Uric acid is an index of chronic diseases or is an index of antioxidant? A mini-review to the recent trends

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Abstract
Abnormal levels of serum uric acid are referred as a main public health problem arising from its role in systemic diseases including cardiovascular disease, chronic kidney disease, hypertension, type 2 diabetes mellitus, ischemia, Alzheimer's disease and Parkinson's disease. Although uric acid is known as an index of chronic diseases, it is also referred as an antioxidant index especially in control of cardiovascular defects. Hence, it seems that uric acid is a double-edged sword. This mini-review is aimed to clarify the pathogenic effect of uric acid on some organs and its positive influence on cardiovascular system.

Keywords: Uric acid, Chronic kidney disease, Hyperuricemia, Type 2 diabetes mellitus, Antioxidant, Oxidative stress, Cardiovascular disease, Inflammation, Reactive oxygen species

Introduction
The serum uric acid level is between 2 and 7 mg/dL in males and between 2 and 6.5 mg/dL in females under physiological conditions (1,2). The concentration of uric acid, either above or below normal levels, has been associated with some diseases (3). Some factors can affect the serum uric acid level including aging (4), the intensity and duration of physical activity (5,6), hormones (7) as well as food type (3,8). The urea concentration in serum is abnormally increased worldwide (9). Hyperuricemia is referred to as the level of uric acid in blood greater than 6 mg/dL in women and 7 mg/dL in men (1) resulting from either overproduction of uric acid or the decreased excretion of uric acid or both. The high intake of fructose leads to a rapid increase in serum uric acid level (10) that is resulted from rising ATP degradation to AMP and consequently activating the pathway of purine degradation to urate (11). Moreover, alcohol intake causes high uric acid concentration via either raising urate synthesis that is resulted from increasing the turnover of adenosine nucleotides (12) or decreasing its excretion (13,14). Serum uric acid is referred to as a main marker of inflammation in various organs (15). Hyperuricemia has been connected with the increased risk of incidence of cardiovascular diseases and death either in non-diabetic individuals or in type 2 diabetic subjects (16-18). On the other hands, hyperuricemia has been demonstrated in individuals with chronic kidney disease (19). In this regard, the development of chronic kidney disease might arise from the pathogenic effects of hyperuricemia (20).

The incidence of chronic kidney disease is higher in patients with hyperuricemia (21). However, it is supposed that uric acid could positively affect cardiovascular system due to its antioxidant activity. Since uric acid acts as a double-edged sword, the aim of this study was to clarify the pathogenic effect of uric acid on some organs and its positive influence on cardiovascular system.

Materials and Methods
For this mini-review we searched PubMed, EBSCO, directory of open access journals (DOAJ), Google Scholar, and Web of Science with key words as uric acid, chronic kidney disease, hyperuricemia, type 2 diabetes mellitus, antioxidant, oxidative stress, cardiovascular disease, inflammation and reactive oxygen species.

The synthesis and transport of uric acid
Uric acid is synthesized by 5-phosphoribosyl pyrophosphate and glutamine. Also, uric acid is generated from xanthine by the activity of xanthine oxidase (22). Uric acid is generally generated in the liver and intestine (23). It always present as monosodium urate in the extracellular fluid compartment (24).

The control of serum urea levels occurs in the kidney via several mechanisms including glomerular filtration, reabsorption and secretion (25). The excretion of uric acid content is reliant on serum urea levels, body weight and size (26). Approximately 90% to 95% of urea, filtered in the kidney, is reabsorbed from the proximal renal tubule (27).
Hyperuricemia and the outbreak of renal dysfunction

Hyperuricemia is known to be a marker of renal dysfunction (28). High uric acid level in serum increases renal dysfunction and progressive renal scarring in rats. Thus, hyperuricemia might be one of the key mechanisms in terms of the activation of rennin-angiotensin and cyclooxygenase-2 systems in renal disease (29). Furthermore, it was reported that about 20% to 60% of patients with gout manifested the elevated uric acid levels in serum and renal disease (30). In a clinical trial on 177,570 patients, individuals with the highest serum uric acid level manifested a 2.14 fold rise in the outbreak of chronic kidney disease when compared to the subjects with the lowest serum uric acid concentration.

Hyperuricemia and the outbreak of hypertension

There is a positive correlation between serum uric acid level and the outbreak of hypertension (31). The increased uric acid in serum leads to induction of early stage of hypertension (32). On the other hands, hypertension causes microvascular disease resulting in local tissue ischemia (33). Serum uric acid level is positively connected with systolic and diastolic blood pressures in Nigerian patients (34). Approximately 20%-89% of hypertensive subjects have the high serum uric acid level (35). Hyperuricemic rats manifested the increased blood pressure after 3 weeks as compared with control rats. This might be occurred as the consequence of stimulation of rennin-angiotensin and the inhibition of neuronal nitric oxide synthase (36).

Hyperuricemia and the outbreak of cardiovascular disease

It has been found that hyperuricemia is one possible cause of cardiovascular disease (37) and myocardial infarction (38). In this regard, the increased uric acid level in serum is known to be a factor in induction of cardiovascular mortality (39). Additionally, patients with coronary heart disease have higher uric acid levels in serum as compared with healthy patients (40). However, the elevated uric acid level in serum might be a defense mechanism against atherosclerosis because of its antioxidant property (41). On the other hands, the elevated uric acid level in serum participates is involved in the development of cardiovascular disease via a detrimental effect on the endothelium; while, serum uric acid stimulates oxygenation of low density lipoprotein cholesterol and consequently lipid peroxidation (42). Moreover, high uric acid concentration in serum induces the release of free radicals that interferes with adhesion molecule expression; in turn, it negatively affects endothelium (43).

Hyperuricemia and the outbreak of diabetes mellitus

Serum uric acid level is known to be relevant with the risk of type 2 diabetes which is characterized by the increase in plasma insulin level, blood glucose concentration and also serum triglyceride content (44). While, uric acid worsens insulin resistance in animals through preventing the bioavailability of nitric oxide required for insulin-stimulated glucose uptake (45).

Uric acid as an antioxidant

Interestingly, at least half of the plasma antioxidant capacity arises from serum uric acid (46). In vitro and in vivo studies have found that uric acid acts as free radical scavenger in humans and plays useful roles in the cardiovascular system (46). Uric acid also serves an important role in ischemic stroke which is resulted from its antioxidant capacity (47). It is supposed that uric acid regulates the rate and activities of free radicals including reactive oxygen species and nitrogen species (48). It acts by giving off an electron to be a urate radical (49). Urate radicals cannot react with oxygen to form other peroxy radical as the result, it elevates the efficiency of uric acid as an antioxidant (50). A reduction in serum uric acid, accompanying with the decreased antioxidants levels, is resulted in the outbreak of defect and induction of oxidative stress (51).

Uric acid can also serve as a pro-oxidant when it loses its antioxidant capacity by electron donation to generate urate radicals (52) leading to induction of oxidative stress; consequently, it causes endothelial dysfunction (52,53).

Conclusion

In spite of much information on uric acid level in serum, it is not clear whether the elevated uric acid concentration in serum participates in the development of diseases or it is an index of diseases? However, several studies reported that high uric acid level is linked to a possible cause of disease development. These studies have concluded that the high uric acid level is responsible for the outbreak and development of diseases.

Author's contribution
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The author declared no competing interests.

Ethical considerations
The author of this manuscript declares that he has followed the ethical requirements for this communication. Also, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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Uric acid and chronic diseases

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