

## Review Article

# Glycated Haemoglobin — a marker and predictor of cardiovascular disease

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### Abstract

Glycated haemoglobin is formed by simple chemical reaction between haemoglobin and blood glucose. It represents a reliable and moving average of blood glucose over preceding three months. In 2009 the International Expert Committee recommended the use of HbA1c to diagnose diabetes with a cut-off of 6.5%. Studies have shown that HbA1c even in the range of 5.5% to 6.5% poses considerably high risk of morbidity and mortality due to cardiovascular disease. HbA1c as a test is important because about 220 million people have diabetes and with increasing life expectancy and emergence of type 2 diabetes in children makes it even more important. Each 1% increase in HbA1c poses 15-18% relative risk of cardiovascular disease in T1DM and T2DM respectively. CVD is a major cause of death and disability among diabetes patients and glycated haemoglobin itself is proportionately linked with excess CV morbidity and mortality. UKPDS-35 demonstrated 14% reduction in the incidence of acute myocardial infarction with only 1% reduction in HbA1c in T2DM patients. The DCCT reported

significant reduction in retinopathy and nephropathy in T1DM, the follow up trial EDIC demonstrated 42% reduction in CVD with intensive reduction of HbA1c. This review is written to remind ourselves of the importance of this simple test which can predict early CV mortality in patients without prior CVD and poor prognosis in established cardiovascular disease. In a country like ours, Pakistan; where diabetes is prevalent with poor health awareness and limited resources, a test like HbA1c which costs Rs, 500.00 twice a year should be considered a cost effective way to avoid the long term diabetes complications, which once start unfolding put enormous burden on already stretched healthcare resources which could easily be avoided by intensive control of diabetes.

**Keywords:** Glycated haemoglobin, Type 2 diabetes mellitus, Cardiovascular disease.

### Introduction

Glycated haemoglobin has been the key measure of glycaemic control in diabetic patients for last two decades. It is considered to be the gold standard test, and most widely

accepted test of glycaemia among clinicians and patients. The glycated Hb concentration levels are also more closely related to the risk of chronic complications than random single or episodic glucose levels.

In 2009, The International Expert Committee recommended the use of HbA1c to diagnose diabetes mellitus with a threshold  $\geq 6.5\%$ .<sup>1</sup> The American Diabetes Association (ADA) adopted this recommendation in its position statement entitled, "Standard of medical care in diabetes-2010".<sup>2</sup> However, the diagnosis should be confirmed by a repeat test unless symptoms of hyperglycaemia and blood glucose level of  $>11.1$  mmol/l ( $>200$ mg/dl) are available. The diagnostic test should be standardized to Diabetes Control and Complication Trial (DCCT) reference assay or the National Glycohaemoglobin Standardisation Programme (NGSP) certified method.<sup>1</sup> In addition, those with an HbA1c level between 6 and 6.5% have been identified as being at very high risk of developing diabetes. Prospective studies indicate that a high normal HbA1c level of 5.5% to 6.5% poses very high risk for subsequent development of diabetes, and the risk increases substantially as the values increase.<sup>3,4</sup>

The ADA's recommended goal for HbA1c is  $< 7\%$  in all patients with diabetes mellitus.<sup>2</sup> The same level is recommended for primary prevention of cardiovascular disease in people with diabetes.<sup>5</sup> The ideal HbA1c goal for individual diabetic patients is as low as  $<6\%$  without causing significant hypoglycaemia. The recommendations are the same for T1DM and T2DM. The ADA recommends checking HbA1c levels at least twice a year in patients with relatively stable glycaemic control and quarterly among those whose HbA1c targets are not achieved, particularly if drugs are changed, to determine the effect of such changes.<sup>2</sup>

### Probable Reasons of Mis-Leading HbA1c Results:

Glycated haemoglobin is formed by non-enzymatic glycation of N-terminus of beta chain of haemoglobin. Different Lab techniques and many clinical conditions may result in under-estimation or over-estimation of HbA1c. Clinicians should interpret very low ( $<4\%$ ) or very high (15%) results with caution and concurrent diseases should be kept in mind. Falsely low HbA1c is seen mainly in conditions with high red cell turn over, such as haemoglobinopathies including variant haemoglobins, sickle cell disease, glucose-6-phosphate dehydrogenase deficiency, treatment of anaemia with iron or erythropoietin, and auto immune haemolytic anaemia. Recent blood loss and blood transfusion result in greater proportion of reticulocytes or transfused red cells in blood stream thereby reducing the average age of red cells. Patients of chronic kidney disease on dialysis and chronic liver failure may also have less than expected level of HbA1c. All these conditions

**Table-1: Take Home Message.**

Sr.No.	Take Home Message
1	T2DM accounts for 90% - 95% of all diabetes mellitus cases
2	T2DM is associated with strong genetic predisposition
3	T1DM accounts for 5% - 10% of all diabetes mellitus cases.
4	HbA1c level 4% - $< 6\%$ is considered as normal
5	High normal HbA1c (5.5% - 6%) is associated with increased risk of CVD regardless of diabetes status.

**Table-2: Comparison of HbA1c in percentage (NGSP) and new mmol/mol (IFCC) units.**

	NGSP HbA1c (%)	IFCC HbA1c (mmol/mol)
Normal	$\leq 5.5\%$	$\leq 36.5\%$
High Normal	5.6% - 6%	37.6% - 42
Elevated	6.1% - 6.4%	42.6% - 45%
Diagnostic of Diabetes	$\geq 6.5\%$	$\geq 47.5\%$

**Table-3: Target of HbA1c set by different diabetic societies.**

	T2DM	T1DM
NICE	$<6.5\%$	$<7.5\%$
IDF	$<6.5\%$	$<6.5\%$
AACE	$<6.5\%$	$<6.5\%$
ADA	$<7.0\%$	$<7.0\%$

**Table-4: Abbreviations used.**

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
ADA	American Diabetes Association
DCCT	Diabetes Control and Complication Trial
UKPDS	United Kingdom Prospective Diabetes Study
NGSP	National Glycohaemoglobin Standardisation Programme
EASD	European Association for study of Diabetes
IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry
AACE	American Association of Clinical Endocrinology
NICE	National Institute of Clinical Excellence
CHD	Coronary heart disease
CVD	Cardiovascular disease.

result in shortened average age of erythrocytes, resulting in decreased exposure time of haemoglobin to glucose and therefore less percentage of HbA1c. Falsely low levels of HbA1c are also observed because glycated Hb variant is separated from HbA1c so it is excluded from calculations.

Anaemia of iron, folic acid, and vitamin B12 deficiency could result in falsely high levels of HbA1c. Haemoglobin variants, eg, Hb Raleigh, Hb Graz and persistence of foetal haemoglobin or rise of HbF during pregnancy may also yield falsely high HbA1c levels. The possible explanation is that HbF is separated from HbA therefore proportion of HbA1c increases. Urea reacts with haemoglobin molecules at the same site as does glucose,

therefore HbA1c and Car Hb have same isoelectric point and assayed together and results in falsely high percentage of HbA1c in uraemic patients.

### **Definition and Prevalence of Diabetes Mellitus:**

Diabetes mellitus as a disease is defined by abnormally high blood glucose and altered fat and protein metabolism. Diabetes is a chronic condition of diverse etiology and pathogenesis; affecting approximately 220 million people world wide. It carries significant morbidity and mortality stemming from long term complications. Organ systems may vary in their susceptibility to damage related to glucometabolic abnormalities, posing different pathophysiological challenges, ranging from trace proteinuria to full nephrotic range proteinuria and end-stage renal failure, from microaneurysms to severe visual impairment and eventual blindness. Complications also include peripheral neuropathy with development of foot ulcers, Charcot joints and eventual amputations and autonomic neuropathy causing gastrointestinal, genitourinary and sexual dysfunction. Furthermore, diabetes increases the risk of accelerated atherosclerosis, which eventually leads to premature cardiovascular disease.

CVD is a global healthcare problem. It is a major cause of death and disability worldwide, especially among diabetics. CVD manifest in three main areas of vascular bed as: Coronary Artery Disease, Cerebrovascular Disease and Peripheral Vascular Disease.

### **Pathophysiological mechanisms of diabetes induced cardiovascular disease:**

Hyperglycaemia is the main metabolic abnormality of diabetes. Hyperglycaemia with other metabolic abnormalities of diabetes e.g. Insulin resistance and dyslipidaemia (characterized by elevated triglycerides and low HDL) plays a role in inhibition of nitric acid (NO) production and excess production of reactive oxygen species in endothelium and vascular smooth muscles.<sup>6</sup> This phenomenon is called oxidative stress when cellular production of reactive oxygen species (ROS) exceeds the ability to neutralise them by antioxidant mechanisms. This may be regarded as first step in production of atherosclerosis. ROS reduces nitric oxide level, causing endothelial dysfunction, it also increases expression of various intracellular adhesion molecules (ICAM-I & VCAM-I). Hyperglycaemia itself activates protein kinase C (PKC) which causes increased expression of platelet derived growth factor- $\beta$  receptor and of transforming growth factor- $\beta$  (TGF- $\beta$ ).<sup>7</sup> PKC also induces up regulation of cyclooxygenase-2 expression, increase production of thromboxane and reduction in NO release.<sup>8</sup> Hyperglycaemia induces non-enzymatic glycation resulting in formation of advanced glycation end products (AGEs) at a faster unchecked pace.

AGEs directly block NO activity and produce ROS in vascular endothelium.<sup>9</sup> Receptors for AGEs are stimulated due to which nuclear factor-kB increases and activator protein I is also stimulated and induce inflammatory gene expression. As a result increased production of inflammatory cytokines and intracellular adhesion molecules occurs. A milieu is created where there is low levels of NO and prostacyclin encounter high levels of inflammatory mediators, vasoconstrictor substances (endothelin I & angiotensinII), and prothrombotic mediators (tissue factor & plasminogen activator inhibitor -I). All these covert activities occurring in endothelium and vascular smooth muscle cells result in vasoconstriction, inflammation, and thrombogenesis; together resulting in atherosclerosis.

### **HbA1c and CHD in Patients with Diabetes:**

Much published data support the conclusion that diabetes puts people at very high risk of coronary heart disease.<sup>10</sup> Diabetic patients without prior myocardial infarction have high risk of having myocardial infarction at rates comparable to non-diabetic patients with previous myocardial infarction.<sup>11</sup> Diabetes patients face an 11% increased risk of mortality from ischaemic heart disease (UKPDS 23).<sup>12</sup> While those with HbA1c > 8% face a 150% increased risk of death from heart disease.<sup>13</sup>

This association is so well established that the Adult Treatment Panel III (NCEP) recommended treating diabetics with hyperlipidaemia as if they already have prior coronary artery disease.<sup>14</sup> Cardiovascular complications are usually present at the diagnosis of T2DM, because diabetes is preceded by long period of asymptomatic hyperglycaemia, called impaired glucose tolerance. Classical CV risk factors such as smoking, hypertension, and hypercholesterolemia do not account for the excess risk of CV morbidity and mortality in patients with elevated HbA1c levels.<sup>15</sup> This association is equally important in both T1DM and T2DM, and exists across ethnic and geographical boundaries. In another very large multiethnic population study (n= 47,904), HbA1c levels were shown to be strongly associated with increased all-cause mortality.<sup>16</sup>

### **HbA1c and CHD in Non-diabetic Population:**

As previously noted, HbA1c levels below the threshold for a diagnosis of diabetes (< 6.5%) are associated with a very high risk of CHD: such patients should receive demonstrably effective preventive treatment.<sup>2</sup> In a study by E. Selvin et al, after 15 years followup of more than 11000 participants, suggested that HbA1c values in normal range without diabetes can identify people at higher risk of CAD, stroke and death.<sup>17</sup>

In the non-diabetic population (in women), HbA1c is a better predictor of CVD and CHD related mortality than

fasting or post prandial glucose levels.<sup>18</sup> Elevated glycated haemoglobin is associated with increased cardiovascular mortality in non-diabetic chronic kidney disease.<sup>19</sup> Every 1% increase in HbA1c is associated with a 20 to 30% increase in cardiovascular events, and all cause mortality in men and women independent of diabetic status.<sup>20</sup> Elevated HbA1c levels have also been associated with increased short-term mortality in post myocardial infarction, non-diabetic patients.<sup>21</sup>

HbA1c showed a continuous relationship with increased CV mortality and extended to non-diabetic subjects.<sup>20</sup> This risk factor indicates excess mortality across the entire population distribution, even at moderately elevated levels.<sup>22</sup> In another epidemiological study of Asian Indian population, a strong association was found between HbA1c and other risk factors of metabolic syndrome including high fasting insulin and insulin resistance, independent of age and sex. The findings of the study become increasingly significant when the study population includes people with normal glucose tolerance.<sup>23</sup>

Although much published data proved the relationship of elevated HbA1c and incidence of coronary artery disease, intervention studies were needed to demonstrate that lowering HbA1c would reduce the risk of cardiovascular morbidity and mortality. Two landmark trials namely, the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM and the Diabetes Control and Complication Trial (DCCT) in T1DM fulfilled the need. UKPDS-33 demonstrated that lowering HbA1c would result in a 10% lower incidence of diabetes related deaths (death from myocardial infarction, stroke, peripheral arterial disease, and sudden death).<sup>24</sup> UKPDS-35 demonstrated a 21% reduction in the risk of diabetes related deaths and 14% reduction in the incidence of myocardial infarction with only a 1% reduction in HbA1c in T2DM.<sup>25</sup> Similarly, in T1DM, DCCT demonstrated intensive treatment delays the onset and progression of retinopathy, nephropathy and neuropathy and also the macro-vascular disease.<sup>26</sup> The DCCT patient population was relatively younger and, therefore, did not have a high incidence of cardiovascular events, which was probably the reason for very trivial reduction in the risk of CVD. However, when the same population sample was followed up for another 12 years in Epidemiology of Diabetes Intervention and Complication trial (EDIC), HbA1c reduction resulted in a 42% reduction in risk of CVD and 57% reduction in nonfatal heart attack, stroke, or death from cardiovascular causes.<sup>27</sup>

### **Glycated Hb and Heart Failure:**

Elevated levels of glycated Hb not only increases incidence of CHD but also extends into subsequent complications of CHD (e.g., congestive heart failure); each

1% rise in HbA1c results in more coronary events and more hospitalizations due to worsening heart failure.<sup>28</sup>

Elevated HbA1c (6.5% to 7%) is associated with poorer prognosis in patients with minimal left ventricular dysfunction (LVEF < 45%).<sup>29</sup> This increased risk of developing heart failure could be explained by two mechanisms: the development of endothelial dysfunction, atherosclerosis, and CHD, and direct toxic damage to the myocardium due to chronic hyperglycaemia.<sup>30</sup> Among diabetics, HbA1c is an independent predictor of heart failure even without pre-existing CHD, although the relative incidence rate of heart failure in people with pre-existing CHD is much higher (15.5 for CHD-negative vs. 56.4 for CHD-positive cases per 1000 person-years).<sup>31</sup> When incidence of heart failure was compared between diabetic and non-diabetic populations, the incidence was 2.5 times higher among diabetic patients with elevated HbA1c.<sup>32</sup> The difference in incidence heart failure was much higher among the younger age group, emphasizing the need for a good glycaemic control just after diagnosis.

### **Glycated Hb and Cerebrovascular Disease:**

Patients of diabetes develop increasing intimal media thickness quicker than non-diabetics. Hard carotid artery plaques develop with increasing level of HbA1c, and risk increases continuously across increasing HbA1c levels.<sup>33</sup> Diabetes particularly puts younger people (<55 years) at risk of stroke and is a cause of poor prognosis post stroke. Raised HbA1c is an independent risk of stroke in people with or without diabetes, unlike CHD this relationship is not linear but it seems more like a threshold dependent association, risk of stroke abruptly increases at HbA1c  $\geq$  7% regardless of diagnosis of diabetes. Although the people with HbA1c 6.5% - 7% are more likely to be undiagnosed diabetics, show significantly increased risk of stroke after adjustment for classic risk factors like hypertension and smoking.<sup>34</sup>

A large meta-analysis of 33040 patients; however showed only non significant reduction in the event of stroke (7%) comparing to quite significant reduction in non-fatal MIs (17%) by only 0.9% reduction in HbA1c concentration after 5 years of treatment.<sup>34</sup>

### **Glycated Hb and Peripheral Vascular Disease:**

Diabetes increases risk of PVD by more than two folds, and is cause of 70% non-traumatic amputations. It is a manifestation of CVD which is not acutely fatal but is associated with serious risk of CHD and stroke. HbA1c is positively associated with low ankle-brachial index and symptomatic PVD,<sup>36</sup> although it is not only due to macrovascular disease but a great element of microvascular disease is also present in processes like neuropathy, foot ulceration, and amputations.

## Conclusion

Glycated haemoglobin has been used to monitor glycaemic control in diabetics for more than two decades. It helps clinicians and their patients to stratify the treatment strategy and avoid long-term complications. Elevated HbA1c increases the risk of micro-vascular and macro-vascular complications in diabetics as well as non-diabetics. This review reminds us of the importance of this valuable test, which can conveniently be carried out in any clinical setting regardless of prandial state, where values > 6.5% are diagnostic of existing diabetes. Such outcomes emphasize the need to lower the HbA1c in our patients to avoid long-term complications and reduce the burden of economic costs as well as provide a better quality of life for patients. The simultaneous use of the IFCC units (mmol/mol) and HbA1c (%) as well as conversion of HbA1c results into estimated average glucose (eAG) would be a significant change and require an enormous amount of work and education to develop a better understanding of glycated haemoglobin and ensure better patient care in the future.

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