IS HbA1c REALLY ESSENTIAL FOR DIAGNOSIS OF DIABETES MELLITUS

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SUMMARY

Various attempts have been made over the years to find a suitable investigation or blood parameter which can be used effectively to characterize the hyperglycemia seen in diabetes and to correlate it with the complications seen in this disease - Blood glucose (fasting and 2 hour post prandial), HbA1c and CGMS (continuous Glucose Monitoring System), have been evaluated in this respect. Currently, the diagnosis of diabetes mellitus is made on the basis of blood glucose cut off values sometimes requiring a 75 gm oral glucose tolerance test. However the results of OGTT are often inconsistent and variable making interpretation difficult. In 1997, ADA expert committee refuted the concept of 2HPg being used as the gold standard for the diagnosis of diabetes mellitus and considered HbA1c for diagnosis. However due to lack of sufficient information and variability of assays used to estimate HbA1c this could not be recommended to be used for diagnosis of diabetes even in 2003. However the assay techniques for HbA1c have improved significantly over the years and represents an accurate and precise measure of chronic glycemic levels which correlates well with risk of complications. Various studies have indicated that at HbA1c level more than 6.5% the risk of "any" retinopathy increases tremendously. Furthermore recent studies also indicate that HbA1c has the same precision as FPG, with less variability, easier sample collection, and less patient preparation. Therefore, the international expert committee has recommended in 2009 that HbA1c should be used for diagnosis of diabetes with value of ≥6.5% being the cut off for diabetes. Values > 6% but < 6.5% should receive effective preventive interventions. This recent change in diagnostic criteria represents a major shift in approach and is likely to affect diabetes care in a big way in the years to come.

INTRODUCTION

Diabetes is a disease characterized by abnormal metabolism, most notably hyperglycemia and an associated increased risk for relatively specific long term complications affecting almost all organ systems especially eyes, kidney and nervous system.

Type 1 diabetes mellitus (T1DM) has a characteristic clinical onset. Hence, specific blood glucose cut points are required mainly for confirmation of diagnosis only. On the other hand Type 2 diabetes mellitus (T2DM) has gradual onset with slowly increasing glucose levels over time. Hence, its diagnosis requires specific criteria to distinguish patients with glucose concentration in diabetic or non-diabetic range. Earlier attempts to standardize the definition of diabetes mellitus were dependent on the oral glucose tolerance test (OGTT), but the performance and interpretation of this test was not reliable and inconsistent and the number of subjects studied was very small (1-6).

In 1979, National Diabetes Data Group (NDDG) stated that there is no clear cut division between diabetic and non-diabetic patients in fasting plasma glucose (FPG) concentration or their response to oral glucose load and consequently an arbitrary decision has been made as to what level justifies the diagnosis of diabetes (7). Diagnosis was made when patient has symptoms of diabetes with a venous FPG of >140 mg/dl or after 75 gm oral glucose load, a venous 2 hour plasma glucose (2 HPg) ≥200 was obtained. Impaired glucose tolerance (IGT) implied FPG <140 mg/dl and 2 HPg 140-200 mg/dl.

In 1997, Expert Committee on Diagnosis and Classification of Diabetes Mellitus refocussed attention on relation between glucose levels and the presence of long term complications as the basis of diagnosis of diabetes (8). It also refuted the widespread concept that 2 HPg was the gold standard for diagnosing diabetes. Accordingly the criteria were revised as follows:

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>FASTING</th>
<th>PP</th>
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<tr>
<td>≥126 mg/dl</td>
<td>≥200 mg/dl</td>
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But still the limitations of OGTT remained.

Rationale for the use of HbA1c to diagnose diabetes mellitus

If chronic hyperglycemia is implicated in causation of diabetes specific complication, then an investigation that can measure long term glycemic exposure should provide a better marker for the presence and severity of the disease than single measure of glucose concentration.

In one study that measured both FPG and HbA1c, there was a stronger correlation between HbA1c and retinopathy than...
between FPG and retinopathy (9). Correlation between HbA1c and complications has also been shown in a setting of controlled clinical trials in type 1 (10) and type 2 diabetes (11).

All these observations suggest that HbA1c which captures the hyperglycemia over time and which is related more intimately to risk of complications than single or episodic measure of glucose levels, may serve as a better biochemical marker of diabetes and should be considered as a diagnostic tool.

1997 Expert Committee considered this option but recommended against it because of lack of standardization (8).

2003 follow-up report reaffirmed the previous recommendation that HbA1c not be used in diagnosis (12).

Current updated examination of HbA1c and glucose measurements indicate that:

- Accuracy and precision of HbA1c assays at least match those of glucose assays.
- HbA1c values are relatively stable after collection and the recent introduction of a new reference method to calibrate all HbA1c assay instruments should further improve HbA1c assay standardization in most of the world.
- Variability of HbA1c is also considerably less than FPG values. <2% day to day within person variability in contrast to 12-15% for FPG.
- Sample collection for HbA1c is convenient, requires no patient preparation and stable at room temperature as compared to FPG.

HbA1c cut point for diagnosis

In 1997, it was stated that retinopathy increased at HbA1c values starting between 6% and 7% (8). In the DETECT2 trial, level at which prevalence of any retinopathy begins to rise above background levels as also for the more diabetes specific moderate retinopathy was 6.5% (13). There is a low prevalence of “any” retinopathy at HbA1c levels <6.5%. This may reflect a continuum of risk for diabetes. Substantial increase in prevalence of moderate retinopathy at HbA1c levels >6.5% supports the threshold level of glycemia that results in retinopathy most characteristic of diabetes mellitus. HbA1c levels of 6.5% is sufficiently sensitive and specific to identify individuals who are at a risk of developing retinopathy and who should be diagnosed as diabetic.

Limitations of HbA1c as means of diagnosing diabetes

- Cost
- Patient’s condition that preclude HbA1c testing
  - Hb traits – Hb S, Hb C, Hb F, HbE
- Conditions that change RBC turnover
  - Hemolytic anemia
  - Chronic malaria

- Major blood loss
- Blood transfusion
- HbA1c levels appears to increase with age (14)
- Racial variability might be present (15)
- In rare conditions like rapidly evolving type 1 diabetes mellitus, HbA1c will not have had time to catch up with glucose values, it may lead to false interpretation
- HbA1c does not provide information about glycemic variability
  - Does not completely represent the risks that patients with diabetes are exposed to on a daily basis
  - HbA1c alone does not indicate the degree of glycemic variability
  - Even at equivalent HbA1c levels, patients receiving intensive therapy
  - Had a reduction in the risk of progression of retinopathy over time compared with patients receiving conventional treatment
- HbA1c does not differentiate among fasting, preprandial, and postprandial glycemia
  - Because HbA1c represents mean glycemic exposure over time, it cannot be used to identify whether a given patient’s abnormal glycemic levels are primarily due to high fasting plasma glucose levels or high postprandial plasma glucose (PPG) levels.
  - It cannot indicate what type of change in therapy is necessary.

Should HbA1c be used to identify increased risk for diabetes

HbA1c testing principles which apply for diagnosis of diabetes can also be used for screening individuals at high risk for diabetes.

Since no criteria exist regarding lower threshold of HbA1c, therapeutic and interventional decision making should be based on how close HbA1c levels are to the diagnosis of diabetes. So individuals with HbA1c levels closer to the 6.5% HbA1c threshold of diabetes should receive effective intervention (16,17).


1. For diagnosis of diabetes

- The HbA1c assay is an accurate, precise measure of chronic glyemic levels and correlates well with the risk of diabetes complications.
- HbA1c assay has several advantages over laboratory measures of glucose.
- Diabetes should be diagnosed with HbA1c >6.5%, diagnosis should be confirmed with a repeat HbA1c test.
Confirmation is not required in symptomatic subjects with plasma glucose >200 mg/dl.

- If HbA1c testing is not possible, previously recommended diagnostic methods are acceptable.
- HbA1c testing is indicated in children in whom diabetes is suspected, but the classic symptoms and a casual plasma glucose >200 mg/dl are not found.

2. For identification of those at high risk for diabetes

- The risk of diabetes based on levels of glycemia is a continuum, therefore, there is no lower glycemic threshold at which risk clearly begins.
- The categorical clinical states prediabetes, IFG and IGT failed to capture the continuum of risk and will be phased out of use as HbA1c measurements replace glucose measurements.
- As for diagnosis of diabetes the HbA1c assay has several advantages over laboratory measures of glucose in identifying individuals at high risk for developing diabetes.
- Those with HbA1c levels below the threshold for diabetes, but >6% should receive demonstrably effective preventive intervention.
- The HbA1c levels at which population based preventive services begin should be based on the nature of intervention, the resources available and the size of the affected population.

In conclusion, it would now appear that HbA1c has finally arrived as a diagnostic tool for the diagnosis of Diabetes Mellitus and the next few years should see it getting established as the primary tool for the purpose. This is also likely to be associated with the evolution of a new system to define diabetes risk and a possible phasing out of the prediabetic classes based on OGTT.

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