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Review Article

Diabetes Mellitus And Glycosylated Hemoglobin A1c

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ABSTRACT

Diabetes mellitus is a global health problem in 21st century. The incidence of diabetes mellitus is in rise and is estimated to be more prevalent in coming years. It is becoming one of the most common non-infectious and non-neoplastic causes of morbidity and mortality. Various complications are associated with diabetes mellitus. With control of blood glucose level, complications of diabetes mellitus can be minimized. In different time frame, different parameters and level have been used to diagnose diabetes. Glycosylated hemoglobin A1c is one of the reliable indicators of chronic hyperglycemia. In 2011, World Health Organization has included HbA1c in the diagnostic criteria. Various methods are used to detect the level of HbA1c.

Glycosylated hemoglobin is being used in the management of diabetes mellitus. Various studies have shown its prognostic implication in micro and macrovascular complications. Here we discuss various methods of estimation of HbA1c, various role of HbA1c in the management of Diabetes Mellitus and limitation of the test.

Keywords: Coronary artery disease; Diabetes; Glycosylated; HbA1c; Hemoglobin; Nephropathy; Prediabetes; Retinopathy

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INTRODUCTION

Diabetes mellitus, a chronic metabolic syndrome, is characterized by persistent hyperglycemia resulting from either insulin deficiency or increased insulin resistant. In 21st century, diabetes mellitus poses a measure global health threat. The number of diabetic patients has risen dramatically from 108 million in 1980 to 422 million in 2014 global prevalence of it was 8.5% in 2014, which was 4.7% in 1980 among population more than 18 years of age.[1] International Diabetes Federation estimated that 1in 11 adults aged 20-79 years has diabetes mellitus globally in 2015 and by 2040, it may rise to 642 million, predominantly from low and middle income societies.[2]

The resulting effects of absolute or related deficiency of insulin include metabolic abnormalities in carbohydrate, protein and lipid. In our body, based upon carbohydrate uptake, tissues can be divided into insulin-dependent and insulin-independent. Decreased carbohydrate in insulin dependent tissue and over-flooding of carbohydrate in insulin independent tissue is the major pathogenesis of organ dysfunction. Since glucose is the major source of energy, lack of it leads to activation of alternative mechanism in that organ/tissue. Hence the severity of symptoms is due to the type and duration of diabetes. Due to lack of glucose inside the insulin dependent tissue, compensatory mechanisms are activated leading to hyperglycemia. Insulin-independent tissue like, vessel wall, brain parenchyma are over-flooded by glucose leading to accumulation of end product of glucose. All these cause the damage to the tissue and remain the pathogenesis of diabetes and its complication.

At various time frames, different values of blood glucose level were implemented for the diagnosis of diabetes mellitus. Recent criteria for the diagnosis of diabetes is:[3]

- Fasting blood glucose ≥126 mg/dL (7.0 mmol/L) or,
- 2-h postprandial blood glucose ≥ 200mg/dL (11.1mmol/L) during OGTT or,
- HbA1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* or
- Presence of classic symptoms of hyperglycemia or hyperglycemic crisis with random blood glucose ≥ 200 mg/dL (11.1 mmol/L).

Diabetes is a major cause of nephropathy, retinopathy, coronary artery disease, cerebrovascular disease, infections, and lower limb amputation. In 2016, an estimated 1.6 million deaths were directly caused by diabetes.[1] Diabetes can be treated and metabolic and microvascular and macrovascular complications can be avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications.

GLYCOSYLATED HEMOGLOBIN

Hyperglycemia leads to attachment of glycosylated end product on various cell surfaces. On one hand it, coats the adhesion molecules present in inflammatory cells, thus promoting immune-compromised state. It also binds with hemoglobin (Hb) of RBCs. In normal healthy adult, RBCs contain approximately HbA - 97%, HbA 2- 2.5% and HbF- 0.5 percent. Among total HbA, approximately 6% are HbA1. Based upon electrophoretic properties, HbA1 are separated into HbA1a1, HbA1a2, HbA1b and HbA1c fractions, among which HbA1c is the predominant fractions and comprises 5% of total HbA. In hemoglobin the major sites of binding of glucose are β-Val-1, β-Lys-66, and α-Lys-61. Glycation of Hb is a physiological process. During the process of glycation of Hb, aldimine is formed and it is a reversible process. Later, aldimine is slowly converted into irreversible ketoamine form.[4] As the blood glucose level increases, level of HbA1c will also increase.

In the patients with Diabetes Mellitus, there were increased levels of HbA1c which was reported by Rahbar et al.[5] in 1969. Bunn et al identified the pathway leading to the formation of HbA1c in 1975.[6] Later in 1976 Koenig et al[7] proposed the use of HbA1c as a biomarker to monitor blood glucose levels among diabetic patients.

The life span of RBC is approximately 120 days. Since formation of glycosylated HbA1c is an irreversible process and RBCs live longer, detection of its level may not only be of diagnostic importance, but also for the assessment of diabetes mellitus during the management. HbA1C can be used as one of the strong predictive tool with regards to diabetic complications. Though, HbA1c has been used to monitor the glucose level, compliance of diets and medications as per physicians' recommendations, it was not included as a diagnostic tool till 2011. World Health Organization, in 2011 along with International expert committee in 2009 and American diabetic association in 2010, included it one of the biomarker in diagnosing diabetes mellitus.[8]

METHODS OF ESTIMATION

In clinical laboratory, HbA1c level is measured by various methods. The basic principal of its estimation is either, method on which Hb fractions are separated or chemical reactions.
Separation method includes ion exchange chromatography, affinity chromatography and capillary electrophoresis. Chemical method includes immunoassay and enzymatic assays. In the later method, HbA1c concentration is measured based on a specific chemical reaction to the glycated N-terminal valine of the β-chain. HbA1c concentration is calculated using HbA1c and total Hb values.[9] In clinical laboratory, boronate affinity chromatography, ion-exchange high-performance liquid chromatography, immunoturbidimetry and enzymatic assay are the commonly used methods.[10-12]

ROLE OF HbA1c AS A DIAGNOSTIC TOOL

In 2011, World Health Organization has included HbA1c in a diagnostic criterion to diagnose diabetes mellitus.[3] A HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.[13] Before that on-going debate was prevalent whether to include the test as a diagnostic tool or not. The main reasons behind were inadequate standardization and its insensitiveness.[14] HbA1c ≥ 6.5% (48 mmol/mol) is considered equivalent to fasting blood glucose level 126mg/dl (7mmol/L).[3] It is quite clear that, increased HbA1c level indicates chronic hyperglycemia. It also has prognostic implication.

Endocrine pancreas functions in two manners. A regular amount of insulin is produced by the endocrine pancreas. Besides that, whenever, hyperglycemia is detected or soon after meal, there is a surge of insulin level. This surge in insulin is necessary to maintain blood glucose level at physiological level. Defect in any of the mechanism leads to diabetes mellitus. Fasting blood glucose (FBG) is time tested test for the diagnosis of diabetes mellitus. However, variation in blood glucose level cannot be recognized by doing FBG. 2-hour post prandial blood glucose test is done to monitor blood glucose level after meal. Tendency to vary blood glucose during the period of the day can be achieved by continual monitoring of the blood glucose level. However, it either requires multiple needle prick or insertion of a chip under the skin, which is not very much cost-effective. Contrary to this, HbA1c is an indicator of blood glucose level in blood for two- to three-months duration.

In a study done by Mostafa SA et al[15], out of total 8696 study population, 3.3% were diagnosed as diabetes mellitus using oral glucose tolerance test (OGTT) and 5.8% using HbA1c test (≥6.5%). In his study, 1.2% had false negative normal HbA1c whereas 3.5% had false negative OGTT test value. Similarly, Khan et al.[16] in his study among 12785 population, found 3.85% false negative prediction using HbA1c (≥6.5%). These finding suggest that HbA1c value between 6 and 6.5% should be considered in a grey zone and hence, combined FBG and HbA1c tests should be performed. Tang et al.[17] conducted a meta-analysis including 11 studies and found that the pooled sensitivity of the diagnostic value with HbA1c ≥ 6.5% were 0.62 (95%CI: 0.60 - 0.64), pooled specificity 0.96 (95%CI: 0.95 - 0.96), diagnostic odds ratio (DOR) 40.25 (95%CI: 20.79 - 77.95) and AUCSROC 0.7702 (sx = 0.0636). According to the analysis, specificity of HbA1c is quite high but sensitivity is low. Hence combination of HbA1c and glucose tests is needed to reduce the missed diagnosis rate.[17]

Benefit of doing HbA1c is that, no fasting blood is required as for FBG and special preparation is not required as for OGTT. A random blood sample is enough to do the test and the value is

Table 1: Common causes which interferes with the HbA1c value[52]

Falsely elevated HbA1c	Falsely decrease HbA1c
Iron deficiency anemia	Hemolytic anemia
Asplenism	Blood loss
Severe hypertriglyceridemia (> 1,750mg/dl)	Splenomegaly
Hyperbilirubinemia (>20 mg/dl)	Recent blood transfusion
Uremia	Vitamin E ingestion
Chronic alcoholism	Ribavirin and α- interferon
Chronic salicylate ingestion	Vitamin C ingestion
Chronic opioid poisoning	
Lead Poisoning	

not affected by recent change in dietary habit or activity. Another superiority of HbA1c is its greater analytic stability and vey less daily variation.[18] Selvin et al.[19] found significantly low variability with HbA1c (CV, 3.6%; 95% CI: 3.2-4.0) levels in comparison to 2-hour PP and FBG which was CV, 16.7%; 95%CI: 15.0-18.3 and CV, 5.7%;95%CI: 5.3-6.1 respectively.

ROLE OF HbA1c IN MANAGEMENT OF DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic syndrome which requires continual evaluation and life style modification, change in dietary habit and pharmacological management. Despite several ways to try and prevent complications of diabetes mellitus, due to wide variation in blood glucose level during day time, compliance of the patient and complications do occur. The optimal way to know the status of blood glucose level for longer duration is HbA1c. The use of HbA1c for monitoring the degree of glucose control in diabetic patients was proposed in 1976. By this time, HbA1c had been shown to decrease as glycemic control improved, and periodical measurement of HbA1c level has become a commonly used tool to monitor the effectiveness of hyperglycemia management.[20] It is recommended to have HbA1c tests done twice a year in a known but controlled diabetes mellitus. In case of uncontrolled diabetes mellitus or if there is change in medication, then HbA1c test is recommended every 3 months.[3] The ADA endorsed HbA1c as a diagnostic test for diabetes at a cut-off of ≥48 mmol/mol (≥6.5%) with the provision that this be measured in a laboratory using a NGSP-certified assay aligned to the DCCT study, and that in the absence of unequivocal hyperglycaemia the test should be repeated.[21] It also recommends to consider HbA1c value of 39–46 mmol/mol (5.7–6.4%) as 'increased risk' category for diabetes as well as cardiovascular disease. These patients should therefore be recommended non-pharmacological means such as weight loss and physical activity, to lower their risks.[21]

HbA1c AS A PROGNOSTIC INDICATOR

Formation of glycated end product in the form of HbA1c gives us a clue of long term status of blood glucose level. It not only indicates the compliance of medication and life style changes as recommended by physician but also predicts about the possible complications. Complications of diabetes mellitus involve multiple organs and tissue not just limited to heart, blood vessels, kidney, retina or central nervous system. These complications not only limit the potential of the individual but also one of the major cause of mortality associated with it. Hence, if forthcoming complications could be predicted, appropriate management to prevent the complications can be initiated. Moreover, direct correlation has been identified between HbA1c and total cholesterol, low-density lipoprotein whereas it has inverse correlation with high-density lipoprotein.[22]

Diabetes mellitus is a risk factor for atherosclerosis. Changes in the atheromatous plaque are the cause of ischemic heart disease and myocardial infarction. Various articles have shown that HbA1c as an independent risk factor for coronary artery disease (CAD).[23-25] Geng et al.[26] in his met analysis found association between high HbA1c level and long-term mortality and myocardial infarction among non-diabetic patients. However, risk for early deaths in non-diabetic patients with CAD was not associated with high level of HbA1c. In his meta-analysis, a total of 18,041 participants were included for the analysis,[27-43] which showed a significantly increased risk of long-term mortality in patients with a high HbA1c level than those with a low HbA1c level (OR 1.76, 95%CI 1.44–2.16, P<.001).

Microalbuminuria and albumin creatinine ratio are the well-established predictor of incipient diabetic nephropathy.[44,45] Chronic hyperglycemia is responsible for the development of diabetic nephropathy. Since HbA1c is well-established test to analyse chronic hyperglycemia, its level may well predict diabetic nephropathy. A meta-analysis done by Cheng et al observed that HbA1c variability, is associated with microalbuminuria in the patient with diabetes mellitus and further nephropathy.[46] In a retrospective study performed by Lin et al in 3,220 type 2 diabetes patients observed annual HbA1c- CV was associated with the incidence of diabetic nephropathy in the duration of 4.4 years.[47] Another study of the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study, which included 8260 type 2 diabetes patients showed correlation between variability in HbA1c and albuminuria and albumin excreting chronic kidney disease.48

Greater HbA1c variability predicts retinopathy, early nephropathy, and coronary artery neuropathy. In a study done by SD-HbA1c was associated with early retinopathy (odds ratio [OR] 1.32; 95% confidence interval, 1.00–1.73), albuminuria (OR 1.81; 1.04–3.14), increased log10 albumin excretion rate (OR 1.10; 1.05–1.15) and coronary artery neuropathy (OR 2.28; 1.23–4.21).[49]

PREDIABETES

If HbA1c value is less than 6.5%, but more than 5.7% (39-47 mmol/mol), then the individual is Prediabetes. Individuals whose blood glucose level do not meet the criteria for diabetes mellitus but are high than normal are considered as Prediabetes.[50,51] Prediabetes are at increased risk for diabetes mellitus. Prediabetes is associated with central obesity, dyslipidemia and hypertension. Hence life style modification, change in dietary habit, treatment of other cardiovascular disease risk factors is recommended. Patients with prediabetes should be tested yearly.[3]

LIMITATIONS Of HbA1c

HbA1c is measurement of glycated hemoglobin due to chronic hyperglycemia. Any defect in the concentration of hemoglobin and factors affecting the non-enzymatic glycosylation alter the HbA1c level. It may either falsely decrease or increase the level of HbA1c. Any condition that prolongs the lifespan of RBCs,

increases the HbA1c level. Various factors falsely may elevate the level of HbA1c which is shown in table 1.[52] Falsely elevated HbA1c is seen in the patients with iron deficiency.[53] The probable underlying mechanism is malondialdehyde, which is increased in iron deficiency anemia. Malanodialdehyde enhances the glycation of hemoglogin,[54] enhances the glycation of hemoglobin.[55]

Similarly increase urea in blood, causes formation of carbamyl-hemoglobin and chronic alcohol consumption leads to formation of acetaldehyde-HbA1 compound formation causing falsely elevated HbA1c.[52]

Hemolytic anemias and splenomegaly are the factors associated with decreased lifespan of RBCs leading to decreased HbA1c level. Ribavirin and α- interferon may also cause hemolysis of RBCs and subsequently decrease in HbA1c level. Vitamin E ingestion inhibits glycation process.

Depending upon methods of estimation of HbA1c, the value may alter. Hemoglobin variant may be the cause of either falsely elevated HbA1c or decreased HbA1c whether it is done by electrophoresis or chromatography. Similarly, in the patient with Vitamin C ingestion, if the test is performed by chromatography method, HbA1c level is falsely decreased due to due to competitive inhibition of glycosylation.[52]

Anemia is quite common in the patient with chronic kidney diseases. The role of renal anemia, erythropoietin intake and routine dialysis complicate the evaluation of HbA1c. Recent reports suggest that glycated albumin is a more appropriate test of glycemic control among that patients.[56-59]

CONCLUSIONS

Since Diabetes Mellitus has multiple complications, early detection and proper management of it may subsequently reduce the economic burden to the society. It also decreases the rate of mortality which occurs due to complications of diabetes mellitus. Since 2011, WHO has included HbA1c as a component of diagnosis criteria for Diabetes mellitus along with FBG and 2-hr postprandial blood glucose level. Since several research articles have pointed false negative rate of HbA1c, exclusion of Diabetes Mellitus should include other tests like FBG, OGTT, 2-hr postprandial blood glucose level, whichever possible. Various complications associated with Diabetes mellitus can be predicted by the routine use of HbA1c value. Hence, HbA1c has both diagnostic and prognostic significance. However, during the evaluation of patient, limitations of HbA1c should be considered depending upon various methods of its estimation.

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