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Short Communication

Serum uric acid as a metabolic regulator of endothelial function in heart failure

Abstract

The development of heart failure (HF) associated with elevated level of serum uric acid (SUA). Additionally, the majority of individuals with traditional cardiovascular risk factors contributing in HF risk exhibited increased levels of SUA. 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 in heart failure (HF) are sufficiently controversial. First SUA plays an important role in inducing oxidative stress, inflammation, neurohumoral activation, and endothelial dysfunction. Secondary, SUA may act as antioxidant contributing in restoring of vascular function. Moreover, SUA is able to epigenetically regulate a survival of endothelial precursors, mediate their mobbing and differentiation, as well as coordinate a turn-over effect of metabolic memory phenomenon into repair capability of cell precursors. However, elevated SUA level was found a predictor of adverse clinical outcomes of HF. The short communication is depicted the importance of new clinical data to confirm the emerging reparative ability of SUA in HF and its role as promising target for treatment in cardiac failure.

Short Communication

There is a large body of evidence regarding the role of serum uric acid (SUA) in pathogenesis of cardiovascular diseases (CVD) including heart failure (HF). 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. acute myocardial infarction, stroke, hypertensive emergencies, acute / chronic heart failure, arrhythmia, shock and sepsis. In contrast, hypouricemia did not associate with increased mortality rate in patient populations with established CVD [1].

In HF an elevated SUA level was found due to several mechanisms including 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). Secondary, decreased kidney clearance of uric acid associated with ACE inhibitor, angiotensin-II receptor blockers or angiotensin-receptor-neprilysin inhibitor (ARNI) [2]. Third, nature evolution of HF related to target organs damage including kidney, fluid retention, and electrolyte disturbance and associated with declined glomerular filtration rate [3]. Fourth, age and metabolic comorbidities including diabetes mellitus, rheumatic diseases, hypertension may lead to kidney insufficiency prior to HF manifestation and worse nature evolution of HF [4].

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 [1,2]. 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 [6,7]. Although uric acid 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 in HF are sufficiently limited.

Whether SUA could be an independent predictor of HF development is not fully clear. Recent clinical studies and some meta-analysis have shown that elevated SUA levels were associated with an increased risk of incident HF, observed in majority of patients with established chronic HF and relate to adverse clinical outcomes in HF [8-11]. However, the impact of uric acid on all-cause mortality and HF-related death was

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insured by co-existing disease predominantly hypertension, abdominal obesity, prediabetes / diabetes mellitus, kidney disease as well as female sex [9,12-14]. Moreover, there are data clarifying that even asymptomatic hyperuricemia associated strongly with long-term survival of CVD patients and individuals with chronic kidney disease throughout pre-dialysis period and whose who undergoing hemodialysis procedures. In the Rotterdam Study high quartiles of normal rages of SUA and mild increased SUA level were more closely related to early-phase mechanisms of insulin resistance and diabetes mellitus rather than CV complications due to target organ damage progression [8]. Thus, predictive value of SUA in different patients at risk of HF is controversial and requires to be elucidated.

The potential molecular mechanisms that explain the role of SUA in development and advance of HF are traditionally structured in follow schematic consequences that are appeared to be counter directed. On the one hand, the hyperuricemia causes inflammation due to direct vascular injury and a production of various inflammatory cytokines and monocyte chemoattractant protein-1, inducing oxidative stress and activation of the local rennin-angiotensin system [15,16]. Additionally, all these factors lead to endothelial dysfunction by a reduction in endothelial levels of vasodilator substances such as nitric oxide, inducing cellular proliferation, accelerating atherosclerosis, activating insulin resistance and microvascular inflammation [17]. On the other hand, urates are physiological substrate for myeloperoxidase acting as regulator of oxidative stress, but molecule of uric acid may act as intracellular scavenger of free radicals diminishing pro-inflammatory effect and increasing cell survival [18]. Thus, SUA links in vascular damage, endothelial dysfunction and oxidative stress that play important role across all stages of HF development and contributes in an impact of co-morbidities on risk of HF onset and advance.

Another way that could probably explain the role of uric acid in pathogenesis of HF relates to an ability of uric acid to epigenetically regulate a survival of endothelial precursors, mediate their mobbing and differentiation, as well as coordinate a turn-over effect of metabolic memory into repair capability of cell precursors [19,20]. Indeed, SUA levels independently and inversely associated with number of circulating endothelial progenitor cells in HF individuals [21]. Moreover, uric acid contributed in shaping of altered ability of endothelial precursors to activate by several stimuli, release cell secretome, regulate endothelial reparation and turn into mature endothelial cells [22,23]. Consequently, uric acid may consider as an endogenous regulator of vascular repair system that undoubtedly opens new sign on the role of uric acid metabolism as integrative asset explaining an impact of various comorbidities on a risk of HF manifestation. As an evidence of the opinion it has been allowed presenting data, which confirm higher predictive value of elevated SUA in HF patients beyond etiology of disease, cardiac pump function, traditional risk factors and estimated glomerular filtration rate [24-26]. Interestingly, large numbers of clinical and observational studies have shown that elevated SUA levels are associated with reduced survival in in-patients and out-patients with several phenotypes of chronic HF, as well as in acute / actually decompensated HF [27-29].

In contrast, in recent meta-analysis lowering SUA levels under treatment did not predict improved surrogate clinical outcomes in HF [30]. Moreover, there was not convincing evidence regarding associations of SUA levels with increased risk of HF and other disease at higher risk of HF and HF mortality [31].

All these facts clarify that uric acid is multiple player with controversial activities that concurrently contribute in HF pathogenesis [32]. The modalities of uric acid cannot be discussed as unconditionally harmful effects supporting inflammation and cell death, but they may produce a favorable result on reparative activity of endothelium and restoring endothelium function and vascular integrity [33]. Whether SUA is a therapeutic target to reduce HF risk in vulnerable population is not fully clear and requires to be explained in the large clinical trials.

In conclusion, there was no strong and available evidence regarding only harmful effect of uric acid in vulnerable population patients at higher risk of HF as well as in individuals with established HF irrespective to left ventricular ejection fraction or isolating diastolic abnormality. The importance of new clinical data that confirm the emerging reparative ability of uric acid and its antioxidant activities across HF development require to be cleared in large investigations. The results of these trials would be intriguing and could open new perspective to use xanthine oxidase inhibitors as adjuvant care in HF management.

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