too quickly for glycation rates to provide an accurate picture, or where a condition is present that will affect the accuracy of HbA1c over the long term. Where serum glucose

**The inter-test variability between HbA1c and fasting glucose**

When choosing the most appropriate diagnostic test for people with suspected type II diabetes, it is important that practitioners understand the limitations of each test.

Multiple studies have shown that HbA1c and fasting plasma glucose tests are frequently discordant when used to diagnose type II diabetes.3 In some populations, such as Indo-Asian people, HbA1c diagnostic cut-off levels of 48 mmol/mol (a lower threshold than is used in New Zealand) identify fewer individuals as having type II diabetes than glucose-based tests.3 However, in the majority of study populations this discordance is minor, and HbA1c and fasting plasma glucose generally identify similar numbers of people with diabetes.4 In addition, the convenience of HbA1c testing is thought to significantly increase the absolute number of people diagnosed with type II diabetes, making it a more effective test for screening populations. HbA1c may not accurately reflect levels of glycaemic control in some situations or individuals (over page), but in comparison with fasting plasma glucose, it has greater analytic stability and less daytime variability in any individual patient, as well as far less stringent patient requirements, particularly the lack of required fasting.
has risen quickly, HbA1c should not be used. In clinical situations where HbA1c may be misleading, measuring glycation rates may still be useful, although consideration should be given to using fasting plasma glucose.

Where serum glucose levels have risen rapidly, do not use HbA1c

A recent UK consensus statement recommended that HbA1c should not be used in the following patients or situations where blood glucose levels may have risen too fast to affect HbA1c:5

- All children and young people or anyone with suspected type 1 diabetes, regardless of age
- People with a short duration of diabetes symptoms
- Women who are pregnant or have been pregnant in the previous two months
- People at high risk of diabetes who are acutely unwell (HbA1c ≥ 50 mmol/mol confirms pre-existing diabetes, but a value < 50 mmol/mol does not exclude it in an unwell patient and such patients should be retested once the acute episode has resolved)
- People taking medicines that may cause rapid glucose rise, e.g. corticosteroids or antipsychotics (for two months or less). HbA1c can be used in people taking such medicines long-term (over two months) who are not clinically unwell.
- People with acute pancreatic damage or who have had pancreatic surgery

In these situations, where symptoms have only been present for a short period (less than three months) and glycation of haemoglobin is unlikely to have occurred, it is more appropriate to request fasting plasma glucose than HbA1c. In addition, in some clinical settings self-monitoring blood glucose (SMBG) measurement, may be indicated to establish glucose levels to guide an acute intervention, such as hospital admission, in patients with suspected hyperglycaemia.

In clinical conditions where HbA1c may be misleading, use with caution

Certain clinical conditions may also affect the accuracy of an HbA1c test – the HbA1c may be falsely low and lead to false-negative results, or falsely elevated and lead to a false-positive result for type II diabetes. Some conditions have variable effects on HbA1c results and may increase or decrease HbA1c levels. Table 1 lists the most common conditions and factors that affect HbA1c. HbA1c may still be useful in these situations, but it should be used with caution, and consideration given to using fasting plasma glucose.

These conditions need to be viewed within the clinical context of the patient. For many, the degree of effect on HbA1c results is modest. For example, iron deficiency tends to modestly raise HbA1c for unknown reasons. However, if the rate of blood loss is enough to cause anaemia then HbA1c will typically fall due to increased red blood cell turnover, i.e. HbA1c will be falsely low, rather than high. A similar situation exists with patients who undergo venesection for haemochromatosis where HbA1c results can be very low. In general, HbA1c will still be useful, however, results should be viewed with caution and when there is clinical suspicion about the validity of the HbA1c result, discussion with a clinical biochemist (pathologist) may be appropriate.

Note that there is also a possible age-related effect when using HbA1c, which rises approximately 0.3% each decade in people with normal glucose tolerance. This does not limit the use of HbA1c in older people, but clinicians should be aware of the possible effect.

Where HbA1c results are borderline or further investigation of the result is necessary, such as in a patient with two discrepant HbA1c results, a fasting plasma glucose test may be useful if the result would change the management of the patient. However, waiting six months before retesting HbA1c with lifestyle interventions in the interim, would generally be the recommended management strategy.

Fasting plasma glucose as a diagnostic test for type II diabetes

If a fasting plasma glucose test is indicated, rather than HbA1c, this can be undertaken and interpreted in accordance with previous type II diabetes testing guidance.

Patients are required to fast (i.e. no caloric intake) for at least eight hours, but ideally 12 hours, prior to testing. Advise patients that they may drink water during the fasting period.
**Table 1: Factors influencing HbA1c results, modified from Gallagher⁶⁻⁷**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Increased</th>
<th>Decreased</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red Cell Survival (erythropoiesis)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Iron deficiency</td>
<td>Iron supplementation</td>
<td>Iron deficiency anaemia⁸⁻¹⁰</td>
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<tr>
<td></td>
<td>Vitamin B12 deficiency</td>
<td>Vitamin B12 or folate supplementation</td>
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<tr>
<td></td>
<td>Renal impairment</td>
<td>EPO treatment</td>
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<tr>
<td></td>
<td>Alcoholism</td>
<td>Reticulocytosis</td>
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<td></td>
<td></td>
<td>Chronic liver disease</td>
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<td><strong>Erythrocyte destruction or removal</strong></td>
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<tr>
<td></td>
<td>Splenectomy</td>
<td>Blood loss</td>
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<tr>
<td></td>
<td></td>
<td>Splenomegaly</td>
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<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
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<td></td>
<td></td>
<td>Certain medicines, e.g. antiretrovirals, dapsone</td>
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<td></td>
<td></td>
<td>Some haemoglobinopathies</td>
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<tr>
<td><strong>Glycation rate</strong></td>
<td>Vitamin C or E deficiency</td>
<td></td>
<td>Some genotypes, e.g. sickle cell disease</td>
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<tr>
<td></td>
<td>Some haemoglobinopathies</td>
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<tr>
<td></td>
<td>Chronic kidney disease</td>
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<tr>
<td><strong>Altered haemoglobin</strong></td>
<td></td>
<td>Recent blood transfusion (previous three months)¹</td>
<td>Some haemoglobinopathies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methaemoglobin</td>
</tr>
<tr>
<td><strong>Assays</strong></td>
<td>Hyperbilirubinaemia</td>
<td></td>
<td>Some haemoglobinopathies</td>
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<tr>
<td></td>
<td>Carbamylated haemoglobin</td>
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<tr>
<td></td>
<td>Alcoholism</td>
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<td></td>
<td>Aspirin (large doses)</td>
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<td></td>
<td>Chronic opiate use</td>
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<td>Hydroxyurea</td>
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</tbody>
</table>
In symptomatic people a single fasting plasma glucose result of ≥7.0 mmol/L can be considered diagnostic of type II diabetes for the majority of people.\(^1\) Repeat testing is recommended where the result is borderline or there is clinical doubt about symptoms.

In asymptomatic people a fasting plasma glucose result of ≥7.0 mmol/L strongly indicates type II diabetes; however, a second test is required for confirmation.\(^1\) The test should be performed on a separate occasion,\(^13\) ideally within two weeks.\(^5\) Lifestyle interventions should be encouraged during the waiting period. If the second result is discordant, repeat testing again in three to six months is recommended, with lifestyle interventions continuing in the interim.

The disadvantages of fasting plasma glucose as a diagnostic test for type II diabetes

The fasting plasma glucose test has several disadvantages, many of which contributed to the NZSSD and WHO decisions to recommend that \(\text{HbA}_1c\) be used as the preferred test for the diagnosis of type II diabetes.\(^1,6\)

The primary disadvantage of fasting plasma glucose is that it requires the patient to fast prior to testing, which can be difficult in practice.

The diagnostic range of fasting plasma glucose is narrow compared with the biological variation between individuals when tested with fasting glucose, which is

### The diagnostic criteria for type II diabetes\(^1\)

<table>
<thead>
<tr>
<th>(\text{HbA}_1c) (\geq ) 50 mmol/mol, with symptoms</th>
<th>(\geq 7.0) mmol/L, with symptoms</th>
<th>Diabetes</th>
<th>A second test above the threshold, with either fasting glucose or (\text{HbA}_1c) is required to confirm diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 50) mmol/mol, no symptoms</td>
<td>(\geq 7.0) mmol/L, no symptoms</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>41 – 49 mmol/mol</td>
<td>6.1 – 6.9 mmol/L</td>
<td>Intermediate hyperglycaemia</td>
<td>Offer lifestyle advice. Perform CVD risk assessment and follow guidelines for treatment. Repeat testing every 6 –12 months</td>
</tr>
<tr>
<td>(\leq 40) mmol/mol</td>
<td>(\leq 6.0) mmol/L</td>
<td>Diabetes unlikely (normoglycaemia)</td>
<td>Normal range</td>
</tr>
</tbody>
</table>

\(\text{HbA}_1c\) and fasting plasma glucose together in at-risk, asymptomatic people is unnecessary and discouraged.\(^5\) However, if \(\text{HbA}_1c\) and fasting plasma glucose are measured together, and results are discrepant with regards to a diagnosis of diabetes, the test above the diagnostic cut point should be repeated after three to six months.\(^1\)

* Requesting both \(\text{HbA}_1c\) and fasting plasma glucose together in at-risk, asymptomatic people is unnecessary and discouraged.\(^5\) However, if \(\text{HbA}_1c\) and fasting plasma glucose are measured together, and results are discrepant with regards to a diagnosis of diabetes, the test above the diagnostic cut point should be repeated after three to six months.\(^1\)
approximately 4.5%. This means that if a group of patients have a fasting plasma glucose level of 7.0 mmol/L, most will have an actual value between 6.7 – 7.3 mmol/L (4.5% biological variation), but some will have a value outside of this range. Given the narrow diagnostic range for diabetes, with fasting plasma glucose, this can be significant.

The sample processing of fasting glucose is more complex than for HbA1c, leading to a greater potential for errors. Variation can be up to 1 mmol/L or more after one to two hours, with an average of approximately 0.4 – 0.5 mmol/L (even if a fluoride tube is used). When added to the biological variation, this difference can have a significant effect on the diagnostic accuracy of the test.

The reproducibility of fasting plasma glucose is lower than HbA1c. An abnormal or borderline HbA1c result is far more likely to be abnormal on repeat than a borderline fasting glucose result.

Fasting plasma glucose has an inferior ability to predict long-term outcomes, particularly beyond 15 years.

Monitoring patients where the use of HbA1c is misleading

All people with type II diabetes should have regular follow-up in general practice to monitor glycaemic control, risk level and disease progression. HbA1c is the recommended test for measuring glycaemic control during follow-up. In the presence of the co-morbidities discussed in Table 1, HbA1c may not accurately reflect the level of glycaemic control. Alternative methods for assessing control may be more appropriate, such as fasting plasma glucose and a series of self-monitoring blood glucose measurements for people using insulin. If therapeutic changes are being considered and there is clinical concern of the validity of the HbA1c test, discussion with a diabetologist is recommended. Measurement of fructosamine may be an alternative option for some people, however, the availability of this test varies, so it should be discussed with a clinical pathologist or diabetologist first. Fructosamine is a glycated protein that indicates glycation levels over the preceding 14 – 21 days.

How regularly should follow-up occur

Follow-up of people with type II diabetes should occur at least annually. In people with multiple co-morbidities

Who should be screened for type II diabetes?

Current recommendations are for asymptomatic men aged over 45 years and women aged over 55 years to be screened for type II diabetes as part of a joint diabetes/cardiovascular risk assessment. Screening of asymptomatic Māori, Pacific and Indo-Asian people should begin at age 35 years for men and age 45 years for women.

Screening should be undertaken every three to five years depending on risk.

New Zealand Guidelines recommend screening ten years earlier in people with multiple risk factors:

- A family history of early onset type II diabetes (more than one first-degree relative)
- A history of gestational diabetes
- Known ischaemic heart disease, cerebrovascular disease, or peripheral vascular disease
- Central obesity or increased BMI (BMI > 30 or >27 kg/m² for Indo-Asian people)
- Long-term steroid or antipsychotic treatment
- Intermediate hyperglycaemia on previous assessment, e.g. HbA1c 41 – 49 mmol/mol or fasting plasma glucose 6.1 – 6.9 mmol/L
- An adverse lipid profile, e.g. TC/HDL ratio ≥7.0
- High blood pressure, e.g. ≥160/95 mm Hg
- Polycystic ovary syndrome
- Current smoker (or have quit within the last twelve months)

NZSSD also recommends that children and young adults with BMI >30 (or >27 kg/m² in Indo-Asian children) should be screened if:

- There is a family history of early onset type II diabetes or;
- They are of Māori, Pacific or Indo-Asian ethnicity

* Screening should be undertaken from age 25 years in people with multiple high risk factors, as indicated
PHO Performance Indicators for diabetes

There are currently two PHO Performance Programme (PPP) indicators involving diabetes; diabetes detection and diabetes follow-up after detection. Both of these indicators are still active under the new funding scheme for diabetes: the Diabetes Care Improvement Package.

The purpose of the diabetes detection PPP indicator is to determine what proportion of the PHO population estimated to have diabetes has been diagnosed.20

The Indicator comprises 7.5% of a PHO’s performance payment, with 2.5% for achieving the target in the total eligible PHO population and 5% in the high needs population.

The purpose of the diabetes follow-up after detection PPP indicator is to determine what proportion of the PHO population expected to have diagnosed diabetes has had a diabetes annual review.20

The Indicator comprises 9% of a PHO’s performance payment, with 3% for achieving the target in the total eligible PHO population and 6% in the high needs population.

References

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