Asymptomatic Hyperuricemia May Flag CV Risk

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VIENNA — The time has come for a change in thinking regarding nongouty asymptomatic hyperuricemia, traditionally dismissed as a clinically irrelevant laboratory abnormality, George Nuki, M.D., asserted at the annual European Congress of Rheumatology.

"We actually need at this time a serious paradigm shift in thinking about the significance of asymptomatic hyperuricemia. We should think of it in terms of being a major prognostic marker. Asymptomatic hyperuricemia, as for gout itself, should be a red flag. When we see such a patient, we should ask ourselves why they're hyperuricemic, but we also need to assess them very well for cardiovascular risk factors and very carefully for metabolic syndrome," said Dr. Nuki, professor of medicine at the University of Edinburgh.

Is uric acid an independent risk factor for cardiovascular and all-cause mortality, or just a biologic marker for other more causal risk factors?

Serum uric acid can be measured simply and inexpensively. But the central question regarding its clinical significance in asymptomatic individuals remains unanswered: Is it an independent risk factor for cardiovascular and all-cause mortality, or merely a biologic marker for other more causal risk factors?

The evidence on this score remains conflicting. A Framingham Study analysis concluded that asymptomatic hyperuricemia was not an independent cardiovascular risk factor. But in several recent studies it was.

For example, in a prospective cohort study of 1,423 healthy middle-aged Finnish men followed for nearly 12 years, Leo K. Niskanen, M.D., professor of medicine at Kuopio (Finland) University, and coworkers found that men in the top one-third in terms of baseline serum uric acid (SUA) levels were an age-adjusted 70% more likely to die of any cause than those in the lowest third. They were also 3.7-fold more likely to die of cardiovascular disease (Arch. Intern. Med. 2004;164:1546-51).

Similarly, in an analysis of data from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, Aud Hoiggen, M.D., of Ullevål University Hospital, Oslo, and coinvestigators reported that baseline SUA was significantly associated with the cardiovascular event rate during 4.8 years of follow-up.

SUA rose over time in hypertensive patients randomized to a losartan-based antihypertensive regimen and in those assigned to an atenolol-based regimen, but the increase in the losartan group was 62% less. The investigators calculated that 29% of losartan's treatment effect on the primary LIFE composite end point of cardiovascular death, nonfatal MI, or stroke was attributable to its effect upon SUA (Kidney Int. 2004;65:1041-9).

Dr. Nuki said these studies are particularly intriguing in light of animal data showing that when SUA levels in rats are raised pharmacologically, the result is hypertension and intrarenal vascular disease, both of which are reversible with SUA-lowering using allopurinol.

Laboratory studies suggest a plausible mechanism by which asymptomatic hyperuricemia might be an independent risk factor for cardiovascular and renal disease. Soluble uric acid activates inflammatory pathways capable of inducing vascular smooth muscle cell proliferation and atherosclerosis. The pathways involve platelet-derived growth factor–A, cyclooxygenase-2, the monocyte chemokine MCP-1, and mitogen-activated protein kinases, he said.

Despite growing evidence implicating nongouty asymptomatic hyperuricemia as a cardiovascular risk factor, Dr. Nuki argued there are insufficient data to warrant using allopurinol or other SUA-lowering drugs in affected individuals.

"At the present time, my view certainly is that uric acid-lowering drug therapy isn't indicated," Dr. Nuki said.

Instead, he advocated lifestyle modification to reduce the hyperuricemia—less dietary intake of high-purine animal protein and alcohol, more exercise, weight reduction—coupled with aggressive pharmacotherapy of any treatment-amenable components of the metabolic syndrome present, including hypertension and dyslipidemia. ■