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STUDY OF GLYCATED HEMOGLOBIN, SIALIC ACID AND LIPID PROFILE IN NON DIABETIC MYOCARDIAL INFARCTION PATIENTS

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ABSTRACT

Background: *Myocardial infarction is one of the commonest diagnosis in hospitalized patients and one of the leading causes of death in industrialized countries. Stress hyperglycemia in non diabetic subjects has important cardiovascular implications. High Sialic acid levels in serum of patients with myocardial infarction indicates not only the disease severity but also prognosis.* ***Aim****: To evaluate the relationship between Glycated haemoglobin, Sialic acid and lipid profile in myocardial infarction patients in the local population.* ***Materials and methods:*** *A total of 100 subjects comprising of 50 non diabetic myocardial infarction patients as cases and 50 age matched healthy people as controls were evaluated for Glycated hemoglobin, Sialic acid and lipid profile.* ***Results:*** *Significant association was found between Glycated haemoglobin, Sialic acid and lipid profile in non diabetic myocardial infarction patients with respect to controls.* ***Conclusions:*** *These newer parameters in conjunction with traditional markers like lipid profile will help to better characterize the disease risk and progression. However more studies with greater sample size need to be done in this regard.*

KEY WORDS

Myocardial infarction, Glycated haemoglobin, Sialic acid, prognostic factors.

INTRODUCTION

Cardiovascular disease is the third most common cause of death in the developed countries. It is fast reaching epidemic proportions in many developing countries. Cardiovascular diseases account for 30 % of deaths worldwide and by 2030, when the global population will be 8.2 billion, WHO estimates that 33% of the deaths will be due to cardiac causes. Although the mortality rate after admission for AMI has declined by 30% overthe past two decades, approximately 1 of every 25 patients who survive the initial hospitalization dies in the first year after AMI1. Mortality is approximately four fold higher in elderly patients (over age 75) compared with younger patients.[1,2]

Epidemiological data suggest that classic cardiovascular risk factors such as hypercholesterolemia, hypertension and smoking alone do not account for the excess of cardiovascular morbidity and mortality in the non – diabetic population. Several investigations as well as prospective studies have shown a significant correlation between glucose metabolism and cardiovascular disease outcome in patients with or without diabetes.

The core of the issue is glycemic control by Glycated haemoglobin has now been established as the most reliable factor in predicting cardiovascular disease risk in individuals without diabetes. High levels of glycated haemoglobin has been found to be associated with

raised atherosclerotic lesions and fatty streaks in coronary arteries. Metabolic changes reflected glycated haemoglobin levels, contribute to the development of hard carotid artery plaques even at moderately elevated levels. Studies associating glycated haemoglobin with left ventricular mass and aortic function have concluded that glycated haemoglobin has a low degree of inflammatory activity - an essential pre-requisite for coronary heart disease to occur.These studies prompted the hypothesis that HbA1c could be considered to be an independent and crucial cardiovascular risk factor both in patients with or without diabetes. This is an important finding as the comprehensive assessment of cardiovascular risk will improve the targeting of preventive treatment.

Sialic acid is a terminal carbohydrate residue of the non reducing end of oligosaccharide chain of glycolipids and glucoproteins in sera and tissues. Sialic acid carries a negative charge at physiological pH. Many of them are important constituents of cell membranes. They affect the conformation of glycoconjugates and play a crucial role in properties of cell surface. They also act as recognition determinants in host pathogen and cell to cell interactions, afford protection from membrane proteolysis and is required for activation of receptors by hormones[3]. Studies done on total serum Sialic acid and sialoglycoproteins, in symptomatic carotid artery atherosclerosis revealed that variations in the degree of sialycation of glycoproteins, may be essential for understanding the relation between serum total sialic acid and atherosclerosis. Other studies showed that Sialic acid concentration predicts coronary heart disease and stroke mortality, independent of major cardiovascular risk factors.

In lipid parameters serum cholesterol was first linked up with cardiovascular pathophysiology, a number of additional markers like LDL, HDL, and triglycerides have been identified, which help in defining the atherogenic potential of lipid profile better. Studies correlating triglyceride levels and risk of coronary disease show that decrease in initial elevated levels are associated with decrease coronary heart disease compared with stable high triglyceride levels. Significant alterations have also been found in serum HDL, cholesterol, triglycerides and ratios of Total cholesterol / HDL cholesterol and myocardial infarction.

Very few studies have been done to determine the influence of glycated haemoglobin on the outcome of acute myocardial infarction in non diabetic patients and whether it can be considered as an independent risk factor for cardiovascular mortality. Serum Sialic acid is an important cardiovascular risk factor; but the reason why it is so, is not clear. We therefore propose to study the relationship of sialic acid with other known cardiovascular risk factors like HBA1C and lipid profile in non diabetic patients with myocardial infarction in an attempt to explore the inter relationship between them and the possibility of using them as serum markers for cardiovascular events in non diabetic population.

MATERIALS AND METHODS

Fifty patients with clinically diagnosed acute myocardial infarction were selected from the ICCU of Hospital. Clinical diagnosis was based on ECG findings and cardiac enzyme. The age of the patient varied from 35-70 years. The cases were selected on the basis of simple random sampling method. The study protocol was approved by the institutional ethical committee and informed consent was obtained from the subjects under study.

The exclusion criterion included diabetic individuals with ECG suggestive of myocardial infarction, non diabetic individuals with ECG suggestive of non ST segment elevation myocardial infarction and any other pre existing comorbid conditions that may alter the course of the study. Myocardial infarction following surgery and major trauma were also excluded from the study. The results were compared with fifty normal, healthy, randomly selected individuals after obtaining due consent. The controls were age and sex matched. Under all aseptic precautions, about 5 ml of venous blood was collected. 3ml of blood, collected in gel tubes was allowed to clot and it was centrifuged at 5000 rpm for 5 minutes. The serum thus separated was used for the estimation of fasting blood sugar, glycated haemoglobin, total cholesterol, triglycerides, low density lipoprotein, high density lipoprotein, and sialic acid. 2 ml of blood, collected in vacutainers

containing EDTA was used for the estimation of glycated haemoglobin.

HBA1c was estimated by Latex agglutination inhibition method, Serum triglyceride was estimated by GPO-PAP method,Serum total cholesterol was estimated by enzymatic end point method ,Serum HDL – cholesterol was estimated by Enzymatic End point method using in the Randox Daytona auto analyzer. Serum sialic acid was estimated manually, using thiobarbituric acid reagent as chromophore by the method of SKOZA and MOHOS as modified by WARREN.

RESULTS

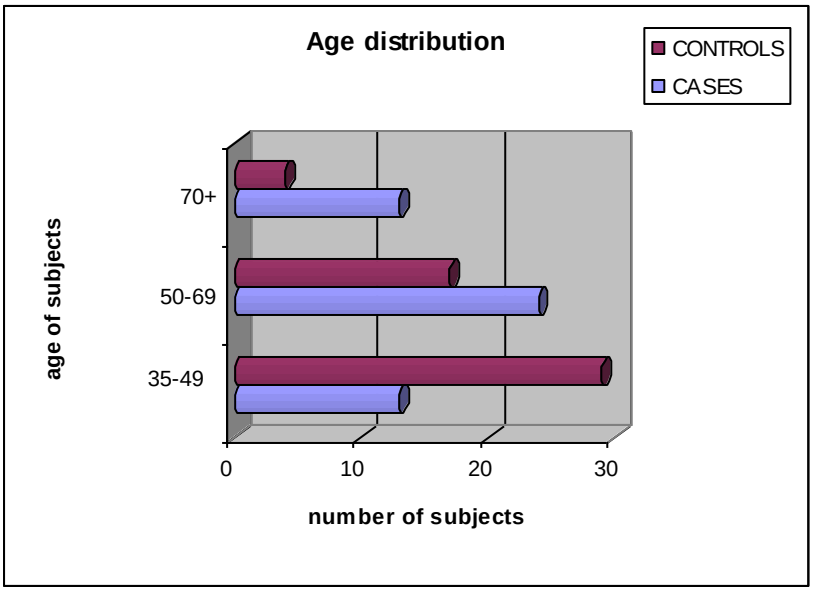
The study was conducted on acute myocardial infarction patients admitted to the ICCU of Hospital. All the patients were non diabetic.

Table 1: Age Distribution

AGE	CASES	CONTROLS
35-49	12	28
50-69	24	18
70+	14	4
Total	50	50

In cases 50-69 age are mainly effected with myocardial infarction.

Figure -1: Bar Diagram Showing Age Distribution



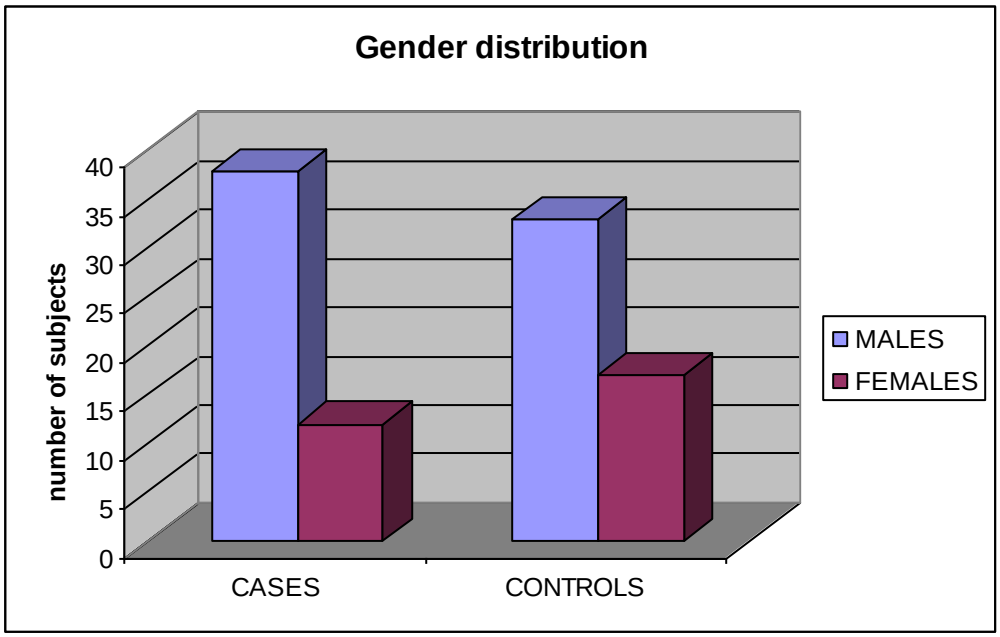
The study group included 50 patients of acute myocardial infarction with a mean age of 58.06 ± 11.45. The gender distribution was 39 males and 11 females. The control group consisted of 32 males and 18 females with a mean age of 48.70 ± 10.49. The maximum number of cases was in the age group of 50-69. This is shown in the bar diagram.

Table 2: Sex Distribution

SEX	CASES	CONTROLS
MALES	38 (74%)	33(665 %)
FEMALES	12 (24%)	17(34%)
TOTAL	50 (100%)	50 (100%)

Males are more in number than females with myocardial infarction.

Graph 2: Sex distribution of the study population



The Bar diagram displays the sex distribution of the study population .In the cases group there were 39 males and 11 females .Among controls 32 were males 18 were females.

Table 3: MEAN ±S.D , and 'p' values of Parameters in Controls and Cases

Parameters	Controls	Cases	'p' value	't ' value
FBS	100.16 ± 8.84	106.74 ± 15.65	<0.05	2.724
HBA1c	3.97 ± 0.44	6.11 ± 0.99	<0.05	13.89
Total cholestrol	152.52 ± 31.24	188.26 ± 44.66	<0.05	4.636
HDL-C	35.24 ± 7.22	27.80 ± 6.94	>0.05*	-5.530
LDL-C	110.76 ± 15.07	165.62 ± 36.18	<0.05	9.897
TAG	121.92 ± 24.26	178.38 ± 58.21	<0.05	6.330
Sialic acid	58.76 ± 6.57	81.16 ± 3.68	<0.05	21.006

*p value -insignificant

All the parameters are significant except HDL which p value is insignificant .

Table -4: Correlation of HBA1c with other parameters

Parameters	Pearson correlation	p-value
Total cholesterol	0.348	.000
HDL	-0.456	.000
LDL	0.617	.000
TAG	0.460	.000
Sialic acid	0.705	.000
Age of subjects	0.426	.000
FBS	0.348	.047

HbA1c correlated significantly with age, fasting blood sugar, sialic acid, total cholesterol, LDL, triglycerides. With HDL it showed a negative correlation

Table -5: Correlation of Sialic acid with other parameters

Parameters	Pearson correlation	p-value
Total cholesterol	0.444	<0.05
HDL	-0.457	<0.05
LDL	0.619	<0.05
TAG	0.525	<0.05
HbA1c	0.705	<0.05
Age of subjects	0.365	<0.05
FBS	0.281	0.005

Sialic acid correlated significantly with age, fasting blood sugar, HbA1c, total cholesterol, LDL, triglycerides. With HDL it had a negative correlation

Table 6: Regression Score of HbA1c and Sialic acid

	Score	p– Value *
HbA1c	66.339	0.997
Sialic acid	81.827	0.994

Logistic Regression Analysis shows that neither values obtained for prediction for groups (cases & controls) by Sialic acid or HbA1c is statistically significant.

DISCUSSION

Cardiovascular diseases are mainly caused by atherosclerosis and the pathophysiology of atherosclerosis is a complicated process governed by several risk factors. As our understanding of this complicated pathophysiology improves, new risk factors/markers are being discovered, many of which have potential clinical utility.

There was an association with male gender and higher age with Myocardial infarction. (**Table1&2**)It is significant in Males and in higher age i.e maximum number of cases was in the age group of 50-69. (**Figure 1&2**)

Glycated haemoglobin concentration is an indicator of average blood glucose concentration over the last three months and has been used as a monitoring test for diabetes. Meta-regression analysis of several studies suggest a continuous relation between fasting and post prandial glucose concentration and macrovascular events even below accepted threshold for diabetes[4,5] but data for glycated haemoglobin in patients without diabetes have been limited. It was in the EPIC –NORFOLK study that the possibility of HBA1C being a predictor of death from cardiovascular diseases, even among non diabetic population, was raised for the first time [6].

In the present study the mean the difference of means was found to be significant at the level of <0.05 as revealed by independent sample t test where cases had higher HBA1C than controls (**Table 3**). Men with glycated haemoglobin concentrations above 5% had greater risk than men with concentration below 5% [5, 6].Our study supported the results of the EPIC-NORFOLK study. We found that HBA1C correlated significantly with fasting blood glucosand serum lipids. It also showed a negative correlation with HDL cholesterol (**Table 4**). Several literatures have claimed that HBA1C is a new cardiovascular risk factor [5, 6, 7, 8].

In our study, we observed that patients who had suffered a myocardial infarction had statistically significant increase of fasting blood sugar. All these patients were non diabetics (**Table 3**). This finding strongly pointed towards a derangement of glycemic controls, which may well have played a crucial role in the pathogenesis of the disease. Many studies have been done on determinants of plasma glucose concentration in patients with confirmed acute myocardial infarction, but without previous glucose

intolerance. These studies have concluded that hyperglycemia in non diabetic patients with acute myocardial infarction was an important prognostic indicator, being mainly determined by raised concentrations of catecholamines and cortisol .These in turn were either a response to extensive infarction or associated with severe myocardial dysfunction[9].

Our study revealed that prevalence of cardio vascular disease was higher among subjects with impaired glucose tolerance. Dysglycemia or stress hyperglycemia are established cardiac risk factors and many meta regression analysis have shown that there was a linear relationship between glucose levels and cardiovascular disease risk [4,10,11,12]. Prospective studies have revealed that HBA1C was a good predictor of total and all cause mortality. Indeed, the study concluded that HBA1C was better predictor of cardiovascular disease mortality than fasting and post prandial plasma glucose [14].

Studies found that HBA1C was strongly and positively related to the prevalence of hard plaques. This observation led them to deduce that there exists a relationship between glycemia and fibrotic process and that glycemia, even at modestly elevated levels contributed to atherogenesis [13, 14].

Serum Sialic acid is a recently identified risk marker for atherosclerosis and cardiovascular mortality. Lennart et. al. in their pioneering work on serum Sialic acid concentration and carotid artery atherosclerosis reported for the first time that in both men and women its serum concentration predicted coronary heart disease and stroke [15, 16].In the present study the difference of means was found to be significant at the level of <0.05 (p value <0.05) as revealed by independent sample t test where cases had higher Sialic acid than controls (**Table 3**). We noted that it significantly correlated with higher age, male sex, fasting blood sugar, HBA1C, and lipids. It had a negative correlation with serum HDL (**Table 5**), supporting the observations by Lennart, Wakabayashi et. al[17]. Our study agrees with these deductions.

We in our study found that Sialic acid, total cholesterol and fasting blood glucose were all significantly elevated in nondiabetic myocardial patients with respect to healthy controls. Based on our observation we concluded that dyslipidemia, dysglycemia and elevated Sialic acid were indeed interlinked in cardiovascular pathophysiology as noted by other workers[18]. Regression Analysis shows that neither values obtained for prediction for groups (cases & controls) by Sialic acid or HbA1c is statistically significant. Hence neither can be treated as an independent cardiovascular risk factor. (**Table-6**)

Over the past few decades, since serum cholesterol was first linked to atherosclerotic disease a number of additional markers have been identified in an attempt to better characterize the atherogenic potential of the lipid profile. Relationships of cholesterol rich lipoproteins (Low density lipoprotein and high density lipoprotein) with atherosclerosis have been clearly established. Our study once again reaffirms these finding. We found that patients who sustained a myocardial infarction had statistically elevated total cholesterol, low density lipoprotein and low high density lipoprotein (**Table 3**) In our study the mean total cholesterol among cases was found to be significant (p value <0.05) at the level of <0.05 as revealed by independent sample t test were cases had higher total cholesterol .

HDL cholesterol was low in both cases and controls .Since there was no variance in the HDL levels in cases and controls t test could not be performed. Means was found to be significant (p value <0.05) at the level of <0.05 as revealed by independent sample t test were cases had higher LDL.

Recent data suggest that triglyceride rich lipoproteins (chylomicrons, chylomicron remnants and very low density lipoprotein) may also play a role in atherogenesis. Most case control and prospective trials that have examined the relationship of fasting triglyceride on risk of cardiovascular risk have reported that a strong crude association exist between the two [19, 20, 21, 22].Triglyceride, total cholesterol and low density cholesterol were significantly, increased whereas high density cholesterol was decreased in our patient group. Thus an altered triglyceride metabolism was noted in our patient group also. Recently, triglyceride has been proven to be an independent cardiovascular risk factor [23].

In our study, we observed that total cholesterol, low density cholesterol was statistically significantly

elevated whereas high density cholesterol was low in the patient group. Thus, our study agrees with the study conducted by N.Wattanasuwan et. al [23]. That acute myocardial infarction did not alter cholesterol ratios.

CONCLUSION

In our study we found a significantly high HBA1C, Sialic acid, fasting blood sugar, total cholesterol, LDL, triglycerides in non diabetic AMI patients. HDL levels were significantly low in the patient group. Since HBA1C is a simple investigation and relatively inexpensive test, we propose the use of HBA1C as an adjunct biochemical parameter in non diabetic AMI patients. Sialic acid is a novel cardiovascular risk factor which has shown promise as a diagnostic and prognostic marker of cardiovascular and cerebrovascular disease including myocardial infarction. We thus recommend that Sialic acid should also be included in the growing armament of biochemical cardiovascular disease markers for a better, early and more objective assessment of the disease.

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