Original Article

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Evaluation of Association of Hyperuricaemia with Metabolic Syndrome and Insulin Resistance

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ABSTRACT

Introduction: The prevalence of Metabolic Syndrome (MetS) ranges from <10% to as much as 84% depending on region and composition of the population studied. The MetS is a growing public health problem in the world.

Aim: To evaluate association of hyperuricaemia with components of MetS and insulin resistance.

Materials and Methods: Sixty patients with MetS were conveniently recruited. MetS was defined as per Adult Treatment Panel III (ATP III) guidelines. For the purpose of analysis study participants were grouped into, group-I (controls - normal serum uric acid levels) and group-II (cases - hyperuricaemia). Hyperuricaemia was defined with cut-off >6.8mg/dl in both men and women. Associated work up for MetS and insulin resistance like fasting blood sugar, fasting lipid profile, fasting insulin, serum uric acid was done. Blood pressure and anthropometric measurements including weight, height and waist circumferences were measured and BMI was calculated. HOMA IR method was used to measure the degree of insulin resistance. Logistic regression analysis was used to evaluate association of hyperuricaemia with MetS and insulin resistance. Receiver Operating Curve (ROC) was plotted to find out optimum cut-off value for insulin resistance.

Results: A significant increase in systolic blood pressure ($p < 0.001$) and triglyceride levels ($p=0.027$) were observed in hyperuricaemia subjects when compared to controls. After adjusting for potential confounders, Insulin resistance (HOMA IR >3.4) was independently associated with hyperuricaemia (OR=5.79, 95% CI=1.6- 20.69, $p=0.007$).

Conclusion: Insulin resistance beyond a threshold is independently associated with hyperuricaemia in subjects with MetS.

Keywords: Homeostasis model assessment of insulin resistance, Public health problem, Serum uric acid

INTRODUCTION

Uric acid is the end product of dietary and endogenous purine metabolism in humans [1]. Serum Uric Acid (SUA) concentrations depend on the balance between the intake, endogenous synthesis, excretion ratio and metabolism of purines. Any alteration in the balance between these factors could trigger hyperuricaemia, defined as a SUA concentration >6.8 mg/dL [2]. Studies have shown that high concentrations of SUA have been associated with an early onset of hypertension and predicts rise in blood pressure, an increase in body and triglyceride levels [3-5]. In several experimental studies it has been observed that, an elevated SUA concentrations precede much before the development of insulin resistance and thus suggests that hyperuricaemia could be a new marker for MetS [6-11].

MetS is an important public health problem affecting nearly 25.9% of the world population. Earlier studies demonstrated high prevalence of MetS among patients with gout [6-8]. Some authors claimed the existence of association between hyperuricaemia and MetS even in healthy individuals [6-8]. Many cross-sectional studies have demonstrated a relationship between increased SUA concentrations and MetS prevalence [9-11].

It is proposed that UA is one of the determinants of the MetS [11]. The odds of developing MetS are 1.6 fold times higher in individuals with elevated levels of SUA [12]. But there was no established relationship between hyperuricaemia, insulin resistance and components of MetS. The present study was aimed to evaluate the association of hyperuricaemia with MetS and insulin resistance.

MATERIALS AND METHODS

In this case control study 60 subjects (30 cases and 30 controls) with MetS aged 19 years and above were included by following convenient sample technique. The sample size was calculated statistically, with power of the study at 80%, 95% Confidence interval, ratio of controls to cases as 1, anticipated odds ratio of 5 and proportion of controls with exposure as 25%. It was calculated from Open Epi, Version 3.0. The MetS was defined according to the diagnostic criteria of ATPIII guidelines [13]. The study was carried out for a period of 2 years from August 2013 to July 2015 in a tertiary care hospital. All the study participants were recruited after obtaining a written informed consent. Prior to the initiation the study protocol was approved by institutional ethics committee. Patients with type-1 diabetes mellitus, chronic kidney disease, lymphoproliferative disorders, haemolytic disorders, myeloproliferative disorders, using drugs like salicylates, diuretics like thiazides, levodopa, ethambutol, cyclosporine, nicotinic acid, pyrazinamide and who consume alcohol≥10 grams per day were excluded from the study. Hyperuricaemia is defined as SUA levels >6.8mg/dL in both males and females [2]. Based on SUA levels the total 60 subjects were divided into two groups namely, controls (n = 30) and cases (n = 30). MetS subjects with serum uric acid < 6.8mg/dL served as controls and > 6.8mg/dL considered as cases. The blood pressure and anthropometric measurements including weight, height, and waist circumferences were noted and accordingly Body Mass Index (BMI) was calculated. Homeostasis model assessment (HOMA-IR) 2.0 computerized method was used to measure insulin resistance [14]. All the other biochemical parameters and SUA levels were measured by using auto analyser.

STATISTICAL ANALYSIS

Data was presented as Mean±SD. The categorical variables were presented as proportions. Independent sample t-test was done to find out difference between group-I and group-II. Chi square test

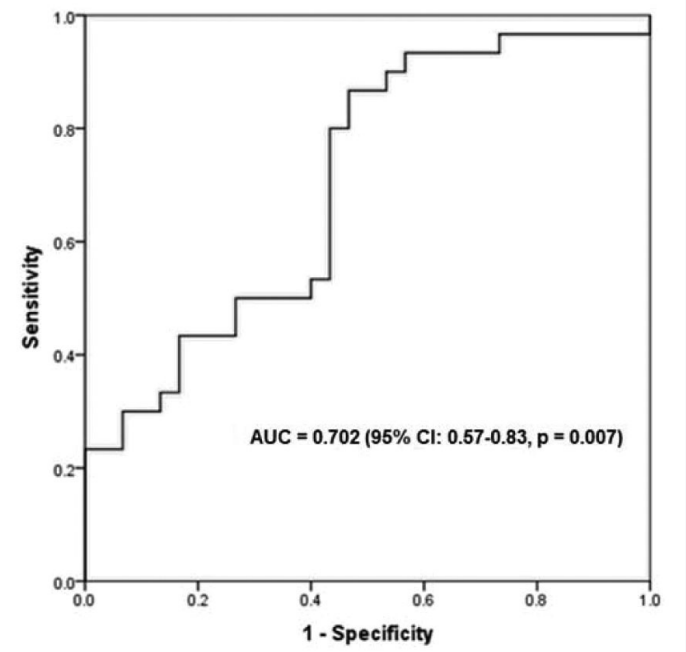
was done for categorical variables. Multiple logistic regression was carried out to find out independent predictors of hyperuricaemia. Receiver Operating Curve (ROC) was plotted to find out the optimal cut-off value for insulin resistance. A p-value <0.05 was considered statistically significant. Data was analysed using statistical package of social sciences (SPSS version 17.0).

RESULTS

The mean age and male: female ratio of the study population was found to be 52.42±10.60 years and 35:25, respectively. Based on SUA levels, 12 (40%) females and 18 (60%) males were found to have hyperuricaemia. A significant difference in mean HOMA-IR (p=0.009), systolic blood pressure (< 0.001), and triglycerides levels (p=0.027) were observed between these two groups [Table/Fig-1]. However, after logistic regression there was no significant association between hyperuricaemia and components of MetS. The ROC curve for insulin resistance was found to be significant with area under the curve 0.702 (p=0.007, 95% CI= 0.56 -0.83) [Table/Fig-2]. Based on ROC curve an optimal cutoff point for HOMA IR was found to be 3.4 with 80% (95% CI=0.59 -0.90) sensitivity and 68% (95% CI= 0.53-0.82) specificity, respectively. Based on HOMA IR cut-off value, 37 subjects had HOMA IR>3.4. Among them 13 (35.1%) were found to have normal uric acid levels and remaining 24 (64.9%) were found to have hyperuricaemia.

Variables	Controls (n =30) Normal uric acid	Cases (n=30) Hyperuricaemia	p-value
Serum Uric acid (mg/dL)	4.63±1.25	8.22±1.37	< 0.001
Systolic blood pressure (mmHg)	138.40±14.63	153.20±9.30	<0.001
HOMA-IR	4.59±3.60	7.79±5.35	0.009
Triglycerides (mg/dL)	162.90±62.07	198.16±58.33	0.027
Weight (kg)	65.36±13.6	70.80±13.36	0.124
Height (cm)	160.63±8.57	161.13±8.43	0.824
Body mass index (kg/m^2)	25.67±4.24	27.28±4.61	0.162
Waist circumference (cm)	90.66±10.54	95.20±6.60	0.05
Fasting blood sugar (mg/dL)	142.43±54.09	165.36±50.94	0.09
Fasting Insulin (µIU/ml)	13.11±9.7	18.63±11.86	0.054
HDL (mg/dL)	39.12±7.42	38.80±6.97	0.079
Males	17	18	0.793
Females	13	12	0.793

[Table/Fig-1]: Clinical characteristics of study population.
* HOMA-IR- Homeostasis model assessment.
HDL-C – High density lipoprotein cholesterol.



[Table/Fig-2]: Receiver operating curve showing optimal cut-off for insulin resistance.

Variables	B (95% CI)	Adjusted Odds Ratio	p-value
HOMA-IR	1.75(1.62-20.69)	5.79	0.007
Fasting blood sugar	0.46(0.20-12.55)	1.59	0.656
Triglycerides	1.03(0.72-11.02)	2.82	0135

[Table/Fig-3]: Multiple logistic regression showing independent predictors of hyperuricaemia.
* HOMA-IR- Homeostasis model assessment

After adjusting for waist circumference, fasting blood sugar and triglycerides, HOMA IR > 3.4 was independently associated with hyperuricaemia (OR=5.79, 95% CI=1.6- 20.69, p = 0.007) [Table/Fig-3]. The other components of MetS were not significantly associated with hyperuricaemia [Table/Fig-3].

DISCUSSION

The present study was aimed to find out the association of hyperuricaemia with MetS and insulin resistance. This study demonstrated that hyperuricaemia is directly proportional to insulin resistance as an independent factor. This association is relevant once the SUA is more than 6.8mg/dL.

Hyperuricaemia is associated with wide range of diseases including MetS [15,16]. Both cross-sectional and prospective studies have consistently shown that uric acid levels were associated with the risk of MetS [17-20]. However, whether the uric acid has the causal effects on MetS still remains to be investigated [21]. Chen LY et al., observed negative correlation between HDL-C and UA [12]. The likely mechanism is the relationship between decreased HDL-C and insulin resistance [22]. In our study there was no correlation between HDL, triglycerides and uric acid. Over all in our study the components of MetS was not associated with hyperuricaemia which is in discordance with previous studies [17-21]. This may be due to their individual life style patterns.

However, in our study it was also observed that insulin resistance was independently associated with hyperuricaemia even after adjusting for other components of MetS. It has been suggested that hyperuricaemia appears to be a part of insulin resistance syndrome due to the resemblance between insulin resistance syndrome and hyperuricaemia [23-25]. A possible explanation has been supported by several epidemiological studies [23-25]. In a study done with Jewish population it has been observed that a significant positive linear correlation was observed between FSA acid levels and plasma insulin responses (sum of 1- and 2-h post oral glucose levels) in both males and females [25]. Subsequent study showed a positive relationship after adjusting for age, gender, overall obesity and abdominal obesity [26]. In a case-control study, Sinagra D et al., demonstrated that insulin resistance to be independently associated with fasting SUA [27]. Experimental studies also indicated that uric acid might play a role in insulin resistance promoting secretion of inflammatory factors and adipocytokine [21,22]. This is in concordance with our study. It has been suggested that the positive association between the insulin resistance syndrome and fasting hyperuricaemia is partly explained by the fact that hyperinsulinemia may decrease the renal excretion of uric acid additionally; insulin could indirectly act on UA, since there is an association between hyperinsulinemia and hypertriglyceridemia [28]. However, in these epidemiological studies optimal cut-off values for insulin resistance was not defined. In the present study, we found that optimal cut-off for insulin resistance was 3.4 and HOMA IR >3.4 were significantly associated with hyperuricaemia.

LIMITATION

Firstly, this study can not be generalised to whole population because insulin resistance varies across different ethnic groups. Secondly it

is a cross sectional study and hence, further prospective studies are required with larger sample size to establish the causal relationship between hyperuricaemia and insulin resistance.

CONCLUSION

Metabolic syndrome is a common disorder in the community associated with insulin resistance. In our study insulin resistance is independently associated with hyperuricaemia in subjects with MetS. Hence, high uric acid levels can be considered as an indirect marker of insulin resistance which is affordable and rapid tool.

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