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Hyperuricemia; the renewed interest in an old enemy

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Treatment with allopurinol may be effective in reversing some of the metabolic derangements of chronic kidney disease patients such as metabolic acidosis.

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Hyperuricemia (defined by serum uric acid levels above 7 mg/dL in men and 5.5 or 6 mg/dL in women) is a common finding in patients with chronic kidney disease (CKD). From the early 1800's hyperuricemia was recognized as a cause of gouty arthritis. At the same time hyperuricemia was suggested to have an underlying relationship with various cardiac and kidney diseases such as arteriosclerosis, hypertension, cardiovascular and kidney diseases (1,2). Some early epidemiological observations found that around 60% to 65% of patients with gout had arterial hypertension, 75% were obese, 20%-60% had mild to moderate degrees of CKD, 10%-25% developed end-stage kidney failure, 25% died with kidney failure, and 90% developed cardiac disease (2-6). Moreover, it is now evident that 25%-50% of hypertensive patients have high serum uric acids, and up to 50% of asymptomatic hyperuricemias (serum uric acid >6.5 mg/dL in females and >7 mg/dL in men) have hypertension (6, 7). The histopathologic findings of "gouty nephropathy" consisted of glomerulosclerosis, renal arteriosclerosis and interstitial fibrosis often containing focal urate crystal deposition in the interstitium was found in the autopsies of 79%-99% of patients with gout (8). However, since both hyperuricemia and cardiovascular diseases are commonly associated with risk factors such as old age, male gender, obesity, metabolic syndrome, type II diabetes, insulin resistance, hypertriglyceridemia, hypertension and CKD, hyperuricemia was considered a bystander and not a causative factor, except for gouty arthritis, and in the late 1980s uric acid was removed from routine chemistries. It took until late 1990s that high serum uric acid was recognized as a surrogate to renal

disease and as a risk factor for developing hypertension, cardiovascular disease and metabolic syndrome (9-12). More recent epidemiologic studies, animal experiments, and human clinical studies have consistently shown that uric acid indeed has a causative role in development of hypertension, development of CKD, and heart diseases (2, 6, 13-15). Some of the inconsistencies in the epidemiologic studies using multivariate analysis models to find an independent role for hyperuricemia in cardiovascular diseases, is partly due to a direct relationship between hyperuricemia and traditional cardiac risk factors such as hypertension, obesity, hyperlipidemia and male gender. However, hyperuricemia can be a causative risk factor for cardiac disorders without simultaneously being an independent risk factor. Moreover, in progressed CKD serum uric acid levels can increase because of the decreased GFR. Hyperuricemia itself might also contribute to the progression of renal disease as has been shown in animal studies (13,15). A number of studies have now shown strong association between hyperuricemia and new onset of hypertension (16,17), CKD and its progression (18-20), metabolic syndrome (21,22), fatty liver (23,24), cardiovascular diseases and the mortality associated with them (11,12,25), and endothelial dysfunction (26, 27). Treatment with allopurinol, a xanthine oxidase inhibitor, has been shown to slow the development of CKD (28,29), decrease blood pressure in the new onset juvenile hypertension (30), improve endothelial function (31-33), and decrease cardiovascular morbidity and mortality (29,34-38). The effect of allopurinol on improving metabolic acidosis was firstly reported by Bayram et al (39). In 30 patients with CKD stages 2-4, they found

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that administration of 300 mg/d of allopurinol for three months resulted in significant improvement in endothelial function as measured by flow-mediated dilation over the forearm, a significant improvement in creatinine clearance and serum bicarbonate levels, compared to a controlled group (39). The randomized controlled clinical trial by Gholami et al, presented in this issue of the journal is of interest. It shows that patients with CKD stages 2-4 and serum uric acid levels between 6-10 mg/dL with documented metabolic acidosis, who received allopurinol 100mg daily, versus placebo control group who received vitamin B1, have a significant rise in serum bicarbonate level and GFR (40). This report adds further evidence to our current knowledge that hyperuricemia is not just an innocent bystander in the CKD patients, and it contributes to its progression and also to some of the metabolic derangements associated with CKD such as metabolic acidosis. Moreover, it shows that treatment with allopurinol may be effective in reversing some of these metabolic derangements such as metabolic acidosis.

Author's contribution

BB is the single author of the paper.

Conflicts of interest

The author declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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