CADTH

CADTH ISSUES IN EMERGING HEALTH TECHNOLOGIES

Informing Decisions About New Health Technologies

Issue 156 June 2017

Point-of-Care Glycated Hemoglobin Testing to Diagnose Type 2 Diabetes

Image courtesy of Alere Canada

CADTH

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Cite as: Point-of-care glycated hemoglobin testing to diagnose type 2 diabetes. Ottawa: CADTH; 2017 Jun. (CADTH issues in emerging health technologies; issue 156)

Acknowledgments: CADTH thanks the external reviewers who kindly provided comments on an earlier draft of this bulletin.

ISSN: 1488-6324 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

- Glycated hemoglobin (A1C) is a marker in the blood used to monitor glycemic, or blood sugar, control in people with diabetes.
- Many point-of-care A1C testing devices have US regulatory approval for use in monitoring glycemic control in people with diabetes, but, as yet, none have been cleared by the FDA for the diagnosis of type 2 diabetes.
- In the US, Alere is seeking FDA clearance for its Afinion HbA1c Dx system for the point-of-care diagnosis of type 2 diabetes and as a test to identify people at risk for developing diabetes.
- The evidence comparing point-of-care A1C devices to laboratory-based testing shows that point-of-care devices performed as well as laboratory devices.
- If point-of-care A1C test systems are approved for diagnosing type 2 diabetes, comparative evidence will be needed to inform purchasing decisions. Quality assurance systems and cost analyses will also be needed.

Issue

Glycated hemoglobin (A1C) is a blood marker used to monitor glycemic (blood glucose or blood sugar) control in people living with both type 1 diabetes and type 2 diabetes. A1C has advantages over blood glucose testing, as it indicates long-term (90-day) blood glucose control. In addition, because A1C is stable throughout the day, measuring it eliminates the need for people to fast or restrict their diets before testing, and there is low variability within an individual's test results.[1]

A1C testing is now widely used to monitor glycemic control in patients with diabetes.[2] In 2011, the World Health Organization determined that A1C could also be used as a diagnostic test at a threshold of 6.5% (48 mmol/mol) provided quality control processes are in place. Quality control should include:

- stringent quality assurance testing
- the use of standardized assays
- ruling out conditions that could preclude accurate A1C measurement.[3,4]

Diabetes Canada (formerly the Canadian Diabetes Association) and the American Diabetes Association have also endorsed the use of A1C for diagnosing type 2 diabetes.[5,6]

Designed for use in a physician's office, a treatment room, or at a bedside, point-of-care A1C analyzers are bench-top instruments that use a finger-prick capillary blood sample. The blood is applied to a test cartridge and the sample is analyzed within several minutes.[7] Point-of-care A1C testing has several potential advantages over laboratory A1C testing:

- It provides rapid test results to expedite medical decision-making.
- It is more convenient for patients.
- It may improve health system efficiency.
- It can improve access to testing for underserved populations.[2,4,8]

One point-of-care A1C analyzer, the Afinion HbA1c Dx system (Alere Technologies AS, Oslo, Norway), is the first to seek US FDA approval for the diagnosis of type 2 diabetes.[9]

The Technology

The Afinion HbA1c Dx system includes:[9,10]

- a compact multi-assay analyzer for point-of-care testing (the Alere Afinion AS100 Analyzer). The analyzer is also capable of testing for lipid levels, albumin/creatinine ratios, and C-reactive protein, and can accept samples of whole blood, plasma, or urine. The Afinion is a desktop-size analyzer that weighs 5 kg and is able to store 500 patient results (as well as internal quality control data for test validation).
- a small connectivity device for automatic transfer of data from the analyzer to a laboratory, information system, or other electronic record systems (the Alere Afinion Data Connectivity Converter)
- single-use Afinion test cartridges used to collect patients' capillary blood samples
- liquid control samples at two levels of A1C for quality control testing.

Availability

The Alere Afinion HbA1c system submission is currently undergoing Health Canada review for a Class III medical device licence (David Smith, Alere Canada, Ottawa, ON: personal communication, 2017 Mar 9).

> **"The Afinion HbA1c Dx system for diagnosis is currently undergoing FDA review…"**

In the US, the Afinion HbA1c test for use with the Afinion AS100 Analyzer (Afinion HbA1c system) was originally cleared by the FDA for monitoring glycemic control in people with diabetes.[9] Many other point-of-care A1C devices are commercially available, but none have yet been approved by Health Canada or the FDA for the diagnosis of diabetes.[11] The Afinion HbA1c Dx system for diagnosis is currently undergoing FDA review[12] and other manufacturers may apply for this expanded indication. The FDA has notified manufacturers that they "believe that certain devices may be able to obtain such a claim with data demonstrating that they are accurate and reliable enough for this purpose."[11]

Cost

The Canadian cost of the Alere Afinion HbA1c Dx system is not available. However, based on online medical supplier retail information, the cost of the Alere Afinion AS100 Analyzer is approximately US$3,700.[13] The system also requires test cartridges (supplied in boxes of 15 at approximately US$10 per cartridge).[14] Control kits are also available (supplied in packages of two at approximately US$30 per control kit).[15]

Who Might Benefit?

An estimated 3.4 million Canadians have diabetes.[16] Approximately 90% to 95% of people with diabetes have type 2, which is characterized by inadequate insulin production and/or inadequate insulin action.[17-19]

Diabetes Canada guidelines recommend laboratory-based A1C testing as one method that may be used to diagnose type 2 diabetes in adults. It may also be used to identify people with pre-diabetes — those who may be more likely to develop diabetes in the future.[17] However, A1C should not replace glucose testing in people with type 1 diabetes, children, pregnant women, or in those with conditions that may affect the accuracy of the test (such as hemoglobinopathies or anemia).[12,17,20]

Undiagnosed diabetes is also an issue, and a point-of-care test might potentially improve access to testing for diabetes in underserved populations.

Current Practice

The most widely accepted tests for the diagnosis of type 2 diabetes are fasting plasma glucose and the oral glucose tolerance test, although the oral glucose tolerance test has fallen out of favour because of its inconvenience, high cost, and poor reproducibility.[5] Reaching a diagnosis involves at least two physician appointments: an initial office visit followed by a laboratory test, and then a return visit, days or weeks later, to follow up on test results to inform treatment decisions. If an elevated A1C is found and there are no other symptoms, the blood test may be repeated, adding to the length of time taken to reach a diagnosis.[7] Once a diagnosis is made, A1C concentration is monitored every three to six months to assess glycemic control, and additional office visits may be needed for medication adjustments.[4,7]

The Evidence

The evidence on use of the Alere Afinion system for the diagnosis of diabetes comes from two studies: a UK systematic review from the University of Oxford,[4] and an observational study from Norway.[1]

The systematic review assessed the diagnostic performance of point-of-care A1C test devices and the implications for their use in clinical practice.[4] The review sought studies that compared results from point-of-care A1C devices with those from a laboratory, with a focus on test bias, precision, and accuracy for the monitoring and diagnosis of diabetes. The review included 60 reports covering 13 different point-of-care devices, including the Alere Afinion system. Twelve of the studies reported data on the Afinion device, and there were sufficient data to carry out meta-analysis on the diagnostic accuracy for five devices, including Afinion.

The Norwegian observational study assessed the diagnostic performance of three types of point-of-care A1C devices (including the Alere Afinion system) used in general practitioners' offices (n = 1,288), compared with testing in hospital laboratories (n = 52).[1] Point-of-care and laboratory data came from 13 A1C external quality assurance surveys conducted from 2006 to 2012, and values were compared with the specifications recommended for the use of A1C to diagnose diabetes.

Test Performance

Sensitivity is the ability of a diagnostic test to correctly identify individuals who have a condition, whereas specificity is the test's ability to correctly identify those who do not have a condition. In the systematic review, sensitivity across the five devices was similar but specificity varied more. The Afinion and one other device (DCA Vantage Analyzer, Siemens) had the highest or most favourable specificity at the diagnostic A1C cut-off value of 6.5% (48 mmol/mol).[4]

Among the 13 devices tested for monitoring, the researchers found that the majority produced results that are typically lower than the results of a laboratory test (negative mean bias). Of the nine devices found to have a negative mean bias, the Afinion and three other devices performed the most favourably. The researchers noted that using a device with a negative bias may lead to fewer short-term episodes of low blood sugar, or hypoglycemia, but some patients may have higher long-term levels of high blood sugar, or hyperglycemia. The researchers concluded that, because most point-of-care devices showed a negative bias, as well as high levels of uncertainty in the results they produce (large standard deviations), their use in a clinical setting may result in different treatment decisions — for example, possible under-treatment — compared with results from laboratory methods.[4]

Results from the Norwegian study showed that, overall, point-of-care devices performed as well as laboratory testing.[1]

Safety

In the literature reviewed, there was no specific discussion of safety related to point-of-care A1C testing in general or the Afinion device specifically. The main concern is the system's performance as a diagnostic test for diabetes because inaccurate results could lead to significant morbidity.

A health technology assessment by the Australian Medical Services Advisory Committee (MSAC) found no studies on the safety of A1C testing versus traditional alternatives in the diagnosis of diabetes.[21] MSAC noted that the A1C test is widely used in Australia for monitoring diabetes and that it has the same or less risk than alternative tests; therefore, MSAC did not consider safety a major concern.

A condition of FDA approval includes mandatory medical devices reporting requirements for manufacturers, importers, and device user facilities; for example, malfunction or contribution to a death or serious injury.[22] The FDA's Manufacturer and User Facility Device Experience (MAUDE) database contains mandatory reports filed by device manufacturers and importers from August 1996 to the present. No reports were found for the Alere Afinion device.[23]

Limitations

The UK systematic review concluded that evidence of the impact of using point-of-care A1C testing on medication use, clinical decision-making, and patient outcomes is lacking and this needed evidence should be determined through a randomized trial with an economic evaluation.[4]

With respect to patient outcomes, both the systematic review and the Norwegian study addressed the performance of point-of-care A1C devices; however, they did not address whether point-of-care testing improves patient care or outcomes in comparison to laboratory-based testing.[7]

Concurrent Developments

A number of point-of-care A1C devices are commercially available for monitoring glycemic control,[4] and it is likely that other manufacturers will seek to expand the approved indications for their devices to include the diagnosis of diabetes.

Implementation Issues

There are several considerations in using A1C systems for the point-of-care diagnosis of type 2 diabetes:

- the suitability of A1C for diagnosing type 2 diabetes (versus its use for monitoring)
- the use of point-of-care tests versus laboratory tests
- the need for methods to ensure sharing test results between information systems and health care providers, and checks to avoid the duplication of testing
- the comparative accuracy and costs of the various devices for point-of-care A1C testing.

The use of point-of-care A1C for the diagnosis of diabetes would enable rapid diagnosis, improved provider and patient convenience, and possibly offer cost savings.[2,4,7] The Norwegian study noted that about 75% of general practitioners in Norway are using point-of-care A1C testing in their offices, presumably for both diagnosis and monitoring, thus providing a possible model of uptake.[1] (About half of the systems in use in Norway are Afinion.) The Norwegian study authors also noted that point-of-care A1C testing quality is closely monitored in their country through a stringent national quality assurance program for laboratory testing in which essentially all general practitioners' offices participate.[1]

> **"There is controversy over whether benefits exist for pre-diabetes screening."**

Physicians report that the Alere Afinion system is easy to use and, in comparison to some of the other systems, superior with respect to rapid analysis time (three minutes) and ease of sample loading.[7] However, in a primary care setting, the cost of purchasing the system and the ongoing cost of test cartridges could be a deterrent unless health system funding is provided.[2]

The cost differences between point-of-care and laboratory testing of A1C for monitoring blood glucose were assessed in a 2014 budget impact analysis by Health Quality Ontario.[2] The analysis included A1C point-of-care devices that were available in Canada at the time (the Afinion system was not included).[2] Results indicated that if all laboratory testing for A1C monitoring in Ontario was replaced by point-of-care testing, the annual cost savings to the province could be $4.7 million ($86.8 million for point-of-care versus $91.5 million for laboratory testing).[2] However, no information on the costs of using point-of-care A1C tests to diagnose diabetes was found and how this use would impact potential cost savings is not yet known.

There is controversy over whether benefits exist for pre-diabetes screening.[24] Over-diagnosis and treatment could be a concern.[25] Moreover, the accuracy of A1C testing in determining pre-diabetes is uncertain.[25] The use of point-of-care devices for this expanded indication could also increase test utilization.

A further consideration in the use of point-of-care A1C testing is that the test cartridges must be refrigerated if they are to be kept for more than 90 days and therefore reliable refrigeration should be available.[26] Control testing must be carried out frequently — at least every 30 days with each new shipment or lot of test kits if testing frequency is low, when training new operators, and any time an unexpected test result is obtained.[26] Broader quality assurance of point-of-care testing is an important consideration. The World Health Organization supports the use of point-of-care A1C assays for diagnosis when it is the only option available or when a stringent quality assurance program is in place.[1] Norway illustrates how this can be accomplished.[1]

Final Remarks

Compared with the traditional tests used to diagnose diabetes (fasting blood glucose, oral glucose tolerance testing, and, more recently, laboratory-based A1C), point-of-care A1C testing offers a number of advantages, particularly rapid diagnosis and early initiation of therapy. Laboratory-based A1C is now an accepted diagnostic test for diabetes, but regulatory authorities and clinical guidelines have yet to endorse point-of-care devices for this use.

Methods — Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library. Grey literature searching included relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012 and January 20, 2017. Conference abstracts published between January 1, 2015 and January 20, 2017 were included in the search results. Regular alerts updated the search until project completion; only citations retrieved before March 6, 2017 were incorporated into the analysis.

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