The level of serum uric acid (UA) has been increasing among people in developed countries, including Japan, and hyperuricemia is prevalent in obese subjects and hypertensive patients. In epidemiological studies, serum UA has been associated with blood pressure (BP) and the incidence of hypertension. It has also been shown that hyperuricemia is a risk factor for cardiovascular disease. The association between serum UA and BP or hypertension may be independent of confounding factors, but the association was not significant on multivariate analysis in some studies. It is known that weight gain, habitual alcohol consumption, and a diet rich in meat and fish raise the level of serum UA.

In this issue of the Journal, Kansui et al investigate the association of serum UA with BP in a large number of male subjects as a cross-sectional study of a work site population. The study group comprised approximately 4,000 Japanese male workers aged 18–64 years old. BP and anthropometric indices were measured, biochemical parameters including serum UA were determined, and completed medical questionnaires, including questions on alcohol consumption, were obtained. In their study, both systolic and diastolic BP significantly correlated with serum UA, and the associations were independent of confounding factors such as body mass index and alcohol intake. Serum UA increased in a linear fashion as BP increased, and was significantly higher in subjects with stage 2 or 3 hypertension compared with those with an optimal BP. Similar results were observed in subjects who were not taking antihypertensive or UA-lowering agents, but not in subjects taking antihypertensive drugs. The authors concluded that serum UA might be associated with an increase in BP.

Their study supports the concept that hyperuricemia is an independent risk factor for hypertension, and that UA itself acts to elevate BP, although their results are largely confirmatory. A number of cross-sectional and longitudinal studies have shown that the level of serum UA is positively related to BP and the prevalence or incidence of hypertension. These associations were observed regardless of age, sex, and ethnicity, and were independent of confounding factors in many but not all studies. The causative role of UA in hypertension is demonstrated in experimental studies. For example, mild hyperuricemia induced by a uricase inhibitor raised the BP in rats. Moreover, a recent clinical trial showed that treatment with allopurinol not only decreases serum UA but also significantly lowers BP in adolescents with newly diagnosed essential hypertension.

The mechanisms of the BP elevation induced by UA have not been completely clarified, but its effects on vascular nitric oxide activity and endothelial function may play a role. It has been shown that hyperuricemia is associated with impaired flow-mediated dilation of the brachial artery in patients with cardiovascular risk factors. A recent study showed that allopurinol improved endothelial function and reduced the central augmentation index and left ventricular mass index in patients with chronic kidney disease. Inflammation and oxidative stress may be involved in the impaired endothelial function in hyperuricemia. Renal damage caused by hyperuricemia also appears to contribute to BP elevation caused by UA.

UA may play a role in the development of target organ damage in hypertensive patients. It has been shown that the level of serum UA or the presence of hyperuricemia is related to left ventricular hypertrophy, microalbuminuria, an increased carotid intima–media thickness, and high pulse wave velocity. High serum UA is also related to incident cardiovascular diseases such as coronary heart disease and stroke, and in the progression of renal failure. These associations of UA with organ damage and cardiovascular and renal diseases have been shown to be independent of BP and other risk factors. Therefore, hyperuricemia itself appears to participate in the development of atherosclerotic cardiovascular disease.

It seems rational to control hyperuricemia in the management of hypertension. Adequate treatment of hyperuricemia might be effective in controlling BP, and thus prevent organ damage and cardiovascular disease. Several agents are available to lower serum UA, and beneficial effects of allopurinol on BP and cardiovascular function have been shown in patients with hypertension or cardiovascular disease. However, lifestyle modifications should be recommended to patients with hyperuricemia as the first step in UA control. Weight loss and restriction of alcohol and meat consumption are effective in lowering serum UA, but weight loss is particularly important. It has been shown that hyperinsulinemia, which is frequently associated with obesity, decreases the renal excretion of UA. In my group’s study, both weight loss and an insulin-sensitizing agent significantly lowered serum UA in overweight hypertensive patients.

Finally, the independent contribution of serum UA to BP and the development of cardiovascular disease may be small. The hypotensive effect of allopurinol is usually not marked in patients with hypertension and hyperuricemia, and is much smaller than that of antihypertensive agents. It has also been shown that thiazide diuretics, which are known to increase UA, have cardiovascular protective effects similar to these agents.

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other antihypertensive drugs without such action. Weight loss but not an insulin-sensitizing agent may lower BP, despite a comparable reduction in serum UA.15

Disclosures
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