

COMMENTARY

The enigma of uric acid in metabolic syndrome

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ABSTRACT

Metabolic syndrome is a group of risk factors including an increased level of triglycerides, fasting blood glucose, blood pressure or waist circumference, and or a decreased level of HDL cholesterol. The level of uric acid in the blood has been associated with the presence of metabolic syndrome, which can aggravate the prognosis of cardiovascular diseases, type 2 diabetes mellitus and stroke. On the interest to identify the early biomarkers of metabolic syndrome, Popovic et al involved 1333 patients and showed using logistic regression that a significant association between the blood levels of uric acid in the subjects diagnosed with metabolic syndrome and in the group of obese patients, who had the body mass index of more than 30 kg/m². This study shed some light in identifying a metabolically unhealthy phenotype.

Keywords: *Uric acid, blood glucose, metabolic syndrome, diabetes, obesity, biomarker*

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Uric acid and metabolic syndrome

Metabolic syndrome (MS) is identified in an individual, who is having three or more of the following five risk factors such as (i) large waist circumference or central adiposity, (ii) higher level of triglycerides, (iii) lower level of HDL cholesterol, (iv) higher level of fasting blood glucose (v) and increased blood pressure.¹ Ultimately, carrying these risk factors can worsen the prognosis of cardiovascular diseases, type-2 diabetes mellitus and stroke. Thus, in order to prevent the development of MS, it is important to identify the early biomarkers, which can increase the incidence of MS. Recently, uric acid has gained some clinical interest as hyperuricemia is comorbid with MS and type-2 diabetes.²

The cross sectional study of Popovic DS et al³ involving 1333 patients from Vojvodina region of Serbia tested the serum uric acid level in separate groups of normal weight (body mass index (BMI) of 18.5 - 25 kg/m²), overweight (BMI of 25-30 kg/m²), and obese (BMI of greater than 30 kg/m²) persons, and further characterized them for the presence or absence of MS. The results show that the serum uric acid level was significantly higher in subjects diagnosed with MS in both overall study group and in the group of obese subjects.

Uric acid: a pro-oxidant or an anti-oxidant?

In humans, uric acid is generated at the end of purine metabolism via the activity of xanthine oxidase

(XO) primarily in the liver. About two thirds of total body urate is produced endogenously (recycling of cellular materials), and the remaining one third is originated from dietary purines (purine rich food include organ meat like kidney, and seafood).

In accordance with the results shown by the Popovic et al³, there has been an association between the level of uric acid and MS risk; and hyperuricaemia alone disturbs the normal metabolism, causing insulin resistance and could lead to MS.⁴ A recent meta-analysis study identified that an elevated serum uric acid level was a causal factor contributed to an increased risk of MS, showing that each 1 mg/dl increase in the serum uric acid level was associated with a 30% increase in the MS risk.⁵ Several *in-vitro* studies show that oxidative stress is the primary mechanism in causing damage to the vascular, renal, liver cells and adipocytes exposed to uric acid.⁶ The role of reactive oxygen species in causing local inflammation, impaired nitric oxide generation, leading to insulin resistance and fat accumulation is well known. Nevertheless, it is paradoxical that uric acid acts as an important antioxidant in the body, by scavenging oxygen radicals such as single oxygen peroxyl and hydroxyl radicals (but not superoxide radicals), and can also react with peroxynitrite to stabilize endothelial nitric oxide synthase (eNOS) activity and prevents peroxynitrite- induced protein nitrosylation.⁶

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Several mechanisms have been suggested for the various physiological and pathological roles of uric acid. Uric acid might function as a pro-oxidant inside the cells (mediated through NADPH oxidase-dependent pathway), whereas it act as an antioxidant in soluble form in the extracellular milieu.⁶ The following three mechanisms have been proposed for the association between serum uric acid and development of MS, such as (i) a decreased renal uric acid excretion, (ii) an impaired endothelial function leading to insulin resistance, and (iii) the inflammation and the changes in the oxidative status of adipocytes induced by uric acid.

Future Directions

Uric acid appears to be a significant independent predictor of vascular and renal disease in hypertensive patients and in subjects with high risk factors, such as diabetes, patients with chronic kidney disease or congestive heart failure.^{7, 8} Although a few studies have mentioned as serum uric acid is a very weak predictor of cardiovascular disease,⁹ the level of uric acid could be used as a marker to identify the “metabolically unhealthy” phenotype, as mentioned by Popovic et al.³ Yet, the exact role of the higher level of uric acid in inducing the metabolic syndrome is unknown, and whether uric acid independently contributes to the development of MS or it is merely a by-product of other processes, and whether uric acid can act as a biomarker to predict the future development of MS is remain to be debated. This is because, currently there is no published results available using uric acid-lowering therapy in a large population, although some randomized controlled studies are ongoing now to examine the etiologic role of hyperuricemia on the progression of cardiovascular, renal and metabolic diseases. Moreover, it would be interesting to study the molecular mechanism that converts uric acid from anti-oxidant to pro-oxidant in hypertensive and/or diabetic subjects with high cardiovascular risk factors

Conflict of interest

None declared.

References

1. Balkau B, Valensi P, Eschwege E, Slama G. A review of the metabolic syndrome. *Diabetes Metab.* 2007;33:405–413. [Full Text](#)
2. Lv Q, Meng XF, He FF, Chen S, Su H, Xiong J, Gao P, Tian XJ, Liu JS, Zhu ZH, Huang K, Zhang C. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. *PLoS One.* 2013;8:e56864. [Full Text](#)
3. Popovic DS, Stokic E, Tomic-Nagic D, Mitrovic M, Vukovic B, Benc D, Icin T, Kovacev-Zaviscic B. Uric acid level and the presence of metabolic syndrome: experiences from Vojvodina Region in Serbia. *Diabesity* 2015; 1(3): 24-28 doi: 10.15562/diabesity.2015.16. [Full Text](#)
4. DeBosch BJ, Kluth O, Fujiwara H, Schurmann A, Moley K. Earlyonset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. *Nat Commun.* 2014;5:4642. [PubMed Full Text](#)
5. Yuan H, Yu C, Li X, Sun L, Zhu X, Zhao C, Zhang Z, Yang Z. Serum Uric Acid Levels and Risk of Metabolic Syndrome: A Dose-Response Meta-analysis of Prospective Studies. *J Clin Endocrinol Metab.* 2015 Aug 26;jc20152527. [PubMed Full Text](#)
6. Kang DH, Ha SK. Uric Acid Puzzle: Dual Role as Anti-oxidant and Pro-oxidant. *Electrolytes & Blood Press.* 2014; 12(1):1-6. [Full Text](#)
7. Silva HA, Carraro JC, Bressan J, Hermsdorff HH. Relation between uric acid and metabolic syndrome in subjects with cardiometabolic risk. *Einstein (Sao Paulo).* 2015; 13(2):202-208. [PubMed Full Text](#)
8. Bickel C, Rupperecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol.* 2002;89:12–17. [PubMed Full Text](#)
9. Baker JK, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, where do they leave us? *Am J Med.* 2005;118:816–826. [PubMed Full Text](#)



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