

Original Research Article

Role of non-lipid risk factors like hs-CRP, uric acid and thyroid stimulating hormone in metabolic syndrome

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ABSTRACT

Background: Metabolic syndrome is the cluster of diseases which arises due to excess of plasma glucose, cholesterol, fatty acids, blood pressure and obesity. The role of lipids in the development of MetS had been extensively studied. Though some non-lipid factors like hsCRP, uric acid and TSH level also remain elevated in the serum of the MetS patients, the role of these non-lipid risk factors remain incompletely understood. The objective of this study was to investigate which of these factors better predicts Mets, in order to help prevention and early detection of MetS and its associated type 2 diabetes mellitus and cardiovascular diseases. Aim and objectives was to study the significance of serum highly sensitive C-reactive protein (hs-CRP), serum uric acid (SUA) and thyroid stimulating hormone (TSH) levels in metabolic syndrome.

Methods: A total of four hundred and fifty subjects (211 men and 239 women) aged ≥ 35 years attending the hospital were divided into three groups based on the components level of MetS as control (CS), normal (MS) and severe (SMS) MetS groups. Their fasting blood sample were taken and analyzed for the serum hs-CRP, uric acid and TSH levels.

Results: The result showed that the mean hs-CRP and uric acid levels were significantly higher in Metabolic Syndrome group (MS) and in Severe Metabolic Syndrome group (SMS) when compared to control group. But the mean TSH levels were more in MS group and in SMS group than the control which was statistically not significant. The analysis of relative significance of these risk factors showed that serum hs-CRP level had a positive linear correlation with the severity of MetS whereas, the TSH level was significantly high only in SMS and the uric acid level was not correlated with the MetS.

Conclusions: In the present study, there was higher mean serum hs-CRP level in patients with metabolic syndrome which showed a linear increase with increasing number of components of the metabolic syndrome. Though available literature indicated that hyperuricemia adult subjects tend to develop MetS more frequently our findings showed this increase was not dependent on the severity of MetS. Also, significantly high TSH levels were found only in severe MetS suggest that as per this study the serum hs-CRP values may be consider as the diagnostic criteria for metabolic syndrome and helps to improve future prediction of development of type 2 DM and cardiovascular diseases.

Keywords: hs-CRP, Metabolic syndrome, Non-lipid risks, Uric acid and TSH

INTRODUCTION

Metabolic syndrome (MetS) is defined as the constellation of diseases having three or more of the

following group of interconnected factors: central adiposity or higher waist circumference, high values of triglycerides, elevated blood pressure, impaired fasting glucose, and decreased high-density lipoprotein (HDL) cholesterol.¹

In the present days, there is a global interest in MetS due to its elevated prevalence in association with impending type 2 diabetes mellitus and cardiovascular complications and determining the risk factors of MetS is of urgent need for the prevention and screening of MetS.

In children, adolescents and adults, serum uric acid (SUA) which is produced in the purine metabolism of hepatic glycolysis, is elevated in type 2 diabetes mellitus and MetS.^{2,3} DeBosch et al, showed through an animal genetic study that hyperuricemia which alters the metabolism via the enterocyte urate transporter GLUT9 that might straight away cause MetS is encoded by the SLCA9 gene.⁴ Further Facchini et al, established that insulin resistance (IR) is accountable for this pathophysiological mechanism.⁵

Elevated levels of high-sensitive C-reactive protein (hs-CRP), an acute phase protein is commonly seen in MetS patients.⁶ Earlier studies have revealed a significant relationship between metabolic disorders and increased levels of hs-CRP.^{7,8} Thyroid hormones have a profound effect on energy homeostasis, lipid and glucose metabolism, and blood pressure. Therefore, it is hypothesized that functional changes in the thyroid gland might have an association with MetS and its related components including obesity, IR, lipid and glucose metabolism abnormalities, and raised blood pressure.⁹

Hence present study aimed to study the role of hs-CRP, uric acid and TSH in metabolic syndrome.

Aim and objective was to study the significance of serum highly sensitive C-reactive protein (hs-CRP), serum uric acid (SUA) and thyroid stimulating hormone (TSH) levels in metabolic syndrome.

METHODS

A total of four hundred and fifty subjects (211 men and 239 women) aged ≥ 35 years attending our institute hospital from 2nd December 2015 to 4th August, 2017 were included in this study. The study protocol was approved by the Institutional Ethics Committee. All the participating subjects in the study gave written informed consent.

As per the guidelines issued by the following international organizations. MetS is defined according to the 2009 harmonizing definition set by a joint statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and

International Association for the Study of Obesity, as the presence of three or more of the following five criteria:¹⁰

- Waist circumference in South Asians >90 cm in men and >80 cm in women,
- Serum triglycerides levels >150 mg/dl,
- Serum HDL cholesterol levels <40 mg/dl in men and <50 mg/dl in women, under treatment is an alternate indicator
- Systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg) under treatment is an alternate indicator, and
- Fasting serum glucose levels >100 mg/dL under treatment.¹¹
- The same standard is also stated in the modified NECP ATP III definition.¹²

The groups were divided into three groups (150 participants in each group), according to the number of components of Metabolic syndrome risk factors mentioned above they acquired.

- Group I: Subjects with less than any of the three components of metabolic syndrome (Control group).
- Group II: Subjects with any three components of metabolic syndrome (MS group)
- Group III: Subjects with more than three components of metabolic syndrome [Severe MS group (SMS)]

Inclusion criteria

Insulin resistance, hypertension, type II diabetes mellitus, increased BMI, is ≥ 23 , Increased waist circumference ≥ 36 inches (90cm) in males and ≥ 32 inches (80cm) in females and age limit is ≥ 35 .

Exclusion criteria

Any recent infections, Active lifestyle, PCOD in women and fatty liver disease.

Parameters

Baseline parameters

Blood pressure and anthropometric data including height, weight, waist circumference was measured using standard techniques.

BMI was calculated by dividing the weight in kilograms by height in meters squared. BMI ≥ 23 kg/m² as overweight individuals according to the revised guideline of WHO Western Pacific region.¹³

Waist circumference was measured using measuring tape with measurements made halfway between the lower border of the ribs and iliac crest in a horizontal plane.¹⁴

Blood Pressure was measured using a Mercury Sphygmomanometer (Diamond, Mumbai, India) with the patients in a sitting position, legs uncrossed. After 5 minutes of rest in the sitting position, BP was measured on both arms and the higher of the two is taken into consideration. If the systolic and diastolic blood pressure were in different categories, the higher of the two was used in the classification and on that visit; fasting blood samples was drawn from the subjects.

Biochemical analysis

Fasting blood samples were obtained from the subjects and centrifuged at 2000×g for 10 min. Samples were analyzed for MetS component of fasting plasma glucose, high density lipoprotein, triglycerides, uric acid using by ERBA EM-360 fully automated analyzer. Also, MetS non-lipid risk factors such as serum TSH, high sensitive C-reactive protein (hs-CRP) were assessed by Enzyme Linked Immuno Sorbent Assay (ELISA). For non-lipid risk factor analytical purpose, the individual having serum level of hs-CRP <1mg/l were considered as low risk, between 1-3 mg/l as medium risk and >3mg/l as high risk person.

Likewise, among the hyperuricemia subjects the risk value was assigned to the subjects who were diagnosed with their SUA value ≥ 6.0 mg/dl in women and ≥ 7.0 mg/dl in men (normal value was 2.6 to 6mg/dl in women and 3.5 to 7.2mg/dl in men). As the normal value of TSH is 0.4-4.2 μ IU/dl; ≤ 0.39 μ IU/dl an increased value of ≥ 4.21 μ IU/dl was considered as abnormal.¹⁵

Statistical analysis

Data were entered on Excel and imported for analysis on SPSS v 16. Distribution was determined by Shaipro-Wilk's Test. All quantitative variables were described as

Mean and Standard Error. One-way ANOVA was used to measure the difference between means of hs-CRP, serum uric acid and TSH values across the three groups, viz, Normal (Controls), Metabolic Syndrome (MS group) and Severe Metabolic Syndrome (SMS group). Differences between groups were determined by post hoc test. Significance was considered at 5%.

RESULTS

One-way ANOVA was used to measure the difference between means of hs-CRP, serum uric acid and TSH values across the three groups, viz, Normal (Controls), Metabolic Syndrome (MS group) and Severe Metabolic Syndrome (SMS group). Differences between groups were determined by post hoc test (Table 1 and Figure 1). Individual risk factor components of MetS were compared between the controls and cases.

Table 1 shows fasting plasma glucose (FPG) to be significantly higher among MS and SMS groups when compared to controls. HDL-C was lower in MS and SMS groups when compared to control group. This was statistically significant. Mean Triglycerides, SBP, DBP and waist circumference (WC) was significantly higher in MS and SMS groups when compared with Controls.

In Figure.1, Mean hs-CRP levels are higher in MS group (2.2 \pm 0.2)** and in SMS group (2.1 \pm 0.1)* when compared to control (1.5 \pm 0.1) group, this difference was statistically significant (P 0.001). Mean uric acid levels are high 5.2 \pm 0.1** and 5 \pm 0.1* in SMS and MS group respectively when compared to control (4.6 \pm 0.1) group which was statistically significant (P 0.008). Similarly the mean TSH levels which are high in MS group (3.2 \pm 0.2)* and in SMS group (3.0 \pm 0.2) compared to that of control group (2.6 \pm 0.1) but the difference was statistically not significant (p 0.66).

Table 1: Comparison of Fasting plasma glucose (FPG), High density lipoprotein (HDL-C), Triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP) and waist circumference (WC) in controls, MS and SMS group.

| Variable | Control Group I (Mean \pm SE) | MS Group II (Mean \pm SE) | SMS Group III (Mean \pm SE) | P value |
|-----------------------|------------------------------------|--------------------------------|----------------------------------|----------|
| FPG (mg/dL) | 81.1 \pm 1.1 | 122.3 \pm 4.4 | 159.5 \pm 4.8 | <0.001** |
| HDL-C (mg/dl) | 45.2 \pm 0.4 | 43.7 \pm 0.2 | 42.9 \pm 0.2 | <0.001** |
| Triglycerides (mg/dL) | 130.6 \pm 3.6 | 185.6 \pm 5.3 | 269.1 \pm 7.9 | <0.001** |
| SBP (mmHg) | 122.5 \pm 1.0 | 137.9 \pm 1.3 | 146.7 \pm 1.3 | <0.001** |
| DBP (mmHg) | 78.1 \pm 0.6 | 82.9 \pm 0.7 | 86.5 \pm 0.8 | <0.001** |
| WC (c.m) | 83.5 \pm 0.5 | 90.3 \pm 0.6 | 97.8 \pm 0.4 | <0.001** |

I-Control group; II-MS (metabolic syndrome) group

III-SMS (severe metabolic syndrome) group

*significant (p<0.05), **highly significant (p <0.001)

Table 2 shows the relative risk of hs-CRP, uric acid and TSH in MetS. For the hs-CRP, the low level group are

the majority (43.6%). This is unlike the other two parameters where subjects belonging to the normal level

group were the majority (81.6% of subjects had normal levels of uric acid, 77.6% of subjects had normal levels of TSH). High risk of hs-CRP in control MS group and SMS group and it is relatively increased from MS (27.3%) and SMS group (28.7%), when compared to control group (13.3%). High values of uric acid were increased from MS (12%) and SMS group (20.7%)

participants when compared to control group (2%). TSH high reference values were also increased from MS (17.3%) and SMS groups (26%) when compared to control group (13.3%). It indicates that all the three non-lipid risk factors increases risk in both MS group to SMS patients and more risk in SMS group.

Table 2: Distribution of hs-CRP, uric acid and TSH values among different risk groups of controls, MS and SMS.

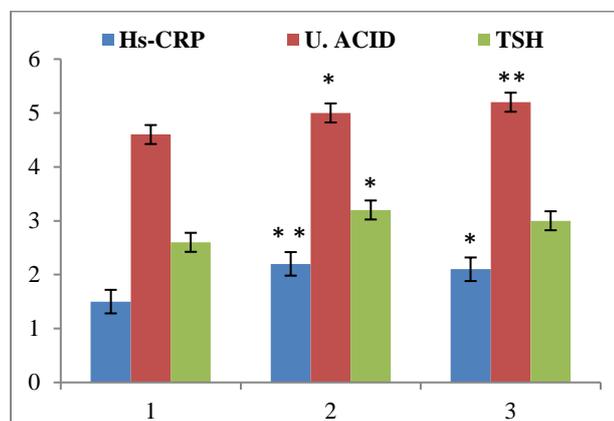
| Non-lipid variable | Risk category | Control Group I n-150 | MS Group II n-150 | SMS Group III n-150 | Total N-450 |
|---------------------------------------|---|--------------------------|----------------------|------------------------|----------------|
| hs-CRP risk-groups (mg/L) | Low (≤ 1) | 85 (56.7%) | 55 (36.7%) | 56 (37.3%) | 196 (43.6%) |
| | Normal (1 to 3) | 45 (30%) | 54 (36%) | 51 (34%) | 150 (33.3%) |
| | High (≥ 3) | 20 (13.3%) | 41 (27.3%) | 43 (28.7%) | 104 (23.1%) |
| Uric acid Risk-groups (mg/dl) | Low (Male- <3.4 (Female- <2.5) | 20 (13.3%) | 10 (6.7%) | 0 (0%) | 30 (6.7%) |
| | Normal (Male-3.5-7) (Female- 2.6-6) | 126 (84%) | 122 (81.3%) | 119 (79.3%) | 367 (81.6%) |
| | High (Male- >7 (Female- >6) | 4 (2.6%) | 18 (12%) | 31(20.7%) | 53 (11.7%) |
| TSH risk- groups (μ IU/dl) | Low (≤ 0.39) | 4 (2.7%) | 4(2.7%) | 8(5.3%) | 16 (3.6%) |
| | Normal (0.4-4.2) | 126 (84%) | 120 (80%) | 103 (68.7%) | 349 (77.6%) |
| | High (≥ 4.3) | 20 (13.3%) | 26 (17.3%) | 39 (26%) | 85 (18.8%) |
| | | 100% | 100% | 100% | 100% |

I-Control group

II-MS (metabolic syndrome) group

III-SMS (severe metabolic syndrome) group

*significant (p<0.05), **highly significant (p <0.001)



1-Control group

2-MS (metabolic syndrome) group

3-SMS (severe metabolic syndrome) group

*significant (p <0.05), **highly significant (p <0.001)

Figure 1: Comparison non-lipid risk factors- high sensitive C-reactive protein (hs-CRPmg/L), serum uric acid (SUA mg/dl) and thyroid stimulating hormone (TSH μ IU/dl) among control, MS and SMS. n=150 each group.

Further in Table 2, non-lipid factors were classified as low, normal and above normal. Distribution of study

population in each category is presented. The risk groups in hs-CRP: Control vs MS group was highly significant (P<0.001, z statistic 3.384 OR=2.259) and control vs SMS group was significant (P 0.001, z statistic 3.275 OR=2.195). Serum uric acid risk group analysis of Control vs MS group was not significant (P 0.542 z statistic 0.609 OR 1.205) and Control vs SMS group was also not significant (P 0.2978 z statistic 1.040 OR 1.368), TSH risk groups analysis it has found Control vs MS group was not significant (P 0.369 z statistic 0.899 OR 1.313) but Control vs SMS group was significant (P 0.002 z statistic 3.017 OR 2.396).

DISCUSSION

MetS is a cluster of risk factors including increased blood pressure, abdominal obesity, lipid abnormalities, and impaired glucose metabolism. Individuals with MS have much higher risk for cardiovascular diseases.¹²

Among the novel risk factors for cardiovascular disease currently under investigation, high-sensitivity C-reactive protein (hs-CRP) is most promising.¹⁷ In the present study, there was higher mean concentration of hs-CRP in patients with metabolic syndrome (1.5 \pm 0.1mg/l v/s 2.2 \pm 0.2mg/l V/S 2.1 \pm 0.1mg/l) and there was a linear

increase in the values with increasing number of components of the metabolic syndrome. These results were in accordance with a study by Gowdaiah PK et al.¹⁸ Similar finding was found by Bo S et al.¹⁹ Anubha Mahajan et al also had similar results where hs-CRP values were significantly elevated in subjects with metabolic syndrome compared to subjects without metabolic syndrome.²⁰ This suggests the fact that higher the number of components of metabolic syndrome in a patient, higher the values of hs-CRP and the risk of development of cardiovascular events.

As the literature reveals that hyperuricemic subjects tend to develop MetS, in this study serum uric acid level was analyzed among the patients. Mean uric acid levels are high ($5.2 \pm 0.1 \text{ mg/dl}$) in SMS group, ($5.0 \pm 0.1 \text{ mg/dl}$) in MS group when compared with the control ($4.6 \pm 0.1 \text{ mg/dl}$) group, the increase being statistically significant ($P=0.008$). Authors findings largely agree with the available literature obtained in adult subjects which suggests that hyperuricemia subjects tend to develop MetS more frequently.^{21,22}

In a scientific report by Cicero AF et al, MetS was more frequent for higher SUA concentrations rather than the population's mean in both men and women.²³ Yuan H et al; in their meta-analysis, concluded that higher SUA levels led to an increased risk of MS regardless of the study characteristics, and were consistent with a linear dose-response relationship. In addition, SUA was also a causal factor for the non alcoholic fatty liver disease (NAFLD) risk.²⁴

Thus, similar to hs-CRP values, the mean serum uric acid levels increased with each additional component. A study by Ford et al was in support of this finding.²⁵

In the present study, mean TSH levels are high ($3.2 \pm 0.2 \mu\text{IU/dl}$) in MS group and ($3.0 \pm 0.2 \mu\text{IU/dl}$) in SMS group compare to control ($2.6 \pm 0.1 \mu\text{IU/dl}$) group. But this difference was statistically not significant ($P=0.66$). We found majority of cases of high risk group in metabolic syndrome and severe metabolic syndrome than the control group (Table 2) i.e. In above normal group ($\geq 4.3 \mu\text{IU/dl}$) majority of cases were found in MS and SMS groups compare to controls. Similar results were found in study by Lee Y K, et al, i.e. the percentage of subjects with metabolic syndrome consistently and significantly increased with TSH concentration ($P < 0.05$).²⁶

Limitations of the present study are with respect to the age of subjects. This study included subjects >35 years. We suggest minimum age of 25 years so that more control subjects without any disease process are available. Also, authors suggest a maximum age restriction of 65 years to get a much clear picture and help in early prediction of Mets in this age group, and also thus avoiding influence of aging process and other geriatric complications.

CONCLUSION

From the results of the present study it can be concluded that, patients with metabolic syndrome have significantly higher levels of hs-CRP and serum uric acid when compared to controls and hs-CRP levels increased linearly with increasing number of metabolic syndrome components. High TSH levels were also found in majority of cases of MS and SMS groups compared to control groups.

There is accumulating evidence that elevated levels of the inflammatory marker hs-CRP and serum uric acid levels are associated with increased risk for development of cardiovascular disease and diabetes mellitus. Adding hs-CRP values in the diagnostic criteria for metabolic syndrome has shown to improve future prediction of development of these diseases.

Future studies would include the role of other non-lipid factors such as T3, T4 levels, urine albumin levels, serum creatinine and albumin-creatinine ratio in Mets.

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Conflict of interest: None declared

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