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STUDY OF LEVELS OF GLYCOSYLATED HB IN CORONARY ARTERY DISEASE AND DIABETES MELLITUS

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ABSTRACT

Coronary Artery Disease (CAD) leads to Angina and Myocardial Infarction (MI). Premature mortality on Coronary Heart Disease (CHD) is more common in diabetic atherosclerosis. In the present study serum level ofGlycosylated Hb was estimated in patients of CAD with DM, CAD without DM, DM without CAD and CAD with DM and other risk factors compared to healthy normal subjects. In present study significant increase in GlycosylatedHb levels was observed in Gr.I, III and IV compared to control group.

KEYWORDS: Coronary Artery Disease, Diabetes Mellitus, Glycosylated Hb.

INTRODUCTION

Diabetes mellitus is a major factor contributing to the predication that cardiovascular disease will become the leading cause of mortality worldwide by 2020.[1] Although coronary artery disease may contribute to the development of heart failure in a proportion of diabetic patients, some patients do not have obvious ischemic insults that lead to progressive heart failure. In the clinical setting, every 1% increase in the baseline glycosylated haemoglobin level translates into a 15% increase in risk of developing heart failure.[2]

Algorithm for management of diabetes in presence of coronary heart disease has not changed much. Diet, exercise, oral hypoglycemia agents and insulin have remained the cornerstone of therapy. However, the paradigm has shifted from mere control of hyperglycemia to correction of a host of associated metabolic and hematologic abnormalities. This approach only could mitigate the devastating consequences of the lethal combination of diabetes and coronary artery disease. Appreciating its importance, American Heart Association, in its scientific statement has pronounced diabetes a cardiovascular disease.[3]

Over the last couple of decades we have understood better the natural history of type-1 and type – 2 diabetes, as well as the pathogenetic mechanism involved in development of both macrovascular and microvascular complications. This has given us insight into developing therapeutic strategies which target key issues in the pathogenesis of diabetes and its complications.[4]

Several studies have indicated that mortality and morbidity rates of Coronary Heart Disease (CHD) were 2 to 4 times higher among patients with type I diabetes whose HbA1C was higher (> 10.4%) than in age matched non diabetic subjects.[5]

Earlier sole method for diagnosis of DM was hyperglycemia but due to its wide biological variations it was found to be inaccurate measure of diabetic load. Subsequently, American Diabetes Association indicated the role of hemoglobin A_1c(HbA_1c), which provides a much better indication of long-term glycemic control and vascular risks of diabetes.[6]

Macrovascular disease is the most important cause of mortality and morbidity in individuals with type 2 diabetes. Even when adjusted for conventional risk factors, diabetic individuals still exhibit a two to four fold increased risk of cardiovascular disease in comparison to the non-diabetic people. Therefore, long-term uncontrolled hyperglycemia, which is indicated by HbA_1c levels, is strongly suspected of promoting atherogenesis. Excess glucose is transformed into advanced glycation end products (AGEs) that not only make blood vessels inelastic and stenotic but also activates chronic inflammation. Furthermore, AGEs have been localized to atherosclerotic lesions, fatty streaks, lipid-containing smooth muscle cells, and macrophages in individuals with diabetes.[7-8] The proposed pathophysiologic mechanism for development of atherosclerosis as mentioned above can be proven by correlation of glycated product of Hb with some reliable marker of atherosclerosis.

Atherosclerosis is the underlying disease process leading to ischemic heart disease (IHD). Atherosclerotic plaques and carotid vessel stenosis are reported to be independent predictors of cerebrovascular accidents.[9] Several studies have also established strong correlation between common carotid artery intima media thickness (IMT) with all types of ischemic stroke, carotid plaque, and cardiovascular deaths.[10] Carotid intima media thickness (CIMT) is a good surrogate marker for cardiovascular disease and can be used to predict myocardial infarction and stroke.[11,12,13] HbA_1c level has been shown to be associated with carotid IMT in a large, multi-ethnic study in an American population. However, in the subgroup analysis, the association between CIMT and HbA_1c levels was not significant in an Asian American population.[14-15]

MATERIALS AND METHODS

The present study was carried out in the Department of Biochemistry, Dr.D.Y.Patil Education Society's Medical College and Hospital, Kolhapur. This study was approved by Institutional ethical committee.

In this study a total number of 200 subjects between age 40 yrs to 60 yrs matched with age and sex were included. They were distributed in controls and four groups.

Controls	**Normal Healthy controls- 100 cases**
Group- I	Patients with CAD and DM- 25 cases
Group- II	Patients with CAD – 25 cases
Group- III	Patients with DM – 25 cases
Group- IV	Patients with CAD and DM + Other risk factors- 25 cases

All controls were from the same age groups as patients, not showing any clinical signs and symptoms suggestive of CAD. They were having normal blood pressure (BP), ECG, blood sugar level and apparently no other cardiac risk factors. Group-I contained patients diagnosed to have CAD (based on angiography)with confirmed DM and were receiving treatment for the same Group- II contained patients with CAD but no DM Group-III contained Type II DM patients receiving treatment for DM, and were not showing any complications of DM, and had normal ECG and BP. Group- IV contained patients with CAD and DM along with other risk factors. (such as smoking, hypertension, family history of CAD, obesity etc.)

Sample collection- 2ml of venous blood was collected in a E.D.T.A. bulb.

Inclusion Criteria: A) Control group: 100 age matched healthy subjects were included in the control group. The subjects were selected after screening for any prior history of

cardiovascular disease or any other disease. B) CAD Patients: Angiographically proven patients by the cardiologists with relevant coronary artery disease showing greater than 50% stenoses in at least one major coronary artery at the time of diagnostic catheterization were enrolled in this study. Each subject was screened by a complete history, physical examination and laboratory analysis. C) Diabetic Patients with CAD: Clinically diagnosed patients whose fasting blood glucose level was above 125 mg/dl.

Exclusion Criteria:-The patients with hemodynamically significant valvular heart disease undergoing catheterization, surgery or trauma, known cardiomyopathy, known cancer, abnormal hepatic and renal function, past or concurrent history of any disease and taking any medication that could influence the oxidant and antioxident status and endothelial functions were exuded from the study group.

RESULT

Table No 1: Showing the levels of Glycosylated Hb (%) in control subjects and different study groups.

Groups	GLYCO Hb (%)
Control	6.8 ± 0.7
Group I (CAD with DM)	11.6 ± 1.8 *
Group II (CAD with out DM)	7.0 ± 0.89 #
Group III (DM with out CAD)	12.8 ± 1.7 * ♣ $
Group IV (CAD with DM and other risk factors)	12.0 ±1.9 * ♠ ♦

Values are expressed as mean ± SD

* P< 0.001 Group I, III, and IV as compared to control.

# P<0.001 Group II as compared to Group I

♣ P<0.001 Group III as compared to Group I

$ P<0.001 Group III as compared to Group II

♠ P<0.001 Group IV as compared to Group II

♦ P<0.05 Group IV as compared to Group III

In present study significant increase in GlycoHb levels was observed in Gr.I, III and IV compared to control group.

In the present study, highly significant increase in the level of glycosylated Hb was observed when Gr. III compared with Gr. I, however no significant change was seen when Gr. IV was compared with Gr.I

Similarly when Gr I, Gr. III and Gr. IV were compared with Gr.II showed highly significant rise.

DISCUSSION

Diabetes and dyslipidaemia are independent risk factors for macrovascular disease. It is clearly evident that the combination may be playing a major role in pathogenesis of CAD.[1]. In the present study, as expected in group II, the level of glycosylated Hb was found to be normal but in other three groups (i.e. I, III and IV) it was significantly raised (Table No-1).

There is an increase in risk of CAD with increased risk for macrovascular disease.[17,18] Klein R. (5) in his study showed an increased risk of 11% for each increment of 1% in HbA_1c and 10% increase in mortality from ischemic heart disease for an increment of 1% in HbA_1c.

Glycosylated proteins can be oxidized to produce free radicals, which may cause cross linking to produce advance glycosylation end products (AGES). Accumulation of AGES in the arterial walls may make it more susceptible to a variety of atherogenic influences. Endothelial dysfunction can be related to both, production of AGES and oxidation stress due to elevated glucose levels, causing free radical damage or can be independent and contribute to progression of CHD.[19]

Hyperglycemia has been the sole diagnostic criterion for diabetes since the development of blood glucose assays 100 years ago. Despite being the gold standard, measurement of blood glucose is less accurate and less precise due to large biological variation. In 2009, an International Expert Committee recommended the use of the HbA_1c test to diagnose diabetes, with a threshold of 6.5% or greater.[20] The American Diabetes Association adopted this criterion in 2010. The diagnostic cut point of 6.5% was recommended based on the risk for developing micro vascular complications such as retinopathy. This HbA_1c criterion identifies one third fewer cases of undiagnosed diabetes than a fasting glucose cut point of 126 mg/dL or greater. However, the advantage of using HbA_1c outweighs this limitation. Compared with fasting glucose, HbA_1c has higher repeatability, can be tested in a non-fasting status, and is a relatively stable marker for glucose level. The disadvantage of the use of HbA_1c in the diagnosis of diabetes might be the fact that the measurement of HbA_1c level is not standardized, which may result in unreliable values in different laboratories and countries.[21] Recent studies have demonstrated that HbA_1c is also a predictor of all-cause, cardiovascular and IHD mortality even at concentrations below the accepted threshold for diabetes.[22] A

recent study in the Annals of Internal Medicine had also validated that HbA_1c is a progressive risk-factor for cardiovascular disease in individuals with and without diabetes.[23] Every 1% absolute increase in HbA_1c above the non-glycemic level of 5% predicts a 20% relative increase in the incidence of cardiovascular events even after adjustment for systolic blood pressure, cholesterol level, body mass index, waist to hip ratio, smoking and previous myocardial infarction or stroke.

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