It is generally accepted that morbidity and mortality from cardiovascular disease (CVD) are significantly higher in patients with hyperuricemia than in the general population\(^1\). However, it has been controversial whether hyperuricemia is a risk factor for CVD independent of other risk factors or a confounding factor. This is because randomized double-blind prospective studies that show medications for hyperuricemia reduce the risk of CVD have been scarce.

Regarding the direct evaluation of coronary atherosclerosis, integrated backscatter intravascular ultrasound (IB-IVUS) was developed for the tissue characterization of coronary plaques\(^2\). In this issue of the Journal, Ando \textit{et al.} reported that increased serum uric acid levels were associated with higher lipid content and lower fibrosis of coronary plaques, as assessed by IB-IVUS in male and female\(^3\). In addition, they found that the prevalence rate of lipid-rich plaques in each tertile was significant in patients with acute coronary syndrome, whereas there was no significant difference in the prevalence rate of lipid-rich plaques among the three groups in the patients with stable angina pectoris. Ando \textit{et al.} suggested that lowering serum uric acid levels may be an option to stabilize coronary plaques\(^3\).

Factors that make the relationship confusing are confounding factors. For instance, insulin resistance induces the production of uric acid and inhibition of uric acid excretion resulting in the increase of serum uric acid\(^4, 5\). Insulin resistance was recently proven to be an independent risk factor of hyperuricemia even after adjustment for baseline serum uric acid, creatinine, hypercholesterolemia and hypertension status, age, alcohol intake, smoking, and exercise habits in a prospective study\(^6\). Therefore, both observational and prospective studies are required to be adjusted by the grade of insulin resistance such as homeostasis model assessment-insulin resistance (HOMA-IR) because insulin resistance is one of the risk factors of CVD\(^7\). Previously, subanalysis of the Japanese Coronary Artery Disease (JCAD) study demonstrated that elevated uric acid level was an independent predictor of cardiovascular events and all-cause mortality combined in patients with coronary artery stenosis for three years after correction for confounding factors (age, smoking, gender, impaired glucose tolerance, hypertension, dyslipidemia, drinking, obesity, family history, heart failure, left main trunk disease, and number of diseased coronary arteries)\(^8\). However, this study was not corrected for insulin resistance because the relationship among serum uric acid level, insulin resistance, and CVD had not been established\(^6, 7\).

A recent prospective study in elderly patients who were affected by advanced atherosclerosis (significant carotid stenosis $>50\%$ and/or lower limb ischemia II or III stages in Leriche-Fontaine classification) demonstrated that serum uric acid level could be considered as a risk of cardiovascular events for 2.5 years\(^9\). The difference between cardiovascular event ratio in patients with lower and higher serum uric acid levels persisted after correction for confounding factors (age, smoking, gender, diabetes, estimated glomerular filtration rate (eGFR), hypertension, dyslipidemia, HOMA-IR, and diuretic treatment)\(^9\).

Recently, some investigators have demonstrated direct relationships between serum uric acid levels and the incidence of CVD. In general, the first step of atherosclerosis has been thought to be an endothelial damage\(^10\). Tomiyama \textit{et al.} demonstrated that...
Increased serum uric acid levels were a risk factor for increased endothelial dysfunction that was evaluated by flow-mediated vasodilatation of the brachial artery independent of other cardiovascular risk factor in middle-aged healthy Japanese men. This endothelial damage that was induced by increased serum uric acid levels may promote the accumulation of lipid content as evaluated by IB-IVUS.

Although evaluation of relative lipid volume in coronary plaques is a surrogate marker for CVD, Ando et al., for the first time, demonstrated the incidence of lipid-rich plaque in coronary arteries in hyperuricemia patients with acute coronary syndrome. This issue of the Journal provided a new insight into the relationship between serum uric acid levels and CVD using IB-IVUS, although the present study was not adjusted for insulin resistance. In the future, studies elucidating the relationship between serum uric acid levels and relative lipid volume by IB-IVUS correcting for confounding factors such as insulin resistance will provide a new insight into a treatment for hyperuricemia.

Conflict of Interest

I have no financial or other relations that could lead to conflict of interest.

References

1) Hakoda M, Masunari N, Yamada M, Fujiwara S, Suzuki G, Kodama K, Kasagi F: Serum uric acid concentration as a risk factor for cardiovascular mortality: a long-term cohort study of atomic bomb survivors. J Rheumatol, 2005; 32: 906-912
2) Kawasaki M, Takatsu H, Noda T, Sano K, Ito Y, Hayakawa K, Tsuchiya K, Arai M, Nishigaki K, Takemura G, Minatoguchi S, Fujiwara T, Fujiwara H: In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. Circulation, 2002; 105: 2487-2492
3) Ando K, Takahashi H, Watanabe T, Daidoji H, Otaki Y, Nishiyama S, Arimoto T, Shishido T, Miyashita T, Miyamoto T, Kubota I: Impact of serum uric acid level on coronary plaque stability evaluated by integrated backscatter intravascular ultrasound in patients with coronary artery disease. J Atherosclerosis Thromb, 2016; 23: 932-939
4) Facchini F, Chen YD, Hollenbeck CB, Reaven GM: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA, 1991; 266: 3008-3011
5) Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, Frascerra S, Giocia D, Ferrannini E: Effect of insulin on renal sodium and uric acid handling in essential hypertension. Am J Hypertens, 1996; 9: 746-752
6) Nakamura K, Sakurai M, Miura K, Morikawa Y, Nagasawa SY, Ishizaki M, Kido T, Naruse Y, Nakashima M, Nogawa K, Suwazono Y, Nakagawa H: HOMA-IR and
the risk of hyperuricemia: a prospective study in non-diabetic Japanese men. Diabetes Res Clin Pract, 2014; 106: 154-160
7) Nakamura K, Sakurai M, Miura K, Morikawa Y, Ishizaki M, Yoshita K, Kido T, Naruse Y, Nakagawa H: Homeostasis model assessment of insulin resistance and the risk of cardiovascular events in middle-aged non-diabetic Japanese men. Diabetologia, 2010; 53: 1894-1902
8) Okura T, Higaki J, Kurata M, Irita J, Miyoshi K, Yamazaki T, Hayashi D, Kohro T, Nagai R; Japanese Coronary Artery Disease Study Investigators: Elevated serum uric acid is an independent predictor for cardiovascular events in patients with severe coronary artery stenosis: subanalysis of the Japanese Coronary Artery Disease (JCAD) Study. Circ J, 2009; 73: 885-891
9) Di Stolfo G, Mastroianno S, Potenza DR, De Luca G, d’Arienzo C, Pacilli MA, Fanelli M, Russo A, Fanelli R: Serum uric acid as a prognostic marker in the setting of advanced vascular disease: a prospective study in the elderly. J Geriatr Cardiol, 2015; 12: 515-520
10) Higashi Y, Yoshizumi M: Exercise and endothelial function: role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. Pharmacol Ther, 2004; 102: 87-96
11) Tomiyama H, Higashi Y, Takase B Node K, Sata M, Inoue T, Ishibashi Y, Ueda S, Shimada K, Yamashina A: Relationships among hyperuricemia, metabolic syndrome, and endothelial function. Am J Hypertens, 2011; 24: 770-774