



Short Communication

Does serum uric acid play a protective role against tissue damage in cardiovascular and metabolic diseases?

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Abstract

Previous clinical, observation and epidemiologic studies have demonstrated strong association between serum uric acid (SUA) and cardiovascular disease (hypertension, heart failure, and asymptomatic atherosclerosis), metabolic states (abdominal obesity, diabetes mellitus, metabolic syndrome, insulin resistance) and kidney disease. There is a large body of evidence regarding the role of SUA as predictor of CV events and CV mortality in general population and individuals with established CV disease and metabolic diseases. However, SUA may exhibit protective effects on endothelium and vasculature as well as attenuate endogenous repair system through mobbing and differentiation of cell precursors. Although SUA lowering drugs are widely used in patients with symptomatic hyperuricemia and gout beyond their etiologies, there is no agreement of SUA below target level 6.0 mg/dL in asymptomatic individuals with kidney injury and CV disease and data of ones are sufficiently limited. The short communication is depicted on the controversial role of SUA as primary cell toxicity agent and secondary cell protector against hypoxia, ischemia and apoptosis.

Serum uric acid (SUA) was recognized an independent risk factor of cardiovascular (CV) events and CV disease in general population [1,2]. Although SUA levels above the current international reference limit equal 6.0 mg/dL are highly prevalent in chronic kidney disease (CKD), hyperuricemia strongly associates with in-hospital CV mortality independently from CKD etiology and renal function in individuals admitted to the hospital due to several causes, i.e. myocardial infarction, stroke, hypertensive emergencies, heart failure, arrhythmia, shock / sepsis [3-6]. There is a large body of evidence regarding that the SUA may be valuable and powerful biomarker of kidney injury, oxidative stress, asymptomatic atherosclerosis, insulin resistance and inflammation [5-9]. Therefore, recent clinical studies have shown that SUA through accumulation of reactive oxygen species in vasculature corresponds to a development of endothelial dysfunction prior to arterial hypertension [10,11]. Although SUA lowering drugs (allopurinol, febuxostat) are widely used in patients with symptomatic hyperuricemia and gout beyond their etiologies, there is no agreement of SUA below target level 6.0 mg/dL in asymptomatic individuals with kidney injury and CV disease and data of ones are sufficiently limited.

However, the role of SUA in CV development appears to be seriously controversial [12]. Being scavenger of free radicals SUA contributes in regulation of oxidative stress and may exhibit a powerful protective effect against hypoxia, ischemia, and apoptosis. Therefore, SUA attenuates generalized microvascular dysfunction in target organs, i.e. heart, lung and kidney, and suppresses a local inflammation in plaque [3,13]. SUA may be an epigenetic regulator of vascular repair system through cooperating with mobbing and differentiation of endothelial progenitor cells and other cells' precursors [14]. There is evidence that the uric acid may regulate secretom compounds and via

innate intracellular signal systems (Akt, STAT3) it mediates releasing of secretomes into circulation including micro particles and micro vesicles [15,16]. Finally, SUA plays a pivotal role in endogenous repair system contributing in enhancement of endothelium and vasculature [17]. Thus, SUA may directly injure of cell membranes through an attenuation of free radicals accumulating, and in it contrast demonstrates indirect effect toward restoration of tissue after hypoxia, ischemia, other damages via involving progenitor cells and improving cell-to-cell cooperation.

Probably, SUA acts as contributor between low-grading inflammation, tissue damage and endogenous repair systems [18]. In fact, an increased activity of xanthine oxidase (XO), which is a key enzyme in uric acid synthesis and is under control of inflammatory cytokines/chemokines, some growth factors, and intermediates (blood glucose), was found in several patients' populations with metabolic syndrome, diabetes mellitus, abdominal obesity, heart failure, atherosclerosis, rheumatic disease. Consequently, XO over expressing could be not only protective putative underlying mechanism against the accumulation of reactive oxygen species, but it may be a specific secretom modifier, which becomes a one of important co-regulator of mobbing and differentiation of cell precursors [19]. In this context, lowering of asymptomatic SUA levels below 6.0 mg/dL regardless of risk of CV events and CV disease as it is alleged requires explanation in details [12].

In conclusion, large clinical trials need to be enter to investigate the controversial role of SUA in pathogenesis and outcomes of CV disease, especially when SUA is not clinically significant elevated and probably does not require decision making to low serum concentrations.

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