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ReviewArticle

The Role of HbA_{1C} 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 micro vascular complications for which a large body of data has been accumulated leading to the endorsement of HbA_{1C} for diagnosis in many countries worldwide, with some variations in cut-offs and testing strategies.

Key words: Type-2 Diabetes mellitus, HbA_{1C}

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[1]. 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[2]. 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[3]. This observation implies that strategies that facilitate early detection of diabetes should result in improved outcomes, with major long term health and cost benefits[1].

Glucose based criteria for the diagnosis of diabetes:

Conventionally, blood glucose is measured based on WHO criteria. WHO recommend FBG is ≥7.0mmol/l and 2HAG ≥ 11.1mmol/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[4, 5].

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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[6,7]. 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[7].

Some drawback of OGTT as a diagnostic test in type-2 diabetes:

However, measuring blood glucose levels is associated with methodological, procedural and practical problems. Day to day variation of blood glucose level should consider and in vitro concentration of blood glucose falls quickly even when the blood sample is collected in a fluoride-oxalate tube, an interlaboratory level can vary[8,9]. As, plasma separated within minutes of taking the sample RBC continue to consume glucose at about 7% per hour in vitro leading to falsely low measured glucose[10]. Secondly, for an oral glucose tolerance test (OGTT) more extensive pre-test preparation is required including an appropriate diet for 3 days before test and a satisfactory overnight fasting. OGTT is time consuming, taking at least 2 hours. The glucose load 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 result. The test often needs to be

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 test[11]. HbA_{1C} in contrast is not affected by prandial status and has no diurnal rhythm, allowing measurement at any time of the day. HbA_{1C} has high pre analytical stability[12] (one week at 4°C).

What is the HbA_{1C} test ?

HbA_{1C} 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 hemoglobin[13]. HbA_{1C} 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 tube[3].

How does HbA_{1C} test is used for diagnose diabetes and prediabetes?

When HbA_{1C} 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 standardized[1]. 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 HbA_{1C} level[3].

Diagnosis*	HbA_{1C} level
Normal	<5.7%
Diabetes	≤6.5%
Prediabetes	5.7-6.4%

*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 HbA_{1C} range of 5.7-6.4%, the higher the HbA_{1C}, the greater the risk of diabetes but they can take steps to prevent or delay diabetes[14].

HbA_{1C} and micro vascular complications:

HbA_{1C} has a relationship with prevalent diabetic retinopathy, as shown in the recent DETECT-2 analysis. This land mark 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 HbA_{1C} (n=28,010). It was found that both FPG and HbA_{1C} 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 HbA_{1C} <6.0% but increased above this level, with an optimal threshold of >6.4%. These findings suggest HbA_{1C} is at least as good as predicting micro vascular complications[15].

Recommendations for HbA_{1C} as a diagnostic test:

HbA_{1C} has recently been endorsed as a diagnostic test for diabetes by the WHO, International Diabetes Federation and the American Diabetes Association[13, 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 HbA_{1C} in the diagnostic pathway. The committee concluded that HbA_{1C} can have an important place in diagnosis of diabetes. They recommend $HbA_{1C} \geq 6.5\%$ 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 diagnosis[3]. Individuals with an HbA_{1C} 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 risk[1].

Cautions and caveats regarding HbA_{1C} as a diagnostic test:

There are some important caveats. If used as a diagnostic test, the HbA_{1C} assay needs to be reliable and consistent across different centers. There have been problems in the past with HbA_{1C} 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 world[11]. In a recent Australian study, whole blood samples were sent to more than 200 laboratories and

more than 90% of HbA_{1C} results fell within the 6% of the median[17]. Further improvements in standardization of HbA_{1C} 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 HbA_{1C} 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[18]. A reduced red blood cell survival time will lower the HbA_{1C} level and may lead to false negative result. It can be 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 HbA_{1C} level[19]. Hemoglobinopathies and sickle cell anemia affect the result to a variable amount, principally due to interference with the laboratory measurement of HbA_{1C}. The NGSP provides a summary of the effect of common hemoglobinopathies on measurement of HbA_{1C} levels using various methods. However any inexplicably high or low HbA_{1C} test result or discrepancy between glucose and HbA_{1C} levels should alert the medical practitioner to a potential problem[20].

Conclusion:

Measurement of HbA_{1C} 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.

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