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A STUDY TO ASSESS THE LEVEL OF URIC ACID AND hs-CRP IN METABOLIC SYNDROME SUBJECTS AND TO COMPARE THE LEVELS IN METABOLIC SYNDROME SUBJECTS WITH AND WITHOUT TYPE 2 DIABETES MELLITUS

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Abstract

A study to assess the level of uric acid and hs-CRP in metabolic syndrome subjects and to compare the levels in metabolic syndrome subjects with and without type 2 diabetes mellitus. Introduction: Metabolic syndrome, also known as syndrome X or insulin resistance syndrome, comprises a group of metabolic abnormalities that heighten the risk of cardiovascular disease (CVD) and diabetes mellitus. C-reactive protein and uric acid levels have been linked to pathogenesis and progression of diabetes and metabolic syndrome. This study is a comparative correlation on Uric acid and hs- CRP levels in metabolic syndrome between diabetics and non- diabetics. Materials & Methods: This cross-sectional comparative study was conducted with a study population 104 subjects, (50 diabetic subjects and 54 non-diabetic subjects) in the Department of Internal Medicine, School of Medical Science and Research, Sharda University, Greater Noida during a period of 2021 to 2023. Results: Present study included total of 104 patients with mean age of 50.01±10.97yrs of age. Among them 51% (53 of 104) were male and 49% (51 of 104) were female. We divided the patients into two groups, Non-diabetic and Diabetic. A total of 50 subjects were in diabetic group while 54 were identified as non-diabetic. There is significant higher mean level of both hs-CRP and UA in diabetic patients compared to non-diabetic individuals. The mean level of hs-CRP in diabetic patients was 5.7±3.6 and in non- diabetic was 3.3±2.7. Similarly the uric acid level in diabetic patients was 6.2±1.9mg/dl and in non-diabetic 5.5±2.2mg/dl.($p<0.05$) Conclusions: Our findings suggest a notable association between diabetes mellitus and elevated levels of serum CRP and uric acid in patients with metabolic syndrome. Further research may delve into the mechanisms underlying this association and explore potential therapeutic interventions targeting these markers in the management of metabolic syndrome and its complications.

Keywords: Metabolic Syndrome, Diabetes Mellitus, hs-CRP, Uric Acid.

INTRODUCTION

Metabolic syndrome, also known as syndrome X or insulin resistance syndrome, comprises a group of metabolic abnormalities that heighten the risk of cardiovascular disease (CVD) and diabetes mellitus. Key features of metabolic syndrome are, central obesity, elevated triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, high blood sugar and hypertension.[1]

In 1988, Reaven coined the term ‘Syndrome X’, denoting the clustering of several metabolic abnormalities and he recognized it as a multiplex risk factor for CVD.

It was further, postulated that insulin resistance underlies Syndrome X (hence the commonly used term insulin resistance syndrome). Individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer.[2,3]

C-reactive protein and uric acid levels have been linked to pathogenesis and progression of diabetes and metabolic syndrome. Metabolic syndrome is now understood as a result of chronic low-grade inflammation, particularly of adipose tissue. It causes release of cytokines which act on liver to release acute phase proteins including hs-CRP.[4] Studies suggest that hs-CRP (a marker of inflammation) level predicts the development of type 2 diabetes in metabolic syndrome. It has effect on atherothrombosis and acts as a useful risk marker for cardiovascular disease.[4,5]

Hyperuricemia, hyperhomocysteinemia, reactive oxygen species, and highly sensitive C-reactive protein (hs-CRP) each play an important role in expanding the original Syndrome X.

Hyperuricemia has been presumed to be a consequence of insulin resistance but recent studies suggest that uric acid is related to development of DM-2. Uric acid has anti-oxidant effect, but it becomes a strong oxidant in the environment of metabolic syndrome. It stimulates vascular smooth muscle proliferation, induces endothelial dysfunction, decreased Nitric Oxide production, insulin resistance and causes TNF-alpha and hs- CRP production.[6] Hyperuricemia is an independent risk factor for development of chronic kidney disease in type 2 diabetes.

Though number of studies have been conducted but comparative correlation studies available on Uric acid and hs- CRP levels in metabolic syndrome between diabetics and non- diabetics is still less.

MATERIALS AND METHODS

This cross-sectional comparative study was conducted, after clearance from board of studies and ethical committee, in the Department of Internal Medicine, School of Medical Science and Research, Sharda University, Greater Noida during a period of 2021 to 2023.

Study Design: Cross-sectional comparative study

Sampling Method: Convenience random sampling.

Sample Size: 104 (50 diabetic subjects and 54 non-diabetic subjects)

Study Population The subjects, who fulfilled the inclusion criteria, were taken from patients presenting to OPD or admitted as IPD, at random, in the Department of Medicine, Sharda Hospital, Greater Noida

Inclusion Criteria:

- Those subjects of age >18, meeting the IDF criteria for metabolic syndrome, who are able to give valid informed written consent.

IDF GUIDELINES FOR METABOLIC SYNDROME (in Indian population)
1. Central obesity:-
2. waist circumference >90 (M), >80 cm in (f) in south Asians and Indians.
PLUS ANY TWO OF THE FOLLOWING:
1. Hypertriglyceridemia: triglycerides ≥150mg/dl or on specific medication.
2. Low HDL:-<40mg/dl (m) and < 50mg/dl (f) or specific medication.
3. Hypertension:-BP ≥130mm systolic or ≥85 mm diastolic or on specific medication.
4. Fasting plasma glucose:-≥100 mg/dl or specific medication or previously diagnosed type 2 diabetes.

Exclusion Criteria:

1. Type 2 diabetes mellitus with chronic kidney disease
2. Subjects who are on non-steroidal anti-inflammatory drugs (NSAID's) or xanthine oxidase inhibitors or uricosuric agents for last 14 days.
3. Known case of gouty arthritis and other arthritis or connective tissue disorders.

Methods of Study:

A pre structured Performa were used to collect the baseline data. Detailed history and clinical examination and routine investigations were carried out. Fasting (at least 12 hours) blood samples (less than 10 ml) were drawn of selected subjects and send for relevant analysis to the Central laboratory at Sharda Hospital. The parameters recorded for this studies are as follows:

- Blood pressure: measured by auscultatory method with sphygmomanometer in supine position.
- Waist circumference: the measurement made in centimetres at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Serum triglycerides
- HDL
- FBS
- Serum uric acid: subjects again divided on basis of uric acid into low uric <6mg/dl and high uric acid >6mg/dl.
- hs- CRP: CRP was measured as hs-CRP test (as hs-CRP is a more sensitive measurement in metabolic syndrome) conventional CRP were measuring only >6mg/l of CRP. While hs-CRP is more sensitive measurement of CRP and measures lower value of CRP, which signifies the low-grade inflammation in metabolic syndrome. Subjects were again divided on the basis of hs-CRP level into

Low risk of CVD: i.e. hs- CRP < 1.0 mg/L,

Intermediate risk of CVD: i.e. hs-CRP 1.0-3.0 mg/L and

High risk of CVD: i.e hs- CRP > 3.0 mg/L.

Statistical Analysis

The data was entered in Microsoft excel sheet and analysed using SPSS v23.0 operating on windows 10. The continuous data was summarised as mean, standard deviation and categorical data using frequency and percentage. The mean difference between the continuous data were compared using unpaired t-test and difference between categorical data were compared using chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Present study included total of 104 patients with mean age of 50.01±10.97yrs of age. Among them 51% (53 of 104) were male and 49% (51 of 104) were female. We divided the patients into two groups, Non-diabetic and Diabetic.

A total of 50 subjects were in diabetic group while 54 were identified as non-diabetic. The mean age of the subjects in non-diabetic and diabetic group were 48.5±11.3 years and 51.5± 10.5 years, respectively. There was no statistically significant difference in age between the two groups (p=0.65).

In our study, there were 29 female and 23 males in non-diabetic group while there were 22 females and 30 males in diabetic group. By gender distribution, there is no significant difference in the male and female distribution between the groups. (p=0.17)

Table 1 shows the comparison of history of hypertension, smoking and alcohol use between the two groups of subjects. As seen in the table there was no statistically significant variation between the two groups in these three parameters.

Table 1: Comparison of History of Hypertension, Smoking and Alcohol between the Groups

		Non-Diabetic		Diabetic		Chi-square (p-value)
		Count	N %	Count	N %	
HTN	No	24	46.2%	19	36.5%	0.99 (0.31)
	Yes	28	53.8%	33	63.5%	
Smoker	No	36	69.2%	29	55.8%	2.01 (0.156)
	Yes	16	30.8%	23	44.2%	
Alcohol	No	40	76.9%	37	71.2%	0.45 (0.502)
	Yes	12	23.1%	15	28.8%	

In the present study we found that the mean waist circumference in the non-diabetic group was 95.2 ±10.5 cms while in the diabetic group it was 99.6 ± 9.9cms. There was no significant difference between the two groups with a p value of 0.61

Table 2: Comparison of Waist Circumference between the Groups

	Non-Diabetic		Diabetic		p-value
	Mean	SD	Mean	SD	
Waist cm	95.2	10.5	99.6	9.9	0.61

In our study on assessment of lipid profile. In the non-diabetic group the mean levels of triglycerides, hdl-c and ldl-c were 162.4±54.2, 40.7±9.3 and 121.8±42.2,

respectively. In the diabetic group the mean levels of triglycerides, HDL-C and LDL-C were 186.7±51.2, 40.9±7.8 and 145.4±44.3, respectively. When we compared the values between the two groups we found that that the levels of triglycerides and LDL-C were significantly increased ($p<0.05$) in the diabetic group.

Table 3: Comparison of Mean Lipid Profile Parameters between the Groups

	Non-Diabetic		Diabetic		p-value
	Mean	SD	Mean	SD	
TG	162.4	54.2	186.7	51.2	0.01*
HDL	40.7	9.3	40.9	7.8	0.91
LDL	121.8	42.2	145.4	44.3	0.01*

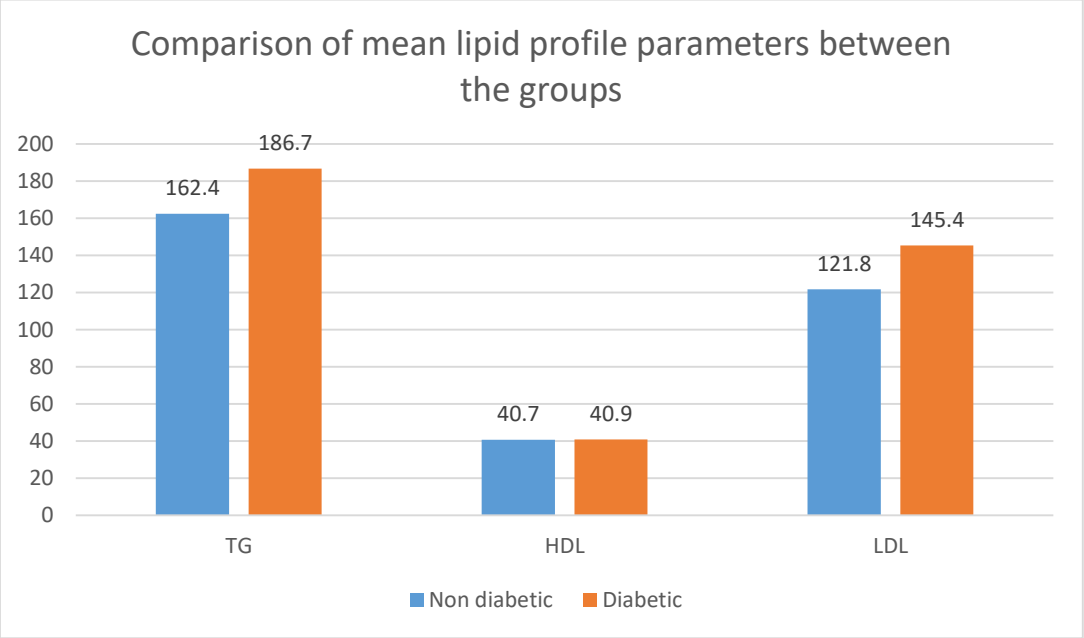

Figure 1: Comparison of Mean Lipid Profile Parameters between the Groups

Table 4 shows that there was no statistically significant difference between the two groups in the mean systolic and diastolic blood pressure.

Table 4: Comparison of Mean Blood Pressure between the Groups

	Non-Diabetic		Diabetic		p-value
	Mean	SD	Mean	SD	
SBP	138.2	18.5	139.3	17.6	0.84
DBP	85.3	10.6	85.4	13.5	0.91

In our study we found that the fasting blood sugar (mg/dl) in the non-diabetic group was 100.6±16.2 mg/dl while in the diabetic group it was 184.6±84.7 mg/dl. The fasting blood sugar was significantly raised in the diabetic group when compared to the subjects in non-diabetic group. ($p<0.05$)

Table 5: Comparison of mean FBS between the groups

	Non-Diabetic		Diabetic		p-value
	Mean	SD	Mean	SD	
FBS	100.6	16.2	184.6	84.7	0.01*

Table 6: Comparison of the Mean hs-CRP and Uric Acid Level between the Groups

	Non-Diabetic		Diabetic		p-value
	Mean	SD	Mean	SD	
hs-CRP	3.3	2.7	5.7	3.6	0.01*
UA	5.5	2.2	6.2	1.9	0.01*

There is significant higher mean level of both hs-CRP and UA in diabetic patients compared to non-diabetic individuals. The mean level of hs-CRP in diabetic patients was 5.7±3.6 and in non- diabetic was 3.3±2.7. Similarly the uric acid level in diabetic patients was 6.2±1.9mg/dl and in non-diabetic 5.5±2.2mg/dl.($p<0.05$)

DISCUSSION

Metabolic syndrome, often referred to as syndrome X or insulin resistance syndrome, encompasses a cluster of metabolic disorders that elevate the risk of cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM). The condition is characterized by central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycaemia, and hypertension. [7,8,9]

Two biomarkers, high-sensitivity C-reactive protein (hs-CRP) and serum uric acid, have garnered attention for their roles in the pathogenesis and progression of metabolic syndrome and its associated conditions.[10,11] hs-CRP is a sensitive marker of systemic inflammation and has been implicated in the development of both atherosclerosis and T2DM. Elevated hs-CRP levels have been observed in patients with metabolic syndrome, reflecting chronic low-grade inflammation predominantly originating from adipose tissue.[12] This inflammation is thought to contribute to insulin resistance, endothelial dysfunction, and subsequent cardiovascular events.

Similarly, serum uric acid, traditionally considered a byproduct of purine metabolism, has emerged as a significant player in metabolic health. Hyperuricemia, or elevated serum uric acid levels, has been linked to increased oxidative stress, endothelial dysfunction, and insulin resistance. Recent research indicates that uric acid may exacerbate inflammatory processes and oxidative stress, further linking it to the metabolic and cardiovascular abnormalities seen in metabolic syndrome.[13,14]

Understanding the roles of hs-CRP and uric acid in metabolic syndrome is crucial for developing targeted interventions. By elucidating the associations between hs-CRP, uric acid, and metabolic syndrome components, particularly in diabetic and non-diabetic populations, we aim to enhance our understanding of the underlying mechanisms and identify potential therapeutic targets to mitigate the risk of CVD and T2DM.

Present study included total of 104 patients with mean age of 50.01±10.97yrs of age. Among them 51% were male and 49% were female with similar distribution of gender in present study. The mean age of patients between the groups were comparable with no significant difference noted. The mean waist circumference of the patients in both the groups were comparable with no significant difference noted.

On assessment of lipid profile, there is significant higher mean total cholesterol and LDL cholesterol level in the patients with diabetes compared to patients without diabetes mellitus.($p<0.05$)

In a study by Sah SK et al., higher incidence of waist circumference, and cholesterol levels was documented in patients with elevated CRP and uric acid. A significant relation was found between these parameters in their study.[15]

On assessment of the serum hs-CRP and uric acid, there is significant higher mean level of both markers in diabetic patients compared to non-diabetic individuals. The mean level of hs-CRP in diabetic patients was 5.7±3.6 and in non-diabetic was 3.3±2.7. Similarly the uric acid level in diabetic patients was 6.2±1.9mg/dl and in non-diabetic 5.5±2.2mg/dl.($p<0.05$)

In a study by Sah SK et al., patients with higher level of CRP and uric acid level was documented with the presence of severity of metabolic syndrome and with components of metabolic syndrome.[50] In concordance to present study Shih Y et al., documented positive correlation with hs-CRP. The logistic regression showing hs-CRP significantly associated with Mets, after adjustment of age, BMI, uric acid levels, gender, smoking status, drinking status, diabetes mellitus, hypertension and dyslipidemia. [16]

Sun M et al., found age, abdominal obesity, physical inactivity, LDL level, fasting glucose, uric acid and ACR were correlated with CRP and relative risk of elevated CRP was 2.4, and 6.23 with more than 3 metabolic syndrome components. Study concluded that the number of metabolic syndrome components were significantly determinant of elevated CRP levels.[17]

Also Sheikh S et al., documented hs-CRP significantly higher in metabolic syndrome cases compared to controls. The Pearson's correlation indicated positive correlation of hs-CRP with BMI, waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood sugar, insulin resistance, insulin level. Significant negative correlation was seen with HDL. Similarly, serum uric acid showed significant higher in subjects compared to controls. The pearson's correlation showed positive correlation with BMI, serum insulin and concluded that the hs—CRP and uric acid have the potential for prediction of metabolic syndrome.[18]

The elevated level of uric acid level were positively associated with prevalence of metabolic syndrome.[19] In line to present study by Ahmadnezhad M et al., showed a significant relation of serum CRP, uric acid significantly associated with parameters of metabolic syndrome. The pro-oxidant and anti-oxidants were strongly associated with serum uric acid and hs-CRP.[20]

Kim Y et al., documented high serum uric acid level correlated with hypertension, hypertriglyceridemia and low HDL. Study found that all metabolic syndrome components were found to be more prevalent in women with high serum uric acid. Study concluded that the low HDL: was more prevalent with high hs-CRP and high serum uric acid level when compared to subjects with hypertension, hypertriglyceridemia and low HDL level.[21] In a study by Li C et al., hyperuricemia was documented as an independent factor in patients with diabetes mellitus.[22] Similarly in meta-analysis by Alemayehu et al., documented higher prevalence of hyperuricemia was documented among the patients with diabetes mellitus.[23]

C-reactive protein (CRP) and uric acid are significant biomarkers in the context of diabetes mellitus. High-sensitivity CRP (hs-CRP) assays detect low levels of CRP indicative of chronic inflammation, which is crucial in the pathogenesis of insulin resistance and type 2 diabetes. Elevated hs-CRP levels are commonly observed in

diabetic individuals, predicting the development of type 2 diabetes and associated with an increased risk of cardiovascular diseases due to atherothrombosis.

Uric acid, a metabolic byproduct of purine metabolism, exhibits a dual role in oxidative stress: as an antioxidant in its soluble form and a pro-oxidant under hyperuricemia conditions, contributing to oxidative stress, endothelial dysfunction, and insulin resistance. Elevated uric acid levels are linked to insulin resistance, production of inflammatory cytokines, and chronic kidney disease progression in diabetic patients.

Both hs-CRP and uric acid highlight the inflammatory and metabolic disruptions in diabetes, providing insights for early identification and management of diabetic complications.

The study highlights a significant association between diabetes mellitus and elevated levels of serum hs-CRP and uric acid in patients with metabolic syndrome. These elevated biomarkers suggest an increased inflammatory state and oxidative stress in diabetic individuals, which may contribute to the progression and complications of metabolic syndrome. Further research should investigate the underlying mechanisms and potential therapeutic interventions targeting hs-CRP and uric acid to better manage and mitigate the risks associated with metabolic syndrome and its complications.

CONCLUSION

The present study examined serum uric acid and hs-C reactive protein (hs-CRP) levels in metabolic syndrome subjects with and without diabetes mellitus. A total of 104 patients participated in the study, with a near-equal distribution of 51% males and 49% females.

In our study, diabetic patients exhibited significantly higher mean total cholesterol and LDL cholesterol levels when compared to non-diabetic patients ($p<0.05$). Although there was no significant difference in mean systolic and diastolic blood pressure between the groups, fasting blood glucose was notably higher among diabetic patients ($p<0.05$). The key findings revolved around serum CRP and uric acid levels.

Diabetic patients demonstrated significantly higher mean levels of both hs-CRP and uric acid compared to non-diabetic individuals ($p<0.05$). Specifically, the mean CRP level in diabetic patients was 5.7±3.6 mg/dl, whereas in non-diabetic patients, it was 3.3±2.7 mg/dl. Similarly, the mean uric acid level in diabetic patients was 6.2±1.9 mg/dl, whereas in non-diabetic patients, it was 5.5±2.2 mg/dl ($p<0.05$).

These findings suggest a notable association between diabetes mellitus and elevated levels of serum CRP and uric acid in patients with metabolic syndrome. Further research may delve into the mechanisms underlying this association and explore potential therapeutic interventions targeting these markers in the management of metabolic syndrome and its complications.

Summary

- Present study included total of 104 patients with mean age of 50.01±10.97yrs of age.
- Among them 51% were male and 49% were female with similar distribution of gender in present study.

- The mean age of patients between the groups were comparable with no significant difference noted.
- By gender distribution, there is no significant difference in the male and female distribution between the groups.
- On assessment of the history of hypertension, smoking and alcohol consumption, these factors were comparable between the groups with no significant difference noted.
- The mean waist circumference of the patients in both the groups were comparable with no significant difference noted.
- On assessment of lipid profile, there is significant higher mean total cholesterol and LDL cholesterol level in the patients with diabetes compared to patients without diabetes mellitus.($p<0.05$)
- On assessment of the blood pressure, there is no significant difference in mean systolic and diastolic blood pressure between the groups.
- The fasting blood glucose was significantly higher among the patients with diabetes mellitus compared to non-diabetic patients.($p<0.05$)
- On assessment of the serum hs-CRP and uric acid, there is significant higher mean level of both in diabetic patients compared to non-diabetic individuals. The mean level of hs-CRP in diabetic patients was 5.7±3.6 and in non-diabetic was 3.3±2.7. Similarly the uric acid level in diabetic patients was 6.2±1.9mg/dl and in non-diabetic 5.5±2.2mg/dl.($p<0.05$).

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