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Could Global Standardization of A1C Help it Become the Preferred Diabetes Screening Method?

The current “gold standard” OGTT is relatively costly, time-consuming, and labor intensive.

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Screening for type 2 diabetes is advantageous as it permits early diagnosis, enabling early diabetes treatment and therefore reducing the risk of complications. Although diabetes is rapidly emerging as a public health issue in both developed and developing countries, consensus has not yet been reached on the most useful and accurate screening test for the detection of type 2 diabetes.

The tests most widely used in clinical practice today are the fasting plasma glucose screening test (FPG) for type 2 diabetes and the confirmatory oral glucose tolerance test (OGTT). Both involve measurement of venous (not capillary) blood glucose, and both require patients to fast overnight for at least 8 hours, be on a normal diet, and be free of intercurrent illness. FPG-based diagnoses also require at least two elevated FPG levels, limiting the practicality of these tests in rural and remote settings where laboratory access is limited.

OGTT IS COSTLY, TIME CONSUMING

The “gold standard” OGTT, on the other hand, is relatively costly, time consuming and labor intensive. Reproducibility for OGTT is also low with intra-individual coefficients of up to 16.7%.¹ These rates are

higher than those reported for FPG (up to 11.4%)¹ and may indicate increased diagnosis error rates,² highlighting the fact that there is no true gold standard diagnostic test for evaluating the sensitivity and specificity of alternative diabetes screening tests.

The glycated hemoglobin test (A1C) is one alternative screening tool that deserves greater attention. Although it has much greater sample stability, it is currently usually only used for monitoring purposes after a diabetes diagnosis has been made. A1C has several additional practical advantages over FPG or OGTT; blood sample collection can be performed more quickly, capillary blood samples are suitable, and sample stability is better than for blood glucose.

A1C ADVANTAGES

A1C has another important advantage in that levels reflect the 2- to 3-month average of blood glucose concentrations, rather than the snapshot view provided by blood glucose tests. A1C has also been demonstrated to have less intraindividual variation (intraindividual coefficient of variation of 4.2%, and even lower in longer-term follow-up¹), and to better predict both micro- and macrovascular diabetes complication risks.³

The accuracy of A1C analysis may be influenced by the presence of hemoglobinopathy or renal failure, as well as laboratory error and/or the use of some medications such as high-dose aspirin and opiates.⁴ These potential confounders, however, are relatively easily and reliably assessed in patients. A1C is also currently a more expensive test option, and it is not readily available to developing countries. Overall, A1C has a number of practical advantages over OGTT; sample collection and measurement is quicker and can be taken regardless of prandial status, A1C can be analyzed with a small blood sample using a portable device,⁵ and blood obtained from a finger stick can be sent to a central laboratory for analysis, allowing screening in remote areas.^{6,7}

DRAWBACK: INCONSISTENCIES IN REPORTING

A current drawback with regard to A1C testing is that there is considerable inconsistency in the reporting of A1C results, making it difficult to compare results across studies and populations. Progress is now being made toward worldwide agreement on standard A1C testing and result reporting.⁸ If this is successful, it might facilitate an increase in the use of A1C as a diabetes screening test that, if substantial enough, could drive the cost of testing down to a level comparable with blood glucose tests. It is therefore timely to assess the performance of A1C as a screening tool for diabetes compared with the blood glucose tests.

In a recent systematic review on the performance of A1C as a diabetes screening tool,⁹ we analyzed the benefits and limitations of the currently available A1C assay. The review examined nine primary cross-sectional studies of the accuracy of the A1C test for the detection of type 2 diabetes using the OGTT as the reference standard and FPG as the comparison.¹⁰⁻¹⁸ Some studies were community based,¹⁰⁻¹³ and others hospital based.¹⁴⁻¹⁸ A barrier to evaluating the relative value of A1C compared with other diabetes diagnostic tests is the current inconsistency in reporting of A1C results. Included studies either reported Diabetes Control and Complications Trial (DCCT)-aligned A1C results, or the published results were converted to the equivalent DCCT-aligned values using conversion regression models.^{19,20}

Multiple A1C cutoff points were analyzed. In the community-based studies, for the majority of cutoff comparisons, A1C was found to have slightly lower sensitivity for detecting diabetes than the FPG for detecting diabetes, but slightly higher specificity. This was seen for all comparisons in community-based

samples except for the A1C cutoff of 6.6% in which specificity was comparable, but sensitivity was higher for A1C (98% sensitivity for A1C in men compared with 91% for FPG at 7 mmol/L¹¹). The pattern was different in the hospital setting, with specificities generally high across all tests and cut-off points compared.

Across community and hospital settings, the sensitivity for A1C at a DCCT-comparable cutoff point of $\geq 6.1\%$ ranged from 78% to 81%, and the specificity ranged from 79% to 84%. For FPG at a cut-off point of ≥ 6.1 mmol/L, the sensitivity ranged from 48% to 64% and specificity from 94% to 98%. Not surprisingly, both A1C and FPG have low sensitivity (around 50%) for the detection of impaired glucose tolerance, which is associated with an increased risk of type 2 diabetes² and perhaps of atherosclerosis.²¹⁻²⁴

A1C, FPG EQUALLY EFFECTIVE

The review confirmed that A1C and FPG are equally effective screening tools for the detection of type 2 diabetes across a range of populations including Australia, Asia, Europe, and the United States. The A1C cutoff point of $>6.1\%$ was the recommended optimum cut-off point for A1C in most of the reviewed studies. There is also an argument, however, for population-specific cutoff points, as reported optimum cutoff points varied according to ethnic group, age, and gender, as well as with the population prevalence of diabetes.

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If global reporting standards for the units reported are successfully introduced in the near future,⁸ it may encourage the more widespread application of A1C as a diabetes screening test. If so, and given the reduced sample collection time relative to an OGTT test, it is likely this will drive down the cost of testing. A1C may then become more widely available as a screening tool, particularly in resource-poor populations who arguably need it most—where diabetes is an emerging public health issue but laboratory facilities are limited.

With increased use across populations, it will be also be important in the future to assess the potential for improving sensitivity and specificity through the identification and application of population-specific cut-

A1C: WHAT IS IT?

A1c is also known as hemoglobin A1c, HbA1c, glycohemoglobin, glycated hemoglobin, and glycosylated hemoglobin

How is it used? The A1C test is used primarily to monitor the glucose control of patients with diabetes over time. The goal of those with diabetes is to keep their blood glucose levels as close to normal as possible. This helps to minimize the complications caused by chronically elevated glucose levels, such as progressive damage to body organs like the kidneys, eyes, cardiovascular system, and nerves. The A1C test gives a picture of the average amount of glucose in the blood over the last few months. It can help patients and physicians know if the measures they are taking to control diabetes are successful or need to be adjusted. The A1C test is frequently ordered for newly diagnosed diabetic patients to help determine how elevated their uncontrolled blood glucose levels have been. It may be ordered several times while control is being achieved and then several times a year to verify that good control is being maintained.

What does the test result mean? A 1% change in an A1C result reflects a change of about 30 mg/dL (1.67 mmol/L) in average blood glucose. For instance, an A1C of 6% corresponds to an average glucose of 135 mg/dL (7.5 mmol/L), while an A1C of 9% corresponds to an average glucose of 240 mg/dL (13.5 mmol/L). The closer a patient with diabetes can keep their A1C to 6%, the better their diabetes is in control. As the A1C increases, so does the risk of complications.

Bear in mind that the correlation between mean plasma glucose (MPG) levels and A1C levels is an estimation only, dependent on methodology used for the calculation as well as other factors, such as the red blood cells' lifespan. The exact MPG value reported on a laboratory report may not coincide exactly with the formula given.

Source: www.labtestsonline.org

off points. In addition, the wider use of diagnostic guidelines, such as the Australian guidelines,²⁵ to identify patients at high risk for diabetes based on age, positive family history, weight, comorbidities such as vascular disease or polycystic ovary syndrome, and prior gestational diabetes, will also result in more targeted testing of high-risk groups, making diabetes screening incorporating A1C (see sidebar) even more efficient. ■

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