A PROSPECTIVE, COMPARATIVE CLINICAL STUDY OF SERUM URIC ACID AND C-REACTIVE PROTEIN LEVELS IN METABOLIC SYNDROME SUBJECTS WITH AND WITHOUT DIABETES IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

Prevalence of metabolic syndrome in India is 30.07%. India has the second maximum number of diabetic patients in the whole world. C-reactive protein and uric acid has been linked to pathogenesis and progression of diabetes and metabolic syndrome. Uric acid and highly sensitive C-reactive protein (hs-CRP) each now share a respected inclusion as two of the novel risk markers - risk factors associated with the metabolic syndrome.

The objective of the study is to assess the level of uric acid and CRP in metabolic syndrome subjects and to compare the levels in metabolic syndrome subjects with and without diabetes mellitus.

MATERIALS AND METHODS

Relevant data obtained from Subjects attending OPD and from the in-patients of Department of Medicine in K. R. Hospital, Mysore, who satisfy the inclusion and exclusion criteria, was studied for a period from 2015 January to December 2015. The subjects were explained about the study and informed written consent was taken from all the subjects. A pre-structured Performa was used to collect the baseline data. Detailed history and clinical examination, routine investigations and the following investigations serum triglycerides, HDL, LDL, FBS, serum uric acid, CRP (CRP was measured as hs-CRP test) were collected.

RESULTS

Mean uric acid value in metabolic syndrome was 6.1 ± 1.75 mg/dL, which was in the upper limit of normal. Mean uric acid level in diabetics was 6.15 ± 1.81 mg/dL and in non-diabetics it was 6.05 ± 1.71 mg/dL. It does not show any significant difference between diabetics and non-diabetics. Males had uric acid level of 6.15 ± 1.81 mg/dL and females had 6.05 ± 1.71 mg/dL. There was no significant difference in uric acid levels in males and females ($p = 0.775$) in the study; 56% of diabetics had higher uric acid (> 6 mg/dL) and 46% of non-diabetics had uric acid > 6 mg/dL. Those with higher uric acid levels had significantly higher systolic blood pressure ($p = 0.027$) and FBS ($p = 0.033$) than those with lower uric acid levels; 76% of patients had hs-CRP > 3 mg/L and none of the patients had hs-CRP < 1 mg/L. Among diabetics, 64% had higher hs-CRP level (> 3 mg/L), while in non-diabetics 88% had hs-CRP > 3 mg/L and high hs-CRP level are significantly more associated with non-diabetics ($p = 0.005$) than diabetics. In those with uric acid > 6 mg/dL, 78.4% had hs-CRP > 3 mg/L.

CONCLUSION

By monitoring uric acid and hs-CRP levels, we can classify the risk and severity of metabolic syndrome. Uric acid at higher level of normal range as seen in the present study will not get clinically treated most of the time. Now uric acid is neither a target of treatment in asymptomatic hyperuricaemia nor a risk marker in clinical practice. Treating this can decrease the progression of metabolic syndrome. Better and more strict lifestyle changes and interventions can be implemented in those with higher uric acid and hs-CRP levels, so that we can prevent complications of metabolic syndrome, specifically atherosclerotic cardiovascular complications.

KEYWORDS

Metabolic Syndrome, Diabetics, Uric Acid, CRP.

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BACKGROUND

Prevalence of metabolic syndrome in India is 30.07%.¹ India holds second place in countries with maximum number of diabetic patients in the world.

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C-reactive protein and uric acid levels have been linked to pathogenesis and progression of diabetes and metabolic syndrome. Both uric acid and highly sensitive C-reactive protein (hs-CRP) are now regarded as the two novel risk markers associated with metabolic syndrome.^{2,3}

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 CRP.⁷ In obesity, excess adipose tissue releases inflammatory cytokines that may elicit higher CRP levels. Increased C-reactive protein has been reported in both type 1 and type 2 diabetes. Studies suggest that CRP (a marker of inflammation) level predicts the development of type 2 diabetes in metabolic syndrome.⁴

It has effect on atherothrombosis and acts as a useful risk marker for cardiovascular disease.^{5,6} Circulating C-reactive protein may predict the development of albuminuria in patients with type 2 DM^{7,8} and it also plays a role in progression of Chronic Kidney disease in diabetics.^{9,10} Hyperuricaemia, hyperhomocysteinaemia, reactive oxygen species and highly sensitive C-reactive protein (hs-CRP); each play an important role in expanding the original Syndrome X.^{11,12,13} Oxidative-redox stress results in impaired endothelium-dependent vasodilation with quenching of endothelial nitric oxide (eNO) and allows the endothelium to become a net producer of ROS, specifically superoxide as the endothelial nitric oxide synthase (eNOS)^{9,10,14} enzyme uncouples to produce superoxide instead of eNO. A similar mechanism applies equally well to that associated with type 2 diabetes and congestive heart failure. It is important to note that allopurinol and oxypurinol (XO inhibitors)^{15,16} are capable of reversing the impaired endothelial nitric oxide production in both heart failure and Type 2 Diabetes Mellitus (T2DM).

Hyperuricaemia has been presumed to be a consequence of insulin resistance, but recent studies suggest that uric acid is related to development of DM-2.¹⁷ Recent study in rats also showed that fructose-induced hyperuricaemia plays a role in the pathogenesis of metabolic syndrome.¹⁸ Uric acid has antioxidant effect, but it becomes a strong oxidant in the environment of metabolic syndrome. It stimulates vascular smooth muscle proliferation, induces endothelial dysfunction, decrease Nitric Oxide production, insulin resistance and causes TNF-alpha and CRP production.^{11,4} Uric acid is also associated with microalbuminuria.¹⁹ Hyperuricaemia is an independent risk factor for development of chronic kidney disease in type 2 diabetes. Now uric acid is neither a target of treatment in asymptomatic hyperuricaemia nor a risk marker in clinical practice.

Combined assessment of CRP and uric acid will help in prediction of diabetic nephropathy and identifying diabetic patients who may require interventions to prevent and delay kidney injury and other complications. The present study is meant to look for the levels of serum uric acid and CRP in metabolic syndrome subjects with diabetes and without diabetes. A study done on North Indian subjects by Shraddha Singh, Pushpalata Sachan, Amit Madeshiya, Dileep Verma, Munna Lal Patel and Sunita Tiwari⁷ shows low uric acid and high C-reactive Protein levels play a significant role in progression of diabetes and these can be used as a predictor of diabetes in early stages. But serum uric acid in diabetics was lower as compared to pre-diabetics ($p < 0.001$) with no significant difference in CRP level between the two groups. A study by Safiqul Islam, Saiful Islam and Yerul Kabir²⁰ shows level of uric acid in diabetics was significantly higher ($p < 0.01$) as compared to non-diabetic subjects. CRP shows significantly positive association with FBS, diastolic blood pressure, HbA1C and CRP in diabetic subjects. Uric acid also shows positive association. So, by monitoring the level of CRP and uric acid levels, whether we can reduce the complication of metabolic syndrome and if we can predict the prognosis or probability of development of diabetes and its complications, particularly chronic kidney disease is an interesting one.

Objectives

1. To assess the serum uric acid and C-reactive protein levels in metabolic syndrome subjects with diabetes and those without diabetes.
2. To compare the levels of serum uric acid and C-reactive protein in metabolic syndrome subjects with diabetes and without diabetes.

MATERIALS AND METHODS

1. **Source of Data** - Relevant data was obtained from randomly selected subjects attending OPD and from the in-patients of Department of Medicine in K. R. Hospital Mysore, who satisfy the inclusion and exclusion criteria, was studied for a period from January 2015 to December 2015 (12 months). Ethical Committee clearance was taken and informed consent was obtained.
2. **Sample Size Calculation**
 - $n = 4 PQ/d^2$.
 - n = the minimum sample size.
 - p = prevalence of metabolic syndrome in India is 30.072.
 - $p = 30.07 = 0.3007$.
 - $q = 1 - p = 0.6993$.
 - $d = 10\% = 0.1$.
 - Minimum sample size (n) = 85.
3. **Method of Collection of Data**
 - Study Design - Cross-sectional study.
 - Sampling Method - Convenience sampling.
 - Sample Size - 100.
 - Duration of Study - Total study period: 12 months: January 2015 to December 2015.
 - Data Collection Time - 1 year (January 2015 to December 2015).
4. **Inclusion Criteria**
 - Those subjects of age > 18 , meeting the IDF criteria for metabolic syndrome, who are able to give valid informed written consent.
 - Those fulfilling IDF criteria of metabolic syndrome.

IDF Guidelines for Metabolic Syndrome (In Indian Population)

Central Obesity

Waist circumference > 90 (M), > 80 cm in (f) in South Asians and Indians.

Plus any two of the following-

1. **Hypertriglyceridaemia** - triglycerides ≥ 150 mg/dL or on specific medication.
2. **Low HDL** - < 40 mg/dL (m) and < 50 mg/dL (f) or specific medication.
3. **Hypertension** - BP ≥ 130 mm 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.
5. **Exclusion Criteria**
 1. Type 2 diabetes 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.

6. Method of Study - Relevant data obtained from subjects attending OPD and from the in-patients of Department of Medicine in K. R. Hospital Mysore, who satisfy the inclusion and exclusion criteria, was studied for a period from 2015 January to December 2015. The subjects were explained about the study and informed written consent was taken from all the subjects. A pre-structured Performa was used to collect the baseline data. An observational method of primary source of information technique was adopted on the blood samples (less than 10 mL) of selected subjects to collect the relevant data. Detailed history and clinical examination, routine investigations and the following investigations were carried out.

- **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 were again divided on basis of uric acid into low uric < 6 mg/dL and high uric acid > 6 mg/dL.
- **CRP** - CRP was measured as hs-CRP test (as hs-CRP is a more sensitive measurement in metabolic syndrome), conventional CRP will measure only > 6 mg/L of CRP. While hs-CRP is a more sensitive measurement of CRP and will measure 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. CRP < 1.0 mg/L, intermediate risk of CVD: i.e. CRP 1.0 - 3.0 mg/L and high risk of CVD: i.e. CRP > 3.0 mg/L.

Statistical Analysis

- Data was entered into Microsoft Excel 2010 and analysis was done on R statistics software {R2.8.0 Statistical Package for the Social Sciences (SPSS) for windows version 17.0}.
- Normality assumption, t-test for sample mean, chi-square or Z-test, ANOVA test (when appropriate) were used to show the association and significance, Histogram and other related statistical tools were used.
- Level of significance was set as 0.05 (p value = .05).

RESULTS

The mean age of the study population is 56.52 +/- 10.13 years. For the diabetic population, mean age was 58.06 +/- 9.25 years and for the non-diabetics the mean age was 54.98 +/- 10.8 years.

There were 46% (n = 46) males and 54% (n = 54) females. In diabetic population, 42% (n = 21) were males and 58% (n = 29) were females. In non-diabetic population, 50% (n = 25) males and 50% (n = 25) were females.

Variables	Mean
Waist circumference	93.86 +/- 6.42 cm
HDL	39.93 +/- 5.08 mg/dL
LDL	175.87 +/- 31.6 mg/dL
Triglyceride	179.50 +/- 23.34 mg/dL
Systolic BP	141.44 +/- 16.19 mmHg
Diastolic BP	81.96 +/- 9.25 mmHg
FBS	139.29 +/- 62.24 mg/dL

Table 1. Mean Value of Variables of Metabolic Syndrome

In diabetic population, the mean levels of waist circumference, HDL, LDL, triglycerides, systolic blood pressure, diastolic blood pressure and FBS were 92.5 +/- 6.21 cm, 41.44 +/- 5.07 mg/dL, 173.04 +/- 34.11 mg/dL, 176.8 +/- 23.34 mg/dL, 139.04 +/- 15.51 mmHg, 81.84 +/- 8.55 mmHg and 185.5 +/- 57.94 mg/dL respectively.

In non-diabetic population, the mean levels of waist circumference, HDL, LDL, triglycerides, systolic BP, diastolic BP and FBS were 95.23 +/- 10.8 cm, 38.42 +/- 6.38 mg/dL, 178.70 +/- 29.01 mg/dL, 182.18 +/- 23.34 mg/dL, 143.84 +/- 16.47 mmHg, 82.08 +/- 9.98 mmHg and 93.05 +/- 10.6 mg/dL respectively with significant difference was noted for FBS (p = 0.001), waist circumference (p = 0.032) and HDL (p = 0.003).

Variables	Diabetic Population	Non-Diabetic Population	P value
Waist circumference	92.5 +/- 6.21 cm	95.23 +/- 6.38 cm	.032
HDL	41.44 +/- 5.07 mg/dL	38.42 +/- 4.67 mg/dL	.003
LDL	173.04 +/- 34.11 mg/dL	178.70 +/- 29.01 mg/dL	.374
Triglyceride	176.80 +/- 23.34 mg/dL	178.70 +/- 23.44 mg/dL	.255
Systolic BP	139.04 +/- 15.51 mmHg	143.84 +/- 16.47 mmHg	.137
Diastolic BP	81.84 +/- 8.55 mmHg	82.08 +/- 9.98 mmHg	.898
FBS	185.5 +/- 57.94 mg/dL	93.08 +/- 10.6 mg/dL	.001

Table 2. Mean of Metabolic Syndrome Variables in Diabetic and Non-Diabetic

History of hypertension was present in 68% (n = 68) of total sample. Hypertension and diabetes was present in 34% (n = 34) of total sample. In diabetic population, hypertension was present in 68% (n = 34) and in non-diabetics, hypertension was present in 68% (n = 34).

In those with hypertension the mean values of waist circumference, HDL, LDL, triglycerides, systolic blood pressure, diastolic blood pressure and FBS were 94.42 +/- 6.06 cm, 40.06 +/- 4.67 mg/dL, 179.88 +/- 32.23 mg/dL, 179.81 +/- 23.84 mg/dL, 143.41 +/- 16.44 mmHg, 82.71 +/- 9.26 mmHg and 138.59 +/- 60.58 mg/dL, respectively. While in non-hypertensives the values were 92.67 +/- 7.06 cm, 39.65 +/- 5.95 mg/dL, 167.34 +/- 28.95 mg/dL, 178.84 +/- 22.87 mg/dL, 137.25 +/- 14.68 mmHg, 80.37 +/- 9.15 mmHg and 140.78 +/- 66.64 mg/dL respectively.

Variable	Hypertensive	Non-Hypertensive	P value
Waist	94.42±6.06 cm	92.67±7.06 cm	.205
HDL	40.06±4.67 mg/dL	39.65±5.95 mg/dL	.714
LDL	179.88±32.23 mg/dL	167.34±28.95 mg/dL	.064
TG	179.81±23.84 mg/dL	178.84±22.87 mg/dL	.849
Systolic BP	143.41±16.44 mmHg	137.25±14.68 mmHg	.074
Diastolic BP	82.71±9.26 mmHg	80.37±9.15 mmHg	.242
FBS	138.59±60.58 mg/dL	140.78±66.64 mg/dL	.870
Table 3. Mean of Metabolic Syndrome Variables in Hypertensives and Non-Hypertensives			

In males, the mean values of waist circumference, HDL, LDL, triglycerides, systolic blood pressure, diastolic blood pressure and FBS were 95.95±4.74 cm, 39.32±4.35 mg/dL, 179.69±32.49 mg/dL, 186.32±21.90 mg/dL, 143.48±17.87 mmHg, 82.30±9.28 mmHg and 135.08±66.22 mg/dL respectively. In females, the values were 92.89±7.01 cm, 40.44±5.63 mg/dL, 172.61±30.81 mg/dL, 176.24±24.40 mg/dL, 139.70±14.35 mmHg, 81.67±9.30 mmHg and 142.87±62.24 mg/dL respectively.

Variable	Male	Female	P value
Waist	95.91±4.74 cm	92.89±7.01 cm	0.072
HDL	39.32±4.35 mg/dL	40.44±5.63 mg/dL	0.275
LDL	179.69±32.49 mg/dL	172.61±30.81 mg/dL	0.260
Triglyceride	186.32±21.90 mg/dL	176.24±24.40 mg/dL	0.260
Systolic BP	143.48±17.87 mmHg	139.70±14.35 mmHg	0.244
Diastolic BP	82.30±9.28 mmHg	81.67±9.30 mmHg	0.733
FBS	135.08±66.22 mm/dL	142.87±62.24 mg/dL	0.536
Table 4. Mean of Metabolic Syndrome Variables in Male and Female			

There were 33% smokers and 30% alcoholics in the total population. In diabetics, 28% (n = 14) were smokers; in non-diabetics 38% were smokers (n = 19); 26% (n = 13) of diabetics and 34% (n = 17) of non-diabetics were alcoholic.

	Diabetic Subjects	% of Subject	Non-Diabetic Subjects	% of Subject
Smoker	14	28%	19	38%
Alcohol	13	26%	17	34%
Table 5. Alcohol User and Smokers in Diabetic and Non-Diabetic Population				

In smokers, the mean values of waist circumference, HDL, LDL, triglycerides, systolic BP, diastolic BP and FBS were 96.45±5.07 cm, 39.33±3.80 mg/dL, 183.58±33.73 mg/dL, 184.64±21.63 mg/dL, 142.73±17.87 mmHg, 83.09±15.23 mmHg and 136.97±63.20 mg/dL respectively. In non-smokers, the values were 92.60±6.66 cm, 40.22±5.61 mg/dL, 172.07±30.07 mg/dL, 176.97±24.01 mg/dL, 140.81±15.23 mmHg, 81.40±9.16 mmHg and 140.43±62.22 mg/dL respectively and significant difference was noted for waist circumference (p = 0.004).

Variable	Smoker	Non-Smoker	P-Value
Waist	96.45±5.07 cm	92.60±6.66 cm	.004
HDL	39.33±3.80 mg/dL	40.22±5.61 mg/dL	.413
LDL	183.58±33.73 mg/dL	172.07±30.07 mg/dL	.087
TG	184.64±21.63 mg/dL	176.97±24.01 mg/dL	.124
Systolic BP	142.73±17.87 mmHg	140.81±15.23 mmHg	.577
Diastolic BP	83.09±9.46 mmHg	81.40±9.16 mmHg	.393
FBS	136.97±63.20 mg/dL	140.43±62.22 mg/dL	.795
Table 6. Mean Value of Metabolic Syndrome Variables in Smokers and Non-Smokers			

In those with alcohol consumption the mean values of waist circumference, HDL, LDL, triglycerides, systolic BP, diastolic BP and FBS were 97.01±5.34 cm, 39.0±3.69 mg/dL, 180.57±52.15 mg/dL, 182.70±21.56 mg/dL, 142.27±16.37 mmHg, 81.73±9.45 mmHg and 132.5±59.48 mg/dL respectively. In non-alcoholics, the mean values of waist circumference, HDL, LDL, triglycerides, systolic BP, diastolic BP and FBS were 92.52±6.40 cm, 40.33±5.55 mg/dL, 173.86±31.42 mg/dL, 178.13±24.20 mg/dL, 141.09±16.07 mmHg, 82.05±9.22 mmHg and 142.2±63.59 mg/dL respectively. Significant difference was noted for waist circumference (p = 0.001) between alcoholics and non-alcoholics.

Variant	Alcoholic	Non-Alcoholic	P value
Waist	97.01±5.34 cm	92.52±6.40 cm	.001
HDL	39.0±3.69 mg/dL	40.33±5.55 mg/dL	.233
LDL	180.57±52.15 mg/dL	173.86±31.42 mg/dL	.334
TG	182.70±21.56 mg/dL	178.13±24.20 mg/dL	.374
Systolic BP	142.27±16.37 mmHg	141.09±16.07 mmHg	.738
Diastolic BP	81.73±9.45 mmHg	82.05±9.22 mmHg	.873
FBS	132.50±59.48 mg/dL	142.20±63.59 mg/dL	.478
Table 7. Mean of Metabolic Syndrome Variables in Alcoholic and Non-Alcoholic			

The mean uric acid level of the total population was 6.1±1.75 mg/dL. Mean uric acid level of diabetic population was 6.15±1.75 mg/dL, while that of non-diabetics was 6.05±1.77 mg/dL. In males and females, mean uric acid levels were 6.16±1.81 mg/dL and 6.05±1.71 mg/dL respectively. The mean uric acid value was 6.2±1.79 mg/dL in hypertensive population. In smokers, mean uric acid level was 6.39±1.92 mg/dL, while in non-smokers it was 5.94±1.66 mg/dL. In alcoholics, it was 6.14±1.79 mg/dL and in non-alcoholics it was 6.06±1.68 mg/dL.

Categories	Uric Acid in mg/dL
Whole group	6.1±1.75
Diabetic	6.15±1.75
Non-Diabetic	6.05±1.77
Hypertensive	6.2±1.79
Smoker	6.39±1.92
Alcoholic	6.14±1.79
Table 8. Mean Uric Acid of Different Categories	

	Uric Acid in mg/dL	P value
Diabetic	6.15±1.75	.775
Non-Diabetic	6.05±1.77	
Hypertensive	6.2±1.79	.546
Non-Hypertensive	5.9±1.66	
Smoker	6.39±1.92	.898
Non-Smoker	5.94±1.66	
Alcoholics	6.14±1.79	.898
Non-Alcoholic	6.06±1.68	
Male	6.15±1.81	.775
Female	6.05±1.71	
Table 9. Uric Acid Level with P value		

51% (n = 51) of total population have uric acid $\geq$ 6 mg/dL. In diabetics 56% (n = 28) have uric acid $\geq$ 6 mg/dL, but in non-diabetics it was 46% (n = 23). In those with uric acid > 6 mg/dL, 76.5% were hypertensives; 54.54% of smokers (n = 18) and 49.25% of non-smokers (n = 33) had uric acid $\geq$ 6 mg/dL; 50% of alcoholics (n = 15) and 70.6% (n = 36) of non-alcoholics were found to have uric acid $\geq$ 6 mg/dL.

	Number of Subjects	Percentage
Uric Acid > 6 mg/dL	51	51%
Uric Acid < 6 mg/dL	49	49%
Table 10. Subjects with Low and High Uric Acid		

In those with uric acid > 6 mg/dL, the mean values of waist circumference, HDL, LDL, triglycerides, systolic blood pressure, diastolic blood pressure and FBS were 94.40±5.76 cm, 41.44±4.94 mg/dL, 182.78±28.67 mg/dL, 182.70±20.17 mg/dL, 143.74 +/- 16.48 mmHg, 83.56±8.42 mmHg, 152.24±47.18 mg/dL. Those with uric acid < 6 mg/dL, the mean values of waist circumference, HDL, LDL, triglycerides, systolic BP and diastolic BP and FBS were 93.71±6.97 cm, 39.48±5.21 mg/dL, 173.81±33.73 mg/dL, 178.55±26.29 mg/dL, 140.75±15.05 mmHg, 81.48±9.75 mmHg and 125.81±72.01 mg/dL. FBS (p = 0.033) and systolic blood pressure (p = 0.027) were significantly higher in those with uric acid > 6 mg/dL.

	Uric Acid < 6 mg/dL	Uric Acid > 6 mg/dL	P value
Waist	93.14±6.54 cm	94.57±5.76 cm	.267
HDL	39.32±4.94 mg/dL	40.50±5.21 mg/dL	.247
LDL	170.59±28.67mg/dL	180.94±33.73 mg/dL	.102
TG	177.97±20.17 mg/dL	180.96±26.29 mg/dL	.527
Systolic BP	137.83±16.48 mmHg	144.90±15.05 mmHg	.027
Diastolic BP	80.20±8.42 mmHg	88.37±9.75 mmHg	.062
FBS	125.81±47.18 mg/dL	152.24±72.01 mg/dL	.033
Table 11. Mean Value of Variables in those with High and Low Uric Acid			

24% (n = 24) of total population had hs-CRP of 1 - 3 mg/L range, 76% (n = 76) had hs-CRP > 3 mg/L. HS-CRP was found to be significantly high in metabolic syndrome.

	No. of Subjects	% of Subjects
Hs-CRP 1 - 3 mg/L	76	76
Hs-CRP $\geq$ 3 mg/L	24	24
Table 12. Subjects with Hs-CRP High and Low		

In diabetics, 64% (n = 32) had hs-CRP > 3 mg/L and remaining 36% (n = 18) had hs-CRP 1 - 3 mg/L. In non-diabetic population 88% (n = 44) had hs-CRP > 3 mg/L, remaining 12% (n = 6) had hs-CRP 1 - 3 mg/L. Hs-CRP was higher in both groups, but significantly higher in non-diabetic population (p = .005). In those with uric acid > 6 mg/dL, 78.4% had hs-CRP > 3 mg/L. Among hypertensives, 72.1% (n = 49) had hs-CRP > 3 mg/L and the remaining had hs-CRP 1 - 3 mg/L. Among smokers, 78.8% (n = 26) had hs-CRP > 3 mg/L. In alcoholics, 83% (n = 25) had higher hs-CRP, i.e. > 3 mg/L.

	Hs-CRP 1 - 3 mg/L	Hs-CRP ≥ 3 mg/L	P value
Diabetic	36%	64%	.005
Non-Diabetic	12%	88%	
Hypertensive	27.9%	72.1%	.179
Non-Hypertensive	15.6%	84.4%	
Smokers	21.20%	78.80%	.647
Non-Smokers	25.40%	74.6%	
Alcoholic	16.7%	83.30%	.261
Non-Alcoholic	72.9%	27.1%	
Table 13. Hs-CRP Levels in Different Categories			

In those with hs-CRP > 3 mg/L the mean values of waist circumference, HDL, LDL, triglycerides, systolic blood pressure, diastolic blood pressure and FBS were 94.25±6.54 cm, 39.83±5.13 mg/dL, 176.59±31.21 mg/dL, 179.97±21.78 mg/dL, 141.87±15.17 mmHg, 82±9.24 mmHg and 167.92±67.71 mg/dL respectively. Uric acid value of those with hs-CRP > 3 mg/dL was 6.2±1.65 mg/dL, which was higher than those with hs-CRP 1 - 3 mg/dL, which was 5.82±2.05 mg/dL.

	Hs-CRP 1 - 3 mg/L	Hs-CRP $\geq$ 3 mg/L	P value
Waist	92.68±5.95 cm	94.25±6.54 cm	.298
HDL	40.25±5.03 mg/dL	39.83±5.13 mg/dL	.726
LDL	173.58±33.5 mg/dL	176.59±31.21 mg/dL	.687
TG	178±28.48 mg/dL	179.97±21.78 mg/dL	.721
Systolic BP	140.08±18.99 mmHg	141.87±15.17 mmHg	.638
Diastolic BP	81.83±9.45 mmHg	82±9.24 mmHg	.939
FBS	167.92±67.71 mg/dL	130.25±57.99 mg/dL	.009
Uric Acid	5.82±2.05 mg/dL	6.2±1.65 mg/dL	.37
Table 14. Mean Value of Metabolic Syndrome Variables in those with Low and High Hs-CRP			

Categories	Waist Circumference
Diabetic	92.50±6.21 cm
Non-Diabetic	95.23±6.38 cm
Alcoholic	97.01±5.34 cm
Non-Alcoholic	92.52±6.40 cm
Smoker	96.45±5.07 cm
Non-Smoker	92.60±6.66 cm
Uric Acid < 6	93.14±5.76 cm
Uric Acid > 6 mg/dL	94.57±6.97 cm
hs-CRP 1 - 3 mg/L	92.68±5.95
hs-CRP > 3 mg/L	94.25±6.54
Table 15. Waist Circumference in Different Categories	

Categories	FBS
Diabetic	185.50±57.94 mg/dL
Non-Diabetic	93.08±10.6 mg/dL
Hypertensive	138.59±60.58 mg/dL
Non-Hypertensive	140.78±66.64 mg/dL
Smoker	136.97±63.20 mg/dL
Non-Smoker	140.20±63.59 mg/dL
Alcoholic	132.50±59.48 mg/dL
Non-Alcoholic	142.20±63.59 mg/dL
Uric Acid < 6 mg/dL	125.81±47.18 mg/dL
Uric Acid > 6 mg/dL	152.24±72.01 mg/dL
hs-CRP 1 - 3 mg/L	167.98±67.71 mg/dL
hs-CRP > 3 mg/L	130.25±57.99 mg/dL

Table 16. FBS in Different Categories

DISCUSSION

- 1. Uric Acid and hs-CRP in Metabolic Syndrome** - In present study, we found that the mean value of uric acid and hs-CRP, both were found to be higher in metabolic syndrome. The mean of uric acid was 6.1±1.75 mg/dL, which was towards the higher side of normal. Similarly, a study done by Santhosh Kumar Sah et al showed mean value of uric acid 6.6±1.8 mg/dL in metabolic syndrome.

	Mean Uric Acid Level
Present Study	6.1±1.75 mg/dL
Santhosh Kumar Sah et al	6.6±1.8 mg/dL
Safiqul Islam et al	7.2 mg/dL
Sharadda Singh et al	12.77 mg/dL

Table 17. Uric Acid Levels in Different Studies

There was not even a single subject with hs-CRP less than 1 mg/L and 76% had hs-CRP > 3 mg/L, which signifies low-grade inflammation is constantly present in adipose tissue of metabolic syndrome subjects. Also the risk of atherosclerotic CVD is higher in metabolic syndrome. Similarly, a study done by Santhosh Kumar Sah et al showed significantly higher proportion of subjects with metabolic syndrome with high risk hs-CRP levels (80%).

	% with Elevated Hs-CRP
Present Study	76%
Santhosh Kumar Sah et al	80%

Table 18. Hs-CRP in Different Studies

- 2. Uric Acid and hs-CRP in Diabetics and Non-Diabetics**
In diabetic subjects, the mean value of uric acid was 6.15±1.81 mg/dL and in non-diabetic subjects it was 6.05±1.71 mg/dL. No significant difference in mean uric acid value was observed between diabetic and non-diabetic subjects. In diabetics, 56% had uric acid > 6 mg/dL, but in non-diabetics 46% had uric acid > 6 mg/dL. But in a study done by Saifqul Islam et al, it was found that level of uric acid was significantly higher ($p < 0.05$ and $p < 0.01$) in diabetics as compared to non-diabetic subjects (in both males and females). In another study done by Sharadda Singh et al, the mean serum uric acid level of Diabetic group was significantly ($p < 0.001$) lower as compared to pre-diabetic (non-diabetic) group.

The present study showed that in those with diabetes, 64% of subjects had hs-CRP > 3 mg/L and in non-diabetics 88% had hs-CRP > 3 mg/L ($p = .005$), which showed higher level of hs-CRP in non-diabetics than in diabetics. Also, the waist circumference was significantly higher in non-diabetic than in diabetic ($p = 0.032$), which means the low-grade inflammation in abdominal adipocytes is more severe in non-diabetics (i.e. more abdominal adipose tissue, more is the underlying chronic inflammation). It means the redox shuttle is more in those with more adipose tissue and it might be the reason for uric acid being also higher in non-diabetics.

Also, abdominal obesity is directly linked to hyperuricaemia, which can cause hyperuricaemia itself. It is like a vicious cycle; abdominal obesity will increase the uric acid which in the milieu of metabolic syndrome (as redox potential changes) acts as anti-oxidant and pro-inflammatory factor and it stimulates production of mediators like IL-6 which can again increase hs-CRP. Hs-CRP in turn will increase inflammation of abdominal fat. So the amount of inflamed abdominal fat is more important.

- 3. Uric Acid and hs-CRP between Male and Female**

Mean value of uric acid in males and females were 6.15±1.81 mg/dL and 6.05±1.71 mg/dL. In males and females, there was no significant difference in the mean uric acid level as well as the hs-CRP level; 50% of males had uric acid > 6 mg/dL and 51.8% of females had uric acid > 6 mg/dL; 82.61% of males and 74.06% of females were having hs-CRP > 3 mg/L. A study done by Santhosh Kumar Sah et al also shows that there was no significant difference in uric acid and hs-CRP levels between males and females.

- 4. Hs-CRP and Uric Acid Groups**

The mean of uric acid in those with hs-CRP > 3 mg/L was 6.2±1.65 mg/dL, which was slightly higher than those with hs-CRP 1 - 3 mg/L. In those with higher uric acid (i.e. > 6 mg/dL), 76.5% were hypertensives. In those with uric acid > 6 mg/dL, 78.4% had hs-CRP > 3 mg/L which showed that higher uric acid was associated with higher levels of hs-CRP. It again implies that when the low-grade inflammation is more, there will be more oxidative stress, redox stress and it worsens the redox shuttle further and it increases uric acid further. Higher CRP further increases atherosclerotic CVD risks in those subjects.

- 5. Metabolic Syndrome Variables in Diabetic and Non-Diabetic**

Waist circumference, LDL, triglyceride, systolic BP, diastolic BP tend to be higher in non-diabetics than diabetics. Waist circumference ($p = 0.032$) showed significant increase in non-diabetic and FBS ($p = 0.032$) showed significant increase in diabetic ($p = 0.001$). According to the study done by Safiqul Islam et al compared to all non-diabetic subjects, systolic and diastolic blood pressure were slightly higher in diabetic subjects and FBS was significantly ($p = 0.002$) higher. HDL is significantly lower in non-diabetics than in diabetics ($p = 0.003$). As non-diabetic subjects in the present study were shown to have significantly higher waist circumference ($p = 0.032$) with most of them

having higher hs-CRP ($p = 0.005$), means they have more abdominal adipose tissue inflammation. As inflammation increases the insulin resistance, metabolic syndrome severity also increases. Those with more waist and more inflammation of abdominal adipocytes will have more risk of atherogenic dyslipidaemia. Also, diabetic subjects might have had more consultations with physicians than non-diabetics as well they might have undergone better lifestyle adjustment than non-diabetic. These might be the reason for higher HDL in diabetics in the present study. LDL triglycerides were higher in non-diabetics than diabetics, even though not significant.

- 6. Metabolic Syndrome Variables in hs-CRP and Uric Acid Group** - In those with hs-CRP > 3 mg/L, waist circumference, LDL, triglycerides, systolic BP tend to be a higher value even though it is not a significant change. FBS ($p = 0.033$) and systolic blood pressure ($p = 0.027$) are significantly higher in those with uric acid > 6 mg/dL. According to the study done by Sah et al, significant difference in metabolic syndrome components; systolic BP ($p = 0.043$), diastolic BP ($p = 0.005$) and HDL cholesterol ($p < 0.001$) was observed among patients with low hs-CRP and high hs-CRP group. In present study, FBS ($p = 0.033$) and systolic blood pressure ($p = 0.027$) were significantly higher in those with uric acid > 6 mg/dL. According to Santhosh Kumar Sah et al, only significant difference ($p = 0.009$) in waist circumference was observed, which was higher among patients with high uric acid.

	Sah et al Uric Acid		Present Study	
	< 6	< 6	< 6	> 6
Waist in cm	101.9	105.3	93.14	94.57
SBP in mmHg	127.5	129.5	137.84	144.9
DBP in mmHg	82.5	85.4	80.2	83.65
FBS in mg/dL	121.1	135.1	125.81	152.24
Triglyceride in mg/dL	210.4	206.6	177.98	180.96
HDL in mg/dL	50.9	49.8	39.92	40.51

- 7. Hypertensives** - 68% of subjects were having hypertension. The mean uric acid level was found to be 6.1 mg/dL in hypertensives. Majority of hypertensives (72.1%) were having hs-CRP > 3 mg/L. Waist circumference, triglyceride and LDL levels tend to be higher in hypertensives than in non-hypertensives. In a study done by Santhosh Kumar Sah et al, they observed significantly higher BP (systolic and diastolic) and increasing prevalence of hypertension with the rise in hs-CRP.
- 8. Alcohol Users** - 26% of diabetics and 34% of non-diabetics use alcohol. The mean uric acid for those who uses alcohol was 6.14 mg/dL. Also 83.3% of alcoholics had hs-CRP > 3 mg/L. Those who uses alcohol had significantly higher waist circumference ($p = 0.001$) when compared to non-alcoholics. It again means that more inflammation occurs in alcoholics and so a more severe metabolic syndrome profile is seen in alcoholics as well as they are having a higher risk of atherosclerotic CVD.

- 9. Smokers** - There were less smokers among diabetics (28%) when compared to non-diabetics (34%). The mean uric acid level in smokers was 6.39 mg/dL; 78.8% of smokers had hs-CRP > 3 mg/L, which again implies presence of more inflammation and more inflamed abdominal adipose tissue in smokers with a much more severe metabolic syndrome profile and a higher risk of atherosclerotic CVD when compared to the non-smokers. Smokers had significantly high waist circumference ($p = 0.004$) than non-smokers. Other metabolic parameters like LDL, triglycerides and systolic blood pressure also tend to be higher in smokers than in non-smokers, even though not significant.

CONCLUSION

By monitoring uric acid and hs-CRP levels, we can classify the risk and severity of metabolic syndrome. Uric acid at higher level of normal range as seen in the present study will not get clinically treated most of the time. Now uric acid is neither a target of treatment in asymptomatic hyperuricaemia nor a risk marker in clinical practice. Treating this can decrease the progression of metabolic syndrome. Better and more strict lifestyle changes and interventions can be implemented in those with higher uric acid and hs-CRP levels so that we can prevent the complications of metabolic syndrome, specifically atherosclerotic cardiovascular complications.

Summary

- Mean uric acid value in metabolic syndrome was 6.1 ± 1.75 mg/dL, which was in the upper limit of normal.
- Mean uric acid level in diabetics was 6.15 ± 1.81 mg/dL and in non-diabetics it was 6.05 ± 1.71 mg/dL. It does not show any significant difference between diabetics and non-diabetics.
- Males had uric acid level of 6.15 ± 1.81 mg/dL and females had 6.05 ± 1.71 mg/dL. There was no significant difference in uric acid levels in males and females ($p = 0.775$) in the study.
- 56% of diabetics had higher uric acid (> 6 mg/dL) and 46% of non-diabetics had uric acid > 6 mg/dL.
- Those with higher uric acid levels had significantly higher systolic blood pressure ($p = 0.027$) and FBS ($p = 0.033$) than those with lower uric acid levels.
- 76% of patients had hs-CRP > 3 mg/L and none of the patients had hs-CRP < 1 mg/L.
- Among diabetics 64% had higher hs-CRP levels (> 3 mg/L), while in non-diabetics 88% had hs-CRP > 3 mg/L and high hs-CRP levels are significantly more associated with non-diabetic ($p = 0.005$) than diabetic.
- In those with uric acid > 6 mg/dL, 78.4% had hs-CRP > 3 mg/L which means those with higher uric acid had higher CRP levels also.

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