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Original Research Article

Exploring the Association of Hyperuricemia with Diabetes, Hyperlipidemia, and Hypertension in Metabolic Syndrome

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Abstract:

Background: Metabolic syndrome is a multifaceted condition characterized by a cluster of cardio metabolic risk factors. This retrospective observational study aimed to examine the prevalence of hyperuricemia in individuals with metabolic syndrome and explore the association between hyperuricemia and various metabolic syndrome characteristics.

Methods: Data were collected from subjects who visited a tertiary care hospital between March 2018 and February 2023. Participants were selected based on the availability of serum uric acid measurements and documented information related to metabolic syndrome criteria as prescribed in National Cholesterol Education Program Adult Treatment Panel III 2005 (ATP III) guidelines. Descriptive statistics and phi coefficient were employed for data analysis.

Results: Out of 300 subjects, 186 (62%) subjects had hyperuricemia. Among patients with metabolic syndrome and hyperuricemia, the majority had hypertension (74%), hyperglycemia (42%), dyslipidemia (38%), and abdominal obesity (48%). In contrast, 114 (48%) metabolic syndrome patients without hyperuricemia had lower prevalence rates for these characteristics: hypertension 66(58%), hyperglycemia 46(40%), dyslipidemia 32(28%), and abdominal obesity 43(38%).

Conclusion: The Phi coefficients indicated a moderate positive association between hyperuricemia and hypertension, while the associations with hyperglycemia, dyslipidemia, and abdominal obesity were relatively weak. These findings suggest that hyperuricemia may play a role in the development and manifestation of certain characteristics in individuals with metabolic syndrome, particularly hypertension.

Keywords: Metabolic Syndrome, Hyperuricemia, Hypertension, Hyperlipidemia, Diabetes Mellitus.

Introduction

Metabolic syndrome is a complex health condition characterized by a cluster of interconnected metabolic abnormalities, including abdominal obesity, elevated blood pressure, high fasting blood sugar levels, dyslipidemia, and insulin resistance.[1] It poses a significant global public health concern due to its association with increased risk of cardiovascular disease, type 2 diabetes, and other chronic conditions. The etiology of metabolic syndrome involves a combination of genetic, metabolic, and lifestyle factors such as sedentary behaviour, poor dietary habits, and obesity.[2] Management of metabolic syndrome requires comprehensive interventions, including lifestyle modifications and pharmacological treatments, to reduce the risk of complications.[3] Understanding and addressing this syndrome are crucial for minimizing its impact on individuals' health. Uric

acid is a compound produced during the breakdown of purines in the body and is excreted through urine. It plays a crucial role in human biology as an antioxidant and contributes to the regulation of blood pressure and vascular health.[4] However, elevated levels of uric acid, known as hyperuricemia, are associated with an increased risk of gout, kidney stones, and cardiovascular diseases.[5]

Elevated uric acid levels have been linked to an increased risk of metabolic syndrome, as hyperuricemia is often observed in individuals with this condition. Studies suggest that uric acid may contribute to the development of metabolic syndrome through its effects on insulin resistance, inflammation, and oxidative stress.[1]

This retrospective observational study aimed to examine the prevalence of hyperuricemia in individuals with metabolic syndrome and explore the association between hyperuricemia and various metabolic syndrome characteristics.

Materials and Methods

This study was conducted using a retrospective observational design. The study involved a total of 300 subjects who visited the hospital over a period spanning from March 2018 to February 2023. The selection of participants was based on their availability of serum uric acid measurements and documented information pertaining to the criteria for metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III 2005 (ATP III) guidelines.

Patient aged 18 and above, diagnosed with metabolic syndrome based on ATP III guidelines, complete medical records, available serum uric acid measurements were included and aged below 18, incomplete medical records, known chronic kidney diseases or renal dysfunction, use of medications affecting serum uric acid levels, pregnancy or pregnancy-related complications, major systemic illnesses or conditions impacting study outcomes were excluded from study.

Data collection was carried out by extracting relevant clinical information, including serum uric acid levels, from the medical records of the participants. Descriptive statistics and the phi coefficient were utilized to analyze the collected data and determine the associations between hyperuricemia and metabolic syndrome characteristics. Institutional review board approval was obtained, Informed consent was waived due to the retrospective nature of the study design.

Result

Total 300 subjects with metabolic syndrome were included in the study. Out of which 186 (62%) subjects had hyperuricemia and 114 (38%) subjects without hyperuricemia. Subjects with and without Hyperuricemia and Metabolic syndrome were studied. It was found that out of 186 such patients, 138 (74%) were having hypertension, 79 (42.4%) were diabetic, 71 (38%) were having dyslipidaemia (elevated triglyceride of more than 150 mg/dL, low high-density lipoproteins <45 in males and less than 55 mg/dL in females) 89 (47.8%) were having abdominal obesity. Among the 114 subjects without hyperuricemia, it was found that 66 (58%) of these subjects had hypertension, 46 (40%) of the subjects had hyperglycemia. In terms of dyslipidemia, 32 (28%) of the subjects had it, and 43 (38%) of the subjects had abdominal obesity.

Table 1: Various characteristic in metabolic syndrome patients

S. No.	Characteristics	Metabolic Syndrome patients with Hyperuricemia		Metabolic Syndrome patients without Hyperuricemia		Phi Coefficient
		Yes	No	Yes	No	
1.	Hypertension	138(74%)	48(26%)	66(58%)	48(42%)	≈ 0.243
2.	Hyperglycaemia	79(42%)	107(58%)	46(40%)	68(54%)	≈ 0.005
3.	Dyslipidaemia	71(38%)	115(62%)	32(28%)	82(72%)	≈ 0.104
4.	Abdominal Obesity	89(48%)	89(52%)	43(38%)	71(62%)	≈ 0.082

Discussion

Hyperuricemia, characterized by elevated uric acid levels in the blood, has been found to be closely associated with hypertension, particularly in the presence of metabolic syndrome. UA displays paradoxical oxidant and anti-oxidant properties, acting as both an antioxidant and a promoter of oxidative stress. Its effects depend on genetic, environmental, and cellular factors. UA scavenges radicals extracellularly, but intracellularly enhances ROS production. It inhibits nitric oxide synthesis while suppressing oxidative stress. The balance between UA's pro and anti-oxidant effects depends on concentration. Elevated SUA levels induce cardiomyocyte apoptosis and release pro-inflammatory cytokines. Hyperuricemia contributes to endothelial dysfunction and macrophage-mediated myocardial fibrosis. [6,7] Insulin resistance leads to increased insulin levels, which promote sodium reabsorption in the kidneys and may contribute to hypertension.[8]

Sanchez-Lozada et al. found that hyperuricemia-induced hypertension is mediated by oxidative stress, endothelial dysfunction, and renin-

angiotensin system activation. Uric acid triggers inflammation and oxidative stress in adipocytes and hepatocytes. [9,10] Hyperuricemia can result from purine nucleotide degradation and insufficient UA excretion. Genetic variations in ABCG2, OAT1/2/3, GLUT9, OAT4, URAT1, ABCG4, NPT1, SLC2A9, SLC22A12, and BCRP genes are linked to hyperuricemia. Factors like diet, enzyme deficiencies, and increased cell turnover contribute to purine breakdown and hyperuricemia. Genetic variants rs7442295 (SLC2A9), rs475688, rs3825016, rs11726117 (SLC22A12), and rs2231142 (BCRP) affect urate secretion and absorption. Rare OAT4 and OAT10 gene mutations are also implicated. [11,12]

The study also explored various characteristics in metabolic syndrome patients with and without hyperuricemia. Among patients with hyperuricemia, the prevalence of hypertension was 74%, while among those without hyperuricemia, it was 58%. The Phi coefficient was approximately 0.243 for hypertension. This suggests a moderate positive association between hyperuricemia and hypertension, indicating that individuals with hyperuricemia tend to have a higher prevalence of hypertension. This aligns with previous research indicating a strong association between hyperuricemia and hypertension within the context of metabolic syndrome. A cross-sectional study conducted by Kuwabara et al. (2017) independently linked elevated serum uric acid levels to an increased risk of hypertension among individuals with metabolic syndrome. Similarly, a prospective cohort study by Choi et al. (2007) identified hyperuricemia as a significant predictor of incident hypertension in individuals with metabolic syndrome components. [13,14] However, it's important to note that the association is not particularly strong based on the Phi coefficient value is the present study.

Meta-analyses have found a significant positive association between serum uric acid levels and the development of type 2 diabetes. Uric acid can be toxic to pancreatic beta cells and induce diabetes in rabbits under conditions of low reductant concentration. Insulin resistance is positively correlated with uric acid levels, and reducing uric acid improves insulin sensitivity. There is a dual correlation: insulin resistance reduces renal excretion of uric acid while increasing its production, and hyperuricemia limits nitric oxide bioavailability, worsening insulin resistance. [15-17]

Several studies have investigated the relationship between hyperuricemia and diabetes within the metabolic syndrome framework. A prospective cohort study by Wang et al. (2011) demonstrated that elevated serum uric acid levels were independently associated with an increased risk of incident diabetes in individuals with metabolic syndrome. Similarly, a systematic review and meta-analysis by Li et al. (2017) found that hyperuricemia was significantly associated with an increased risk of developing diabetes in patients with metabolic syndrome. [18, 19]

In present study we observed a very weak positive association between hyperuricemia and hyperglycemia. The association is close to zero (φ =0.005), suggesting that there is minimal relationship between these two characteristics.

Despite its antioxidant properties, uric acid can also act as prooxidant, generating oxidants on reaction with peroxynitrite and myeloperoxidase. The main source of oxidative stress is NOX4-expressing NADPH oxidase, which leads to mitochondrial oxidative stress and impairment of lipogenesis and fatty acid oxidation in hepatocytes. Uric acid inhibits AMP-activated protein kinase, stimulates gluconeogenesis, and impairs fatty acid oxidation. Mitochondrial oxidative stress also affects insulin-dependent nitric oxide release and glucose delivery. [20, 21]

Insulin resistance and elevated circulating free fatty acids are key mechanisms underlying metabolic dysfunction. Insulin resistance can stem from genetic factors or age-related changes, while increased free fatty acids are often associated with obesity or abdominal obesity due to a sedentary lifestyle. Adipose tissue produces pro-inflammatory cytokines, leading to insulin resistance, lipolysis, and liver production of pro-thrombotic factors. This chronic inflammatory state, driven by abnormal adipokine production, results in endothelial dysfunction and a pro-thrombotic environment. Lipolysis affects hepatic metabolism, promoting glucose production and very low-density lipoprotein synthesis, contributing to hypertriglyceridemia and altered HDL composition. Elevated free fatty acids and impaired insulin activity further contribute to hyperglycemia by increasing glucose production and reducing uptake by muscle and adipose tissue. [22-24]

Several studies have investigated the relationship between hyperuricemia and dyslipidemia within the metabolic syndrome framework. For instance, a cross-sectional study by Wu et al. (2000) demonstrated that hyperuricemia was significantly associated with unfavorable lipid profiles, including elevated total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels, as well as decreased high-density lipoprotein cholesterol levels. Identical finding also reflected in our study. 35% subjects were shown dyslipidemia along with hyperuricemia. Similarly, a meta-analysis by Wang et al. (2014) showed a positive association between hyperuricemia and dyslipidemia, with hyperuricemia being a risk

factor for the development of dyslipidemia. [25, 26]

Abdominal obesity, also known as central obesity, is a key component of metabolic syndrome and is characterized by the accumulation of excess fat in the abdominal region. In the present study 48% subjects were present with abdominal obesity.

Several studies have investigated the relationship between hyperuricemia and abdominal obesity within the metabolic syndrome framework. For example, a cross-sectional study by Li F et al. (2021) demonstrated a positive association between serum uric acid levels and waist circumference, a marker of abdominal obesity. Similarly, a longitudinal study by Kodama et al. (2009) found that hyperuricemia was independently associated with the development of abdominal obesity over time. [16, 27]

In the present study we observed a weak positive association between hyperuricemia and dyslipidemia, as indicated by a Phi coefficient of approximately 0.104. This implies that individuals with hyperuricemia tend to have a slightly higher prevalence of dyslipidemia. Similarly, there was a weak positive association between hyperuricemia and abdominal obesity, with a Phi coefficient of approximately 0.082. This suggests that individuals with hyperuricemia may be slightly more likely to have abdominal obesity.

However, it is important to note that the associations between hyperuricemia and both dyslipidemia and abdominal obesity are considered weak, indicating that the relationships are not particularly strong. The retrospective design of this study may limit the ability to establish causality. Furthermore, the study was conducted at a single tertiary care hospital, which may affect the generalizability of the findings.

Conclusion:

In conclusion, this study explored the association between hyperuricemia and various characteristics of metabolic syndrome. Among the study participants, a significant proportion had hyperuricemia, indicating its relevance within the context of metabolic syndrome.

The findings revealed a moderate positive association between hyperuricemia and hypertension, indicating that individuals with hyperuricemia are more likely to have hypertension. However, the associations between hyperuricemia and hyperglycemia, dyslipidemia, and abdominal obesity were weak, suggesting only slight tendencies for individuals with hyperuricemia to have higher prevalence rates of these characteristics. These results contribute to the understanding of the relationship between hyperuricemia and metabolic syndrome and highlight the importance of monitoring serum uric acid levels in individuals with metabolic syndrome, particularly in relation to hypertension. Further research is warranted to explore the underlying mechanisms and potential clinical implications of these associations.

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