The relationship between chronic kidney disease, uric acid, and dietary factors; an updated review

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Abstract
Chronic kidney disease (CKD) is one of the important illnesses that several risk factors have been suggested for its incident and progression, including lifestyle, obesity, metabolic syndrome, diabetes mellitus, hypertension, family history of illness, and age more than 60 years. Recently, a large and growing body of literature has investigated the relation between serum uric acid (SUA) and CKD. Numerous studies have found that SUA is as a possible risk factor for CKD but other studies did not show. Therefore, whether hyperuricemia (HUA) is a marker of chronic renal failure or independent risk factors for CKD is controversial, while, the relationship between the high uric acid levels and CKD is more complex than a simple cause-and-effect association. Uric acid is the end-product oxidation of purine metabolism. Endogenous processes with high cell turnover and environmental factors such as diet and prescribed drugs are associated with uric acid levels. Previous studies have shown that some dietary factors such as soy foods, vitamin C, and low-fat dairy products decrease SUA and other factors such as caffeine, fructose, and meat increase SUA. The purpose of this paper is to review recent research into the relationship between CKD, SUA, and dietary factors that influence on SUA.
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Introduction

Chronic kidney disease (CKD) is one of the important illnesses and a worldwide public health problem. CKD or chronic renal failure is described as kidney injury which can be determined by the existence of albuminuria "defined as an albumin-to-creatinine ratio > 30 mg/g in two of three urine samples" or a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for three months or more, regardless of the reason according to the Kidney Disease Outcomes Quality Initiative (KDOQI) explanation (1). The prevalence of chronic renal failure is expanding worldwide, and it is a risk factor for cardiovascular disease, end-stage kidney diseases, and all-reason mortality. There are several risk factors for the incident and progression of chronic renal failure, including life style, obesity, diabetes mellitus, metabolic syndrome, hypertension, family history of illness, and age more than 60 years. Recently, a large and growing body of literature has investigated a relation between serum uric acid (SUA) and chronic renal failure. A number of studies have found that SUA is a possible risk factor for chronic renal failure but other studies did not show (2). The purpose of this paper is to review recent research into the relationship between CKD, SUA, and dietary factors that influence on SUA.

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 chronic kidney disease, uric acid, type II diabetes mellitus, obesity, metabolic syndrome, hypertension, hyperuricemia, chronic renal failure and cardiovascular disease.

Production of uric acid

Uric acid is the end-product oxidation of purine metabolism. Purines are produced via two pathways; de novo production from non-purine combinations, and the salvage pathways to recover purines that are respectively regulated by the phosphoribosyl-pyrophosphate synthetase, and the hypoxanthine-xanthine phosphoribosyl-transferase (3). Catabolism of purines is controlled generally by the xanthine oxidoreductase that changes hypoxanthine to xanthine, and xanthine to uric acid. Urate has the anti-oxidant effect but xanthine oxidase that is an isoform of xanthine oxidoreductase employs molecular oxygen as an electron acceptor, making superoxide anion and other reactive oxygen species. Thus, uric acid would play a role as antioxidant or pro-oxidant depending on dealings with other factors, and the intracellular or extracellular location. It is a strong antioxidant in the extra cell while being a pro-oxidant inside the cell by inducing stimulation of NADPH oxidases. This double function has been expressed as the 'uric acid paradox'(4). Uric acid is excreted through both intestinal and renal elimination. The nor-

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mal reference interval of blood uric acid in human is 1.5 to 6.0 mg/dL and 2.5 to 7.0 mg/dL in women and men, respectively (3).

Hyperuricemia (HUA) is defined as a SUA level > 7.0 mg/dL in males and >6.0 mg/dL in females (5). HUA may happen due to decreased excretion, increased production, or a combination of both mechanisms. Decreased excretion is responsible for most causes of HUA. Urate handling by the kidneys consists of filtration, reabsorption, and secretion at the glomerulus, and lastly, post-secretory reabsorption. Altered uric acid excretion can result from reduced glomerular filtration, diminished tubular secretion, or enhanced tubular reabsorption. While decreased urate filtration may not cause primary HUA, it can contribute to the kidney insufficiency (1). Epidemiologic investigations have exhibited that high SUA level is a marker of tissue injury, oxidative stress and kidney failure (6,7).

CKD and hyperuricemia

Results from observational studies indicated that raised levels of SUA may forecast the development and progression of chronic renal failure. Weiner et al performed a community-based cohorts study on 13 338 participants with normal kidney and determined that raised SUA level is a modest, an independent risk factor for occurrence of chronic renal failure (8). In another cohort study, which performed on 2337 type II diabetes mellitus patients with a mean follow-up interval of 4.6 years, it was detected that the SUA level is significantly related to CKD progression (9). Furthermore, a meta-analysis containing 15 cohort studies with 99 205 persons and 3492 incident CKD cases exhibited that the relative risk of CKD was 22% higher per one mg/dL increase in serum UA level, thus advocated a positive relation between chronic renal failure and SUA (10).

Zoppini et al in a large prospective study, showed that baseline HUA predicts the incidence of chronic renal failure in type II diabetes mellitus patients in the future (11). In a cohort study, which was done on 17 000 patients in a Kaiser Permanente database, showed the decline of uric acid below 6 mg/dL was associated with a 37% reduction in renal endpoints (12).

In addition to the observational studies, results from several interventional studies suggest that effectual medical treatment of HUA may slow the progress of chronic renal failure, therefore, delaying the dialysis in chronic renal failure patients. In a prospective study of 21 475 healthy person in a 7-year follow up duration, SUA was associated with more presence of kidney disease. Additionally, higher SUA level was accompanied with higher probability of CKD incidence (13). Furthermore, analysis of data from 656 108 patients followed for a mean of 8.0 years in Taiwan revealed that uric acid deposition was associated with 57% increase in the incidence of end-stage renal disease (14).

The result of a randomized controlled trial (RCT) that was performed on 54 chronic renal failure patients with HUA to investigate the impact of allopurinol on kidney disease progression showed SUA significantly decreased, and kidney function was preserved in cured patients after 12 months (15).

Other risk factors such as obesity, hypertension, and metabolic syndrome are strongly associated with HUA (10,16). Therefore, whether HUA is a marker of chronic renal failure or may be an independent risk factors for chronic renal failure is controversial and relationship between the high uric acid levels, and chronic renal failure is more complex than a simple cause-and-effect association (2,17-19).

Some possible mechanisms have been proposed to elucidate the causative relationship between HUA and chronic renal failure, extracted from primarily studies in cell culture systems. These mechanisms include; first, vascular smooth cell proliferation with the production of oxidants, chemotactic factors, and the activation of the RAS (a GTPase) (20,21). Second, endothelial dysfunction through a diversity of mechanisms: stimulating the release of alarmins (endogenous molecules that release upon tissue destruction) from endothelial cells that activate Toll-like receptor pathways (22), impaired endothelial nitric oxide construction (20), enhanced synthesis of interleukin-6, and increased insulin resistance. Endogenous processes with high cell turnover and environmental factors such as diet and prescribed drugs are associated with high uric acid levels. Diet that is the most important factor may increase or decrease blood uric acid. However, the evidence on the relationship between particular food intake and HUA is inadequate and inconsistent.

Dietary Factors

Although it has been proposed that dietary factors play the main role in the improvement and development of HUA, investigations on association food intake and HUA is scarce.

Caffeine

Caffeine is a bitter, white crystalline purine, a methylxanthine alkaloid, which is related chemically to the adenine and guanine comprised in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It is extracted from seeds, nuts, or leaves of a number of plants native to South America and East Asia. Products included caffeine are coffee, tea, soft drinks ("colas"), energy drinks, and chocolate. Coffee is one of the most widely consumed beverages in the world. Coffee and tea are major source

of caffeine but the content of caffeine in tea is lower than that in coffee.

Studies have established that moderate caffeine drinking has favorable health effects, including mental alertness, enhanced tolerance to fatigue, and improved physical activity (5,23-27). Conversely, the excessive consumption of caffeine might also be related to adverse effects, such as restlessness, anxiety, and an increased danger of hypertension (23).

The influence of caffeine on the SUA level is controversial. The most studies exhibited that common coffee intake might reduce SUA levels (24-27). In contrast, some study determined that the drinking of green tea or coffee was associated with a higher level of SUA (28,29). Two epidemiological observations suggested no association existed between caffeine intake and SUA level in the US population (25,30).

The mechanism of caffeine on the regulation of SUA level has not exactly been determined. One possible mechanism is demethylation caffeine (1,3,7-trimethylxanthine) into three dimethylxanthine (i.e., paraxanthine, theobromine and theophylline), which result of the inhibitory effect of methylxanthine on xanthine oxidase in vitro and in vivo (31). Another mechanism for this effect may be the existence of many different types of antioxidants in tea and phenolic chlorogenic acid in coffee that has strong antioxidant properties (32). Previous studies have suggested that antioxidants may improve insulin sensitivity (33), and decrease insulin levels in rats (34).

Fructose

Fructose is a monosaccharide naturally occurring in fruits and is commonly consumed as table sugar (sucrose) or high-fructose corn syrup. Global fructose consumption, particularly in the form of high-fructose corn syrup, has paralleled the increase in HUA (35). This sugar, unlike other monosaccharide sugars, is exclusively metabolized in the liver. Fructokinase enzyme unregulates phosphorylation of fructose so causes local ATP depletion and increases AMP production. Analysis of 21 controlled trials in 425 subjects demonstrated that the effect of fructose feeding on the uric acid level is different between isocaloric and hypercaloric diet. The uric acid level did not increase in isocaloric diet, whereas in the hypercaloric diet increased. However, these conclusions are limited for the reason the short follow-up of the most of trials and weak quality of some of the experiments comprised in the meta-analysis (35). Thus, further trial with longer follow-up and higher quality is required to establish the effects of fructose on uric acid.

Soy food

Soy is a food rich in purines and often believed less suitable for individuals with HUA. Several clinical trials have assessed the impression of soy foods' ingestion on UA levels (36,37), and most of them reported an increase in blood urate levels after soy ingestion. However, the duration of these studies is short and sample size is small

or the amount of soy protein considerably exceeds the usual utilization at a single meal. Some of the observational studies indicated that purine-rich vegetables (26,38) or regular soy foods' intake (39) were not associated with blood UA levels. However, observational data may have several limitations. A review on epidemiologic and intervention studies indicated that soy did not increase SUA levels in response to quantities comparable to customary Asian consumption (40). A meta-analysis in menopausal women advocated that long-term soy foods intake did not raise serum urate levels, and thus, soy foods do not require to be restricted (41). Lack of relationship between purine-rich vegetables such as soy and serum urate could be due to the co-linearity between purine-rich plant and useful plant ingredients (such as dietary fiber, vitamin C or some phytochemicals) that may have covered an influence of purine on UA (42).

Vitamin C

Vitamin C is an essential micronutrient that participates in a number of physiologic processes. It also plays a role as an antioxidant to inhibit oxidative impairment by free radicals, nitrogen species, and reactive oxygen. The effect of vitamin C on SUA concentrations has been investigated in various types of studies. Clinical studies in humans have shown that ascorbic acid decreases SUA (43). The same observational studies have also described an inverse relationship between vitamin C intake, plasma ascorbic acid, and SUA concentrations (44). Furthermore, a meta-analysis assessed the influence of vitamin C supplementation on SUA by pooling the results from published RCTs and determined vitamin C supplementation significantly decreased SUA (45). However, future studies of longer duration and larger sample size are suggested to determine the effect of vitamin C supplementation on HUA.

Several mechanisms have been suggested for the SUA reducing effect of vitamin C, including increase in the glomerular filtration rate, competitive inhibition of an anion exchange transport system at uric acid reabsorption sites in the proximal tubule in the nephron, and decrease in free radical-induced injury to body cells due to its antioxidant properties (46,47).

Dietary patterns

The investigation of the relationship between dietary patterns and SUA concentrations is scarce. In a cross-sectional study in Taiwan, it was demonstrated that dietary patterns were derived from a validated FFQ; and the uric acid-rich pattern and the vegetable and fruit pattern were not significantly related with SUA concentrations after adjustments. In another study that assessed probable associations between Mediterranean diet and SUA levels, adherence to the Mediterranean diet was related to lower serum UA levels (48,49).

Meat

Recent studies revealed the association between meat

intake and seafood intake and higher uric acid level. In one investigation performed in China. The risk of HUA was respectively 26%, 28%, and 34% more in groups with higher consumption of meat, fish, and shellfish. A study from the Third National Health and Nutrition Examination Survey (NHANES-III) that performed on 14 809 participants stated that SUA level was respectively increased 41% and 51% in higher versus the lower quintile for ingestion of meat and seafood (50). In a cross-sectional study that was done on 3978 middle-aged men in Shanghai, it was realized that the prevalence of HUA was more in groups with higher animal protein and seafood intake. However, the result of a study in Taiwan showed no association of meat and seafood with HUA (51).

Dairy product

Numerous studies suggest that there is an inverse relationship between dairy product consumption and SUA levels (52-54). In a recent large prospective study of incident gout among men, they found that higher dairy intake was protective of the risk (12). The study from the NHANES-III suggested that dairy consumption was inversely associated with the SUA level. Ingestion of milk proteins (casein and lactalbumin) has been shown to decrease SUA levels in healthy subjects via the uricosuric effect of these proteins (55). In a population-based case-control study in Scotland, an inverse association between dairy consumption and plasma urate concentration, especially with skimmed milk and yoghurt was seen. The absenteeism of association between full-fat dairy products and SUA might arise from the effect of saturated fats (56). The result of a prospective study determined that the risk of gout in men who drank two or more glasses of skim milk per day was 46% fewer as compared with who drank less than one glass per month (38).

Some of the possible mechanisms were suggested for this effect; first, the uricosuric effect of casein and lactalbumin, second promotion renal urate excretion by orotic acid .Third urate-lowering effect of phosphorus, calcium, magnesium, and lactose (38,57,58).

Conclusion

A number of studies have found that SUA is a possible risk factor for CKD and dietary factors such as soy foods, vitamin C, and low-fat dairy products decrease SUA and other factors such as caffeine, fructose, and meat increase SUA. Most of the studies done in this regard are epidemiology-based, and controversial. Hence, further trials with higher quality are suggested to establish the effects of these factors on uric acid and CKD.

Author's contribution
MK 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.

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