DIAGNOSTIC TESTS

Glycated haemoglobin for the diagnosis of diabetes

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SUMMARY

The development of specific diabetes complications correlates with glycated haemoglobin (HbA1c), the most accepted measure of chronic glycaemia.

An HbA1c of 48 mmol/mol (6.5%) or greater has now been recommended in Australia for diagnosis of type 2 diabetes.

The HbA1c test should greatly simplify the diagnostic pathway, negating the need for oral glucose tolerance tests in the majority of patients. However, improved performance and precision of the assay with its standardisation across Australia is required.

Many clinical situations can impact on the HbA1c assay and the clinician needs to be aware of these if it is to be used appropriately for diagnosis.

Introduction

Diabetes results from elevated blood glucose and its diagnosis has traditionally been estabished by measuring blood glucose. The current blood glucose criteria used for diagnosis are associated with an increased risk of diabetes-related complications.

The major disease burden of type 2 diabetes is from macrovascular disease. There is a strong relationship between elevated blood glucose and coronary heart disease. Unfortunately, there is no threshold of blood glucose concentration associated with the development of coronary heart disease so the diagnosis cannot be related to macrovascular risk.[1]

In contrast, there is a clear glycaemic threshold for the development of microvascular complications, particularly diabetic retinopathy. There are also excellent outcome data showing that glucose-lowering therapy effectively prevents these complications.[2] The modern diagnosis of diabetes has therefore been based on blood glucose criteria associated with the development of retinopathy.[3,4] Over time, these blood glucose criteria have changed as the understanding of their relationship to retinopathy has improved.[5]

Blood glucose testing

The reliability of a blood glucose test performed in a laboratory is taken for granted by most medical practitioners. However, there are major practical problems with the fasting blood glucose and the oral glucose tolerance tests.

The day to day variation of blood glucose is considerable. The concentration of blood glucose ex vivo falls quickly even when collected in a fluoride tube, and the inter-laboratory results vary by at least 14% in a third of cases.[6,7]

With the oral glucose tolerance test, the patient should be on an appropriate diet for three days beforehand and have had a satisfactory period of overnight fasting. The test is time consuming to perform, taking at least two hours and involving three blood glucose samples. It is also labour intensive for pathology laboratories. The test is poorly tolerated by a significant number of people, with nausea, vomiting, delayed gastric emptying and issues of venous access all contributing to an invalid test. It often needs to be repeated and has poor patient compliance. A recent study from the Flinders Medical Centre in South Australia showed that only 27% of patients identified on admission as potentially having diabetes presented for a diagnostic oral glucose tolerance test despite repeated contact.[8]

Glycated haemoglobin (HbA1c) testing

Glycated haemoglobin (HbA1c) is produced by the non-enzymatic glycation of haemoglobin. The degree of glycation reflects the mean plasma glucose over the life of the red blood cell (approximately three months). Testing HbA1c is attractive as it measures chronic glycaemia rather than instantaneous blood glucose. It has been used as an objective marker of average glycaemic control for many years and has an accepted place in the monitoring of patients with diabetes. A review of eight studies conducted between 1988 and 2004 reported that HbA1c concentrations above 48 mmol/mol (6.5%) were at

least as strongly correlated with the development of diabetic retinopathy as blood glucose concentrations.[9] HbA1c is also associated with macrovascular outcomes and mortality, although there is no threshold below which there is no risk.[1,10,11]

HbA1c testing provides significant practical advantages over blood glucose measurement. It can be performed at any time of the day and does not require any special pre-test preparation by the patient. The blood sample is stable once collected – essentially in the same tube used for a full blood count. When access to an appropriate laboratory is limited, the test can be performed using a point-of-care testing machine. This may be particularly useful in rural and remote areas.

Standardisation

HbA1c testing must be reliable and consistent across Australia. The US National Glycohemoglobin Standardization Program has driven improvements in assays.[12] The variability of different tests for HbA1c within Australia is now acceptable. In a recent Australian study, whole blood samples were sent to more than 200 laboratories for testing. More than 90% of HbA1c results fell within 6% of the median.[13] Further improvements in standardisation should be achieved following the development of a national quality control program by the Royal College of Pathologists of Australasia, the Australian Association of Clinical Biochemists and the Australian Diabetes Society. Standardisation and calibration are extremely important if point-of-care testing is used for establishing the diagnosis.

Limitations

There are a number of clinical conditions which may affect the accuracy of the test, resulting in falsely high or low readings. The major concern is of a falsely low HbA1c result being interpreted as being normal in a patient with true diabetes. This may delay diagnosis, with the potential for significant long-term consequences. It is very important that clinicians are fully aware of the test's limitations. Any condition that leads to a shortened red cell survival time can interfere with the HbA1c assay. This includes the haemoglobinopathies, therapeutic venesection, anaemia, haemolysis, recent transfusion, and chronic renal failure. If any of these conditions are thought to exist, the diagnosis should be made on measures of blood glucose.[6,7,14] The effect of haemoglobinopathies is complex, varying with the type of haemoglobinopathy, the instrument and the method used in the laboratory. If suspected, discuss this issue with your local chemical pathology laboratory. If a patient has had a therapeutic venesection or a transfusion, the test should be delayed for three months, until the HbA1c measurement will be valid.

Recommendations

Along with other international organisations,[15,16] the Australian Diabetes Society has recommended that an HbA1c of 48 mmol/mol (6.5%) can be used to establish the diagnosis.[13] This recommendation is to be used in conjunction with National Health and Medical Research Council guidelines for the management of type 2 diabetes.[17] In the absence of symptoms, a second elevated HbA1c is necessary to confirm the diagnosis.

Currently in Australia, an HbA1c test can only be reimbursed by Medicare in patients with established diabetes. The Australian Diabetes Society has submitted a proposal to Medicare to accept the measurement of HbA1c for diagnosis but this proposal is still under consideration.

Discrepancies between blood glucose and HbA1c tests

HbA1c is a measure of chronic glycaemia whereas blood glucose tests are acute measurements at one point in time. These tests will identify different populations of patients. Most people with elevated blood glucose will have a raised HbA1c. However, some patients with a minor elevation on the fasting blood glucose or oral glucose tolerance tests will have an HbA1c of less than 48 mmol/mol (6.5%) (the diagnostic threshold). How does a practitioner resolve this discrepancy? Usually, the blood glucose concentrations are only minimally raised in these patients and the HbA1c result implies that they are at minimal or no risk of developing microvascular complications.[9-11] Although their blood glucose results are consistent with the biochemical diagnosis, they do not have chronic hyperglycaemia which is associated with an increased risk of developing microvascular complications. This means they do not have clinically relevant diabetes. These patients should still be assessed for their risk of macrovascular diseases, and their blood pressure and lipids managed appropriately. The test should be repeated.

Pregnancy

HbA1c cannot be used to diagnose diabetes in pregnancy. If true diabetes in pregnancy is suspected, blood glucose criteria must be used.

Conclusion

The acceptance of HbA1c testing will provide an additional tool to assist in the early diagnosis of diabetes. But it should not be the only tool. There remains a very important role for blood glucose testing, and the medical practitioner needs to be aware of the

benefits and limitations of both strategies. However, the HbA1c test does overcome many of the practical problems associated with the fasting blood glucose or oral glucose tolerance tests and its correct use should enhance the early diagnosis of type 2 diabetes. ◀

Conflict of interest: none declared

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New drugs

Crizotinib

Approved indication: non-small cell lung cancer
Xalkori (Pfizer)
200 mg and 250 mg capsules
Australian Medicines Handbook section 14.2.3

Along with erlotinib (Aust Prescr 2006;29:53-5) and gefitinib (Aust Prescr 2003;26:94-5), crizotinib is an oral tyrosine kinase inhibitor for non-small cell lung cancer – it is indicated for people with anaplastic lymphoma kinase (ALK)-positive advanced disease. Rearrangements in this gene lead to continuous activation of the kinase which promotes cell proliferation and inhibits apoptosis. Up to 5% of people with non-small cell lung cancer will have mutated ALK. These are mainly adenocarcinomas and are more likely to occur in non-smokers.

Following an oral dose, peak concentrations are reached after 4–6 hours. Steady state is reached after 15 days with twice-daily dosing. After extensive metabolism in the liver, most of the dose is eliminated in the faeces (63%) and urine (22%). The terminal half-life is 42 hours. Drug concentrations are likely to increase in hepatic impairment so caution is urged in these patients. Dose reduction is needed in people