

# Correlation Between Serum Uric Acid Levels with Metabolic syndrome and its Components

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**Background.** Metabolic syndrome (MetS) encompasses various metabolic abnormalities linked to an increased risk of type 2 diabetes mellitus and cardiovascular diseases, involving insulin resistance, central obesity, dyslipidemia, hypertension, and inflammatory factors. While different diagnostic criteria exist, ongoing debate persists regarding additional risk factors such as uric acid levels. This study aimed to determine the correlation between serum uric acid (SUA) levels and the presence of metabolic syndrome (MetS) among adult Filipino patients.

**Method.** A single-center, retrospective, cross-sectional analytical study was conducted, including 99 Filipino subjects from the database of an insulin resistance study. Demographic, relevant anthropometrics and biochemical characteristics were obtained. Pearson correlation was performed to assess associations between SUA levels, MetS diagnosis and MetS components. Stepwise logistic regression analysis was done, which used age, sex and SUA to determine whether these variables can account for MetS classification.

**Conclusion.** Serum uric acid was not associated with the MetS; however, associations were observed with specific components of MetS.

**Keywords.** Uric acid, metabolic syndrome, hyperuricemia, metabolic health, Philippines

## Introduction

Metabolic syndrome (MetS) refers to the co-occurrence of metabolic abnormalities that identify individuals at risk of developing type 2 diabetes mellitus and cardiovascular diseases.<sup>1</sup> The pathophysiologic mechanisms involved in the metabolic syndrome are related to insulin resistance, central obesity, dyslipidemia, hypertension, and the presence of prothrombotic and proinflammatory factors.<sup>2</sup>

The earliest definition of metabolic syndrome was proposed by the World Health Organization in 1998 which required evidence of insulin resistance with the addition of two or more of the following: obesity, dyslipidemia, hypertension and microalbuminuria. Insulin resistance could be in the form of impaired fasting glucose, impaired glucose tolerance, an elevated homeostatic model of assessment of insulin resistance (HOMA-IR) or hyperinsulinemic euglycemic clamp studies.<sup>3</sup> The obesity criteria used waist-hip-ratio or body mass index, later on simplified to measurements of waist circumference.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) diagnostic criterion is currently the widely used definition for metabolic syndrome in epidemiological studies. In this criteria, diagnosis is established in the presence of three out of five traits: abdominal obesity, defined as an enlarged waist circumference; serum triglycerides  $\geq 150$  mg/dL or drug treatment for elevated triglycerides; serum high-density lipoprotein cholesterol (HDL-c)  $< 40$  mg/dL in men and 50 mg/dL in women; blood pressure  $\geq 130/85$  mmHg or on anti-hypertensive medication; and fasting plasma glucose of  $> 100$  mg/dL or on drug treatment for elevated blood glucose. Unlike the WHO criteria, no single factor was required as a prerequisite for diagnosis.

Other definitions for metabolic syndrome utilize different parameters and threshold values. In order to unify criteria, a Harmonization definition was published in a joint statement in 2009 by the International Diabetes Federation (IDF); National Heart, Lung, and Blood Institute (NHLBI); American Heart Association (AHA); World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. According to this definition, metabolic syndrome diagnosis is made when any three of the five following risk factors are present: enlarged waist circumference with population-specific and country-

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specific criteria; elevated triglycerides, defined as  $\geq 150$  mg/dL, decreased HDL-C, defined as  $< 40$  mg/dL in men and  $< 50$  mg/dL in women, elevated blood pressure, defined as systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 85$  mm Hg and elevated fasting glucose, defined as blood glucose  $> 100$  mg/dL, patients on drug treatment to manage hypertriglyceridemia, low HDL-C, hypertension, and hyperglycemia were also included as alternative indicators.<sup>4</sup>

The current MetS components such as insulin resistance, obesity, and dyslipidemia promote the development of cardiovascular disease and type 2 diabetes mellitus. However, a previous study reported that the currently defined traits cannot explain all these events.<sup>5</sup> Thus, other risk factors associated with the metabolic syndrome such as inflammatory markers, microalbuminuria, and hyperuricemia have been extensively studied and debated for inclusion in the MetS criteria.<sup>6-10</sup>

It has been suggested that MetS is a consequence of excessive fat storage. Excess fat is stored in adipose tissues, liver, and serum, often in association with the development of insulin resistance and hypertension.<sup>10</sup> Mechanisms in fat storage involve multiple genetic factors, but recent studies suggest a role for nucleic acid metabolism, in which stimulation of adenosine monophosphate (AMP) deaminase promotes fat storage and insulin resistance.<sup>10-13</sup> Uric acid, a product of AMP deaminase, is identified as a key factor that promotes this fat storage.<sup>11,12,14,15</sup> Epidemiologic studies have consistently shown associations of uric acid with cardiovascular and cerebrovascular disease, including its risk factors such as hypertension, diabetes, dyslipidemia, kidney disease, smoking, and obesity.<sup>16-25</sup> This relationship is observed not only with hyperuricemia but also in normal to high normal levels of serum uric acid.<sup>25</sup>

Multiple studies including different Asian population groups have reported strong associations between metabolic syndrome and its components with serum uric acid elevation.<sup>26-32</sup> However, as of the present, no study has been performed to examine this relationship among the Filipino population. This study could provide unique insights into the metabolic health of this specific demographic group and can help inform targeted screening programs and interventions to improve metabolic health outcomes in the Filipino population.

This study aims to determine the association of serum uric acid levels and the presence of metabolic syndrome and its associated components among Filipino individuals seen in an outpatient clinic.

## Methodology

This is a single-center, retrospective, cross-sectional analytical study done at Chong Hua Hospital, a tertiary hospital in the Philippines from October 2019 to January 2020. The study subjects were Filipino adults  $\geq 18$  years old, seen at the Executive Check-Up Unit with no prior diagnosis of hypertension, diabetes or dyslipidemia and

not taking any maintenance medications. The relevant biochemical measurements of the patients were reviewed using electronic medical records. Patients whose medical records cannot be retrieved or with missing information were excluded. A total of 99 patients were included in the final analysis. In this study, the 2009 harmonizing definition of metabolic syndrome (MetS) was used to identify patients with the diagnosis and the waist circumference thresholds were based on the current recommendations by the World Health Organization for the Asian population.<sup>4</sup> The clinical protocol was reviewed and approved by the Institutional Ethics Review Committee of Chong Hua Hospital.

## Sample Size

The paper employed purposive sampling as a sampling method. Patients were selected from a patient pool obtained from a previous insulin resistance study which included Filipino patients 18 years old and above seen at the Executive Check-up Unit (ECU). Among the 100 subjects in the patient pool, one did not have uric acid levels taken and was thus excluded. As a result, a total of 99 subjects were included in the final analysis and out of the 99, 15 were classified to have metabolic syndrome while 84 of the subjects did not have metabolic syndrome.

## Data Collection

Data was collected through chart review, following the criteria of study inclusion and exclusion. Information retrieved included the demographic data and anthropometric measurements of the study subjects, including the age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, body mass index (BMI) and waist circumference (WC). Blood results for fasting insulin, fasting plasma glucose, lipid profile, and serum uric acid analyzed at the hospital laboratory were also collected. HOMA-IR was calculated using the formula:  $\text{HOMA-IR} = \frac{\text{fasting insulin concentration (mIU/L)} \times \text{fasting plasma glucose concentration (mg/dL)}}{22.5}$ .

## Data Processing and Analysis

Analysis was done using SPSS software. Relevant descriptive statistics were computed for each variable of interest. Normality of distribution of continuous variables was tested using the Shapiro-Wilks test. Pearson correlation was done to determine associations between uric acid and the other variables of interest. The strength of association is determined based on the correlation coefficient,  $r$ . Mild associations are considered for  $r$  values at 0.1 – 0.3, moderate at 0.4 – 0.6, strong at 0.7 – 0.99. As the 0.05 was the chosen alpha for the entire study, these associations were deemed statistically significant if it were less than the aforementioned threshold. A stepwise logistic regression analysis was done in order to ascertain if a model containing demographics and serum uric acid can account for metabolic syndrome diagnosis. Entering the demographic variables in block one was essential in that results would later inform the need to control these

variables. Block two contained serum uric acid levels which was central to the current study.

## Results

### Baseline Characteristics

The demographic and anthropometric profile of the study population ( $n = 99$ ) are summarized in Table 1. The study subjects were generally middle adults ( $M = 44.38$  years,  $SD = 11.92$ ), and were nearly even distributed across sex (50 males and 49 females). Mean values for the anthropometric measurements are: waist circumference ( $M = 85.73$  cm,  $SD = 11.65$ ), weight ( $M = 69.65$  kg,  $SD = 16.127$ ), height ( $M = 162.08$  cm,  $SD = 9.35$ ), body mass index ( $M = 26.230$  kg/m<sup>2</sup>,  $SD = 4.51$ ), systolic blood pressure ( $M = 113.84$  mmHg,  $SD = 11.31$ ), diastolic blood pressure ( $M = 76.16$  mmHg,  $SD = 8.17$ ). The table also shows that age, weight, BMI, SBP and DBP were statistically different between the subjects. The waist circumference and the weight were not statistically different.

**Table 1.** Demographic and Anthropometric Characteristics of the Study Population ( $n = 99$ )

|                         | Mean $\pm$ SD; Frequency (%) |
|-------------------------|------------------------------|
| Age, years              | 44.38 $\pm$ 11.92            |
| Sex                     |                              |
| Male                    | 50 (50.51)                   |
| Female                  | 49 (49.49)                   |
| Waist Circumference, cm | 85.73 $\pm$ 11.65            |
| Weight, kg              | 69.65 $\pm$ 16.13            |
| Height, cm              | 162.09 $\pm$ 9.35            |
| BMI, kg/m <sup>2</sup>  | 26.23 $\pm$ 4.51             |
| SBP, mmHg               | 113.84 $\pm$ 11.31           |
| DBP, mmHg               | 76.16 $\pm$ 8.17             |

**Table 2.** Biochemical Characteristics of the Study Population ( $n = 99$ )

|         | Mean $\pm$ SD      |
|---------|--------------------|
| Insulin | 11.09 $\pm$ 6.00   |
| FPG     | 93.17 $\pm$ 9.28   |
| HOMA-IR | 2.61 $\pm$ 1.54    |
| TC      | 202.46 $\pm$ 45.80 |
| Tg      | 111.82 $\pm$ 73.62 |
| LDL     | 125.15 $\pm$ 40.73 |
| HDL     | 57.42 $\pm$ 17.49  |
| SUA     | 5.92 $\pm$ 1.58    |

Insulin, uIU/mL; FPG, fasting plasma glucose; HOMA-IR, homeostatic model of assessment for insulin resistance; TC, total cholesterol; Tg, triglycerides; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; SUA, serum uric acid

Table 2 shows the biochemical parameters of the subjects included in the study. Mean values of the biochemical tests taken are: insulin ( $M = 11.09$  mIU/L,  $SD = 6.00$ ), fasting plasma glucose ( $M = 93.17$  mg/dL,  $SD = 9.28$ ), HOMA-IR ( $M = 2.61$ ,  $SD = 1.54$ ), total cholesterol ( $M = 202.46$  mg/dL,  $SD = 45.80$ ), triglycerides ( $M = 111.82$  mg/dL,  $SD = 73.62$ ), LDL ( $M = 125.15$  mg/dL,  $SD = 40.73$ ), HDL ( $M = 57.42$  mg/dL,  $SD = 17.49$ ), and serum uric acid

( $M = 5.92$  mg/dL,  $SD = 1.58$ ). The fasting plasma glucose, total cholesterol and SUA were not statistically different in the population. In contrast, insulin, HOMA-IR, triglycerides and HDL showed statistical difference.

### Metabolic Syndrome Prevalence

The prevalence rate of metabolic syndrome in the sample is 15.16% ( $n = 15$ ). Majority are males ( $n = 11$ ) and have a mean age of 45.87 ( $SD = 12.21$ ) years old. The average BMI for this group is 29.67 ( $SD = 12.21$ ) suggesting that they are classified under the obese category. A detailed comparison of the demographic and biochemical characteristics of the metabolic syndrome (MetS) group and non-metabolic syndrome (No MetS) are presented in Tables 3 and 4.

Patients under the MetS group had higher average waist circumferences (96.6 vs 83.786 cm), SBP (121.33 vs 112.5 mmHg) and DBP (83.333 vs 74.881 mmHg). Mean levels of the atherogenic lipids were also higher in this group. Mean total cholesterol among MetS subjects was higher (203.13 vs 202.23 mg/dL) as well as the average LDL (130.51 vs 124.18 mg/dL) and triglycerides (197 vs 96.61 mg/dL). However, mean HDL cholesterol in the MetS group appeared lower (42.287 vs 60.124 mg/dL). Mean serum uric acid levels were also noted to be higher in the MetS group (6.63 vs 5.79 mg/dL).

**Table 3.** Demographic and Anthropometric Characteristics of the Study Population ( $n = 99$ )

|                         | No MetS            | MetS               |
|-------------------------|--------------------|--------------------|
|                         | Mean $\pm$ SD      |                    |
| Age, years              | 44.12 $\pm$ 12.21  | 45.87 $\pm$ 10.34  |
| Waist Circumference, cm | 83.79 $\pm$ 10.43  | 96.60 $\pm$ 12.49  |
| Weight, kg              | 67.15 $\pm$ 12.95  | 83.65 $\pm$ 24.08  |
| Height, cm              | 161.12 $\pm$ 8.34  | 167.50 $\pm$ 12.72 |
| BMI, kg/m <sup>2</sup>  | 25.69 $\pm$ 4.00   | 29.27 $\pm$ 6.01   |
| SBP, mmHg               | 112.50 $\pm$ 11.07 | 121.33 $\pm$ 9.90  |
| DBP, mmHg               | 74.88 $\pm$ 7.84   | 83.33 $\pm$ 6.17   |

**Table 4.** Baseline Biochemical Characteristics of the Study Population According to Presence of Metabolic Syndrome ( $n = 99$ )

|         | No MetS           | MetS             |
|---------|-------------------|------------------|
|         | Mean $\pm$ SD     |                  |
| FBS     | 92.31 $\pm$ 9.24  | 98 $\pm$ 8.19    |
| TG      | 96.61 $\pm$ 61.57 | 497 $\pm$ 79.42  |
| HDL     | 60.12 $\pm$ 17.46 | 42.29 $\pm$ 6.53 |
| Insulin | 10.69 $\pm$ 5.78  | 13.34 $\pm$ 6.87 |
| HOMA-IR | 2.49 $\pm$ 1.46   | 3.28 $\pm$ 1.81  |
| BUA     | 5.79 $\pm$ 1.57   | 6.63 $\pm$ 1.53  |

### Serum Uric Acid Level-Metabolic Syndrome Relationship

As indicated in Table 4, subjects with MetS had higher mean serum uric acid levels compared to those with No MetS. Bivariate analysis was done to evaluate the association between SUA levels and the presence of MetS. The point biserial correlation is 0.192 ( $p = 0.057$ ) is weak and insignificant (though approaching significance)

- indicating that there is no relationship between metabolic syndrome classification and serum uric acid levels.

### Correlations of Serum Uric Acid Levels Among The Factors Associated with MetS

Table 5 provides a summary of the correlations between the SUA and all demographic and biochemical parameters measured in the study. Several parameters were noted to be significant. Moderate positive correlations were found between SUA and waist circumference ( $r = 0.42$ ), as well as weight ( $r = 0.46$ ). Furthermore, mild positive correlations were noted with height ( $r = 0.39$ ), body mass index ( $r = 0.35$ ), systolic blood pressure ( $r = 0.25$ ), diastolic blood pressure ( $r = 0.32$ ), total cholesterol ( $r = 0.22$ ), triglycerides ( $r = 0.38$ ), and LDL-c ( $r = 0.30$ ). Mild negative correlation was noted with SUA and HDL-c levels ( $r = -0.33$ ). However, no significant associations were found for fasting blood sugar ( $r = 0.13$ ), fasting insulin ( $r = 0.07$ ) and HOMA-IR ( $r = 0.08$ ).

**Table 5.** Correlations Between SUA and Factors Associated with the Metabolic Syndrome

| SUA and                  | Correlation Coefficient |
|--------------------------|-------------------------|
| Age                      | -0.032                  |
| Waist Circumference      | 0.417                   |
| Height                   | 0.389***                |
| Weight                   | 0.456***                |
| Body Mass Index          | 0.348***                |
| Systolic Blood Pressure  | 0.246*                  |
| Diastolic Blood Pressure | 0.316**                 |
| Insulin                  | 0.066                   |
| Fasting Plasma Glucose   | 0.130                   |
| HOMA-IR                  | 0.078                   |
| Total Cholesterol        | 0.229*                  |
| TG                       | 0.384***                |
| LDL                      | 0.301**                 |
| HDL                      | -0.332***               |

Note: \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

### Logistic Regression Analysis

As shown in Table 6, a hierarchical logistic regression analysis was done on the following variables: age, sex and SUA. For SUA, looking at the odds ratio, a point-increase in SUA level is associated with a higher likelihood for metabolic syndrome classification – about 1.29 times higher to be precise (or the odds are increased by 29%) – however, this is not significant. The confidence intervals show that true odds ratio may fall between 0.0827 to 2.019–crossing the threshold of 1, indicating that in the population, no effect exists. The confidence intervals for age (95% CI 0.966 - 1.063) as well as the sex (95% CI. 0.119 - 2.064) also cross the threshold of 1, suggesting that there is no effect

**Table 6.** Logistic Regression Model Coefficients – Metabolic Syndrome by Age, Sex and SUA Levels

| Predictor | Odds Ratios (95% CI) | p-value |
|-----------|----------------------|---------|
| Age       | 1.01 (0.97-1.06)     | .597    |
| Sex:      |                      |         |
| F - M     | 0.496 (0.12-2.06)    | .335    |
| BUA       | 1.29 (0.83-2.02)     | .260    |

### Discussion

In this retrospective cross-sectional study, the relationship between serum uric acid levels and metabolic syndrome diagnosis was examined among adult Filipino subjects in a health checkup clinic. The results demonstrated that MetS was not associated with serum uric acid levels, a similar finding observed in a study conducted on 102 Indonesian patients.<sup>33</sup> However, multiple studies that enrolled a larger population yielded conflicting results. There was an independent association of hyperuricemia with metabolic syndrome prevalence in a study of Taiwanese participants.<sup>28</sup> Another report which involved a Korean cohort also found strong associations between serum uric acid levels with the presence of metabolic syndrome.<sup>29</sup> Two Japanese studies consistently reported uric acid as a predictor of future metabolic syndrome.<sup>26, 31</sup> Despite these contrasting outcomes, one key observation noted in our study, which was also seen in the Indonesian report, was higher average serum uric acid levels among the subjects who had MetS.

Correlations between factors associated with the metabolic syndrome were also investigated. The current study showed that serum uric acid levels were associated with the parameters of metabolic syndrome. A negative association with SUA and HDL was found while positive correlations were noted with waist circumference, weight, height, body mass index, systolic blood pressure, diastolic blood pressure, LDL, and triglycerides. One of the underlying causes of metabolic syndrome is visceral obesity, which can be measured using waist circumference.<sup>2</sup> Among the parameters examined in the study, stronger correlations with waist circumference and weight were noted. The findings of this study confirmed significant positive relationships between SUA and obesity in several reports.<sup>34-36</sup> Hyperuricemia induces redox-dependent signaling and oxidative stress among adipocytes. Oxidative stress in the adipose tissue has been recognized as a major cause of insulin resistance and cardiovascular disease.<sup>32</sup> Another measure of adiposity such as body mass index showed positive correlations with SUA. Height likewise showed positive correlations with SUA. In a previous report, BMI and waist circumference were independently found to contribute to the prediction of visceral fat.<sup>37</sup> However, another study showed that an increased volume of visceral tissue in the abdomen corresponded not only to the presence of overweight but also normal body weight, especially among women.<sup>38</sup> In this report, correlations were found with waist circumference rather than BMI. Our data thus

supports the importance of obtaining measurements of waist circumference rather than the BMI alone.

The dyslipidemia characteristic of metabolic syndrome is that of low HDL with high triglyceride levels. This lipid pattern induces both an increase in small HDL particles and an increase in small, dense LDL particles, a feature that was found in visceraally obese subjects.<sup>39</sup> We found in our study positive associations of SUA with triglycerides and LDL and negative associations with HDL. The mechanism by which uric acid causes an increase in triglyceride levels is said to result from increased fat synthesis brought about by effects of oxidative stress in the Krebs cycle. In particular, aconitase is inhibited, leading to citrate accumulation and stimulation of ATP citrate lyase resulting in increased fat synthesis.<sup>10</sup>

One of the earliest associations of hyperuricemia was with hypertension.<sup>10</sup> The mechanisms for hyperuricemia-induced hypertension include inhibition of nitric oxide, enhanced activity of the renin-angiotensin system, and endothelial dysfunction from direct vascular endothelial injury due to uric acid crystal deposition.<sup>40</sup> In this study, positive correlations were found with SBP and DBP, confirming this relationship.

Hyperuricemia was also reported to be strongly associated with insulin resistance and abnormal glucose metabolism.<sup>40</sup> The reason behind this association is that elevated uric acid levels are associated with a decrease in endothelial nitric oxide levels, which is a key regulator for insulin sensitivity as it increases blood flow to peripheral tissues and enhance glucose uptake by cells. It was also reported that elevated uric acid levels were thought to induce beta cell damage and death. However, in this study, we did not find any significant relationships between uric acid levels and parameters of insulin resistance and diabetes. This contradicts the current evidence that shows that hyperuricemia is both present and predicts the development of insulin resistance and type 2 diabetes.<sup>41</sup>

There are several limitations identified in the present study that warrant consideration. First is sample adequacy. There were only 99 subjects recruited for analysis which did not meet the calculated sample size ( $n = 385$ ). The chart records of patients at the ECU revealed incomplete anthropometrics particularly waist circumferences as these were not routinely taken. Fasting insulin, which is required to determine the HOMA-IR to identify insulin resistance, was also not available among ECU patients. Thus, in this retrospective analysis, recruitment of subjects that will fit the inclusion criteria was limited to a pool of patients in a previous insulin resistance study which only involved 100 individuals.

Secondly, some of the variables were not normally distributed and significant outliers were present among them. Thus, caution should be taken in generalizing the results of this study. We recommend that for future studies, a bigger cohort should be considered and for the majority of the regions be represented.

## Conclusion

In conclusion, while no direct association between serum uric acid levels and MetS was found, our study highlights the importance of considering serum uric acid levels as a potential biomarker in assessing metabolic health and its associations with individual components of MetS.

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