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Original Research Article

Association of Glycosylated Haemoglobin, Non-High-Density Lipoprotein and Uric Acid in Diabetic Patients Presenting with Acute Coronary Syndrome

Uday B. Nayak[1], Aswathi Kamal[2]

[1]Professor, Department of General Medicine, AJ Institute of Medical Sciences, Mangalore, Karnataka, India.
[2]Senior Resident, Department of General Medicine, AJ Institute of Medical Sciences, Mangalore, Karnataka, India.

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Corresponding author: Dr. Aswathi Kamal
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Abstract

Background: In this study, we wanted to evaluate the association between glycosylated haemoglobin, non-high-density lipoprotein and uric acid in diabetic patients presenting with acute coronary syndrome and study the clinical profile of diabetic patients with acute coronary syndrome.

Materials and Methods: This was a hospital based single centric, observational, cross-sectional study conducted among 105 diabetic patients who presented with acute coronary syndrome to the Department of General Medicine of a tertiary care hospital over a period of 12 months from December 2018 to December 2019 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Results: The average serum fasting blood sugar level (BSL) among enrolled patients was 215.01 ± 67.00 mg/dl. The average serum post prandial BSL among enrolled patients was 292.85 ± 85.38 mg/dl. The average serum HbA1c among enrolled patients was 8.13 ± 2.22 %. The average uric acid among enrolled patients was 8.5 ± 2.55 mg/dl. The average serum total cholesterol among enrolled patients was 188.37 ± 25.57 mg/dl. The average serum HDL among enrolled patients was 40.77 ± 8.96 mg/dl. The average serum non-HDL among enrolled patients was 147.6 ± 25.90 mg/dl. The average serum LDL among enrolled patients was 109.55 ± 25.65 mg/dl. The average serum triglyceride among enrolled patients was 190.75 ± 29.09 mg/dl. Uric acid was directly correlated with HbA1c, total cholesterol, non-HDL, LDL and triglyceride. Uric acid was inversely correlated with HDL.

Conclusion: Serum uric acid level was increased in diabetic patients with acute coronary syndrome. Serum uric acid directly correlated with HbA1c, total cholesterol, non-HDL, LDL and triglyceride. Serum uric acid was inversely correlated with HDL.

Keywords: Glycosylated Haemoglobin, Non-High-Density Lipoprotein, Uric Acid, Acute Coronary Syndrome

Introduction

Myocardial Infarction is one of the key components of cardiovascular disease burden all around the world. Coronary heart disease constitutes an immense

public health problem. [1] coronary heart disease mortality has now decreased over the years, but the huge burden of its associated complications is on the rise. Effective utilization of multifaceted approaches (like drug discovery, clinical trials, and clinical policies) is necessary to reduce cardiac disease burden along with proper identification of patients with cardiovascular events, and also the incidence and outcome of such disease. The epidemiology of myocardial infarction plays an immense role in proper investigation of such cardiovascular disease burden. [2] Majority of deaths from cardiac events, including coronary vascular disease and cerebrovascular accidents occur in developing countries. Coronary artery disease has achieved epidemic proportion in India. Comparing the Indian subcontinent with other countries, coronary artery disease related mortality is still high with cardiac disease manifesting 10 years earlier than the rest of the world. The huge burden in Indian subcontinent may be attributed to its large population and high prevalence of cardiovascular risk factors which has emerged as a part of urbanization. As per the current scenario, cardiovascular death accounts for about 50 % of total death, and it is predicted that, it may go up to 2/3rd of total death by 2030.[3] Despite advances in management, acute coronary syndrome (ACS) remains a life-threatening condition with high mortality and morbidity rates. The long-term mortality for patients presenting with ACS is around 25%. [4, 5] The mortality rate for patients with diabetes mellitus (DM) presenting with acute coronary syndrome is even higher. Over the past 30 years, there has been a 27 percent decrease in age-adjusted heart disease mortality in non-diabetic patients. In contrast, patients with diabetes have experienced a 23 percent increase in age-adjusted heart disease mortality. [6,7] Diabetes mellitus is associated with endothelial dysfunction of vessels promoting atherosclerosis. The risk of developing coronary artery disease (CAD) has increased 2 – 4-fold by developing diabetes. Among persons with CAD, diabetes increases the risk of developing an acute cardiovascular event and of death after an acute myocardial infarction. [8] The relationship between ACS and glucometabolic disorders was noted as far back as 1931, when an unusually high prevalence of glycosuria was observed in patients without diabetes presenting with acute myocardial infarction. [9] Subsequent studies have shown a positive relation between the glucose level at admission and long-term mortality in patients without diabetes presenting with ACS. [10] Similarly, post-prandial hyperglycaemia is an important predictor of cardiovascular risk, even within non-diabetic threshold. [11,12] Evidence of macro and micro-vascular disease involving the cardiovascular system has been observed with hyperglycaemia. [13,14] These findings suggest a more complex relationship between glucometabolic status and cardiovascular disease than previously thought, especially in the context of ACS. On the molecular level, uric acid acts an antioxidant and can result in the dysfunction of endothelial cells, proliferation of vascular smooth muscles and aggregation of platelets on vessel walls resulting in micro inflammation and tubulo-interstitial inflammation. Increased serum uric acid has been associated with increased incidence of metabolic syndrome, chronic kidney diseases (CKD), diabetes mellitus and cerebro-vascular accidents proving uric acid as an important secondary marker of cardiovascular disease on the basis of pathophysiological and etiological processes, according to some researchers. [15] Uric acid promotes vascular smooth muscle proliferation and also upregulates the expression of platelet-derived growth factor and monocyte derived chemotactic protein. [16-18] This would enhance the

atherogenesis and its progression. As a result of insulin resistance, there is a decrease in excretion of uric acid due to reduced effect of insulin. [19,20] Dyslipidaemia is an important risk factor for cardiovascular disease (CVD) and plays a major role in the progress of atherosclerosis. For decades, the role of LDL cholesterol in predicting the risk of coronary and cerebrovascular events has been well established. It is now clear that LDL is not the only atherogenic particle. [21] But other particles that contain apoprotein B such as VLDL, VLDL remnants, IDL, and Chylomicron remnants are important. This is reflected in the non-HDL cholesterol value which is a simple measure. The terminology non-HDL cholesterol which includes all cholesterols other than HDL has a significant role in assessing the second risk for subsequent development of coronary or cerebrovascular events. Non-HDL cholesterol has significant contribution in risk assessment and therapeutic goal monitoring especially when the triglycerides are high and in diabetes and in patients with metabolic syndrome and hence non-HDL cholesterol is a surrogate marker for all the major atherogenic lipoproteins. Thus, hyperuricemia and hyperlipidaemia are the metabolic abnormalities frequently associated with type 2 diabetic patients. In present study, the levels of biochemical parameters like serum uric acid, serum lipid profile especially non-HDL and glycosylated haemoglobin were evaluated and correlated for the risk of cardiovascular disease in patients with type 2 diabetes mellitus.

Aims and Objectives

To study association between glycosylated haemoglobin, non-high-density lipoprotein and uric acid in diabetic patients presenting with acute coronary syndrome.

To study clinical profile of diabetic patients with acute coronary syndrome.

Materials and Methods

This was a hospital based single centric, observational, cross sectional study conducted among 105 diabetic patients who presented with acute coronary syndrome to the Department of General Medicine of a tertiary care hospital over a period of 12 months from December 2018 to December 2019 after obtaining clearance from institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

Type 2 diabetic patients presenting with acute coronary syndrome (ACS)

Patients ready to give written informed consent

Patients willing to be part of the study

Exclusion Criteria

Type 2 diabetic patients with CKD/nephrotic syndrome

Patients with hypothyroidism

Patients with malignancy

Patients less than 18 years of age

Patients with old CAD cases

Patients not willing to be part of the study

Statistical Methods

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality is rejected, then nonparametric tests were used. Statistical tests applied as follows-Quantitative variables were compared using unpaired t-test/Mann-Whitney test (when the data sets were not normally distributed). Qualitative variables were compared using Chi-Square test /Fisher's exact test. Pearson's correlation coefficient/Spearman rank correlation coefficient (when the data sets were not normally distributed) was used to

correlate glycosylated haemoglobin, non-high-density lipoprotein and uric acid. A p value of < 0.05 was be considered statistically significant. The data was entered in MS excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Study Procedure

After approval from IEC and after obtaining a written informed consent from the study subject and maintaining confidentiality, diabetic patients presenting in emergency department with symptoms of ACS were considered. Medical records and case sheets were referred whenever necessary to collect additional information. Diabetes was defined according to the American Diabetic Association (ADA) diabetes by the following criteria:

Fasting plasma glucose > 126 mg/dl

2-hour post prandial blood glucose > 200 mg/ dl

HbA1c > 6.5 %

Random blood sugar > 200 mg/dl

Diagnosis of ACS made on the basis of ECG, cardiac biomarkers, and clinical examination.

Patients were further investigated with ECG, cardiac troponins, hba1c, fasting lipid panel (FLP), uric acid, liver function test (LFT), renal function test (RFT), complete blood count (CBC) and thyroid stimulating hormone (TSH). Non-HDL level was also calculated. The above parameters were later correlated and analyzed according to the aims and objective of the study.

Results

The average age of enrolled patient was 62.66 ± 8.52 years. Majority of the patients were in the age group of 61 to 70 years, followed by those in 51 to 60 years of age. Male patients were relatively higher in our study as compared to females. Male to female ratio was 2 : 1.

Table 1: Demographic Distribution

Age (Years)	No of Patients	Percentage
41 - 50	12	11.42
51 - 60	30	28.57
61 - 70	44	41.90
70	19	18.09
Average age	62.66 ± 8.52	
Age Distribution		
Gender	No of Patients	Percentage
Male	70	66.66
Female	35	33.33
Total	105	100
Sex Distribution		

Table 2: Past History of Hypertension

Duration of Diabetes (Years)	No of Patients	Percentage
≤ 5	43	40.95
5.1 to 10	39	37.14
10.1 to 15	8	7.61
15	15	14.28
Average (years)	8.35 ± 6.52	
Duration of Diabetes		

Past History of Hypertension	No of Patients	Percentage
Yes	75	71.42
No	30	28.57
Total	105	100

The average duration of diabetes among our study patients was 8.35 ± 6.52 years. Majority of the patients have diabetes of up to 10 years. Majority, 71.42 % patients had pre-existing hypertension.

Table 3: Blood Parameter among Enrolled Patients

General Examination	Average Value
SBP (mmHg)	132.85 ± 23.25
DBP (mmHg)	82.47 ± 11.07
PR (per min)	86.42 ± 6.45
General Examination among Enrolled Patients	
Blood Parameter	Value
Hb (g/dl)	10.99 ± 2.21
WBC (/mcl)	10021.31 ± 3629.78
Platelets (/mcl)	257761.9 ± 111025

The average systolic blood pressure was 132.85 ± 23.25 mmHg. The average diastolic blood pressure was 82.47 ± 11.07 mmHg. The average pulse rate was 86.42 ± 6.45 per min. The average Hb level among enrolled patients was 10.99 ± 2.21 g/dl. The average WBC count among enrolled patients was 10021.31 ± 3629.78 /mcl. The average platelet among enrolled patients was 257761.9 ± 111025 /mcl.

Table 4: Liver Function Test among Patients

RFT Parameter	Average Value
Serum creatinine (mg/dl)	1.88 ± 1.48
Serum urea (mg/dl)	49.36 ±32.67
Serum sodium (mEq/L)	137.54 ± 5.15
Serum potassium (mmol/L)	4.29 ± 0.57
Renal Function Test among Patients	
LFT parameter	Average value
Serum total bilirubin (mg/dl)	0.44 ± 0.25
SGOT (U/L)	21.26 ± 13.78
SGPT (U/L)	± 1.96

The average serum creatinine among enrolled patients was 1.88 ± 1.48 mg/dl. The average serum urea among enrolled patients was 49.36 ± 32.67 mg/dl. The average serum sodium among enrolled patients was 137.54 ± 5.15 mEq/L. The average serum potassium among enrolled patients was 4.29 ± 0.57 mmol/L. The average serum total bilirubin among enrolled patients was 0.44 ± 0.25 mg/dl. The average serum SGOT among enrolled patients was 21.26 ± 13.78 U/L. The average serum SGPT among enrolled patients was 21.67 ± 1.96 U/L.

Table 5: Uric Acid among Enrolled Patients

Blood Sugar Parameter	Average Value
Fasting BSL (mg/dl)	215.01 ± 67.00
Post prandial BSL (mg/dl)	292.85 ± 85.38
HbA1c (%)	8.13 ± 2.22
Blood Sugar among Patients	
Uric acid	Average value
Uric acid (mg/dl)	8.5 ± 2.55

The average serum fasting BSL among enrolled patients was 215.01 ± 67.00 mg/dl. The average serum post prandial BSL among enrolled patients was 292.85 ± 85.38 mg/dl. The average serum HbA1c among enrolled patients was 8.13 ± 2.22 %. The average uric acid among enrolled patients was 8.5 ± 2.55 mg/dl.

Table 6: Correlation between Uric Acid and HbA1c and Lipid Parameters

Lipid Parameter	Average Value	
Total cholesterol (mg/dl)	188.37 ± 25.57	
HDL (mg/dl)	40.77 ± 8.96	
Non-HDL (mg/dl)	147.6 ± 25.90	
LDL (mg/dl)	109.55 ± 25.65	
Triglyceride (mg/dl)	± 29.09	
Lipid Parameter among Enrolled Patient		
Correlation of Uric Acid with	Correlation Coefficient r (CI)	P Value
HbA1C	0.12 (-0.09677 to 0.2937)	0.29
Total cholesterol	0.06 (-0.1380 to 0.2551)	0.53
HDL	-0.18 (-0.3663 to 0.01551)	0.06
Non-HDL	0.10 (-0.08994 to 0.3000)	0.26
LDL	0.09 (0.1073 to 0.2839)	0.35
Triglyceride	0.07 – (0.1239 to 0.2684)	0.44

The average serum total cholesterol among enrolled patients was 188.37 ± 25.57 mg/dl. The average serum HDL among enrolled patients was 40.77 ± 8.96 mg/dl. The average serum non-HDL among enrolled patients was 147.6 ± 25.90 mg/dl. The average serum LDL among enrolled patients was 109.55 ± 25.65 mg/dl. The average serum triglyceride among enrolled patients was 190.75 ± 29.09 mg/dl. Uric acid was directly correlated with HbA1c, total cholesterol, non-HDL, LDL, and triglyceride. Uric acid was inversely correlated with HDL.

Discussion

The present study was thus conducted to estimate and correlate the level of serum uric acid, serum lipid profile especially non-HDL and glycosylated haemoglobin for the risk of cardiovascular disease in patients with type 2 diabetes mellitus. In these, 105 diabetic patients with acute coronary syndrome were evaluated and analysed for possible correlation of HbA1C with uric acid and non-HDL lipoprotein. The average age of enrolled patient in our study was 62.66 ± 8.52 years with majority of patients in the age group of 61 to 70 years, followed by those in 51 to 60 years of age. Male patients were relatively higher in our study as compared to females. Male to female ratio was 2:1.

Thus, male diabetics in the age group of 50 to 70 years were relatively higher in our study. This was very much similar to another Indian study conducted by Baligar B [22] where majority of the patients (42 %) were in the age group of 50 to 70 years. Also, males were relatively more diagnosed with ACS. Several studies have highlighted the risk of increasing age and its association with coronary artery disease. Among the conventional risk factors, Framingham heart study has clearly increased age and male gender at greater risk of coronary artery disease. [23] Duration of diabetes is also associated with increased risk of cardiovascular and other complications. In our study, the average duration was 8.35 ± 6.52 year. The Framingham Heart Study highlighting the significant effect of diabetes duration on coronary heart disease and associated mortality reports after adjustment for age, sex, and CHD risk factors, the risk of CHD was 1.38 times higher for each 10-year increase in duration of diabetes (95 % CI 0.99–1.92) and highlights, duration of diabetes is an independent risk for diabetes associated cardiovascular complication. [24] Patients with pre-existing hypertension increase the risk of coronary heart disease. In our study, 71.42 % patients had pre-existing hypertension. The two independent risk factors associated with CAD include diabetes and hypertension. Compared with those who do not have diabetes, hypertension is twice as common in patients with diabetes. In addition, patients with hypertension also have insulin resistance and are at a higher risk of developing diabetes than those with normo-tension. [25] Thus, because of related risk factors, such as endothelial dysfunction, artery inflammation, arterial remodelling, atherosclerosis, dyslipidaemia, obesity, diabetes, and hypertension are strongly interlinked. The cardiovascular risks of diabetes and hypertension are also greatly overlapping, especially linked to micro vascular and macro vascular diseases. The close association between diabetes and hypertension is likely to lead to common mechanisms, such as renin-angiotensin - aldosterone upregulation, oxidative stress, inflammation, and activation of the immune system. Baligar B reported that 64 % of the patients were diabetic patients with hypertension who presented with ACS in his study. General and systemic examination of study participants highlighted that majority of parameters were within normal limit while SBP and DBP were marginally elevated. Liver function parameters were within normal limit, serum sodium-potassium were within normal limit, but serum urea and creatinine were marginally increase than normal in our study group. Since majority of the patients in our study group had hypertension, the blood pressure was relatively higher and long-standing diabetes does affect the functioning of renal function. A common complication of type 2 diabetes is diabetic nephropathy. Poorly regulated diabetes can cause damage to clusters of blood vessels in the kidneys that remove waste from your blood over time. This can cause damage to the kidneys and cause high blood pressure. Diabetic nephropathy patients are at significantly increased risk of cardiovascular disease and of progression to end-stage renal disease (ESRD). [26]

For patients enrolled in our study, uncontrolled long-term diabetes was clearly illustrated. Average fasting, post-prandial fasting, and HbA1c were higher than normal. Hypercholesteremia was also highlighted in our study participants, in addition to uncontrolled diabetes. All other lipid parameters were elevated except HDL which was within the usual limit. Among the metabolic disorders that typically accompany diabetes are abnormalities in plasma lipoprotein production and clearance. The development of dyslipidaemia, in addition,

may be a precursor to possible diabetes. A characteristic phenomenon called diabetic dyslipidaemia is low HDL, elevated triglycerides, and postprandial lipemia. This pattern is seen most often in type 2 diabetes and can be a treatable risk factor for subsequent cardiovascular disease. Defect in insulin and hyperglycaemia could lead to changes in plasma lipoproteins in patients with diabetes. Alternatively, obesity / insulin-resistant metabolic disorder, which is at the root of this type of diabetes, may lead to lipid abnormalities other than hyperglycaemia, especially in the case of type 2 diabetes. [27] In diabetic patients, since it correlates strongly with atherogenic lipoproteins, non-HDL cholesterol can be a better indicator of CVD than LDL cholesterol or triglycerides. A single index of all atherogenic, apolipoprotein (apo) B-containing lipoproteins-LDL, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and lipoprotein(a) [28] is given by non-HDL cholesterol measurements (calculated as total cholesterol minus HDL cholesterol). Since apo B-containing lipoproteins are assessed by non-HDL cholesterol, this may serve as an additional tool for cardiovascular risk assessment in people whose risk is not adequately defined by LDL cholesterol alone. This is particularly relevant in patients with diabetes who may not have significantly elevated LDL levels. Moreover, in the presence of hypertriglyceridaemia that typically accompanies diabetes, non-HDL cholesterol is especially atherogenic. [29] The level of uric acid (8.5 ± 2.55 mg/dl) was also higher than normal and was directly correlated with HbA1c, total cholesterol, non-HDL, LDL and triglyceride and inversely correlated with HDL supporting the fact that elevated morbidity and mortality could be due to lipid profile distortions contributing to metabolic complications. By stimulating granulocyte adherence to the endothelium, uric acid can promote LDL oxidation, thereby triggering the progression of atherosclerosis. Similar to our study outcome, Babiker W et al. [30] reported that the level of serum uric acid was found to correlate positively with HbA1c in diabetic patients, possibly indicating the adverse effect of elevated serum uric acid in glycaemic regulation, although other researchers believe that the potential mechanism for associating increased serum uric acid with uncontrolled hyperglycaemia in diabetes mellitus has been identified. In order to explain the independent association between serum uric acid levels and diabetes mellitus, a study performed by Bandaru et al. concluded that there was a statistically non-significant adverse correlation between uric acid and FBS and a positive correlation with HbA1c. [31] These findings are consistent with the results obtained in a study conducted by Safi et al. [32] who found a mean serum uric acid level of 6.07 mg/dl in diabetic patients as opposed to 5.01 mg/dl in the control group. Serum uric acid has been shown to be positively associated with type 2 diabetes mellitus and to have a relatively greater correlation in patients with hyperlipidaemia. High levels of glycaemia can facilitate non-enzymatic LDL glycosylation, which can be phagocytised into the arterial wall independently of the mechanism of the receptor. Dysfunctional endothelium can be transmitted by phagocytosed uric acid, which in turn contributes to plaque formation. [33,34] Thus, the findings of our study have shown that hyperuricemia in type 2 diabetes mellitus is associated with dyslipidaemia and these patients are at high risk of developing CVD. The findings of this study will help to prove the framework for similar studies in the future which will assist in the early detection of diabetes-related complications, especially CAD. [35]

Conclusion

Serum uric acid level was increased in diabetic patients with acute coronary syndrome. Serum uric acid directly correlated with HbA1c, total cholesterol, non-HDL, LDL and triglyceride but inversely correlated with HDL.

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