Uric Acid: Is It a True Cardiovascular Risk Factor?

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The notion that elevated uric acid (a product of purine metabolism) is a risk factor for cardiovascular disease (CVD) has been much debated. It has been observed that an increased uric acid concentration is associated with hypertension, cardiovascular and renal disease, though there has been no direct proof of causality. Furthermore, several studies found that uric acid is not an independent risk factor for CVD after controlling for other conventional risk factors. Some even went as far as suggesting raised uric acid (associated with low-dose thiazide diuretics usage) may be beneficial for CVD based on assumptions made from the ALLHAT (Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack Trial) study in which thiazide treatment group had the best cardiovascular outcome. At present, routine measurement of serum uric acid has not been included as part of CVD risk assessment in clinical practice. Over recent years, accumulating evidence from animal research, human experimental studies to large-scale randomized clinical trials suggests that raised uric acid is perhaps an underestimated true CVD risk factor.

Uric acid, endothelial dysfunction, systemic inflammation & VSMC proliferation

Endothelial dysfunction is a widely accepted precursor for CVD. Infusion of uric acid into the human forearm resulted in impaired endothelium-dependent vasodilatation in healthy individuals. Allopurinol, a xanthine oxidase inhibitor, blocks uric acid synthesis and reverses impaired endothelial nitric oxide production in both heart failure and type 2 diabetes. In addition, uric acid has been shown to have proinflammatory effects. Infusion of uric acid leads to a marked increase in circulating tumour necrosis factor-α, a proinflammatory cytokine that has been implicated in the pathogenesis of insulin resistance and CVD. Uric acid also stimulates synthesis of monocyte chemoattractant protein-1 (MCP-1), a chemokine involved in atherogenesis, in rat vascular smooth muscle cells. Uric acid also stimulates vascular smooth muscle cell (VSMC) proliferation, another key process in atherogenesis. Thus uric acid may have a pathogenic role in atherosclerosis through its effects on endothelial function, inflammation and VSMC proliferation.

Uric acid and CVD endpoint reduction: insight from LIFE and GREACE

The results of an important landmark study, LIFE (Losartan Intervention for Endpoint Reduction), showed that incidence of fatal and non-fatal stroke is significantly reduced in losartan-treated hypertensive subjects with ECG-evidence of left ventricular hypertrophy (LVH) over a mean follow up period of 4.8 years compared with atenolol-treated subjects. This was achieved despite very similar blood pressure reduction between groups. Significantly, up to 29% of the reduction in the primary composite endpoint (death, myocardial infarction or stroke) seen in LIFE study was attributable to a fall in serum uric acid concentrations in the losartan-treated group. The difference in serum uric acid concentrations in the LIFE study was observed despite the fact that the final serum creatinine concentrations were very similar (97.0 vs 96.2 µmol/L in the losartan and atenolol group respectively). Hence it is very likely that reduction in serum uric acid concentrations was due to pharmacological effects rather than differences in renal function. This has important practical implications in the therapeutic management of high-risk hypertensive subjects. This uricosuric effect of losartan appears to be a drug effect rather than a class effect. Further insight of the importance of uric acid reduction is evident from the GREACE (The GREek Atorvastatin and Coronary-heart-disease Evaluation) study. In this study, two groups of patients with coronary heart disease were compared. One group received atorvastatin titrated to lower LDL-c to below 2.6 mmol/L and another group was assigned for “usual care”. Over the trial period of 3 years, there was a fall in both serum creatinine and serum uric acid concentrations in the atorvastatin group compared to a rise in both variables in the “usual care” group. The net difference between the two groups in serum uric acid concentrations was 39 µmol/L which exceeds the magnitude seen in the LIFE study (28 µmol/L). Hence, it can be argued that the reduction in serum uric acid may have directly contributed to the reduction in mortality seen in the atorvastatin-treated group (average dose 24 mg/day). Furthermore, results from the recent Heart Protection Study showed that stoke is significantly reduced by simvastatin (40 mg/day). It is likely that this beneficial effect is also mediated through a reduction in serum uric acid concentration since in the Heart Protection Study, those taking simvastatin had a smaller rise in serum creatinine levels compared to placebo. Fibrates generally do not have uricosuric effects with the exception of fenofibrate. Indeed, fenofibrate diminishes the reabsorption of uric acid in the proximal renal tubule and hence augments uricosuria and lowers serum uric acid. Micronised fenofibrate at a daily dose of 200 mg reduces diuretic-induced elevation of serum uric acid. Although the mechanisms of losartan and statin-induced reduction in uric acid are not fully understood, it is possible that combination therapy with losartan and statins
or fenofibrate have synergistic effect in uric acid reduction. This may confer greater cardiovascular protection in specific patient groups. Future randomized controlled trial will be required to test this hypothesis.

Relevance to Hong Kong Chinese

In Hong Kong, the prevalence of obesity (and thus the metabolic syndrome) is increasing at an alarming rate. This suggests that high uric acid associated with high body mass index and insulin resistance is probably quite common. There are no official local data for the prevalence of high uric acid in Hong Kong or in China. Data from the Nutritional and Health Survey in Taiwan conducted between 1993-1996 showed that 26% of adult males and 17% of adult females have raised uric acid, which cannot be explained by obesity and alcohol intake. Personal experience from Qualigenics Diabetes Centre reveals that approximately one in four obese (BMI > 25 kg/m²) subjects who undergo routine metabolic assessment have raised uric acid.

There are additional dietary reasons to account for the high uric acid concentrations in Hong Kong Chinese, given the amount of shellfish, red meat and organ meats the local population consumes (Table 1). Therefore, in addition to choice of drug therapy, dietary modulation is essential in managing these individuals (Table 2).

### Low purine food (10-25 mg purine per 100 g portion)
- Milk, cheese, yogurt
- Egg
- Most vegetables
- All fruits
- Cereal grains, e.g. rice, noodle and bread
- Fats and oil
- Water, tea and coffee

### Medium purine food (25-100 mg purine/100 g portion)
- Lean beef, pork, lamb, poultry
- Other fishes, shrimp, crab, lobster
- Dried beans, tofu, soy milk
- Spinach, green peas, cauliflower, asparagus
- Mushroom, bamboo shoot, seaweed
- Peanuts, almond, chestnut, lotus seed

### High purine food (150-1000 mg purine/100 g portion)
- Game meat and goose
- Organ meats: liver, kidney, intestine, heart and brain
- Sardine, herring, eel
- Fish roe, fish skin, dried shrimp and dried fish
- Shellfish: scallop, oyster, mussel, clam
- Concentrated meaty soup, gravy, meat essence
- Yeast

### Table 1 Purine content of various foods

<table>
<thead>
<tr>
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### Table 2 Dietary therapy for managing hyperuricemia

<table>
<thead>
<tr>
<th>Moderate protein intake</th>
<th>Limit to 0.8 g/kg ideal body weight (i.e. 50 g protein per day for a 60 kg man)</th>
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<tbody>
<tr>
<td>Avoid or decrease alcohol consumption</td>
<td>Limit to 1-2 drinks per day (1 standard drink = 12 oz beer, 5 oz wine or 1 oz distilled liquor)</td>
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<tr>
<td>Limit fat intake (&lt;30% fat from total kcal)</td>
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<tr>
<td>Increase fluid intake to at least 2L per day (8-10 cups) and urine output</td>
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<td>Maintain a healthy weight but avoid rapid weight loss which may increase breakdown of tissue and temporarily increase plasma uric acid level</td>
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### Conclusions

There is emerging evidence from large-scale clinical trials to support uric acid as a true CVD risk factor. Compelling evidence will need to be provided by randomized controlled trials with solid endpoints. Measuring and targeting uric acid as part of CVD risk evaluation may soon be standard practice.

### References