Open Access Mini-Review

Journal of Renal Endocrinology

J Renal Endocrinol 2016;2:e04.

http://www.jrenendo.com

Nickan Research Institute

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

Hamid Nasri*

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

Citation: Nasri H. Uric acid is an index of chronic diseases or is an index of antioxidant? A mini-review to the recent trends. J Renal Endocrinol. 2016;2:e04.

Copyright © 2016 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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).

Received: 14 March 2016, Accepted: 4 May 2016, ePublished: 19 May 2016

Nickan Research Institute, Isfahan, Iran.

***Corresponding Author:** Prof. Hamid Nasri, Email: hamidnasri@med.mui.ac.ir

Implication for health policy/practice/research/ medical education

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.

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 ride 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 radial (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 (32,38). These studies have concluded that the high uric acid level is responsible for the outbreak and development of diseases.

Author's contribution

HN was the single author of the manuscript.

Conflicts of interest

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.

Funding/Support

None.

References

1. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser- braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol. 2008;19:2407-13.
2. Fini MA, Ellias A, Johnson RJ, Wright RM. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med. 2012;1:16.
3. Kutzing MK, Firestein BL. Altered uric acid levels and disease states. J Pharmacol Exp Ther. 2008;324:1-7.
4. Beavers KM, Beavers DP, Serra MC, Bowden RG, Wilson RL. Low relative skeletal muscle mass indicative of sarcopenia is associated with elevations in serum uric acid levels: findings from NHANES III. J Nutr Health Aging. 2009;13:177.
5. Sutton JR, Toews CJ, Ward GR, Fox IH. Purine metabolism during strenuous muscular exercise in man. Metab Clin Exp. 1980;29:254-60.
6. Green HJ, Fraser IG. Differential effects of exercise intensity on serum uric acid concentration. Med Sci Sports Exercise. 1988;20:55-9.
7. Mumford SL, Dasharathy SS, Pollack AZ, Perkins NJ, Cole SR, Wactawski-Wende J, et al. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle:findings from the BioCycle study. Hum Reprod. 2013;28:1853-62.
8. Jacome MA, Uehera SK, Monteiro WL, de Maria CA, Rosa G. Effects of green coffee beans extracts in some biomarkers of adult brazilian subjects. Aliment Nutr Araraquara. 2009;20:185-90.
9. Ekpenyong C, Akpan E. Abnormal serum uric acid levels in health and disease: a double-edged sword. Am J Intern Med. 2014;2:113-30.
10. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Johnson RJ, et al. The causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol. 2006;290:F625-31.
11. Mayes PA. Intermediary metabolism of fructose. Am J Clin Nutr. 1993;58:754S-65S.
12. Faller J, Fox IH. Ethanol-induced hyperuricemia:urate production by activation of adenine nucleotide turnover. N Engl J Med. 1982;307:1598-602.
13. Drum DE, Goldman PA, Jankowski CB. Elevation of serum uric acid as a clue to alcohol abuse. Arch Int Med. 1981;141:477-9.
14. Eastmond CJ, Garton M, Robbins S, Riddoch S. The effects of alcoholic beverages on urate metabolism in gout sufferers. Br J Rheumatol. 1995;34:756-9.
15. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. J Am Soc Nephrol. 2008;19:1204-11.
16. Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. Arthritis Care Res. 2009;61:225-32.
17. Ioachimescu AG, Brennan DM, Hoar BM, Kashyap SR, Hoogwerf BJ. Serum uric acid, mortality and glucose control in patients with type 2 diabetes mellitus: a PreCIS database study. Diabetic Med. 2007;24:1369-74.
18. Zoppini G, Targher G, Negri C, Stoico V, Perrone F, Muggeo M, et al. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care. 2009;32:1716-20.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266.
20. Tangri N, Weiner DE. Uric acid, CKD, and cardiovascular disease: confounders, culprits, and circles. Am J Kidney Dis. 2010;56:247- 50.
21. Zoppini G, Targher G, Chonchol M, Ortalad V, Abaterusso C, Pichiri I, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. Diabetes Care. 2012;35:99-104.
22. Ganong WF. Review of medical physiology. 22nd ed. McGraw Hill Professionals; 2005.
23. Hosomi A, Nakanishi T, Fujita T, Tamal I. Extrarenal elimination of uric acid via intestinal efflux transporter BLRP/ABCG2. PLoS One. 2012;7:e30456.
24. Barr WG. Uric acid. In: Walker HK, Hall HD, Hurst JW, eds. Clinical Methods: The History, Physical and Laboratory Examinations. 3rd ed. Boston: Butterworth; 1990.
25. Mount DB, Kwon CY, Ziandi-Nejad K. Renal urate transport. Clin Rheum Dis. 2006;32:313-31.
26. Jeanin G, Chiarelli N, Gaggiotti M, Ritteli M, Maiorca P, Quinzani FV, et al. Recurrent exercise-induced acute induced renal failure in a young Pakistani man with severe renal hypouricemia and SLC2A9 compound heterozygosity. BMC Med Genet. 2014;15:1-8.
27. Steele TH. Hyperuricemic nephropathies. Nephron. 1999;81:45-49.
28. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002;13:2888-97.
29. Kang DH, Nakagawa T. Uric acid and chronic renal disease:possible implication of hyperuricemia on progression of renal disease. Semin Nephrol. 2005;25:43-9.
30. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol. 2000;27:1501-5.
31. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Int Med. 2009 ;169:342-50.
32. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, et al. Serum uric acid and hypertension: the Olivetti heart study. J Hum Hypertens. 1994;8:677-81.
33. Puig JG, Ruilope LM. Uric acid as a cardiovascular risk factor in arterial hypertension. J Hypertens. 1999;17:869-72.
34. Emokpae AM, Abdu A. Serum uric acid levels among Nigerians with essential hypertension. Niger J Physiol Sci 2013;28:41-4.
35. Oppatham S, Bancha S, Choovichian P. The relationship of hyperuricaemia and blood pressure in the Thai Army population. J Postgraduate Med. 2008;54:259-62.
36. Mazzali M, Hughes J, Kim YG, Jefferson A, Kang DH, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001;38:1101-06.
37. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 1995;141:637-44.
38. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke. 2006;37:1503-7.
39. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. JAMA. 2000;283:2404-10.
40. Torun M, Yardim S, Simsek B, Burgaz S. Serum uric acid levels in cardiovascular diseases. J Clin Pharm Ther. 1998;23:25-9.
41. Davies KJ, Sevanian A, Muakkassah-Kelly SF, Hochstein P. Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid. Biochem J. 1986;235:747-54.
42. De Scheerder IK, van de Kraay AM, Lamers JM, Koster JF, de Jong JW, Serruys PW. Myocardial malondialdehyde and uric acid release after short-lasting coronary occlusions during coronary angioplasty:potential mechanisms for free radical generation. Am J Cardiol. 1991;68:392-5.
43. Waring WS, Webb DJ, Maxwell SR. Uric acid as a risk factor

for cardiovascular disease. Q J Med. 2000;93:707-13.
44. Galvan QA, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. Am J Physiol. 1995;268:1-5.
45. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005;67:1739-42.
46. Ames BN, Cathcart R, Schewiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A. 1981;78:6858-62.
47. Waring WS. Uric acid: an important antioxidant in acute ischaemic stroke. Q J Med. 2002;95:691-3.
48. Hayden MR, Tyagi SC. Uric acid: a new look at an old risk marker for cardiovascular, metabolic syndrome and type 2 diabetes mellitus:the urate redox shuttle. Nutr Metab. 2004;1:10
49. Proctor PH. Uric acid: neuroprotective or neurotoxic? Stroke. 2008;39:e88.
50. Batool S, Ahmed I, Sarwar M, Ul Hassan H. Relationship of uric acid with superoxide dismutase (SOD) in induced hyperuricemic rat model. Pharmacol Pharm. 2012;3:404-8.
51. Nan H, Qiao Q, Dong Y, Gao W, Tang B, Qian R, et al. The prevalence of hyperuricemia in a population of the coastal city of Qingdao. China J Rheumatol. 2006;33:1346-50.
52. Sautin YY, Imaram V, Kim KM, Angerhofer A, Henderson G, Johnson R. Uric acid and oxidative stress. In: Miyata T, Eckhart KN, Nangaku M, eds. Studies in Renal Disorders. Oxidative Stress in Applied Basic Research Practice. Springer Science + Business Media LLC; 2011.
53. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens. 2008;26:269-75.