Abstract:
For many years, the diagnosis of diabetes has been made through the laboratory-based measurement of fasting or random blood glucose levels or using OGTT. In the case of diabetes, the major outcome of interest is long-term microvascular complications for which a large body of data has been accumulated leading to the endorsement of HbA1c for diagnosis in many countries worldwide, with some variations in cut-offs and testing strategies.

Key words: Type-2 Diabetes mellitus, HbA1c

Introduction:
Type-1 diabetes usually presents with symptoms and unequivocal hyperglycemia, thus diagnosis is usually uncomplicated. But type-2 diabetes has slower onset with a more gradual increase in glucose level over time. It is important to establish the diagnosis of diabetes early in its development, as effective management of the disease has been shown in the United Kingdom Prospective Diabetes Study (UKPDS) to significantly reduce the risk of developing complications. Furthermore, long-term follow-up of UKPDS participants demonstrated that more effective glycaemic control from the time of diagnosis in people with type-2 diabetes conferred a long-term benefit that persisted even though glycaemic control may deteriorate over time. This observation implies that strategies that facilitate early detection of diabetes should result in improved outcomes, with major long term health and cost benefits.

Glucose based criteria for the diagnosis of diabetes:
Conventionally, blood glucose is measured based on WHO criteria. WHO recommend FBG is $\geq 7.0\text{mmol/l}$ and 2HAG $\geq 11.1\text{mmol/l}$ for diagnosis of diabetes mellitus. Prediabetic category by WHO is IFG (impaired fasting glycemia) ranges 6.1-6.9 mmol/l and IGT (impaired glucose tolerance) ranges 7.8-11.0 mmol/l.

Some drawback of OGTT as a diagnostic test in type-2 diabetes:
Though, we have relied on measurement of blood glucose parameters to make the diagnosis of diabetes but there is highly significant relationship between blood glucose level and diabetes related complications. However, there is no threshold level at which cardiovascular disease will occur but microvascular complications particularly retinopathy, show a much clearer threshold of glycaemia above which they occur and where glucose lowering therapy is clearly effective in preventing them. Thus, the diagnosis of diabetes has been based on blood glucose threshold levels associated with the presence of retinopathy.

The Role of HbA1c for Diagnosis of Type-2 Diabetes Mellitus - A Review
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Abstract:
For many years, the diagnosis of diabetes has been made through the laboratory-based measurement of fasting or random blood glucose levels or using OGTT. In the case of diabetes, the major outcome of interest is long-term microvascular complications for which a large body of data has been accumulated leading to the endorsement of HbA1c for diagnosis in many countries worldwide, with some variations in cut-offs and testing strategies.

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repeated and has a poor patient compliance. A recent study from South Australia showed that only 27% of patients identified on admission to hospital as potentially having diabetes presented for a diagnostic OGTT despite consenting to undertake the test11. HbA1c in contrast is not affected by prandial status and has no diurnal rhythm, allowing measurement at any time of the day. HbA1c has high pre analytical stability12 (one week at 4°C).

What is the HbA1c test?

HbA1c is a blood test that provides information about a person's average level of blood glucose, over the past three months. This test is based on the attachment of glucose to hemoglobin13. HbA1c test is attractive as it measures chronic glycaemia rather than instantaneous blood glucose level. Practically it provides significant advantages over blood glucose measurement for diabetes diagnosis and taking management decisions, such as initiation of insulin therapy. It can be performed at any time of the day, does not require special pretest preparation such as diet or fasting, and is stable when collected in the appropriate specimen tube3.

How does HbA1c test is used for diagnose diabetes and prediabetes?

When HbA1c test is used for diagnosis, the blood sample must be sent to laboratory that uses an NGSP (National Glycohemoglobin Standardization Program) certified method for analysis to ensure the results are standardized1. Blood sample analyzed in a health care provider's office known as point of care (POC) tests are not standardized for diagnosing diabetes. The following table provides the percentages that indicate the diagnosis of normal, diabetes and prediabetes according to HbA1c level3.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HbA1C level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;5.7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≤6.5%</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>5.7-6.4%</td>
</tr>
</tbody>
</table>

*Any test for diagnosis of diabetes requires confirmation with a second measurement unless there are clear symptoms of diabetes.

People with prediabetes may be retested each year as there is a risk of getting type 2 diabetes mellitus. Within the prediabetes HbA1c range of 5.7-6.4%, the higher the HbA1c, the greater the risk of diabetes but they can take steps to prevent or delay diabetes14.

HbA1c and micro vascular complications:

HbA1c has a relationship with prevalent diabetic retinopathy, as shown in the recent DETECT-2 analysis. This landmark study involved data pooling of nine studies from five countries, with 44,623 participants aged 20-79 years with gradable retinal photographs. The study examined the relationship between diabetes specific retinopathy (defined as moderate or more severe retinopathy) and three glycaemic measures: FPG (n=41,411), 2HAG (n=21,334) and HbA1c (n=28,010). It was found that both FPG and HbA1c have narrow threshold ranges within which the prevalence of diabetes specific retinopathy begins to increase significantly. The study showed that prevalence of retinopathy was low with HbA1c <6.0% but increased above this level, with an optimal threshold of >6.4%. These findings suggest HbA1c is at least as good as predicting micro vascular complications15.

Recommendations for HbA1c as a diagnostic test:

HbA1c has recently been endorsed as a diagnostic test for diabetes by the WHO, International Diabetes Federation and the American Diabetes Association13,16. The Australian diabetes society established an expert committee in 2011, including invited representatives of the Royal College of Pathologists of Australasia (RCPA) and Australasian Association of Clinical Biochemists (AACB), to review the available evidence and provide this position statement concerning the role of HbA1c in the diagnostic pathway. The committee concluded that HbA1c can have an important place in diagnosis of diabetes. They recommend HbA1c ≥ 6.5% as the cut-off point for diagnosing diabetes. In an asymptomatic patient with a positive test result, the test should be repeated to confirm the diagnosis3. Individuals with an HbA1c 5.7-6.4% are considered to be at increased risk for diabetes as well as cardiovascular disease and should be counseled about effective strategies, such as weight loss and physical activity, to lower their risk1.

Cautions and caveats regarding HbA1c as a diagnostic test:

There are some important caveats. If used as a diagnostic test, the HbA1c assay needs to be reliable and consistent across different centers. There have been problems in the past with HbA1c test results varying considerably between laboratories. In the United States, NGSP (National Glycohemoglobin Standardization Program) has progressively driven improvement in assays, resulting in better quality results around the world11. In a recent Australian study, whole blood samples were sent to more than 200 laboratories and
more than 90% of HbA1c results fell within the 6% of the median\textsuperscript{17}. Further improvements in standardization of HbA1c measurements should be achieved following the development of national whole blood external quality control program by the RCPA Quality Assurance Program and the AACB.

When applying HbA1c testing for the diagnosis of diabetes, some medical conditions may affect the test and cause falsely high or low readings. The tests accuracy is affected principally by conditions that affect red blood cell survival time or non-enzymatic glycation of hemoglobin\textsuperscript{18}. A reduced red blood cell survival time will lower the HbA1c level and may lead to false negative result. It can occur in hemolytic anemia, chronic renal failure, severe liver disease, megaloblastic anemia. Iron deficiency may also have an impact on red blood cell survival and increase HbA1c level\textsuperscript{19}. Hemoglobinopathies and sickle cell anemia affect the result to a variable amount, principally due to interference with the laboratory measurement of HbA1c. The NGSP provides a summary of the effect of common hemoglobinopathies on measurement of HbA1c levels using various methods. However any inexplicably high or low HbA1c test result or discrepancy between glucose and HbA1c levels should alert the medical practitioner to a potential problem\textsuperscript{20}.

**Conclusion:**

Measurement of HbA1c can be used as a diagnostic test for diabetes if analysis is performed in a facility producing acceptable performance in external quality assurance, assays are standardized to criteria aligned to international reference values, and if no conditions which preclude its accuracy are present.

**References :**


