# 高尿酸血症、痛風、與心血管疾病的三角關係

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According to the Nutrition and Health Survey in Taiwan (NAHSIT) [1], the prevalence of hyperuricemia in men (sUA >7.0 mg/dl) and women (sUA >6.0 mg/dl) were as high as 42.1% and 27.4%, respectively. Both the mean sUA levels and prevalence of hyperuricemia were higher in the Taiwanese population compared to those of other ethnic groups [2-4]. The prevalence of gout in Kin-Men 1996 –97 was estimated as 1.7% for the general population from the reported gout prevalence among hyperuricemic subjects [5]. NAHSIT 1993 –96 also reported the prevalence of gout as 3.3% in men and 1.1% in women [1]. These data were higher than those of 0.16, 0.67, and 0.67% among rural, suburban, and urban areas, respectively, in Taiwan prior to 1994 [6].

Known risk factors for gout include hyperuricemia, male gender, hypertension, renal insufficiency, obesity, diuretic use, lead exposure, and family history [7]. The Normative Aging Study suggests the annual incidence of gout increases with increasing sUA levels, especially sUA above 9 mg/dl [8]. However, most gout-related reports studied men as contrasted to the limited description on women. Previous research indicates women not only tend to develop gout later in life, but also use more diuretics, and have more co-morbidity of obesity, hypertension, dyslipidemia, cardiovascular disease (CVD), peripheral artery disease, diabetes mellitus, renal insufficiency, and habitual alcoholic intake [9]. The gender-specific risk of gout in relation to abnormalities of various metabolic risk factors, including sUA, cholesterol, triglyceride, glucose, blood pressure and overweight is noted [10]. Gender-specific risk thresholds of serum uric acid (sUA) levels for gout development are provided for the optimal sUA levels to prevent gout attack.

Elevated sUA level has been associated with cardiovascular disease (CVD) in high-risk subgroups, including patients with gout. The population-based study of NHANES I (First National Health and Nutrition Examination Survey) further demonstrated an independent relationship between sUA and CVD mortality [11-12]. In Taiwan, sUA is claimed to be a significant risk for incident stroke in women (hazard ratio [HR], 1.3) [13-14]. We recently reported hyperuricemia (sUA >7mg/dl) as an independent predictor for CVD and ischemic stroke with respective HR of 1.39 ($p < 0.001$) and 1.35 ($p = 0.02$) in subjects aged >35 years after a mean follow-up of 8.2 years [15]. These estimates are parallel to those derived from recent meta-analysis for stroke and coronary heart disease [16-17].

Phagocytosis of monosodium urate crystals activates Toll-like receptor and inflammasome-NALP3 to release interleukin-1β and to initiate gouty arthritis [18]. In vitro, uric acid may be a signal of danger, and can act as an adjuvant of the damaged cells, when it was presented by the dendritic cells to T lymphocytes [19]. In vivo, uric acid shows an antioxidant capacity with reduction of singlet oxygen consumption [20]. In response to reduced ascorbic acid synthesis, the urate level increases [20] which may stop the stress-induced cell transformation and prevent oxidant-induced cardiac and renal toxicity [21]. On the other hand, synthesis of uric acid may result in the generation of superoxide [22] and offset the anti-oxidant effect [23]. The pro-oxidant effect of uric acid may increase oxygen radical formation in circulation, in-turn promote the lipid oxidation, lead to vascular endothelial dysfunction, inflammation, impaired nitric oxide production, atherosclerosis, and thrombogenesis [21]. In response to increased sUA level, systolic blood pressure increases through the activation of renin-angiotensin system [24] which further results in increase of sodium resorption [21]. In animal models, the pro-inflammatory and proliferative effect of soluble uric acid influences vascular smooth muscle cells and inhibits the nitric oxide synthesis from vascular endothelium [25]. Hypertension develops thereafter in association with both direct effect from urate on the endothelium and renal injury from intra-renal vascular diseases [21, 26].

The commonly used urate lowering therapy (ULT) for symptomatic hyperuricemia and chronic gouty arthritis, includes allopurinol, probenecid, sulphinpyrazone, benzbromarone and uricase [27]; however, the role of urate lowering in preventing CVD is still inconclusive. A randomized control trial of allopurinol, a xanthine oxidase inhibitor, in hypertensive adolescents has demonstrated its effect in reducing systolic and diastolic blood pressure [28]. Allopurinol can reduce oxygen consumption in the myocardium and improve systolic function of congestive heart failure (CHF), with which sUA has been associated as a poor prognostic factor [29].

Therefore, this talk will focus on defining the role of sUA on CVD through exploring the risk of sUA on CVD mortality and discussing if controlling sUA with ULT can improve this outcome.

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