Review Article

Glycated Haemoglobin : It's Diagnostic and Prognostic Efficacy in Various Clinical Scenarios

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Glycated Haemoglobin (HbA1c) gives a measure of long term Glycemic control. However, how the values of HbA1c affects the outcome in various comorbidities and its effect on the short term and long term outcome of these comorbidities remains a matter of Grey Zone. Cardiovascular Diseases, Chronic Kidney Disease, Anemia, Chronic Liver Disease etc, can alter the interpretation of HbA1C level, where it may not reflect the appropriate Glycemic control. Hence this review is done to look for the evidence and appropriateness of HbA1c as Diagnostic and Prognostic marker for Glycemic control in various clinical scenario.

Glycated Haemoglobin (HbA1c) is a form of haemoglobin which gives a measure of long term Glycemic control. It has been seen that it is produced in a Non-enzymatic Glycationpathway in an interaction between haemoglobin and Plasma Glucose. Biochemically, HbA1c reflects the beta-N1-deoxy fructosyl component of haemoglobin[1]. In 1976, a study has shown that it can be used as a mean for monitoring the Glycemic control among Diabetic patients[2]. Currently Diabetes Mellitus is diagnosed if a patient has one of the following[3].

- Fasting Blood Glucose level $\geq$126 mg/dl*
- Postprandial Blood Sugar $\geq$200 mg/dl*
- HbA1c $\geq$6.5%*
- Random Blood sugar value $\geq$200 mg/dl with classic symptoms of Hyperglycemia or Hyperglycemic crisis

[*"In the absence of unequivocal Hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples".]

As compared to the test of Random Blood Glucose level, Hba1c can give a better assessment of the long term diabetic control. Many trials including the famous prospective studies eg. Diabetes Control and Complications Trial (DCCT), the UK Prospective Diabetes Study Group (UKPDS) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, have given definite evidence that diabetic

> **Editor's Comment :**
> - HbA1c gives the measurement of long term Diabetic Control as well as diagnosis of Diabetes. However, in special clinical scenarios such as Chronic Kidney Disease, Chronic Liver Disease, Anemia, we must be cautious while interpretatiing the result of Hba1c. Other molecules such as fructosamine and Glycated Albumin can give a better prediction of Glycemic Control in such condition. Hence before ordering and interpreting HbA1c report one must be aware of the patients comorbid conditions.

complications are directly related to mean glycemic control, as measured by the HbA1c value[4-6]. However, how the values of HbA1c affects the outcome in various comorbidities and its effect on the short term and long term outcome of these comorbidities was a matter of Gray Zone. Hence, these reviews are aiming to find the association between the levels of Hba1c with various comorbidities.

Methods of HbA1c Measurement :

Hba1c measurement depends on mainly the two methods[7] —

(a) Separation methods — HbA1c and Non-glycated Haemoglobin have different chemical properties which allows for the chemical separation of the two and quantification of HbA1c. The methods based on this principle are : Ion Exchange Chromatography (IEC), Capillary Electrophoresis (CE) and Affinity Chromatography (AC).

(b) Chemical methods — Here, HbA1c concentration is measured by specific chemical reaction to the Glycated N-terminal valine of the β-chain. Total Haemoglobin concentration is measured with Photometry. Two independent tests, HbA1c and total Haemoglobin tests are required in this method of calculating the HbA1c value. Immunochemical and

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Enzymatic Assays are based on this technique.

Standardization- Interpretation of HbA1c value needs appropriate standardization. The normal reference range and clinical decision limits for International Federation of Clinical Chemistry (IFCC) and National Glycohemoglobin Standardization Program (NGSP)-standardized HbA1c values are shown below. The normal reference range is derived from the landmark Diabetes Control and Complications Trial (DCCT) Study[4].

	IFCC (mmol/mol)	NGSP (%)
Normal	20-24	4-6
Diabetes	>40	>6.5
Target for Treatment**	<53	<7
Hgh Risk	40-46	5.8-6.4

(IFCC-International Federation of Clinical Chemistry, NGSP-National Glycoprotein Standardization Program) [**American Diabetes Association.6.Glycemic targets. standards of medical care in diabetes—2018. Diabetes care. 2018, Jan 1; 41(Supplement 1): S55-64.]

The major advantage of measuring HbA1c over any Random Blood Sugar value is the lack of influence of Fluctuating Plasma Glucose after meals and with illness. However, there are many conditions where interpretation of the HbA1c value needs caution. Especially in those conditions where the erythrocyte lifespan gets shorter (eg, renal anemia with use of Erythropoietin, Chronic and Hemolytic Anemia, Acute Blood Loss and Recent Transfusion), results will show a false, low level of HbA1c. Similarly, Liver disease, Dialysis and Chronic Malaria may also cause a false, Low-level HbA1c. Iron deficiency anemia may cause a false, high-level HbA1c, cause of which is presumed to be altered glycation rates[8-9]. These conditions should be kept in mind while interpretation of result of HbA1c concentration while assessing the Diabetic control .

HbA1c In Various Comorbidities :

Cardiovascular Morbidity —

Diabetes Mellitus is an independent risk factor for Cardiovascular events and Hba1c value acts as a strong predictive marker[10]. A Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P)based systemic review and Meta-analysis, which was registered with PROSPERO, the MOOSE (Meta-analysis of observational studies in epidemiology: a proposal for reporting), PRISMA and Cochrane Collaboration Handbook, have provided a clear and structured procedure for analyzing the

relevant information and providing summarized information on the importance of HbA1c levels for controlling the risk of CVD outcomes and mortality[11-14]. They have shown that high Hba1c is associated with an increased risk of all form of Cardiovascular events. There was a famous study, named "Syntax trial" where the HbA1c of Non-diabetic patients were assessed in terms of Cardiovascular events and it has shown a positive correlation using SynTAx (Synergy between PCI with Taxus and Cardiac Surgery) score. To characterize and objectively quantify the severity and extent of CAD,Syntax Score (SS) was developed as part of theSyntax trial[15] (Fig 1).
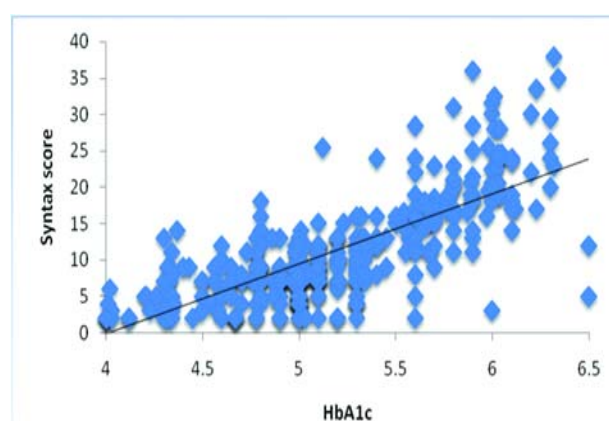

Fig 1 — Linear regression analysis between HbA1c and SYNTAX score in non diabetic patients[15]

Cerebrovascular Disease —

Diabetes Mellitus is an important risk factor for atherosclerotic changes in the Cerebral Vasculature with literature showing 20% of Stroke cases associated with Diabetes Mellitus[16]. A recently concluded cohort study comprising of more than 40,000 diabetic patients has shown that there is an increased risk of stroke among young Diabetic females as evidenced by Hazard ratio of 2.32 among females and 2.08 among male. The increase in risk was found to be highest among young women with Hazard ratio of 8.18 and it decreased with age[17]. The pattern of stroke is different in Diabetics than Non-diabetics. Measurement of HbA1c in every Ischemic Stroke patient is very important even if the patient is not a known case of Diabetes Mellitus, because the Pre-stroke Glycemic Control is an independent predictor of Stroke severity along with poor long term outcome[18]. Kamouchi et al in their study on 3627 patients, have shown that neurological improvement is less associated with age or sex as compared to the HbA1c value on admission[19]. Another study has showed that the

NIHSS value is directly proportional to the HbA1c value, means a better prognosis (ie, lower NIHSS) with lower HbA1c and vice versa[20]. The correlation of NIHSS scoring and hba1c level from their study is shown below (Fig 2).

Hence, routine monitoring of HbA1c level may be used as a measure of Secondary Prevention of Stroke in Diabetic patients.

Chronic Renal Failure —

Patients with Chronic Kidney Disease (CKD) are usually anaemic due to a variety of reasons, including Anaemia of Chronic Disease, iron deficiency due to maintenance Haemodialysis and Erythropoietin insuûciency[21].There are several studies that have documented a fall of HbA1C in patients treated with Erythropoietin Stimulating Agent (ESA) and iron therapy. The hypothesis behind this fall in HbA1c value following either treatment has been postulated to be secondary to the formation of new Erythrocytes in the blood stream, causing a change of proportion of young to old cells and also from an alteration in the Red-cell gyration rates and which is independent of glycemic changes in patients, Hence continuous glucose monitoring can be a better option for those patient[22]. Similarly another study has shown the similar result with a preference for Glycated Albuminas a better indicator than HbA1c in patients with Diabetes who are on Dialysis and Erythropoetin Therapy. Since CKD is a known complication of Diabetes, so interpretation of Hba1c should be done in caution[23] (Fig 3).

In Chronic Liver Disease —

The prevalence of Diabetes is higher in patients with Chronic Liver Disease than in those without the disease, especially after discovery of Non Alcoholic Steato Hepatits (NASH) as a cause of it[24]. Cirrhosis is associated with Porto-systemic Shunts and Shrunken Hepatic Mass, both of which can impair Insulin clearance by the Liver, Leading to peripheral
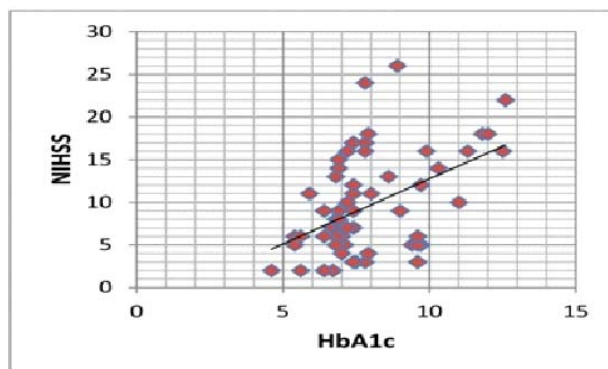
Fig 2 — Correlation between levels of serum HbA1c and NIHSS[20]

Insulin resistance by Insulin receptor down regulation[25]. Moreover, Cirrhosis is also associated with increased levels of advanced glycation end products[26]. There was a study that has found that the sensitivity of HbA1c for diagnosing Diabetes in hospitalized patient (sensitivity 58.3%) is much lower as compared to the Outpatients (sensitivity 87.0%)and they have given recommendation that OGTT as better diagnostic tool[27]. In fact, now a days, a term called 'hepatogenous diabetes is coming into the literature[28]. Studies have shown that there is a higher value of PPPG:FPG (Postprandial Plasma Glucose to Fasting Plasma Glucose ratio), Fasting plasma Insulin and Insulin Resistance (IR) in cirrhotic patients with Hepatogenous diabetes as compared to those with T2DM[29].

In ICU and Critical Care —

There are studies that have shown that HbA1c is a useful tool predicting the mortality among critically ill patients. There was a study that showed, Non-survivors had significantly higher HbA1c values compared to survivors irrespective of prior history of Diabetes[30]. The study also revealed that with each increase in HbA1c level, the risk of death also doubled, however, the relationship was not statistically significant. There was a recent study that compared predictive value of HbA1c for hospital mortality and length of stay among diabetic patients with Sepsis. They have found that HbA1c and APACHE II score are independently related to length of hospital stay. HbA1c was found as an independent predictive factor for hospital mortality and longer stay in hospital among the study
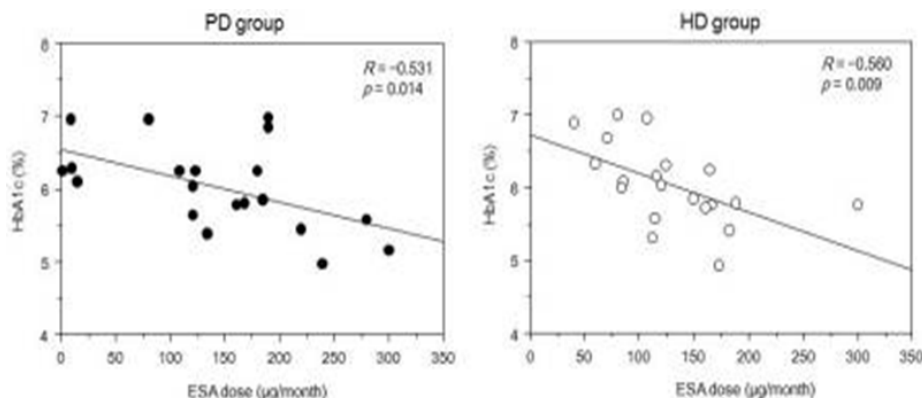
Fig 3 — Relationship between mean HbA1c level and mean dose of monthly Erythropoiesis-Stimulating Agent (ESA) in diabetic patients on dialysis. HD-Hemodialysis; PD-Peritoneal Dialysis[23]

population[31]. It can be said that mortality of critically ill patients are definitely affected by acute Hyperglycemia, and is Influenced by Chronic Hyperglycemia.

In perioperative and postoperative period —

Although it is considered that the current blood sugar can only affect the perioperative care, but it has also been suggested that optimizing a patient's pre-operative Glycemic Control. A recently published systemic review comprising of seven studies showed that higher Pre-operative HbA1c levels in patients without prior diagnosis of diabetes acts as a predictor of Postoperative complications and a potentially modifiable factor[32]. While another study showed that pre-operative HbA1c level is not associated with the risk of Postoperative infection in a statistically significant manner[33]. Hence further studies are needed to verify this factor more precisely (Table 1).

Table 1 — *Statistical analysis of pre-operative predictors of Postoperative infection*			
Potential pre-operative predictor	Odds ratio	95% confidence interval	p-Value
Gender : Male	1.01	0.65–1.56	p = 0.98
Wound (vs clean wound) :			
Clean/Contaminated	2.04	1.02–4.09	p < 0.05
Dirty	12.59	5.77–27.46	p < 0.001
Surgical risk (vs low risk) :			
Moderate	1.84	1.09–3.10	p < 0.05
High	2.57	1.34–4.92	p < 0.005
Age (linear regression analysis)	1.02	1.01–1.04	p < 0.005
Haemoglobin A1c (linear regression analysis)	0.93	0.80–1.07	p = 0.313

[Source-Blankush JM, Leitman IM, Soleiman A, Tran T — Association between elevated pre-operative glycosylated hemoglobin and Postoperative infections after non-emergent surgery. Annals of medicine and surgery 2016 Sep 1; 10: 77-82.]

CONCLUSION

Diabetes Mellitus is one of the most Widely Prevalent Non-communicable Disease in this era and is considered to a silent killer . It is one of those few diseases that affects almost all the system. Similarly diagnostic, therapeutic and prognostic value of Diabates also get affected by different comorbid conditions. HbA1c is one of the most important parameters used for diagnosis and monitoring of patients. However, since it'svalue depends on the function and Pathophysiology of Red Blood Cell (RBC) and Haemoglobin, in some conditions as elaborated above, some caution must be taken before final interpretation. While most of the co-morbidities are associated independently with high HbA1c (eg, Cardiovascular, Neurological, Peripheral Arterial

Disease) but there are some condition (eg, Renal Disease, Chronic Liver Disease, Anemia), which may underestimate the glycemic control with the level of Hba1c. A clinician must be aware of these conditions before proceeding for the therapeutic intervention.

Limitations :

• Relatively small number of studies were included and only published article were taken for review

• Most of the data obtained is from the studies on western population

• All the previous publications considered here for review are not randomized and some observational studies were also included

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