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A Study of Glycosylated Haemoglobin (HbA1C) in Acute Coronary Syndrome.

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Abstract

Introduction

The World Health Organization (WHO) defines Diabetes Mellitus (DM) as: "a metabolic disorder of multiple aetiology characterized by chronichyperglycaemiawithdisturbancesofcarbohydrate,fatandprotein metabolism resulting from defects in insulin secretion, insulin action, or both[(1)]. It is a complex disorder. Genetic and environmental factors play a major part in the pathogenesis of DM. Insulin resistance (IR) and pancreatic beta cell dysfunction are said to be the mechanism behind DM[(2).] Glycosylated Haemoglobin (HbA1c) is a biomarker reflecting both fasting and post prandial plasma glucose concentration over preceding 3months and also it has been regarded as an important tool in management of diabetes. HbA1c can be used to diagnose diabetes and the diagnosis can be made if HbA1c level is>6.5%. HbA1c between 5.8 to 6.5% indicates prediabetes.[(3)]The HbA1c is recommended as a standard of care (SOC) for testing and monitoring DM[(4)].

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina (UA), ST segment elevated myocardial infarction (STEMI) and non ST segment elevated myocardial infarction (NSTEMI).The main difference among these conditions is based on the underlying severity of the disease and resulting myocardial damage. Compared to non-diabetics, persons having diabetes have a two to four fold increased risk of death from CAD. In acute coronary syndrome, stress hyperglycaemia commonly occurs secondary to increased catecholamine levels. Due to stress hyperglycaemia, a method looking only at plasma glucose levels at the time of ACS cannot be used to predict the prognosis [(5)]. Coronary Artery Disease (CAD) has emerged as the single most important cause of death worldwide and as well as in India. In 2013 CAD caused an estimated 7.5 million deaths accounting for 13.3% deaths worldwide [(6)]. Epidemiological evidence now suggests HbA1c levels to be an independent risk factor for cardiovascular events [(7)]. Present study was undertaken to find out the relationship of HbA1c and in-hospital outcome of ACS.

Aims And Objectives

Aim: To find out relationship of HbA1c with outcome of Acute Coronary Syndrome.

Objectives: To asses HbA1c in patients of Acute CoronarySyndrome.To compare the relation between levels of HbA1c and outcome of Acute Coronary

Syndrome. To determine the relation of HbA1c and outcome of Acute Coronary Syndrome.

Review of Literature

Diabetes is an ancient disease first described in an Egyptian manuscript in 1500BC. The word diabetes is derived from the Greek word "diabetes" which means "a passer through a siphon" or "to pass through"(8). At around the same time in India the disease was identified and classified as "*madhumeha"* or "honey urine".(8) In1776 Dobson confirmed the presence of sugar in samples of urine and blood as a cause of their sweetness. Type II DM was first described as a component of metabolic syndrome in 1988. Claude Bernard discovered that diabetes is due to excess production of glucose and also established the role of the liver in glycogenesis. Mering and Minkowski in 1889 established the role of the pancreas in pathogenesis of diabetes. Banting and Best in 1921 isolated insulin for the first time.(8)

Epidemiology and prevalence of type II diabetes: As per International Diabetes Federation, the prevalence of DM has increased dramatically worldwide in last 30 years, from an estimated 30 million cases in1985 to 425 million of adult population (aged20-79years) in 2017. It is estimated that by the year 2045, this will further increase to 629 million adults. (9)

Classification of Diabetes Mellitus: (10).

1) Type I diabetes (β-cell destruction): a) Immune-mediated. b) Idiopathic
2) Type II diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
3) Other specific types of diabetes:

1) Genetic defects of β-cell function, Characterized by mutations in: a)Chromosome 12, HNF1 α (MODY3). b) Chromosome 20, HNF4 α (MODY1). c) Chromosome 7, glucokinase (MODY2). d) Other very rare forms of MODY [e.g. MODY 4, MODY 6, MODY7]. e) Transient neonatal diabetes. f)Permanent neonatal diabetes.Mitochondrial DNA mutation. g)others.
2) Genetic defects in insulin action.
3) Diseases of the exocrine pancreas.
4) Endocrinopathies.
5) Drug or chemical induced.
6) Infections.
7) Uncommon forms of immune-mediated diabetes – "stiff-man" syndrome, anti-insulin receptor antibodies.
8) Genetic syndromes sometimes associated with diabetes – Down syndrome, Friedreich ataxia, Huntington Choreaetc.
4) Gestational diabetes mellitus (GDM).

Criteria for the diagnosis of diabetes (15)-

1) FPG 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8h.
2) Or 2-h PG 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
3) 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.

Type I Diabetes Mellitus(15-16)

Immune Mediated Diabetes (TypeIA) -This form of diabetes accounts for only 5-10 % of those with diabetes. It results from a cell mediated autoimmune destruction of the ß- cellofpancreas.Markersofimmunedestructionoftheß-cellsincludeislet cell auto antibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase-65

(GAD65) and autoantibodies to the tyrosine phosphates. One or more of these auto antibodies are present in about 85-90% of individuals when fasting hyperglycemia is first recognized. HLA associations with linkage to DQA and DQB genes have been found (11).

Idiopathic type I diabetes mellitus (Type Ib) - TherearesomeformsoftypeIdiabeteswhichhavenoknownaetiologies. Only a minority of patients with type I diabetes mellitus have been found to have this property and most are of African or Asian ancestry.

TYPE II Diabetes mellitus - Type II diabetes mellitus is a heterogeneous group of disorders characterized by:

Variable degrees of

(i) Resistance to insulin.

(ii) Impaired secretion of insulin.

(iii) Increased production of glucose.

Insulin resistance is present in type II diabetes mellitus and is present even before the development of the disease. It is manifested by a decreased insulin stimulated glucose transport and metabolism inskeletal muscle and adipocytes and by impaired suppression of hepatic glucose production and output. Insulin sensitivity is multi factorial with factors including age, weight, ethnicity, abdominal fat, physical activity and medication.(12)

Insulin secretion initially increases in Type II DM in response to insulin resistance to maintain normal glucose tolerance.[13]But this insulin secretory defect progresses further to a stage of highly inadequate insulin secretion. The reason for this decrement in insulin secretory capacity inType II DM is unclear, but is being attributed to the amyloid fibrillar deposits found in the is lets of the patients with long standing DM.

As demonstrated by studies, kidneys can contribute up to 25% of the glucose production, but the defect in type II diabetes mellitus is primarily in defective regulation of glucose production in the liver or hepatic glucose output. Glycogenolysis (of stored glycogen) and gluconeogenes is (from two and three carbon derivatives from muscle) are the two routes of production of glucose from liver.(14)

Epidemiological Determinants and Risk Factors of Type-2 Diabetes Mellitus (13) : Genetic markers, family history (i.e., parent or sibling with type IIDM). Obesity (BMI > 25Kg/M2). Habitual Physical in activity. Demographic determinants (sex / age / race /ethnicity). Previously identifiedIGT. History of Gestational Diabetes Mellitus or delivery of baby with weight > 4Kg. Hypertension (BP ≥ 140/90mmHg). HDL cholesterol level < 35 mg/dl and / or triglyceride level > 250 mg/dl. Polycystic ovarian syndrome or acanthosis Nigericans. History of vascular disease.

Genetic factors in development of type 2 diabetes mellitus.(15) Type II Diabetes Mellitus is a polygenic and multi factorial disease with has strong genetic component, but with limited genetic knowledge as major genes that predispose to it have not been identified yet.

Obesity And Type Ii Diabetes. (16) It is known from decades there exists a close association between the obesity and type II diabetes mellitus in all ethnic group, body weight, age and gender. Excess intra- abdominal fat is being considered as the reason for insulin resistance in obese. But, various studies suggest that other than percent body fat, no obesity indices (BMI, WHR and WC) are significantly correlated with CAD in diabetic patients.

Hypertension And Diabetes Mellitus. (17) Patients with diabetes mellitus have an increased peripheral artery resistance due to vascular remodeling and hyperglycaemia induced increased body fluid volume. These mechanisms cause an elevation of systemic blood pressure.

Metabolic Syndrome (Syndrome X). [18-19]Metabolic syndrome is a complex of abnormalities including obesity, abdominal body fat distribution, hypertension, atherogenic dyslipidemia and insulin resistance, causing alteration in hepatic metabolism, lipoprotein levels and circulating insulin levels.

Complications of Diabetes. [20] :Diabetes has both acute and long term complications.

Acute -Diabetic ketoacidosis,Hyperglycaemic hyperosmolarstate,Hypoglycaemia.

Long term-Retinopathy,Neuropathy,Nephropathy,Ischemic heart disease,Cerebro vascular disease,Peripheral vascular disease.

Glycosylated Haemoglobin (Hba1c). [21-22]. HbA1c is considered a sensitive and specific indicator of hyperglycemia - recent as well as chronic - at least 3 months old.

Table 1: Historical aspects of HbA1c.

Name of scientist	*Work done*
Allen (approx65yrs ago)	HbA contains three minor components; HbA1a HbA1b, and HbA1c.
HuismanandMeyring (1958)	HbA1c was first separated.
Bokchinand Gallop (1968)	Identified as a glycoprotein
Samuel Rahbar (1969)	Noted that diabetes is clearly associated with an elevation in glycatedhaemoglobin.
Cerami and Koenig	Proposed the use of HbA1c for control of blood sugar (1976) in diabetic patients.
Kahn Fonseca (2008);Tran etal.(2004)	1C represents the order of Hb detection on Chromatography.
Saudeketal.(2006)	HbA1c measures long-term glycemiccontrol.
Gallagher et al.(2009)	HbA comprises 97% of the total Hb and HbA1c is an irreversible non enzymatic complex between glucose &Hb.

HbA1C is the non-enzymatic glycated product of the hemoglobin beta–chain. Normally, it is present at low levels in circulating red cells as there is glycosylation reaction between haemoglobin and circulating glucose, but when there is presence of excess plasma glucose like in diabetes, this glycation is increased, thus raising its levels and making it a useful index of glycaemic control.

Factors Affecting HBA1C.

1)Erythropoiesis:a) Increased HbA1c: Iron deficiency, vitamin B12 deficiency and decreased erythropoiesis.b) Decreased HbA1c: Erythropoietin administration, iron and vitamin B12 intake, reticulocytosis, and chronic liver disease.

2) Altered Haemoglobin: Haemoglobinopathies, HbF, methaemoglobin levels may increase or decrease HbA1c.

3) Glycation: a) Increased HbA1c: Alcohol intake, chronic renal failure and decrease in intra-erythrocyte pH. b)Decreased HbA1c: Aspirin intake, vitamin C and E, increase in intra-erythrocyte pH. c)Variable HbA1c: Genetic determinants.

4) Erythrocytedestruction.a)Increased HbA1c: Post Splenectomy status.b) Decreased HbA1c:Haemoglobinopathies, splenomegaly, rheumatoidarthritisordrugssuchasantiretrovirals,ribavirinanddapsone.

5) Assays. a) Increased HbA1c: Hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiateuse. b) Variable HbA1c: Haemoglobinopathies. Decreased HbA1c: Hypertriglyceridemia.

Table 2: HbA1c and estimated average blood glucose levels

HbA1c	Estimated average glucose	
%	Mg/dl	Mmol/l
6	126	7.0
7	154	8.6
8	183	10.1
9	212	11.8
10	240	13.4

Epidemiologic studies suggest that with each 1% increase in the HbA1C value, there is 18% increase in the relative risk of cardiovascular diseases for type II diabetes patients and 15% for type I diabetes.

Material And Methods

Study Centre: Department of General Medicine, Sri Aurobindo Medical College and P.G Institute, Indore, Madhya Pradesh, India.

Study Population: Patients aged more than 18 years diagnosed with acute coronary syndrome were included in this study.

Sample size: A sample size of 144 patients was taken. This sample size was calculated seeing the number of patients admitted with acute coronary syndrome in previous year.

Study design: It is an observational study.

Duration of study: The period of study was 18 months from December 2016 to May 2018.

Inclusion Criteria- Patients who gave informed consent, Patients equal to or above 18 years of age, Patients diagnosed with acute coronary Syndrome.

Exclusion Criteria- Patients with haemoglobinopathies, sepsis, hypothyroidism, chronic renal failure on hemodialysis and iron deficiency anemia.Patients on erythropoietin therapy, NRTI therapy, ribavirin therapy.

Sampling: Purposive sampling (non-probability) technique was used to recruit a sample from the population of patients who were admitted with acute coronary syndrome at Sri Aurobindo Medical College and Post Graduate Institute during the period of study that met inclusion-exclusion criterion for this study.

Study tools: History, Examination, CBC, Electro Cardiogram (ECG), Cardiac enzymes – Troponin T (Trop T) / Troponin I (Trop I) / CreatinePhosphokinase MB (CPKMB), Fasting Blood Sugar (FBS) levels, Glycosylated haemoglobin (HbA1c), Serum Creatinine / Blood Urea levels, 2DECHO. HbA1c was calculatedon admission for each patient by HPLC (High performance liquid chromatography) method .Based on the HbA1c levels, patients were divided into two groups of High HbA1c (HbA1c More than equal to 6.5%) and low HbA1c (HbA1c less than 6.5%) irrespective of their diabetes status and their relation with outcome of ACS was recorded.Theabovedatawasrecordedonapretestedandstructuredproforma and tabulated in the master chart for eachpatient.Microsoft word and excel files were used to prepare tables, graphs and descriptive statistics.Forstatisticalanalysis,ttestwasusedandassociation wasobserved using quantitative parameters. A p value of less than 0.05 was considered statisticallysignificant.Ethical and legal considerations: The protocol of the present study was submitted to the Ethics Committee of Sri Aurobindo Medical College & Post Graduate Institute Indore. After getting their due approval, the study was initiated in the institute. A patient information and consent form was given to the patients in

his/her local language which, when all their queries were satisfactorily answered, signature of patients was obtained and study related procedures were initiated.

Observations And Results

The present study entitled "**A Study of Glycosylated Haemoglobin (Hba1c) In Acute Coronary Syndrome**" was carried out in Department of General Medicine in Sri Aurobindo Medical College and P.G. Institute, Indore (M.P.), One Hundred and forty four patients who met the inclusion criteria were purposively selected during the specified period. The organisation and analysis of findings in the selected patients is determined in the following tables and legends. The present chapter is dedicated to the tabulated and statistically analysed data.

Table 3: Age distribution of patients with ACS.

S. No.	Age Category (Years)	Frequency (N)	Percent (%)
1	≤40	**8**	**5.56**
2	40-59	**52**	**36.11**
3	60-79	**79**	**54.86**
4	≥80	**5**	**3.47**
	Total	**144**	**100.0**

The distribution of age of studied patients of acute coronary syndrome is shown in table 3. Youngest patient in our study was 27 year old and oldest patient was 85 year old. The mean age of patients in our study was 58.56±11.7years. The table above indicates that maximum number of patients i.e. 79 patients (54.86%) in our study were in the age group of 60-79 years of age and least number of patients were in age group of ≥80 years.

Table 4: Gender distribution of patients with ACS.

Gender	Frequency (N)	Percent (%)
Male	**104**	**72.2**
Female	**40**	**27.8**
Total	**144**	**100**

It is clear from the table that in our study, more than two third (72.2%) of the patients of acute coronary syndrome were male. Rest were female. Male to female ratio is 2.6:1

Table 5: Mortality in each HbA1c category.

	Mortality		
HbA1c	Yes	No	TOTAL
<6.5%	2 (3.03%)	64 (96.97%)	66 (100%)
≥6.5%	13 (16.37%)	65 (83.33%)	78 (100%)
TOTAL	15 (10.42%)	129 (89.58%)	144 (100%)

Of the total 144 patients in our study, 66 were in the HbA1c group of <6.5% and 78 were in group of ≥6.5%. Over all 15 mortalities were noted in our study. Of these, only 2 were from HbA1c <6.5% group and 13 were from ≥6.5% group.

Table 6: Association between means of HbA1c in survived and died patients by T-Test

Group Statistics					
	Mortality	N	Mean	Std. Deviat	Std. Error Mean
HBA1c	YES	15	8.63	2.520	0.651
	NO	129	6.82	1.796	0.158

A total of 144 patients of acute coronary syndrome were included in our study, out of these 15 mortalities were reported. The mean HbA1c of patients with mortality was 8.63±2.52, while those who survived was 6.80± 1.796.

After applying independent t-test, it suggests that mean HbA1c was statistically significantly more in patients who died than in survived patients with p value of 0.001.

Discussion

144 patients with ACS were studied in this study to correlate HbA1c with in-hospital outcome of patients.The mortality and morbidity due to Coronary artery disease and specifically Acute Coronary Syndrome have significantly fallen with advances in treatment facilities

and understanding of disease. But despite these advances, patients of diabetes with cardiovascular disease are at a significant risk. We observed that the mean age of patients with ACS in our study was 58.56±11.7 years, which was comparable with studies done by Cakmak M et al [23]and Vora S D et al [24] where average age were 59.5±9.6 years and 55.73±12.69 years respectively. Males we affected more than twice of female with male to female ratio of 2.6:1, which was also seen in study by Cakmak M et al [23] with male to female ratio of 2.1:1. We observed that 15 patients out of 144 died during the hospital stay. Their mean HbA1c value was 8.63±2.520 while the Mean HbA1c of those who survived was 6.80±1.796. On applying t test, it suggested that HbA1c was statistically significantly more in patients with in hospital mortality than those who survived. This is in agreement with Choudhary TA et al [25] and Cakmak M et al [23] who suggested that HbA1c level is a potent predictor of in-hospital and short term mortality in patients with ACS. Gosavi S et al[26] also suggested HbA1c to be associated with higher mortality in age of more than 60 years. A Meta-analysis done by Liu Y et al [27] suggested that elevatedHbA1clevelsweresignificantlyassociatedwithover allmortality in patients withCAD.Whereas studies done by Dubey T. N. et al [7], Corpus RA et al [28] and Timmer JR et al [29] suggested that HbA1c values failed to predict in- hospital mortality

Summary And Conclusion

On the basis of our study, we found that higher HbA1C is associated with poor in hospital outcome in patients with Acute Coronary Syndrome. This observation suggests that routine screening of glycaemic status by HbA1C should be done in patients with Acute Coronary Syndrome and active management should be done to keep HbA1C level below 6.5 in these patients. Also a high HbA1C is associated with higher chances of short term/ in- hospital mortality.

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