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Editorial

Clinical implications of the metabolic syndrome and hyperuricemia

A cluster of risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus, which occur together more often than by chance alone, have become known as the metabolic syndrome.[1] These factors include high blood pressure, raised blood glucose, elevated triglyceride levels, decreased high-density lipoprotein cholesterol and obesity. The metabolic syndrome has been proposed as a means to identify people with increased risk of CVD and diabetes and to guide clinical management decisions. It has been shown to predict CVD morbidity, CVD mortality, type 2 diabetes and all-cause mortality in a number of populations.[2] However, it does not enhance risk prediction, being outperformed by traditional cardiovascular risk prediction algorithms.[3] The association of the metabolic syndrome with the risk of CVD was much less than that of low-density lipoprotein cholesterol, and most published reports indicate that the metabolic syndrome does not predict cardiovascular events or disease progression any better than its components.[4] The metabolic syndrome is also not an absolute risk indicator, because it does not contain many of the factors that determine absolute risk; for example, age, cigarette smoking and low-density lipoprotein cholesterol levels. As described in the National Cholesterol Education Program Adult Treatment Panel in 2001, metabolic syndrome played a role only in the guidance of the therapeutic goal of cholesterol.[5]

In this issue of JCMA, Lin et al. report their study designed to evaluate the use of several simple indicators in identifying postmenopausal women with insulin resistance estimated by HOMA-IR. The investigators sought to provide clues for clinicians to identify postmenopausal women who are susceptible to diabetes and CVD.[6] They recruited 262 naturally postmenopausal women without frank diabetes, and HOMA-IR values were calculated to estimate insulin resistance, which was defined as the upper quartile of the HOMA-IR values, and the diagnostic power was examined by constructing receiver operating characteristic curves. They found that 45% of patients with insulin resistance had silent diabetes, and the odds ratio was 6.09 compared to those without insulin resistance. As expected, uric acid, body mass index, waist circumference, alanine aminotransferase, triglycerides and high-density lipoprotein cholesterol were important determinants of HOMA-IR in these women. Lin et al. also found that using uric acid levels with $\geq$5.0 mg/dl as a cut-off point, they could diagnose insulin resistance with 75.4% sensitivity and 73.1% specificity. This issue picks up right individuals who are major target population for prevention of diabetes and CVD. (This approach identifies individuals who are part of a major target population for the prevention of diabetes and CVD).

It has been postulated that insulin resistance is a key underlying pathophysiology in metabolic syndrome. Recent interest has focused on the possible involvement of insulin resistance as a linking factor, although the pathogenesis remains unclear. Uric acid levels are known to be elevated in subjects with metabolic syndrome, and subjects with hyperuricemia frequently have metabolic syndrome.[7] Hyperinsulinemia reduces the renal excretion of uric acid and sodium. Hyperuricemia resulting from euglycemic hyperinsulinemia may precede the onset of type 2 diabetes, hypertension, coronary artery disease and gout in individuals with metabolic syndrome.[8] Hyperuricemia reflects insulin resistance, and uric acid has been demonstrated to be associated with several components of the metabolic syndrome.[9] Many authorities have described the elevation of uric acid in metabolic syndrome as a secondary phenomenon; however, some studies have reported that an elevated uric acid level predicts the development of metabolic syndrome *per se*.[10,11]

The question arises of whether physicians should routinely screen the serum uric acid level or insulin resistance in postmenopausal women, and whether treatment of asymptomatic hyperuricemia or metabolic syndrome has benefit in the clinical setting. Metabolic syndrome is characterized by abdominal obesity with visceral adiposity, impaired glucose tolerance due to insulin resistance with hyperinsulinemia, hypertriglyceridemia, increased blood pressure, decreased high-density lipoprotein cholesterol and, possibly, hyperuricemia. Type 2 diabetes develops when insulin-resistant individuals cannot produce the increased amounts of insulin needed to compensate for the insulin resistance.[12] In my view, metabolic syndrome should be defined as a pre-disease, a concept proposed also by some authorities. Recently, a WHO report concluded that metabolic syndrome is a pre-morbid condition rather than a clinical diagnosis, and should thus exclude individuals with established diabetes, hypertension or dyslipidemia.[3] Reaven also suggested that metabolic syndrome should not include type 2 diabetes as a component.[13] He has attempted to explain why CVD was increased in insulin-resistant individuals who were not diabetic by virtue of compensatory hyperinsulinemia. According to this definition, people with metabolic syndrome must be given advice to

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modify lifestyle and increase physical activity to reduce obesity. Once the metabolic syndrome progresses to hypertension or diabetes, patients should be treated with medication along with lifestyle modification.

People with hyperuricemia, especially those with higher serum urate levels, are at risk of developing gouty arthritis. In the past, the association of hyperuricemia with CVD and renal failure led to the use of urate-lowering agents for patients with asymptomatic hyperuricemia. However, most hyperuricemic people do not develop gout or renal stones, and prophylactic treatment is not indicated. Structural kidney damage or tophi are not identifiable before the first attack.[8] Reduced renal function cannot be attributed to asymptomatic hyperuricemia, and treatment of asymptomatic hyperuricemia does not alter the progression of renal dysfunction in patients.[8] Increased risk of renal stone formation in patients with asymptomatic hyperuricemia is not established. In addition, treatment with specific antihyperuricemic agents entails inconvenience, cost and potential toxicity; therefore, routine treatment of asymptomatic hyperuricemia cannot be justified for the prevention of acute uric acid nephropathy.[8] Therefore, this approach is no longer recommended except for individuals receiving cytolytic therapy for neoplastic disease.

In conclusion, hyperuricemia may be a component of metabolic syndrome, and its presence is an indication to screen for and aggressively treat any accompanying hypertension, dyslipidemia or diabetes mellitus. Routine screening for asymptomatic hyperuricemia is not recommended. If hyperuricemia is diagnosed, the cause should be determined and associated problems, such as hypertension, hypercholesterolemia, diabetes mellitus and obesity should be treated.[8] Metabolic syndrome is a premorbid condition rather than a clinical diagnosis. Currently, there is no class of medication that can treat all components of metabolic syndrome. Drug treatment might not be required, and lifestyle intervention remains the primary therapy. At a clinical level, hypercholesterolemia, diabetes, hypertension or symptomatic hyperuricemia need to be treated with appropriate drugs.

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References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;**37**:1595–607.
2. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 2005;**28**:1769–78.
3. Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia* 2010;**53**:600–5.
4. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2010;**375**:181–3.
5. Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection. Evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–97.
6. Lin KH, Liou TL, Hsiao LC, Hwu CM. Clinical and biochemical indicators of homeostasis model assessment-established insulin resistance in postmenopausal women. *J Chin Med Assoc* 2011;**74**:442–7.
7. Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, et al. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 2009;**30**:96–116.
8. Wortmann RL. Disorders of purine and pyrimidine metabolism. In: Fauci AS, Longo DL, editors. *Harrison's internal medicine*. 17th ed. New York: McGraw-Hill Professional; 2008. p. 2444–9.
9. Liu PW, Chang TY, Chen JD. Serum uric acid and metabolic syndrome in Taiwanese adults. *Metabolism* 2010;**59**:802–7.
10. Ryu S, Song J, Choi BY, Lee SJ, Kim WS, Chang Y, et al. Incidence and risk factors for metabolic syndrome in Korean male workers, ages 30 to 39. *Ann Epidemiol* 2007;**17**:245–52.
11. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic syndrome in women and men. *Metabolism* 2008;**57**:845–82.
12. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med* 1993;**329**:1988–92.
13. Reaven GM. The metabolic syndrome: time to get off the merry-go-round? *J Intern Med* 2011;**269**:127–36.