Glucose and Glycated Haemoglobin Point-of-care Testing and Early Diagnosis of Diabetes and Pre-diabetes

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Abstract
The number of individuals with impaired glucose metabolism (‘pre-diabetes’) and type 2 diabetes is reaching epidemic proportions. This increase is associated with higher cardiovascular morbidity and mortality. Early screening for diabetes and pre-diabetes (i.e. elevated glucose and/or glycated haemoglobin [HbA1c]) may aid in the reduction of diabetes-related complications. Point-of-care testing, defined as testing at or near the site of the patient, is able to bring diagnostic tests and its associated therapeutic actions immediately to the patient and may aid in the detection of diabetes and the reduction of complications. However, the majority of available point-of-care testing devices for glucose and HbA1c do not meet generally accepted analytical performance criteria and may underestimate the true risk of diabetes. Until these analytical performance issues have been addressed properly, caution should be exercised in the use of point-of-care testing of glucose and HbA1c in the diagnosis of and screening for pre-diabetes and diabetes.

Keywords
Point-of-care testing, oral glucose tolerance test, glucose, glycated haemoglobin (HbA1c), pre-diabetes, diabetes, diagnosis, sensitivity, specificity, performance, quality assurance

Over the last few decades the prevalence of diabetes has reached epidemic proportions in western societies and is even higher in developing countries,1–3 mainly due to population growth, ageing and obesity.1,4 The World Health Organization (WHO) has estimated that the global prevalence of diabetes will increase from 2.8% in 2000 to 4.4% by 2030.1 The increases in both obesity and diabetes will have a profound impact on diabetes- and obesity-related complications,1,5 the use of healthcare resources8 and the quality of life of affected patients.9

Diabetes comprises a group of metabolic diseases characterised by elevated blood glucose levels, and the diagnosis is based on increased fasting and/or post-load (after an oral glucose tolerance test [OGTT]) plasma glucose values (see Table 1).10–12 Type 2 diabetes, which accounts for 90–95% of all diabetes cases, is characterised by inappropriate insulin secretion due to a decline in β-cell function and the presence of (obesity-related) insulin resistance,13,14 resulting, among other metabolic disturbances, in fasting and post-prandial hyperglycaemia. Glycaemic control, as reflected by glycated haemoglobin (HbA1c), is common practice in the management of diabetes to adjust therapy regimens and to aid in patient education.

Recently, the American Diabetes Association (ADA) has advocated the use of HbA1c in the diagnosis of diabetes13–15 as a result of the global standardisation of the HbA1c assay with associated improvement of the analytical performance of the assay.16–18 However, the WHO and the International Diabetes Federation (IDF) recommend against the use of HbA1c in the diagnosis of diabetes in their 2006 consensus report.19 Individuals with type 2 diabetes have an increased risk of developing macrovascular and/or microvascular complications and mortality,20,21 and the risk of developing these complications may increase if good glycaemic control is not adequately maintained. Studies such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have supported the notion that adequate glycaemic control in the general patient population may aid in the prevention or reduction of the risk of developing diabetes-related vascular complications.22,23 Early detection of high-risk patients with elevated glucose levels may aid in the prevention or reduction of diabetes-related complications. This could be achieved by screening individuals who are at high risk of developing diabetes by for example capillary glucose testing by point-of-care testing.

This article focuses on the potential role of point-of-care testing of glucose and HbA1c in the diagnosis of pre-diabetes and diabetes. It gives an overview of the principles, pitfalls and analytical performance of glucose and HbA1c point-of-care testing and summarises the studies that have applied point-of-care testing of glucose and HbA1c in the diagnosis of (pre-) diabetes. Finally, the article concludes with the authors’ recommendations on the applicability of point-of-care testing of glucose and HbA1c in the diagnosis of diabetes.

Point-of-care Testing of Glucose and Glycated Haemoglobin – Principles, Practice and Pitfalls

Point-of-care or near-patient testing can be defined as diagnostic testing at or near the site of the patient and is able to bring the
Developments in Glucose Point-of-care Testing Devices

Over the last four to five decades the principles of point-of-care testing of glucose have changed considerably.37,38 The first-generation quantitative point-of-care testing devices for glucose included a modified dipstick originally designed for detecting glucose in urine that is based on an enzymatic reaction with a change of colour of the pad of the dipstick. A blood sample was applied to the strip and whipped off. Subsequently, the change in colour intensity was measured and compared with an internal calibration and translated to a quantitative result. The second-generation point-of-care glucose testing devices provided automatic timing and no need for wiping off the strip, which considerably improved the performance of the device. The latest point-of-care glucose testing devices are based on enzymatic methods (glucose dehydrogenase and glucose oxidase) and electrochemical sensors instead of colorimetric assays.39–41 These technical advances have led to an improved performance with respect to operation and sample handling and to improvement of the analytical performance of these devices. However, even state-of-the-art devices can still be improved.

Developments in Glycated Haemoglobin Point-of-care Testing Devices

Laboratory analysers for HbA1c utilise technologies that are based on either charge differences (high-pressure liquid chromatography) or structure (boronate affinity or immunoassay combined with general chemistry). In the last five to 10 years these technologies have been incorporated into point-of-care testing devices, allowing for immediate availability of HbA1c measurements.42–44 The first HbA1c point-of-care devices needed several manual handleings, while the newly developed devices are easy to use and are provided with tools to make it possible to be connected with other information systems.

Practice and Pitfalls of Point-of-care Testing of Glucose and Glycated Haemoglobin

Point-of-care testing for glucose has been used in a variety of settings, including hospitalised patients with diabetes, self-management of patients with diabetes, outpatient diabetes clinics, emergency departments, general practitioners’ offices and pharmacies,52,53 whereas the use of point-of-care testing of HbA1c is less common in clinical practice. In The Netherlands, HbA1c point-of-care devices are mainly used in paediatric diabetes centres in children with type 1 diabetes. The major advantages of point-of-care testing include portability, small sample volume (whole blood) and immediate result with appropriate therapeutic action.27 However, in general point-of-care testing of glucose is still more expensive than the laboratory reference method and higher analytical variability has been reported. In addition, quality assurance issues should be addressed properly.27,28

Although the performance of glucose point-of-care testing devices has improved, some pitfalls in point-of-care testing should still be acknowledged. The operators should be properly trained and certified to obtain an optimal whole-blood sample and to apply the correct amount of blood volume on the point-of-care testing device.48,49 Furthermore, patient characteristics that may adversely influence the result should be noted, including haematocrit levels,50,51 interfering drugs52 and metabolic disorders (e.g. uraemia, hyperlipidaemia).53,54 Low (<0.35) and high (>0.55) haematocrit levels may significantly influence the result of glucose measurement by point-of-care devices as illustrated in Figure 1, and should be evaluated in patients in whom the point-of-care devices are to be applied. Finally, factors that might adversely affect the operation of the devices and the performance of the strips such as temperature, humidity and high altitude should be taken into account.55–57 Although the use of point-of-care testing of HbA1c is less common than that of glucose, similar limitations and pitfalls of point-of-care testing of HbA1c may apply. In addition, immunoassay-based HbA1c point-of-care devices may interfere with haemoglobin variants, which is not the case with affinity-based point-of-care testing devices.50,56

Although the technical specifications of the point-of-care devices have improved considerably, pre-analytical, analytical and post-analytical issues should still be acknowledged and quality assurance systems should be implemented.

Analytical Performance of Point-of-care Testing of Glucose and Glycated Haemoglobin

Although glucose point-of-care testing devices can provide immediate results, these results may not be equivalent to the results produced by laboratory analysers.54–56 Over the past few years various regulatory affairs bodies have issued guidelines for the analytical performance of
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The Dutch guideline issued by the Netherlands Organisation for Applied Scientific Research (TNO) Centre for Medical Technology recommends a maximum of a 15% average deviation from a hexokinase laboratory value >6.5 mmol/l and within 1 mmol/l for values <6.5 mmol/l. Finally, the ADA has proposed the most stringent guidelines and recommends an agreement within ±10% of a laboratory method, with an eventual goal of <5% deviation. Based on the TNO guidelines, an overview of the current minimal criteria for assessment of the performance of point-of-care glucose devices is presented in Table 2.

As yet, there is no consensus on what should be considered the maximum deviation of the point-of-care devices. Currently, the ISO 15197 guideline is under revision and a maximum deviation of 15% in point-of-care testing devices for home use versus a reference method is proposed. In our view, for point-of-care testing devices for clinical uses a lower deviation should be implemented (<10%).

Performance of Glucose and Glycated Haemoglobin Point-of-care Testing Devices

Slingerland and co-workers found that only 60% of 30 available point-of-care testing devices available in The Netherlands complied with the TNO guidelines (15% deviation). If all criteria as set out in the TNO guidelines were tested, including reproducibility (maximum coefficient of variation of 10%), haematocrit dependency and under-filling protection, only 20% of the devices would comply with the TNO guideline. HbA1c point-of-care testing devices have been made available over the last few years and only a number of validation studies have been published. One of the most extensive validation studies was performed by Lenters-Westra and Slingerland. They reported that the majority of HbA1c point-of-care testing devices do not comply with the generally accepted performance criteria, and these results imply that these devices should be used with caution in the screening of diabetes and pre-diabetes. Unfortunately, the most stringent ADA criteria may not be met by most glucose point-of-care testing devices. In addition, the majority of HbA1c point-of-care devices do not meet generally accepted analytical performance criteria.

Point-of-care Testing of Glucose and Glycated Haemoglobin in the Diagnosis of Diabetes and Pre-diabetes

Diagnosis of Pre-diabetes with Point-of-care Testing of Glucose

The diagnosis of diabetes and pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance) is based on elevated fasting plasma glucose and/or post-load (after a 75g OGTT) glucose levels and/or hyperglycaemia related symptoms (see Table 1). The OGTT is regarded as the gold standard in the diagnosis of diabetes, and is preferably performed on two separate occasions. The reproducibility of the OGTT is relatively low (95% of the random test and re-test differences were less than 15% with fasting glucose and 46% with post-load glucose), mainly due to intra-individual biological variability and, to a lesser extent, to analytical variability if glucose is measured in venous plasma with a laboratory reference method with low analytical co-efficients of variation (<2%). Indeed, an analysis of the DCCT data demonstrated that the biological variation was higher than the variation of the glucose measurements.

The co-efficients of variation of glucose measured by point-of-care testing devices may be considerably higher and therefore may contribute to further lowering the reproducibility of the OGTT.
Indeed, a number of studies that compared venous plasma glucose assessed by a laboratory reference method with glucose measured in capillary whole blood by point-of-care devices showed an acceptable correlation between both values, but significantly higher co-efficients of variation in the point-of-care-measured glucose values.

To date, only a limited number of studies have addressed the applicability of point-of-care glucose testing in the diagnosis of diabetes and pre-diabetes (see Table 3). Rush and co-workers studied the performance of glucose point-of-care testing in an outpatient setting for the diagnosis of diabetes and pre-diabetes. An OGTT was performed in more than 3,000 individuals with a laboratory-based glucose reference method and with point-of-care glucose testing to assess the comparability of the two methods. The glucose levels as measured by the point-of-care device were significantly lower compared with the laboratory reference method, and the authors recommended against the use of point-of-care glucose testing for the diagnosis of diabetes and pre-diabetes. By contrast, based on their study of 200 participants in an area of Western Australia, Marley and co-workers concluded that point-of-care glucose testing could be used in the diagnosis and exclusion of diabetes if based on locally established reference values.

A recently published study conducted by Zhou and co-workers compared HbA1c (laboratory reference method) with point-of-care glucose testing with plasma glucose values after an OGTT to diagnose diabetes and pre-diabetes. The authors concluded that point-of-care glucose testing performed significantly better than HbA1c for the diagnosis of diabetes and/or pre-diabetes. Unfortunately, the authors did not present data on the comparability of point-of-care-derived glucose values with the plasma glucose values of the reference method at diagnostic values (i.e. ≥7.0 mmol/l). Overall, the reported areas under the receiver operating characteristics curve were less than 0.81 and 0.68 for detecting diabetes and pre-diabetes, respectively.

Based on these studies it can be concluded that the performance of point-of-care glucose testing may suffice for epidemiological studies in the screening of diabetes and pre-diabetes, and that local cut-off values of point-of-care glucose testing may, to some extent, enhance the performance of point-of-care glucose testing. However, in screening and diagnosis of individual patients the performance of point-of-care testing of glucose may lead to a significant misclassification of patients.

**Table 3: Overview of Studies Assessing the Value of Point-of-care Testing of Glucose in the Diagnosis of Diabetes**

<table>
<thead>
<tr>
<th>Author(s), Year, Site, Population</th>
<th>Year</th>
<th>Cohort/Population</th>
<th>n</th>
<th>Diagnostic Criteria</th>
<th>Reference</th>
<th>(Pre-) Diabetes</th>
<th>Sensitivity/ Specificity</th>
<th>AUC</th>
<th>Authors’ Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rush et al., 2008, Te Wario Rona</td>
<td>3,225</td>
<td>WHO 2000, Single OGTT</td>
<td>NDM 161 (5.0%)</td>
<td>NDM 9%</td>
<td>Not reported</td>
<td>POCT cannot be recommended as a means of screening for (pre-) diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou et al., 2010, Qingdao</td>
<td>2,332</td>
<td>WHO 1999, Single OGTT</td>
<td>NDM 278 (11.9%)</td>
<td>Not reported</td>
<td>POCT of glucose, as a screening tool for diabetes and pre-diabetes, performed better than HbA1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kruiskoop, 2004, CoDAM</td>
<td>350</td>
<td>WHO 1999, Single OGTT</td>
<td>NDM 97 (27.7%)</td>
<td>NDM 84%</td>
<td>Not reported</td>
<td>Cost-effective inclusion schemes for epidemiological studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marley, 2007, Australian cohort</td>
<td>200</td>
<td>Glucose ≥11.1</td>
<td>Not reported</td>
<td>NDM 83.3%</td>
<td>Not reported</td>
<td>Can be used in the process of diagnosis or excluding diabetes using locally established reference values</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

AUC = area under curve; HbA1c = glycated haemoglobin; IFG = impaired fasting glycaemia; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; NDM = newly detected diabetic mellitus; POCT = point-of-care testing; WHO = World Health Organization.

**Diagnosis of (Pre-) Diabetes with Point-of-care Testing of Glycated Haemoglobin**

An elegant alternative to fasting and post-glucose testing in the diagnosis of diabetes and pre-diabetes is the use of HbA1c. The patient does not need to fast or to undergo an OGTT, which can be associated with some discomfort. Instead, a non-fasting blood sample can be drawn to measure HbA1c, which has an overall lower analytical variability than glucose measurements (either capillary or venous plasma). Recently, the ADA has proposed the use of HbA1c in the diagnosis of diabetes. However, the applicability of HbA1c and the optimal cut-off value (≥6.5% as proposed by the ADA) in diagnosing diabetes seem to depend on ethnicity, age, sex and diabetes prevalence, and therefore other HbA1c cut-off values have been proposed. Furthermore, the life span of the erythrocyte should be taken into account, which may differ between individuals and may influence HbA1c. In addition, recent studies that applied the cut-off value of ≥6.5% reported low sensitivity and specificity of HbA1c in the diagnosis of diabetes.

To the best of our knowledge, no studies that used point-of-care HbA1c testing in the diagnosis of diabetes and pre-diabetes have been published to date. Given the recent observation that the majority of point-of-care HbA1c devices performed poorly with respect to generally accepted analytical performance criteria, the applicability of these point-of-care testing devices in the diagnosis of diabetes and pre-diabetes may be very limited or may even discouraged until these performance issues have been properly addressed.

Based on these observations with respect to HbA1c testing in the diagnosis of diabetes and pre-diabetes, we can conclude that HbA1c assessed by reference laboratory methods may underestimate...
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or overestimate the prevalence of undiagnosed diabetes and pre-diabetes. Given the low analytical performance of point-of-care HbA1c devices, their use in diagnosing diabetes and pre-diabetes is not recommended.

Conclusions

The number of patients with type 2 diabetes is reaching epidemic proportions and this increase is associated with an increase in cardiovascular morbidity and mortality. Early screening of patients with undetected diabetes and pre-diabetes (i.e. elevated glucose and/or HbA1c) may eventually lead to a reduction in diabetes-related complications. Point-of-care testing of glucose and HbA1c have been introduced and could lead to improvement of patient care. However, currently the majority of available point-of-care testing devices for glucose and HbA1c do not meet generally accepted analytical performance criteria, and may therefore underestimate or overestimate the risk of diabetes. Until these analytically accepted procedures have been addressed properly, we recommend against the use of point-of-care testing of glucose and HbA1c. In the diagnosis and screening of pre-diabetes and diabetes.