Guidance concerning the use of glycated haemoglobin for the diagnosis of diabetes mellitus

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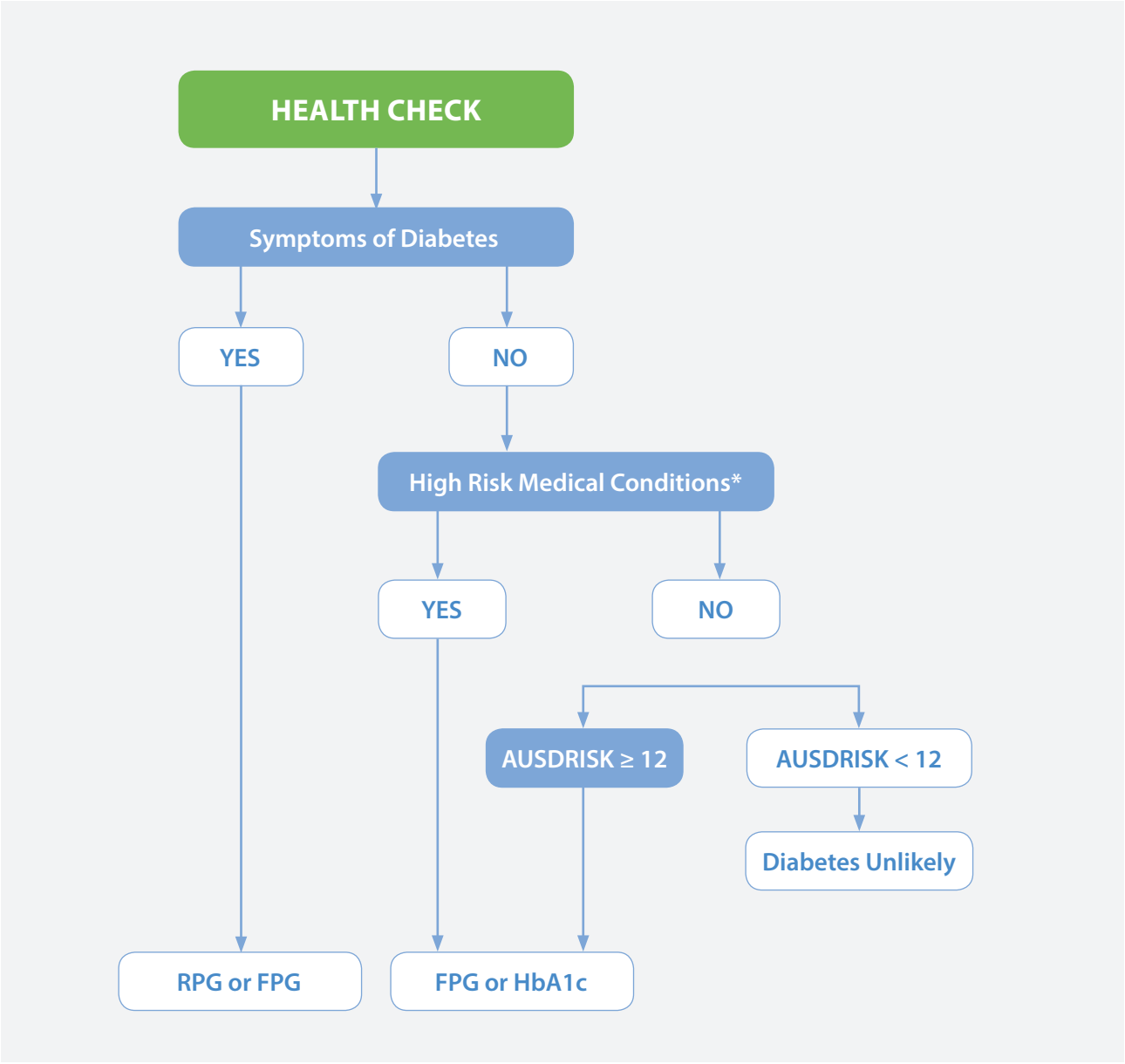
Australian Diabetes Society

Figure 1: Pathway For Diagnosis of Diabetes Mellitus



Diagnostic ranges

RPG: Diabetes ≥11.1 mmol/l

FPG: Diabetes ≥ 7.0 mmol/l; Impaired Fasting Glucose 6.0-6.9 mmol/l

HbA1c: Diabetes ≥ 6.5%

RPG = Random Plasma Glucose

FPG = Fasting Plasma Glucose

* High risk conditions include cardiovascular disease, prior gestational diabetes mellitus, impaired glucose tolerance or impaired fasting glucose, polycystic ovarian disease, and patients on antipsychotic medication.

In asymptomatic individuals, two blood tests on separate days, both within the diabetes diagnostic range, are required to make a clinical diagnosis.

BOX 1

CONDITIONS THAT MAY REDUCE GLYCATED HAEMOGLOBIN

A. Increased erythropoiesis
Iron administration, Vitamin B12/ Folate administration, Erythropoietin therapy, Chronic liver disease, Reticulocytosis

B. Abnormal Haemoglobin
Haemoglobinopathies, Haemoglobin F, methaemoglobin

C. Decreased Glycation
Aspirin, Vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH

D. Increased Erythrocyte Destruction
Haemolytic anaemia, haemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs (e.g., antiretrovirals, ribavirin and dapsone).

E. Assay Issues
Haemoglobinopathies*, hypertriglyceridaemia.

*The common heterozygote haemoglobinopathies do not cause problems with most current assays but for further information contact your laboratory. Adapted from Gallagher et al [11]

BOX 2

SUMMARY OF IMPLEMENTATION RECOMMENDATIONS

- The HbA1c should be considered in people considered at high risk, i.e. having an AUSDRISK score >12, or a pre-existing high-risk condition or being of a high-risk ethnicity.
- If one or more symptoms are present in a patient at low risk, blood glucose should be used for diagnosis.
- Patients who have symptoms suggestive of diabetes mellitus**,** should have diabetes confirmed by measurement of blood glucose.
- A HbA1c result less than 6.5% suggests that the patient does not have diabetes mellitus. As the test has been performed in a high-risk patient the test should be repeated 12 months later.
- Be aware of conditions which may invalidate the test.

INTRODUCTION

The measurement of glycated haemoglobin (HbA1c) provides an alternative to traditional glucose-based methods for diagnosis of diabetes. It does not replace them. The correct use of the test may facilitate the earlier diagnosis of patients with elevated mean blood glucose levels at increased risk of long-term diabetes-specific microvascular complications. It is used predominantly for the diagnosis of type 2 diabetes mellitus.

It is important that medical practitioners who elect to use the test for diagnosis understand the nature of the test, its limitations and its benefits. The major benefits of using HbA1c for diagnosis have been outlined by the HbA1c Committee of the Australian Diabetes Society [1], and relate mainly to the lack of the need to fast, the measurement of glycaemia over a period of weeks-months, and the low level of test-to-test variability.

Practitioners are recommended to read that paper in conjunction with this implementation document.

The Medicare Wording for Reimbursement

The wording for reimbursement states that the test is for "Quantitation of HbA1c (glycated haemoglobin) performed for the diagnosis of diabetes in asymptomatic patients at high risk." The test when used for diagnosis can be performed not more than once in a 12-month period [2]. The brevity of this statement raises certain issues that need to be considered.

1. Identification of patients at high risk

The intent of the statement is that only people at high risk of having un-diagnosed diabetes should be tested. As outlined in the original position statement, there are two groups of people at high risk: (i) those with an underlying medical condition or ethnic background associated with high rates of type 2 diabetes, and (ii) those people with characteristics placing them at increased risk of diabetes [1, 3]. The latter group is best identified using the AUSDRISK score available at https://www.health.gov.au/resources/apps-and-tools/the-australian-type-2-diabetes-risk-assessment-tool-ausdrisk

Patients considered to be at high risk have a score ≥ 12. However, the tool may not be reliable for people aged under 25 years.

The HbA1c should not be used to randomly or systematically screen un-differentiated, community-based groups of people for diabetes. Without prior knowledge of the medical status of patients, the test may not correctly diagnose patients as having diabetes (see below, section 5). It also represents a more expensive approach to screening compared with using blood glucose levels (BGLs) based on current costs [2].

2. Asymptomatic patients

The wording for reimbursement states that only asymptomatic patients should be considered for this test. Many of the symptoms in isolation are not specific for diabetes mellitus. For example, there may be many reasons for the development of tiredness or blurred vision as isolated symptoms. The ADS recommends that these patients be considered asymptomatic and are suitable for the test, but only if they fulfil the high-risk requirement as outlined above. If one or more symptoms are present in a patient at low risk, blood glucose should be used if diabetes is suspected.

Patients who have multiple symptoms highly suggestive of diabetes mellitus (weight loss, polyuria, polydypsia, blurred vision etc) are not asymptomatic and should have diabetes confirmed by measurement of blood glucose. These patients would be expected to have very high BGLs. There is the theoretical possibility that a patient with rapidly evolving diabetes could become symptomatic yet have a normal HbA1c as BGLs have not been elevated for a significant duration of time. Thus, it may not be clinically appropriate to measure HbA1c for diagnosis in symptomatic patients, especially if symptoms have only been present for a short period of time, as is often the case in type 1 diabetes.

3. Re-measurement

A result less than 6.5% (48 mmol/mol) suggests the patient does not have diabetes mellitus. As the test has been performed in a patient at high risk of developing diabetes in the next 5 years, the test should be repeated 12 months later as recommended in the National Health and Medical Research Council (NHMRC) guidelines for diagnosis of type 2 diabetes [3], irrespective of the HbA1c result. These people are at high risk of developing diabetes in the future and should be given lifestyle advice to reduce their risk of developing diabetes [4, 5].

People having a result just less than 6.5% do not need to have the test repeated in less than 12 months unless there is a significant change in their medical condition e.g. sudden change of weight or development of symptoms suggestive of diabetes. If the HbA1c is in the range of 6.0-6.4%, there is likely to be an even higher risk for developing diabetes than that based on their AUSDRISK score alone. If consideration would be given to enrolling the patient in an intensive lifestyle program to prevent the development of type 2 diabetes, an oral glucose tolerance test is recommended, as evidence for the benefits of such a program has only been established for impaired glucose tolerance [6]. If such a program is not appropriate, general advice about lifestyle measures (weight loss, dietary changes, exercise) should still be given, and the person should be assessed for other modifiable cardiovascular risk factors (hypertension, dyslipidaemia, smoking). The HbA1c should be repeated 12 months later.

4. Confirmation of Diabetes Mellitus

The NHMRC guidelines suggest that an abnormal blood glucose in an asymptomatic patient should be confirmed by a second test before the diagnosis of diabetes mellitus is established. However, a confirmatory HbA1c is not reimbursed by Medicare. A single elevated HbA1c result is accepted by Medicare as evidence of established diabetes. However, other organisations such as the World Health Organization and the American Diabetes Association recommend that diagnoses made by HbA1c be confirmed [7, 11].

Diabetes is a lifelong condition and there are employment, insurance, financial and lifestyle implications of being diagnosed with diabetes. It is important that the diagnosis is correct.

Although HbA1c is a more reliable laboratory measure of mean blood glucose [1], it does have a small coefficient of variation even in the best laboratories. Additionally, sample handling errors can occur. In consideration of all these issues, the ADS recommends that a confirmatory test is performed on another day. The confirmatory test can be either a glucose test or an HbA1c. However, since substantial numbers of people are positive on one test, but not on a different test of glycaemia (e.g. HbA1c is above the threshold, and fasting glucose is below the threshold), using an HbA1c as the confirmatory test for an initial HbA1c result is usually the most efficient process. Ideally, this test should be performed as soon as possible before any lifestyle or pharmacological interventions are commenced. If delayed, a subsequent normal result may simply reflect the improvement in glycaemia following initiation of management.

If the result is below 6.5%, then the diagnosis of diabetes has not been confirmed. In general, the patient should be advised that they do not have diabetes but they are at high risk of its development, and managed as outlined above in section 3.

There is an apparent conflict between these practice guidelines and the Medicare regulations (one diagnostic HbA1c test in a 12-month period). Medicare recognises a single elevated HbA1c measurement as establishing a diabetes diagnosis; this entitles the patient to four monitoring HbA1c tests in each subsequent 12-month period. We therefore recommend that the first monitoring test be performed before any interventions are initiated. A positive result in this test confirms the diagnosis and sets the baseline for clinical management. A result below 6.5%, if the test is performed appropriately, means that the patient should be classified as not having clinical diabetes, but they should have a further diagnostic HbA1c test 12 months later.

5. Abnormal glycated haemoglobin measurements

In the context of establishing the diagnosis of diabetes based on the HbA1c, an inappropriately low result is the major concern as the diagnosis will be missed. In all patients having an HbA1c performed, the possibility that the patient may have an associated medical condition that may render the HbA1c measurement invalid should be considered. These conditions have been previously discussed [1]. In summary, HbA1c may not be the appropriate test in patients with any significant chronic medical disease, any anaemia or any abnormality of red blood cell structure or turnover (Box 1). This possibility should certainly be considered in any patient who has a high AUSDRISK score with an unexpectedly low HbA1c. A full blood count (FBC) may reveal red blood cell abnormalities suggestive of a haemoglobinopathy or haemolytic anaemia but a normal FBC does not exclude the possibility. Some medications (e.g. dapsone) can also lead to erroneously low HbA1c results.

SUMMARY

The use of the HbA1c for diagnosis overcomes many practical problems associated with traditional blood glucose measurements. However, the test is not without its own limitations of which the medical practitioner needs to be aware. The possibility of having a medical condition that may interfere with the test should always be considered, even though these are rare in most Australian communities. Appropriately used, it provides a cost-effective, efficient and simple tool for the early diagnosis of type 2 diabetes.

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