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Review Paper

HbA1c IS A RISK FACTOR FOR CARDIOVASCULAR DISEASE PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Globally, the proportion of impairment in tolerance of glucose is found to be 7.5% (374 million) in 2019 and projected to touch 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045. Estimation of haemoglobin A1C is accomplished as a procedure to monitor long term sugar control in patients with diabetes mellitus (a persistent disorder correlate with defects in carbohydrate, fat, or protein metabolism and characterized by hyperglycaemia). Determination of haemoglobin A1C affords an essential symptomatic means to study the efficiency of dietary control and therapy during treatment of diabetes mellitus. Long term treatment of the disease emphasizes control of blood glucose levels in preventing the acute complications of ketosis and hyperglycaemia. In addition, long term complications such as retinopathy, neuropathy and cardiovascular disease can be minimised, if blood glucose levels are effectively controlled. Elevated levels of % HbA1c suggests the need for more aggressive treatment of glycemic state. The American Diabetic Association ADA recommends that a primary goal of therapy should be a %HbA1c < 7% and that physicians should re-evaluate the treatment regimen in patients with %HbA1c values consistently >8%. However, the role of HbA1c as a predictor of macrovascular complications (e.g., myocardial infarction or stroke) in these patients is not clearly defined. In contrast new evidence suggests that HbA1c can predict the risk of cardiovascular disease in the general population. The potential applications of this test in vascular disease prevention are discussed here in this scientific review.

Key words: Diabetes mellitus, glycated haemoglobin, cardiovascular diseases.

DIABETES: AN ENIGMA OF COMPLICATIONS

Diabetes is of major and increasing public health importance with a major impact on the lives and well-being of individuals, families, and societies worldwide [1]. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The three main types of diabetes are type 1 diabetes (T1D), type 2 diabetes mellitus (T2D), and gestational diabetes mellitus (GDM), with T2D accounting for approximately 90% of the total. India is known as the diabetic capital of the world with more than 30 million people have been diagnosed with diabetes. In India type II diabetes is most common, while type I diabetes is very rare. Moreover, the crude prevalence rate of diabetes in urban and rural areas is 9% and 3% of the total Indian population respectively. Persons with diabetes are at increased risk for premature disability and death associated with vascular, renal, retinal and neuropathic complications and other cardiovascular diseases (CVDs) (**figure 1**). Diabetes also increases the risk of macro vascular diseases, such as coronary heart disease and stroke [2]. Diabetic patients with accompanied dyslipidemia are soft targets for cardiovascular deaths which represent the top killer in this population. In contrast to micro-vascular disease, increased evidence suggests that the relationship between blood glucose level and macro-vascular disease is continuous and does not have an obvious threshold [3].

Glycemia is an important risk factor for cardiovascular disease (CVD), not only in those with diabetes but across the range of blood glucose values [4 5]. Previous studies have suggested that HbA1c has a continuous and graded relationship with CVD, with 1% higher HbA1c levels associated with a 20% and 26% increased risk of CHD and total mortality, respectively [6, 7]. Systematic reviews of randomised controlled trials of tight glycemic control among patients with diabetes provide further evidence of a causal relationship between glucose and CVD [8]. However, there are no trials of glucose lowering therapy in people with non-diabetic hyperglycaemia that have reported a reduction in cardiovascular events [9].

HBA1C AS A DIAGNOSTIC MARKER FOR DIABETES

Raised fasting and post challenge blood glucose levels in an oral glucose tolerance test are used to diagnose diabetes. The diagnostic threshold is based on the shape of the risk curve between glucose levels and specific micro vascular complications of diabetes [10]. Haemoglobin A1c (HbA1c) an indicator of average blood glucose concentrations over the preceding 3 months; is significant for characterizing dysglycemia in population studies simpler to perform than the oral glucose tolerance test [11]. Elevated glucose in circulation enters inside RBCs and binds to hemoglobin A (HbA) forming glycated haemoglobin (HbA1c) **(figure 2**). As average life span of RBCs is 3 months, the average blood glucose level in a patient over the past three months can be estimated by detection of HbA1c percentage. The **Table-1** shows the level of HbA1c in diabetic, prediabetic and nondiabetic people. It has been observed that chances of getting diabetes increase with increase in HbA1c percentage. Moreover, Lowering HbA1c level by diet, exercise and medication can reduce the diabetes associated complications. So emphasis is now given to have HbA1c test every three months [12-14]. Glycated haemoglobin is a predictor of microvascular complications in diabetic individuals [15]. However, it is not yet clear whether the HbA1c is an indicator of the risk of the macro vascular complications associated with diabetes mellitus [16]. In addition, the concentration of this long term index of glycaemia has recently been shown to predict cardiovascular disease (CVD) risk in individuals without diabetes. This is an important finding because the comprehensive assessment of vascular risk will improve the targeting of preventive treatment.

Methods of HBA1C estimation

Glycated haemoglobin is quantified most commonly with methods that distinguish it from non-glycated haemoglobin on the basis of ion exchange chromatography (high pressure liquid chromatography (HPLC), low pressure liquid chromatography (LPLC), immunoassay (turbidometry), agar gel electrophoresis or affinity chromatography. HbA1c does not reflect blood glucose levels equally over the previous 120 days.; rather, recent changes in glycaemic control are over represented in HbA1c. Mathematic formulae have been developed to quantitate their weighing and suggest that the mean glycaemia during the month preceding the HbA1c measurement contributes approximately 50% of the result, during 30-60 prior to HbA1c measurement

contributes to another 25% and during 60-120 days prior to the measurement contributes the final 25%.

Reliable standardisation of the previous estimation of correlation between HbA1c and mean plasma glucose levels based on data of the Diabetes Control and Complication Trial (DCCT) had limitations due to sparse data. Recently results of multicentre AIC Derived Average Glucose (ADAG) trial has shown a relationship between A1C and average glucose (eAG) levels. HbA1c levels can be expressed as eAG for most patients with type 1 and type 2 diabetes.

GLUCOSE METABOLISM AND CARDIOVASCULAR DISEASE

The most convincing evidence that disorders of glucose metabolism are risk factors for CVD was provided by the European DECODE study [17, 18]. Increased mortality was observed in DM and IGT but not in impaired fasting glucose (IFG). A high 2h PG predicted all cause and CVD mortality after adjustment for other major cardiovascular risk factors. While a FPG alone was not predictive, once 2 hPG was taken into account. The highest excess CVD mortality in the population was observed in people with IGT especially those with normal FPG [18]. Several studies show that increasing HbA1C is associated with increasing CVD risk [19, 20]. Studies that compared all three glycaemic parameters (FPG, 2hPG and HbA1C) for mortality and CVD risk revealed that the association is strongest for 2hPG and that the risk observed with FPG and HbA1C is not significant after controlling for the effect of 2hPG [21, 22]. A review of the impact of gender on the occurrence of coronary artery disease (CAD) mortality reported that the overall relative risk (the ratio of risk in women to risk in men) was 1.46 (95%confidence interval) in people with DM and 2.29 (95% C12.05 to 2.55). In those without suggesting that the well-known gender differential in CAD is reduced in DM {20}. A meta-analysis of 37 prospective cohort studies (N ¼ 447 064 DM patients). Estimated gender related risk of fatal CAD and reported higher mortality in patients with DM than those without (5.4 Vs 1.6% respectively). The relative risk in DM was significantly greater among women (3.50) than in men (2.06). A recent study revealed a greater adverse influence of DM on adiposity. Homeostatic model of assessment/insulin resistance (HOMA/IR) and downstream blood pressure, lipids, endothelial dysfunction and systemic inflammation in women than in men, which may contribute to their greater relative risk of CAD [23].

Also, it seems that women put on more weight before developing diabetes and consequently undergo bigger changes in risk factor status. Diabetic patients with accompanied dyslipidaemia are soft targets for cardiovascular deaths which represent the top killer in this population [24].

Patients with Type-2 diabetes often exhibit a heterogenic lipid profile, which greatly increases their CVD risk compared with people without diabetes. Individuals with co-existing diabetes and metabolic syndrome (dyslipidaemia + hyperglycaemia+ hypertension) have the higher prevalence of CVD. Early therapeutic interventions, aiming to reduce triglycerides and LDL and to increase HDL, significantly reduce mortality in type 2 diabetic patients [25, 26]. A significant association between dyslipidaemia and systolic BP has been observed in type 2 diabetic patients, suggesting their increased susceptibility to vascular diseases associated with LDL. It is likely that the combination of hyperglycaemia, diabetic dyslipidaemia, insulin resistance, and hypertension atrial wall and dermal tissue has been implicated in atherosclerosis and xanthomata respectively. Severe hyperlipidaemia in diabetes may also lead to lipid infiltration into the retina causing macular edema, retinal hard exudates, and blindness [27]. The diabetes complications and control Trial (DCCT) established glycosylated haemoglobin (HbA1C) as the gold standard of glycaemic control, with levels ≤ 7% deemed appropriate for reducing the risk of vascular complications [27]. HbA1C is directly related to the severity of CAD in diabetic patients [28]. Whereas, improving the glycaemic control can substantially reduce the risk of CVD events in diabetics [29]. Moreover, attempts to reduce cardiovascular risks resulted in the improvement of HbA1C even in the absence of any specific intervention targeted at improving glycaemic control [30]. A soluble form of receptor for advanced glycation end products (sRAGE) in type 2 diabetic patients with CAD was found to be elevated with significant association between sRAGE and HbA1C as well as serum lipids [31]. **Figure-3_**describes various factors which increase the risk of CVD in patients suffering from diabetes (heart.org.in). CVD can be avoided or at least delayed by managing these risk factors.

HBA1C CVD AND DIABETIC INDIVIDUALS

CVD is the main cause of mortality among Type 2 diabetic patients (32, 33). Although HbA1c is a well-established risk factor for micro vascular complications in diabetes

mellitus, there is no clear evidence regarding the predictive role for diabetic macro vascular complications. The diabetic Control and Complications Trial-I (DCCt) and the United Kingdom Prospective Diabetes Study 2 (UKPDS) evaluated the role of glycaemic control in type 1 and 2 diabetes, respectively. These trials showed a non-significant reduction of CVD risk with more intensive glycaemic control (lower HbA1C). In the DCCT the CVD risk reduction was 40% (P= 0.08). This reduction was not significant probably because the patients were young and accordingly there were few cardiovascular events. In contrast in the UKPDS 2 there were more CVD events but the variation in HbA1C values was smaller than in the DCCT (the intensive treatment group in the UKPDS had a HbA1C < 7% while the control group had a HbA1C between 7% to 9 %). The risk reduction (16%) in the UKPDS 2 failed to reach significance (p = 0.052) for myocardial infarction. However, a recent meta-analysis 12 showed that when the whole range of the HbA1C concentrations in the UKPDS was considered, there was a highly significant relation between HbA1C and CVD risk. In conclusion, the evidence suggests but does not confirm a role for HbA1c as a predictor of CVD in the diabetic population. As far as macro vascular complications are concerned, diabetic patients are more likely to benefit from tight blood pressure control and the modification of the other major risk factors (e.g., dyslipidaemia and smoking) than from improved glycaemic control. [10, 34]. **Figure-4** describes various strategies to manage diabetes and its associated complications including CVD.

FUTURE PROSPECT OF HBA1C IN CARDIOVASCULAR DISEASE MONITORING

There is still a need to confirm that HbA1C measurements can predict the risk of microvascular events in both diabetic and non-diabetic individuals. The need to use HbA1C measurements to assess cardiovascular risk in non-diabetic individuals may lead to the development of ultrasensitive assays. This is because small changes in this variable (possibly below an HbA1C value of 5%) may be relevant (see comments above regarding the EPIC – Norfolk study [6]. It will also be necessary to assess if HbA1C is stronger and more cost effective predictor of cardiovascular risk than making a diagnosis of IGT or IFG using simple glucose measurements. A fasting glucose is currently recommended as part of the assessment of cardiovascular risk. However, for screening purposes, the need for fasting may be a disadvantage for glucose measurement but not when using HbA1c assays.

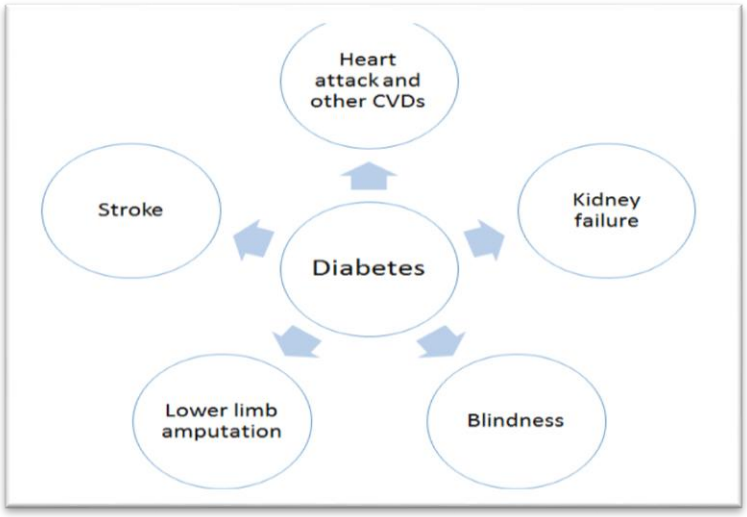

Figure 1: Major complications associated with diabetes.

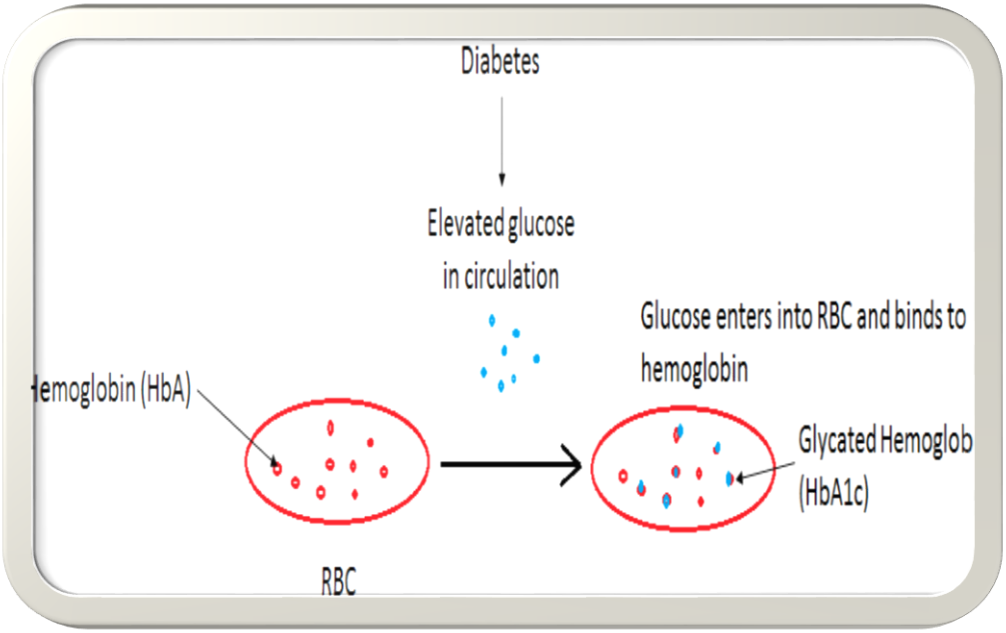

Figure 2: Mechanism of formation of HbA1c in Diabetes

Table 1: Percentage of HbA1c in blood and its interpretation

% HbA1c	Interpretation
6.5% or higher	Diabetes
5.7% to 6.4%	Prediabetes
4.0% to 5.6%	Normal

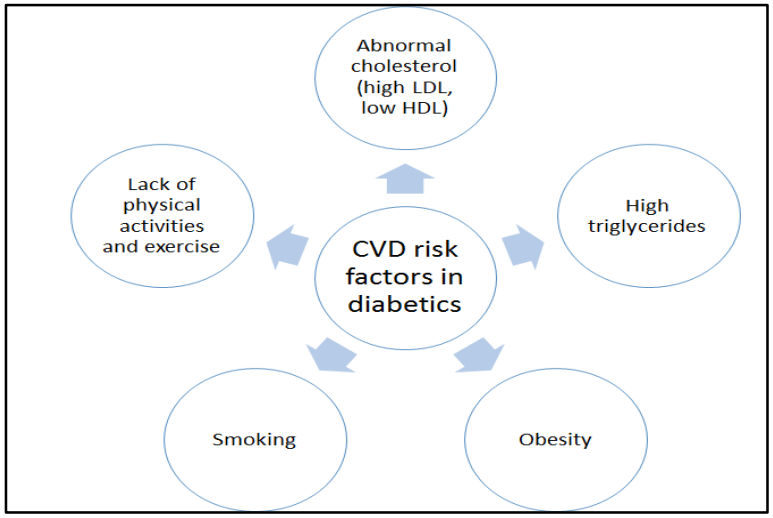

Figure 3: Factors increasing risk of cardiovascular disease in Diabetic patients (The American Heart Association).

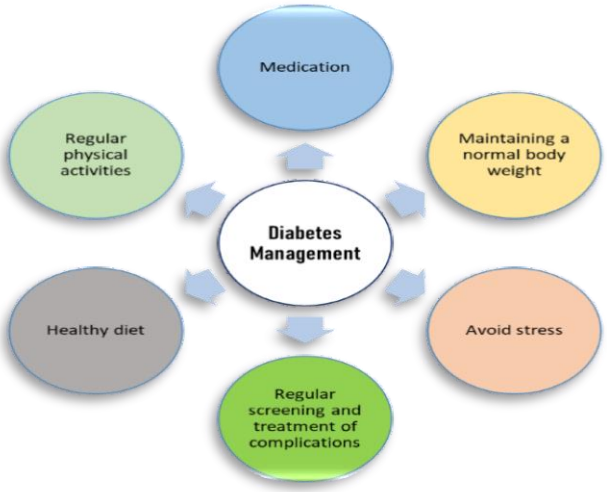

Figure 4: strategies to manage diabetes and its associated complications including CVD

CONCLUSION

One in two (50.1%) people living with diabetes do not know that they have diabetes, and HbA1c is used only for monitoring and not for diagnosis and screening of diabetes. Current evidence suggests that HbA1C could be used together with other variables to assess cardiovascular risk in diabetic and non-diabetic individuals. Reducing blood HbA1C levels, in conjunction with other interventions, should prove beneficial in decreasing the risk of vascular events in all populations. Further, there is an urgent need for developing multi-sectoral strategies to educated patients about the association between coronary artery disease and diabetes and the importance of glycaemic control.

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