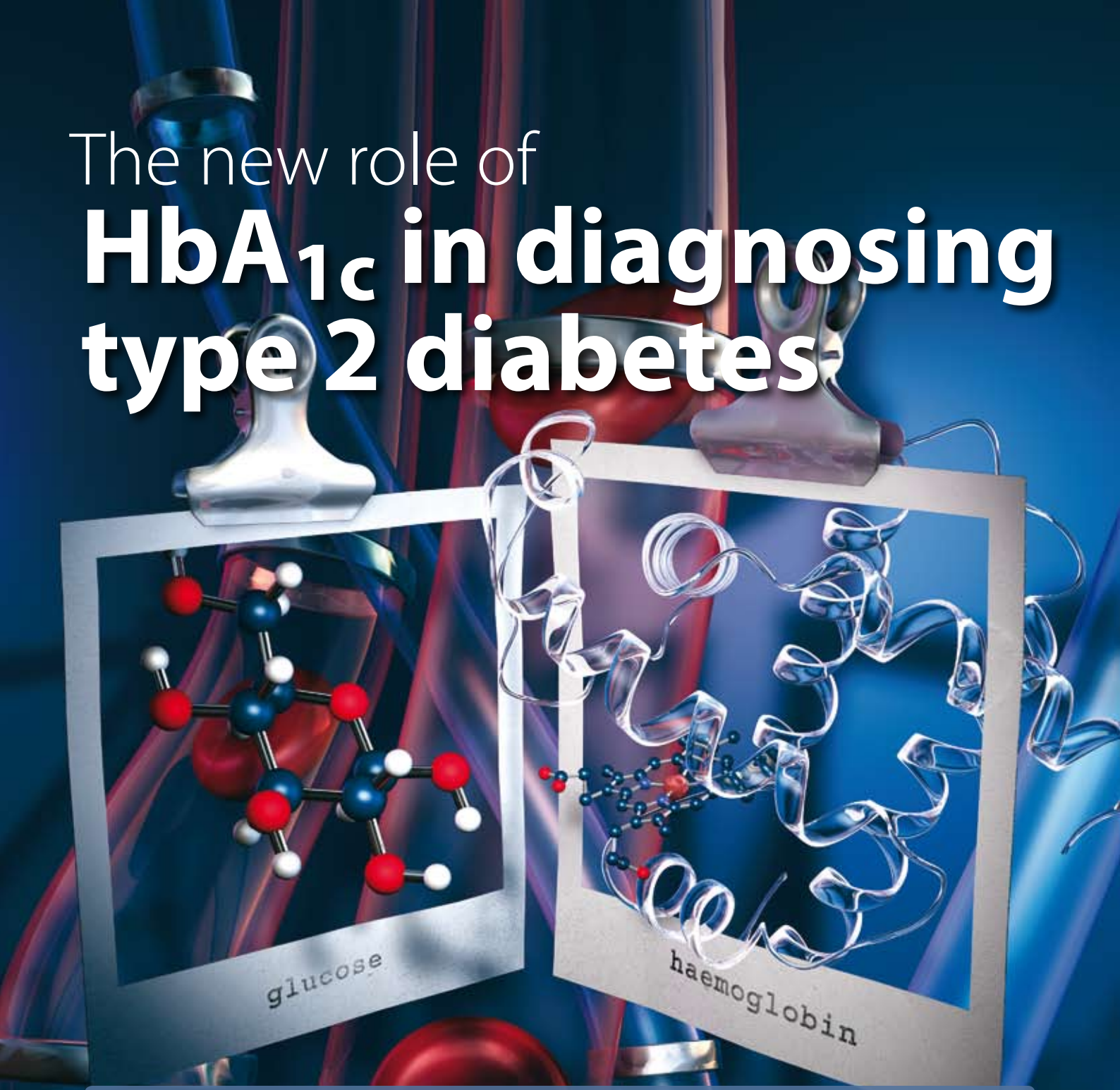
The new role of HbA$_{1c}$ in diagnosing type 2 diabetes



A position statement released in September 2011 from the New Zealand Society for the Study of Diabetes (NZSSD) now recommends the use of glycated haemoglobin (HbA$_{1c}$) for the diagnosis of type 2 diabetes. In addition, HbA$_{1c}$ should also be the test of choice for opportunistic screening in the majority of people. This use, particularly for opportunistic screening, may help address the rapidly growing epidemic of type 2 diabetes in New Zealand,[1, 2] and assist with the detection of the estimated 20 – 40% of all people with type 2 diabetes who remain undiagnosed.[1, 3] The use of HbA$_{1c}$ for screening and diagnosis in type 2 diabetes has been widely debated in the international literature. The decision to recommend this change is based on the advantages of HbA$_{1c}$, such as the lack of need for fasting, reduced biological variability and simpler laboratory requirements. Existing glucose criteria remain valid but the statement emphasises the necessity of having two separate diagnostic readings when a patient is asymptomatic.

HbA_{1c} is now the recommended test for the screening and diagnosis of type 2 diabetes

NZSSD has recommended that, in most cases, HbA_{1c} should be the first-line test for screening and diagnosis of type 2 diabetes.[4] This recommendation aims to complement and update current guidance from the New Zealand Guidelines Group and is also broadly in line with many international guidelines.[5–7] Until now, the recommended diagnostic and screening tests for type 2 diabetes have been fasting plasma glucose levels or the two hour post-oral glucose tolerance test. However HbA_{1c} has several advantages over these tests for the majority of patients.[8, 9]

The advantages of HbA_{1c} for screening and diagnosis of type 2 diabetes

HbA_{1c} testing offers several significant advantages over fasting plasma glucose. Firstly, there is **no need for fasting**. Research and anecdotal evidence suggests that many people are not compliant with the requirement for fasting, thereby reducing the accuracy of fasting plasma and oral glucose tolerance tests.[10]

HbA_{1c} is less affected by day to day variation in plasma glucose, due to exercise, smoking, medicines and diet patterns, than fasting plasma glucose testing, because it reflects the average level of glycaemia over six to eight weeks rather than measuring it at a single moment in time.[10]

There is also less **biological variability associated with HbA_{1c}** than with fasting plasma glucose testing.[4, 10] The variability between two tests, in the same person, is approximately four times greater with fasting plasma glucose than with HbA_{1c}.[10, 11] This means that the likelihood of false negatives and positives, with repeat testing, is lower with HbA_{1c} than with fasting plasma glucose.

HbA_{1c} measures chronic glycaemic exposure rather than an acute value, therefore providing a more relevant view of long-term glycaemia and future risk of complications.[10] As with fasting plasma glucose, there is a well established, and accurate **relationship between HbA_{1c} and future retinopathy risk**.[4, 5, 12–14] For example, in previously undiagnosed people with HbA_{1c} values above 50 mmol/mol the prevalence of moderate retinopathy begins to increase exponentially. A value above this level is therefore strongly predictive of a risk of development of clinically significant retinopathy. There is also overwhelming evidence that HbA_{1c} levels are predictive of the prevalence of other microvascular complications such as nephropathy and neuropathy.[5] HbA_{1c} is a superior indicator of future cardiovascular (CVD) risk than fasting plasma glucose, although the relationship is not as well defined as with retinopathy.[10,15]

HbA_{1c} has simpler sampling and analysis requirements.[4] As it is very stable, a blood sample for HbA_{1c} can be collected either at a laboratory or during a consultation at a general practice clinic, allowing for more opportunistic testing. While fasting plasma glucose samples can also be taken at the practice, the requirements are more complex than with HbA_{1c} and values can be misleading if the sample is not processed immediately, due to pre-analytical instability**.** This is because glucose consumption continues to occur in blood after sampling, even when anti-glycolyic fixatives are applied to the tube.[16] The pre-analytic variability of fasting plasma

PHO Performance Indicator

Diabetes detection is a PHO Performance Programme (PPP) indicator. Its purpose is to determine what proportion of the PHO population estimated to have diabetes has been diagnosed.[19]

As HbA_{1c} testing can be done opportunistically, ideally as part of an overall cardiovascular risk assessment, the number of people tested and diagnosed with diabetes is likely to rise, meaning that the Indicator performance should improve (along with a potential improvement in refining the estimate of people with diabetes, which forms the denominator for this indicator).

The Indicator currently 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 (N.B. Indicator weightings are subject to change).

glucose testing is approximately 5 – 10%, with New Zealand laboratories generally accepting approximately 5% variability as inherent.[10,17] In comparison, the pre-analytic variability of HbA_{1c} is negligible.

Concerns about the use of HbA_{1c} for screening and diagnosis

One of the main concerns expressed about the use of HbA_{1c} for screening and diagnosis is that there has previously been a lack of standardisation with the test. There is now a level of quality standardisation equal to that of fasting plasma glucose testing.[10] This has been driven by:[4]

- Improvement in the technologies used for processing and analysing samples
- An overall effort and agreement by laboratories towards international standardisation
- The change to international units (mmol/mol)

A further concern has been that the HbA_{1c} test is more expensive than fasting plasma glucose – although still less expensive than oral glucose tolerance testing.[5] However, the long-term cost of diabetes is high, and effective screening aims to reduce the incidence of diabetes through detection of people with pre-diabetes and reduce the risk of complications post-diagnosis through early detection.[4] The cost in terms of time and inconvenience to the patient is also less for HbA_{1c}.

HbA_{1c} is not, however, suitable for patients with some haemoglobinopathies and disorders with abnormal red-cell turnover such as many anaemias, as these falsely alter the value. There is also some evidence of individual and ethnic variations in HbA_{1c}, although local data on this is very limited.

Table 1 compares the attributes of HbA_{1c} and fasting glucose assays.

Using HbA_{1c} for diagnosis of type 2 diabetes

NZSSD and the Ministry of Health have recommended that the threshold for a diagnosis of diabetes using HbA_{1c} is ≥ 50 mmol/mol.[4,9] This slightly differs from other international bodies and is designed to have high specificity for the diagnosis; sensitivity issues are addressed by the repeat requirements for patients with borderline levels of HbA_{1c}.

All tests should be performed in an accredited laboratory, i.e. point-of-care testing is not acceptable for diagnostic purposes.[4]

In symptomatic people a single HbA_{1c} ≥50 mmol/mol can be considered diagnostic of diabetes in New Zealand for the majority of people (see below for exceptions).[4]

In asymptomatic people a HbA_{1c} ≥50 mmol/mol strongly indicates diabetes; however, a second test, ideally HbA_{1c} (at least three months later), or alternatively fasting plasma glucose, is needed for confirmation.[4] Lifestyle interventions should be encouraged during the three month wait for a second HbA_{1c}. If the second result is discordant, repeat testing again in three to six months is recommended.[4]

Table 2 summarises diagnostic criteria for diabetes using HbA_{1c}.

HbA_{1c} results may be falsely low in people:[4, 5, 7]

- With a high red blood cell turnover
- Taking iron, vitamin B12 or any other product that temporarily increases red blood cell production
- Who have undergone a blood transfusion any time in the previous three months

HbA_{1c} results may be falsely high in people with:[4, 5, 7]

- Iron deficiency* anaemia
- Vitamin B12 or folate deficiency
- Alcoholism or chronic renal failure
- With certain haemoglobinopathies, e.g. sickle cell anaemia, methaemoglobinaemia

Fasting plasma glucose testing remains a valuable test

Fasting plasma glucose testing is still a valid test for diagnosing people with type 2 diabetes, including when HbA_{1c} is not appropriate or cannot be used.[4, 5] The use of fasting plasma glucose is recommended where HbA_{1c} results are borderline or further investigation of the result is necessary, such as in a patient with two discrepant HbA_{1c} results. In this situation, a fasting plasma glucose test may be used to clarify the diagnosis. Fasting plasma glucose is also the preferred initial test if the patient has a specific condition or complication that may lead to an inaccurate HbA_{1c} result.[4, 5, 7]

The criteria for diagnosing diabetes using fasting plasma glucose and oral glucose tolerance testing (if indicated) remain unchanged. However, other than in pregnancy, oral glucose tolerance testing should now only be used if HbA_{1c} is contraindicated and fasting plasma glucose results are inconclusive.[4]

* Amended 5/12/2012 from "Severe anaemia"

Table 1. Advantages and disadvantages of HbA_{1c} and fasting glucose assays.[4, 5, 17]

	Fasting glucose	HbA_{1c}
Patient preparation	Fasting required, this is often misunderstood or not adhered to	None
Sample processing	Stringent requirements for processing and separation; rarely achieved	Relatively simple
Standardisation	Fully standardised	Fully standardised
Variability	Moderate pre-analytic and biological variation	Little to no variation
Effect of illness	Severe illness may increase glucose concentration in hours or days	Severe illness may shorten red-cell lifespan, reducing HbA_{1c} levels in days or weeks
Haemoglobinopathies and disorders of red blood cell turnover	Few problems	May interfere with values in some cases
Cost to laboratory (approximate)	$2.30	$11.40

Table 2. Recommended guidelines for the diagnosis of diabetes[4–6]

HbA_{1c} results	Glucose Equivalent	Diagnosis	Comments
≥50 mmol/ mol, **with symptoms**	≥7.0 mmol/L, **with symptoms**	Diabetes	
≥50 mmol/ mol, **no symptoms**	≥7.0 mmol/L, **no symptoms**	Diabetes	A second HbA_{1c} test ≥50 mmol/mol is required to confirm diagnosis (after three months)
41 – 49 mmol/mol	6.1 – 6.9 mmol/L	Pre-diabetes	Offer lifestyle advice. Perform CVD risk assessment and follow guidelines for treatment of risk. Repeat testing of HbA_{1c} every 6 – 12 months
≤40 mmol/mol	≤6.0 mmol/L	Diabetes unlikely	Normal range. Repeat HbA_{1c} at next CVD assessment or when clinically indicated

A single fasting plasma glucose result ≥7 mmol/L is indicative of diabetes in **symptomatic** people; in **asymptomatic** people two fasting plasma glucose results ≥7 mmol/L, on separate days, are required to confirm the diagnosis. A fasting glucose of 6.1 – 6.9 mmol/L indicates impaired fasting glucose/pre-diabetes.

Testing for diabetes in women who are pregnant

HbA_{1c} testing is not currently recommended for diagnosis of diabetes in pregnant women because glucose tolerance is altered in pregnancy; a separate glucose-based diagnostic algorithm is used. Oral glucose tolerance testing (75 g) is still used for diagnosis of gestational diabetes in women with an abnormal initial polycose screen (50 g), although there are controversial proposals to change this.

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Monitoring glycaemic control

HbA_{1c} remains the preferred, and only really useful, test for monitoring glycaemic control in people with diabetes, in primary care. Glycaemic control targets should be discussed with the patient, with the aim of deciding on a realistic goal that lowers long-term risk.

New Zealand guidelines and NZSSD recommend a target HbA_{1c} of 50 – 55 mmol/mol or as individually agreed.[4, 9]

Table 3. HbA_{1c} values and associated outcomes[4, 5, 20, 21]

HbA_{1c} (mmol/mol)	Individual targets and possible patient outcomes
<50	Exceptional control, if taking insulin there is an increased risk of hypoglycaemia
50 – 54	Very good control, some risk of hypoglycaemia if on insulin
55 – 64	Acceptable in many individuals but higher than recommended. Long-term risk of microvascular complications increases exponentially from this point
65 – 79	Suboptimal glycaemic control. More intensive control may be required. Risk of retinopathy, CVD and other complications very high
80 – 99	Poor glycaemic control. More intensive control recommended
≥100	Extremely poor glycaemic control. Immediate action required

For further information see: "HbA_{1c} targets in people with type 2 diabetes", BPJ 30 (Aug, 2010).

Who should be screened for type 2 diabetes?

Current recommendations are for asymptomatic men aged over 45 years and women aged over 55 years to be screened for diabetes as part of a joint diabetes/cardiovascular risk assessment.[4] 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. In addition, NZSSD recommends screening should be undertaken opportunistically at age 25 years in people with the following specific risk factors:[4]

- Ischaemic heart disease (angina or myocardial infarction), cerebrovascular disease or peripheral vascular disease
- Long-term steroid or antipsychotic treatment
- BMI ≥30 or BMI ≥27 kg/m^2 for Indo-Asian peoples
- Family history of early age of onset type 2 diabetes in more than one first degree relative
- Past personal history of gestational diabetes mellitus

Additional risk factors for diabetes include:[7, 18]

- Central obesity
- Impaired glucose tolerance on previous assessment, e.g. HbA_{1c} 41 – 49 mmol/mol or fasting glucose 6.1 – 6.9 mmol/L
- 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)

Children and young adults with BMI >30 (or >27 kg/m^2 in Indo-Asian children) should be screened for diabetes if:[4]

- There is a family history of early onset type 2 diabetes or
- They are of Māori, Pacific or Indo-Asian ethnicity

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