

Hyperuricemia as a Potential Determinant of Metabolic Syndrome

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Recent studies have focused on hyperuricemia as a modulator for metabolic syndrome. Hyperuricemia has reported in many studies as a causal marker in a higher prevalence of metabolic syndrome. In fact, insulin resistance, dyslipidemia, obesity and hypertension, each of these variables of metabolic syndrome gets influenced by the serum uric acid level. High level of uric acid has been associated with metabolic syndrome, type 2 diabetes and cardiovascular diseases. Hyperuricemia has attributed to hyperinsulinemia in metabolic syndrome and decreased excretion of uric acid causing endothelial dysfunction in kidney leads to renal disease and cardiovascular disorders. This review focus on the role of uric acid in the development of metabolic syndrome and on the possible pathophysiology.

Key Words: Hyperuricemia, Uric acid, Metabolic syndrome, Hypertension, Obesity

INTRODUCTION

Uric acid is an end product of purine metabolism in human and higher primates. Human lost uricase gene due to mutation occurred about 15 million years ago [1] and hence the level of uric acid in humans are much higher than other species. The uric acid is formed in the liver by the breakdown of nucleic acid and proteins. When the level of uric acid increases in blood beyond allowable level the condition is called as hyperuricemia. The uric acid level is higher in men compared to women which clearly show a link of uricosuric effect of estrogen [2].

Johnson et al. suggested the role of uric acid as an antioxidant, the increased level of uric acid has shown advantageous effects [3] on compensatory pathway in cardiovascular

disease in response to the stress conditions [4]. Uric acid has detrimental effect in adipocytes and vascular smooth muscle cells [5,6] which clearly shows its proinflammatory nature. Hyperuricemia also leads to endothelial dysfunction by the impairment of nitric acid generation [7]. Oliveira et al. suggested that acute elevation of uric acid has protective effect while chronic elevation of uric acid exacerbates the risk of disease [8].

The association of hyperuricemia and the prediction for the development of metabolic syndrome has been seen [9-11]. Uric acid acts as an identifying factor for the high risk asymptomatic individuals in the prognosis of metabolic syndrome that leads to an improvement in the treatment for the upcoming cardiovascular events [12]. Until now the pathogenic role of uric acid in the development of the metabolic syndrome is not completely comprehended. Hence this review would provide an insight into the linked pathways between hyperuricemia and each component of metabolic syndrome.

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HYPERURICEMIA AND INSULIN RESISTANCE

Insulin resistance is a condition in which a normal amount of insulin produces a subnormal biological response. It is one of the most important factors for uric acid regulation in the body. Studies have demonstrated the association between high serum uric acid and insulin resistance but the causal relation is less reviewed.

Facchini et al. discussed that insulin resistance is inversely proportional to the uric acid clearance from the kidney [13] and hence the level of uric acid gets accumulated in the kidney. Studies also revealed the positive correlation of hyperuricemia with elevated fasting insulin level [14]. The mechanism of insulin resistance induces hyperinsulinemia suggested by animal as well as human studies. Some of them conclude that insulin resistance promotes hyperinsulinemia, which may enhance renal urate reabsorption by the activation of urate-anion exchange URAT1 [17] and Na dependent anion cotransporter in renal proximal tubules [15,16]. It has been reported that insulin increases renal tubular sodium reabsorption [15,20] reduces the uric acid excretion which increases the serum uric acid level.

Carnethon et al. observed a follow-up study on increasing uric acid among non-diabetic individuals which had higher risk for developing hyperinsulinemia [18]. Another study on animal professed the lowering of uric acid by xanthine oxidase inhibitors which reduces insulin resistance in obese mice demonstrated by Baldwin et al. [19].

Johnson et al. proposed a mechanism through which fructose accumulates uric acid and induce insulin resistance. Increase in uric acid cause proinflammatory effect on adipocytes. As has been discussed earlier hyperuricemia leads to the endothelial dysfunction that impairs the bioavailability of nitric oxide, and lead to insulin resistance. While the systemic effect of uric acid on skeletal muscle impairs glucose uptake, further it leads to insulin resistance [7,21,22]. In addition to this insulin resistance may occur by alcohol intake, obesity and from various other reasons but the process of development of hyperuricemia and insulin resistance shares the convertible bidirectional causal effects.

HYPERURICEMIA AND HYPERTENSION

The most researchers have studied about uric acid as an inducible factor that helped to understand the pathogenesis of hypertension [23,33,36]. Hyperuricemia could be one of the culprits and it is well known as an independent risk factor for hypertension [23]. Kim et al. observed a significant positive correlation between hyperuricemia and the incidence of hypertension [24-26]. Yeh et al. suggested that plasma uric acid relates with diastolic blood pressure not the systolic hypertension [27]. The possible reason behind this is unknown.

Surprisingly the association of hyperuricemia and blood pressure diminished in the elderly patients [28-30]. The possible mechanism was that uric acid damages small renal vessels, which leads to an irreversible salt sensitive hypertension. The reason for not lowering uric acid by specific uric acid inhibitor in these subjects concludes that there must be some other pathophysiological mechanism of hypertension [31]. Dietary habits and specific foods (table sugar and high-fructose corn syrup) are also important factors in determining hyperuricemia induced hypertension. Nakagawa et al. observed the role of uric acid in fructose induced metabolic syndrome in rats. Animals fed with high fructose elevated the level of uric acid along with insulin, triglyceride, and blood pressure [32]. Mazzali et al. observed that when rats were fed with uricase inhibitor for developing hyperuricemia, few weeks after developing hyperuricemia these animals developed the hypertension too. A xanthine oxidase inhibitor or a uricosuric drug decreased blood pressure by reducing uric acid level in animals. It means that hypertension was developed due to vasoconstriction mediated by uric acid, with the reduction in the bioavailability of nitric oxide level and activation of the renal - angiotensin system [36].

Another mechanism published by Daniel et al. about the linking pathway of uric acid mediated hypertension suggests that purine rich meat or excessive fructose may result chronic hyperuricemia. Obese mother with preexisting hypertension or preeclampsia may pass the uric acid into infant circulation and it leads to intrauterine growth retardation and reduction in the nephron number. Further hyperuricemia develops in the new born babies may be due

to genetic and environmental factors. This chronic hyperuricemia stimulates renin angiotensin system and block the endothelial nitric oxide production, which contribute renal vasoconstriction and hypertension [33].

Until now there is no common agreement for the laboratory measurement of uric acid in the hypertensive subjects. Serum uric acid is not considered as a risk factor for hypertension by American Heart Association or the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood pressure [34]. However, the guideline of European Society of Hypertension and Cardiology recommends serum uric acid as a laboratory measurement for hypertension [35].

HYPERURICEMIA AND OBESITY

Obesity is one of the pivotal causative of metabolic syndrome. It has been proven as a risk factor for hypertension, dyslipidemia and hyperuricemia. The positive association of obesity with increasing uric acid level has been found among several recent studies [48,49].

Waist circumference have been suggested as a measure of intra-abdominal fat mass, body mass index and waist-to-hip ratio is a simple indicator for the assessment of cardiovascular risk [37,38]. Indeed the prevalence of insulin resistance is increased in overweight/obese individuals [39,40]. The association of insulin resistance and obesity leads to the further development of the other factors of metabolic syndrome. Wajchenberg suggested that insulin resistance in adipose tissue leads to an inability to suppress the release of fatty acids from adipose tissue and thus it induced decrease in the clearance of triglyceride-rich lipoproteins [41]. Ultimately, abdominal obesity associated with insulin resistance and triglyceride may increase the uric acid level by the decreased insulin sensitivity (Fig. 1).

Matsuura et al. and Bonora et al. reported that obesity and central body fat distribution were associated with hyperuricemia [42,43]. Bedir et al. and Fruehwald-Schultes et al. conducted studies in the evaluation of relationship between leptin and the cluster of hyperuricemia in order to clarify the causative mechanisms associating obesity with hyperuricemia. They found that the serum uric acid concentration is independently associated with the serum leptin

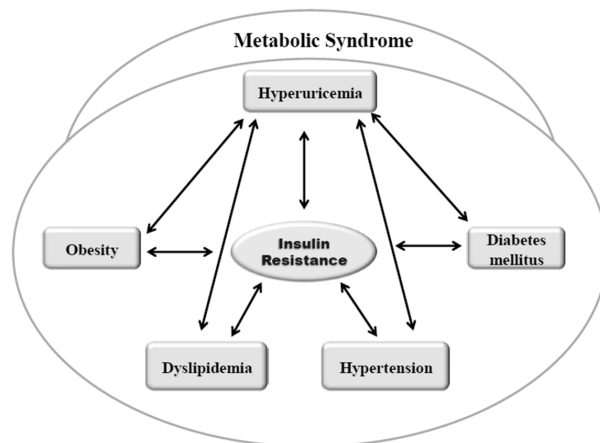


Fig. 1. Multiple bidirectional association between higher level of uric acid and different component of metabolic syndrome. Insulin resistance is a central component that is associated with hyperuricemia and further development of metabolic syndrome. Hyperuricemia may develop metabolic syndrome by inducing endothelial dysfunction and also through activating proinflammatory pathways.

concentration [44,45]. This study suggested that leptin could be a pathogenic factor responsible for hyperuricemia in obese patients. Chen et al. reported the relationship between hyperuricemia and waist circumference in hospital based cross-sectional study. The study showed that elevated waist circumference was significantly associated with hyperuricemia in both men and women [46]. In a study which was conducted in Portugal [47] for the association between waist circumference and uric acid, only high waist circumference remained significantly and positively associated with hyperuricemia.

Qian et al. explained [50] the pathophysiology of obesity that causes hyperuricemia: firstly obesity directly obstructs with urate protein synthesis and excretion [51], secondly obesity causes renal damage via glomerulus dysfunction [52] and thirdly, obesity leads to the dysfunction of the renin-angiotensin system, which would eventually result in the insignificant clearance of uric acid [53].

Studies regarding abdominal obesity done in lean and obese Japanese men showed that visceral adiposity measured by computerized tomography was a strong contributor to the elevated uric acid concentration possibly due to the reduction in its excretion [54,55]. In the Turkish Adult Risk Factor Study, abdominal obesity was the most important determi-

nant of uric acid concentration variability after the adjustment for 13 variables, including the use of alcohol, diuretics, high blood pressure, glucose regulation and gamma glutamyl transferase levels [56]. This study suggested that abdominal obesity is the main determinant of elevated plasma uric acid levels in the general population. A possible explanation would be that hyperinsulinemia, due to insulin resistance and visceral adiposity, leads to an increased uric acid absorption in renal tubules [16]. Masuo et al. have noted that hyperuricemia predicts the development of obesity following weight gain and high blood pressure [9]. It is now widely believed that increasing prevalence of obesity causes the hypertension [57]. Dietary habits are also responsible for the increasing prevalence of hyperuricemia. There has been a large increase of fructose intake in the developed world during the past 200 years which correlates with the increase in the prevalence of hypertension and obesity [58,59].

Ryu et al. published a prospective study in Korean population, a cohort relating to hyperuricemia in middle aged Korean men. Subject with incident hyperuricemia were more likely to have high body mass index after 7 year follow up study [60]. It suggests that uric acid is associated with increase in the obesity.

HYPERURICEMIA AND DYSLIPIDEMIA

Dyslipidemia associated with insulin resistance is characterized by increased levels of VLDL, triglyceride, remnant particles and decreased levels of HDL-cholesterol. Epidemiological studies revealed the link between dyslipidemia and uric acid. Among men, uric acid concentration was positively correlated with waist circumference, blood pressure, and triglyceride. Uric acid concentration was strongly correlated with serum triglyceride. Conen et al. and Schechter showed the similar observation of correlation between triglyceride and hyperuricemia [61,62].

Leyva et al. suggested the pathway of glycolysis in uric acid production. Phosphoribosylpyrophosphate (PPRP) is an important metabolite in this process. Its availability depends on ribose-5-phosphate (R-5-P), governed by glycolytic flux. Disturbances in the intermediates like R-5-P, PPRP, diminish the activity of GA3PDH (glyceraldehyde-3-phosphate dehydrogenase), which is regulated by insulin. Accumulation

of glycerol-3-phosphate leads to an increase in serum triglyceride concentrations. The defects in GA3PDH and a loss of its responsiveness to insulin by causing the accumulation of glycolytic intermediates could explain the assortment among insulin resistance, hyperuricemia, and hypertriglyceridemia [63]. Chen et al. showed that serum uric acid level was negatively correlated with HDL-C level, but this association was not evident among women. This finding was consistent with Rho et al. [64,65].

During triglycerides synthesis there would be a greater need for NADPH [66] and the synthesis of fatty acids in the liver which is associated with the *de novo* synthesis of purine, thus hastening uric acid production [42]. Tsouli et al. & Lin et al. suggested genetic and environmental factors to be responsible for this association [67] while some studies support the fact that dietary habit and alcohol consumption is the main reason for the increment of uric acid and triglyceride level [68,69]. The free fatty acid produced by lipolysis is metabolized through beta oxidation with increased production of NADPH which further get metabolized to uric acid resulting in hyperuricemia [66,70].

HYPERURICEMIA AND METABOLIC SYNDROME

The concept of the metabolic syndrome is existent since the last 80 years. In 1920, Kylin, a Swedish physician, first described a constellation of metabolic disturbance, which entailed the risk factors of cardiovascular disease, atherosclerotic cardiovascular disease and the clustering of hyperglycemia, hypertension and gout [71]. In 1988 Reaven [72] postulated that several risk factors-dyslipidemia, hyperglycemia, and hypertension commonly clustered together and recognized as the multiple risk factors for CVD. Some recent studies report that the prevalence of metabolic syndrome was high among the patients with gout [73,74]. Sex related variations for metabolic syndrome prevalence has been seen by different studies. Uaratanawong et al. observed that the higher prevalence of metabolic syndrome was found in men with hyperuricemia [74]. Fig. 1 shows the close association of hyperuricemia with the individual component of metabolic syndrome.

Yang et al. in a follow up of Chinese population for 5.41

years stepwise increase in the incidence of metabolic syndrome across the tertiles of serum uric acid. Among women, this association was stronger than men. After adjusting variations in age, blood pressure, triglycerides, HDL-C, glucose, and waist circumference, females in the middle and upper tertiles of serum uric acid had significantly higher risk of developing metabolic syndrome when compared with subjects in the lowest tertile. Certain other studies showed positive relations between metabolic syndrome and uric acid [56,75-77].

A 1.6-fold higher risk for metabolic syndrome was noted in the individuals with serum uric acid levels in the highest compared with the lowest quartile [60]. Associations between serum uric acid level and metabolic syndrome have been reported in cross-sectional studies [56,75,78]. Choi et al. found that the prevalence of the metabolic syndrome was higher across the levels of serum uric acid in a nationally representative sample of NHANES III [75]. Sui et al. reported a follow up study in USA individuals for 5.7 years [79] where men with serum uric acid concentrations ≥ 6.5 mg/dl had a 1.60-fold increase in the risk of metabolic syndrome, as compared with those who had concentrations < 5.5 mg/dl. The risk of metabolic syndrome was at least 2 folds higher in the women with serum uric acid concentrations ≥ 4.6 mg/dl. The study also suggests that hyperuricemia is a strong and independent predictor of incident metabolic syndrome in men and women [78]. Future predictor for CVD is one of the reasons to focus in these aspects [80,81] from the studies above mentioned risk populations. Although some researchers have debated on this issue whether uric acid should be an additional metabolic syndrome component [82,83] however, it has not been included in any of the diagnostic criteria like NCEP-ATP, IDF and WHO criteria.

The specific biologic mechanisms by which hyperuricemia increase the risk of developing metabolic syndrome remain ambiguous. Recently, an observation has linked to table sugar, high fructose corn syrup, and natural sources which provide fructose for the development of metabolic syndrome by predisposition of uric acid. The ingestion of fructose is strongly associated with obesity and insulin resistance epidemic [84]. Fructose-1-phosphate is formed by phosphorylation in fructose metabolism. Then enzyme aldolase B

breaks fructose 1 phosphate into dihydroxyacetone phosphate (DHAP) and D glyceraldehydes. The reaction of aldolase is slow for the conversion of DHAP and glyceraldehyde. Thus, in the condition of high fructose intake, fructose -1-phosphate gets accumulated and further decreases the concentration of intracellular phosphate which limits the ATP formation. ADP or AMP resulting from such metabolism is catabolized, thus leading to hyperuricemia [85].

Hyperuricemia could play a role in the development of insulin resistance through urate-induced inhibition of endothelial nitric oxide [86]. A decrease in the endothelial nitric oxide may interrupt the normal functioning of insulin in the skeletal muscle [87]. Cook et al. observed the features of the metabolic syndrome in mice lacking endothelial nitric oxide synthase [88]. Further treatment with allopurinol can improve endothelial function in the patients with hyperuricemia [7,89]. In addition to this result Nakagawa et al. [32] found that lowering uric acid in fructose-fed rats improves the components of the metabolic syndrome, which clearly suggests that uric acid has a causal role in the metabolic syndrome. Sautin and Furukawa et al. observed inflammatory and oxidative changes in adipocytes after the treatment of uric acid; it suggested that they might be a process in causing metabolic syndrome [5,90]. Recent studies also [91-94] conclude that upper normal range of uric acid could be an indicating factor for the development of metabolic syndrome. Our group suggests that high quartile of uric acid within normal range may be surrogate markers of metabolic syndrome in general population. However this apprehension needs to be substantiated with ethnic-based cross sectional as well as follow-up study.

CONCLUSION

This review focuses on the association between hyperuricemia and the further development of individual variables of metabolic syndrome. The uric acid is one of the important markers to predict metabolic syndrome, diabetes and cardiovascular disease. Insulin resistance and uric acid interactions are crucial factor for determining the development of other metabolic syndrome components. The various defining criteria for the metabolic syndrome independently predict the cardiovascular disease and uric acid could also

include in the parameters of metabolic syndrome. Better definitions should be given so as not to confuse with different international criteria's. Many studies clearly conclude that uric acid is not an innocent observer rather a culprit. Available study suggests that hyperuricemia appears to potentially contribute to obesity, hypertension, diabetes, renal and cardiovascular diseases. Hence, there should be an effective implementation in all aspects to reduce the adverse effects of uric acid in metabolic syndrome.

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