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Editorial

EDITORIAL

Uric acid and cardiovascular risk in rheumatoid arthritis

An association between hyperuricaemia and cardiovascular disease (CVD) was suggested more than a hundred years ago but did not receive much attention, mainly because there was no known mechanism that could link it pathogenically to CVD. On the contrary, uric acid (UA) was thought to be an antioxidant, leading many experts to propose that increased serum UA (SUA) levels in patients with CVD was actually a mechanism to counterbalance increased oxidative stress in these patients [1].

Up until the early 1990s, there was no reliable *in vivo* experimental model to study the effects of chronic hyperuricaemia on the cardiovascular system. A major breakthrough though came with the use of the uricase inhibitor oxonic acid: mice fed with oxonic acid developed chronic mild hyperuricaemia, with SUA levels comparable to those of humans, with no crystal deposition. This animal model of induced hyperuricaemia has provided us with novel insights about the role of UA in CVD [2]. In elegant experiments, investigators have found that these mice develop systemic hypertension, with every 0.5 mg/dl of SUA increase leading to a 10 mmHg blood pressure (BP) rise [3]. Moreover, these mice displayed endothelial dysfunction and renal changes such as afferent arteriolopathy, strikingly similar to those observed in human essential hypertension. Intriguingly, allopurinol was effective in lowering BP and preventing vascular changes in this animal model, suggesting a pathogenic role for UA [4].

Further *in vitro* studies have shown that UA can enter cells and stimulate several intracellular pathways. For example, UA can enter vascular smooth muscle cells and stimulate their proliferation by activating the mitogen-activated protein kinase pathway [5]. Moreover, UA can stimulate pro-inflammatory pathways and induce CRP production and redox pathways, thus promoting intracellular oxidative stress [6]. The latter interaction may reconcile the two opposing views (antioxidant *vs* pro-oxidant) regarding UA and oxidative stress: it has been proposed that UA may act as an antioxidant extracellularly and as a pro-oxidant intracellularly [7].

These basic research data have provided a strong mechanistic link between UA and CVD and led to a reappraisal of UA's role. Moreover, epidemiologic studies have also shown a strong association between SUA levels and CVD, especially in high-risk populations; this association is less profound, but still significant, in low-risk groups [8]. Intriguingly, allopurinol, the most widely used urate-lowering agent, was recently shown to be effective in patients with angina pectoris [9].

Little work has been done on the potential association of UA and CVD in RA. RA is characterized by increased cardiovascular morbidity and mortality that cannot be fully explained by the presence of classical CVD risk factors, suggesting that novel risk factors may also be implicated [10]. Evidence accumulated over the past decade points to the conclusion that SUA may be such a novel CVD risk factor, and therefore one may hypothesize that hyperuricaemia contributes, at least to some extent, to the increased CVD burden in RA. In support of this, we have shown in a cross-sectional study that SUA levels are a strong, independent predictor of CVD in patients with RA, after full adjustment for multiple other CVD risk factors and RA characteristics [11]. This association appeared to be stronger than that observed in the general population: patients in the highest SUA quintile show a 6.5-fold increase in the odds of having CVD compared with patients in the lowest SUA quintile.

How might UA mediate deleterious effects on the cardiovascular system in patients with RA? Several links may exist, but it is likely that the strongest one is hypertension. A large amount of data from basic research indicate that increased SUA levels can promote the development of hypertension by causing vascular smooth muscle cell proliferation, activating the renin–angiotensin system and inducing salt sensitivity [12]. Clinical data also support a potential link between SUA and hypertension. Recently, a randomized controlled study assessing the efficacy of allopurinol in adolescents with hypertension and hyperuricaemia showed that lowering SUA levels was an effective treatment of hypertension [13]. Hypertension is highly prevalent among RA patients [14]. A study by our group showed that SUA levels were a significant independent predictor of hypertension in patients with RA, with a 1.6-fold increase in the odds of being hypertensive per 1 mg/dl increase in SUA levels [15].

Even though hypertension appears to be the most important potential link between hyperuricaemia and CVD in RA, other links may also apply. A second potential link is metabolic syndrome/insulin resistance. The prevalence of metabolic syndrome, an established CVD risk factor, may be as high as 40% in RA [16]. It has been proposed that hyperinsulinaemia stimulates UA reabsorption in the proximal tubule; however, hyperuricaemia may be not only a consequence but also a promoter of insulin resistance [17]. Therefore, high(er) SUA levels could contribute to increased CVD risk in RA by enhancing insulin resistance. A third potential link is endothelial dysfunction, which is also common in RA [18]. Evidence from both basic research and clinical studies indicates that hypeuricaemia promotes endothelial dysfunction. UA may have pro-inflammatory effects on the endothelium and thus

promote endothelial dysfunction and atherogenesis [19]. Interestingly, we have shown a link between SUA and CRP levels in patients with RA (unpublished observations). Finally, another link could be renal dysfunction. The potential role of renal dysfunction as a risk factor for CVD has increasingly been recognized in the general population. Regarding RA, we have shown that UA is a strong, independent predictor of renal dysfunction. It is noteworthy that UA ranked as the strongest predictor of GFR among all variables tested, including age [20].

It appears therefore that UA is not just an innocent bystander but may be an active player in the pathogenesis of CVD, including CVD in patients with RA. However, all RA studies are cross-sectional and have not assessed long-term mortality, while mechanistic studies in the context of high-grade inflammation are lacking; therefore, further corroboration is required before any definite conclusions are drawn. Whether SUA should be targeted therapeutically as a means of reducing CVD risk in patients with RA should be investigated in prospective studies designed specifically for the purpose.

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