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Review Article

Is vitamin C able to reduce hyperuricemia

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ABSTRACT

Hyperuricemia is defined as high levels of blood uric acid, the product of purine metabolism, which can form uric acid crystals and lead to become gout. Gout is a systemic disease that results from chronic elevation of uric acid levels above the threshold point and form the deposition of monosodium urate (MSU) crystals in tissues, mainly in and around the joints forming tophi. The impact of gout and its associated conditions can cause deformity, morbidity and mortality. Vitamin C is shown to has beneficial effect in lowering serum uric acid level in hyperuricemia patients with unknown mechanism. But it is still debatable whether using or not using and the dose of vitamin C because giving large doses also had no effect on serum uric acid concentration, uric acid excretion and clearance by the kidney, and even can cause adverse effects.

Keywords: Dosage, Hyperuricemia, Gout, Uric acid, Uricosuric effects, Vitamin C

INTRODUCTION

Hyperuricemia is defined as high levels of blood uric acid, the product of purine metabolism, which can form uric acid crystals and lead to become gout. In adults, it is greater than 7.0 mg/dL in men and 6.0 mg/dL in women.[1] Gout is a systemic disease that results from chronic elevation of uric acid levels above the threshold point and form the deposition of monosodium urate (MSU) crystals in tissues, mainly in and around the joints forming tophi.[2,3] Gout incidence and prevalence have surged in recent years, and the global burden of gout is substantial and increases in many parts of the world over the past 50 years and also differ between countries. The prevalence of gout among US adults in 2007-2008 was 3.9% (8.3 million individuals) and has increased until today.[4] Prevalence of hyperuricemia and gout in Asia in the last decade around 13%-25% and 1%-2%. Prevalence of hyperuricemia and gout in Indonesia still unknown because limited available data.[5] The impact of gout and its associated conditions can obviously cause deformity, morbidity and mortality.[6]

Since, hyperuricemia is the major etiological factor of gout and precursors of other vascular diseases, lowering high blood uric acid level become the main goal for prevention of gout incidence.[7] Vitamin C is shown to has beneficial effect in lowering serum uric acid level in hyperuricemia patients with unknown mechanism, but it is still a debatable entity. Treatment of gout especially is more challenging and is considered higher cost than its prevention. Hence, it becomes imperative to carry out review about relationship between the efficacy of vitamin C and hyperuricemia.

URIC ACID

Uric acid is produced through hepatic metabolism of purine, which comes from endogenous and exogenous sources.[8] In humans, serum uric acid levels are

determined by the balance between urate production and excretion. Hyperuricemia can occur from urate overproduction (10%) or impaired urate excretion (90%) or often the combination of the two, through the kidney (2/3) and gastrointestinal tract (1/3).[9] Factors related to increased risk of hyperuricemia include intake of purine-rich foods, alcohol, and fructose-containing products. Intake of vitamin C and dairy products can lower serum uric acid levels. Several studies in humans suggest that vitamin C supplementation reduces serum uric acid level.[10] The exact mechanism of uricosuric of vitamin C is still unknown, possible explanation is competitive interaction between vitamin C and urate-reabsorbing transporters, such as URAT1, SLC2A9 and ABCG2, which are responsible for urate-anion exchange in apical membranes of renal tubular cells.[11] Beside its uricosuric effects, there are also so many different opinions reported that ascorbic acid could inhibit synthesis of urate.[12]

URIC ACID PRODUCTION, METABOLISM AND ITS EXCRETION

Uric acid production and metabolism are complex processes involving various factors that regulate hepatic production, as well as renal and gut excretion of this compound. Uric acid is the end product of an exogenous pool of purines and endogenous purine metabolism. The exogenous pool varies significantly with diet especially animal proteins. The endogenous production of uric acid is mainly from the liver, intestines and other tissues like muscles, kidneys and the vascular endothelium.[13]

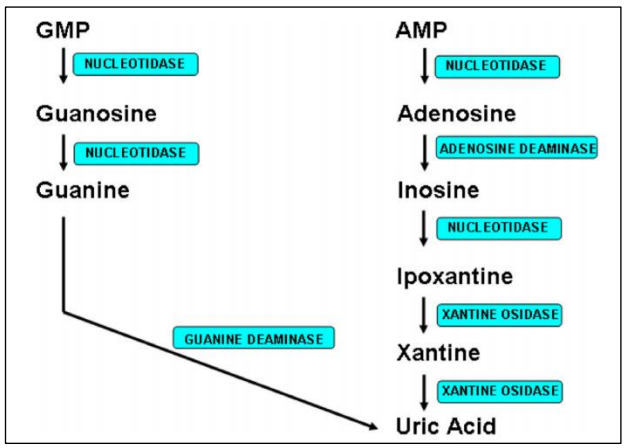

Figure 1: Enzymatic degradation of purine in human.

Many enzymes are involved in the conversion of the two purine nucleic acids, adenine and guanine, become uric acid (Figure 1).[14] Xanthine is oxidized by xanthine oxidase to form the final product, uric acid. Uric acid exists majorly as urate, the salt of uric acid. As urate concentration increases in blood, uric acid crystal formation increases. The normal reference interval of uric acid in human blood is 1.5 to 6.0 mg/dL in women and 2.5 to 7.0 mg/dL in men. The solubility of uric acid in water is low, and in humans, the average concentration of uric acid in blood is close to the solubility limit (6.8 mg/dL). When the level of uric acid is higher than 6.8 mg/dL, crystals of uric acid form as monosodium urate (MSU). Humans cannot oxidize uric acid to the more soluble compound allantoin due to the lack of uricase enzyme.[1]

Excretion of uric acid is approximately two-thirds by kidneys, while the gastrointestinal tract eliminates one-third of the uric acid load. Almost all uric acid is filtered from glomeruli, then post-glomerular reabsorption and secretion regulate the amount of uric acid excretion. The proximal tubule is the site of uric acid reabsorption and secretion, approximately 90% is reabsorbed into blood and approximately 10% of the filtered uric acid appears in the urine.[13]

Three urate transporters, URAT1/SLC22A12, GLUT9/SLC2A9, and ABCG2/BCRP, have been reported to play important roles in the regulation of serum uric acid (SUA), and their dysfunctions cause urate transport disorders. Among them, common dysfunction of ABCG2 exporter has proved to be a major cause of hyperuricemia and gout.[14] The molecular identification of URAT1 as the dominant apical urate exchanger of the human proximal tubule was a landmark event in the physiology of urate homeostasis. The URAT1 protein is encoded by the SLC22A12 gene, part of the large SLC22 family of organic ion transporters.[15] GLUT9 (SLC2A9) membrane transporter is shown to transport essentially urate. Genetic variation in human ABCG2 has also become major factor in human hyperuricemia. A loss of or reduction in ABCG2-mediated renal urate secretion would lead to increased renal urate reabsorption, given that reduced renal excretion of urate is considered to be the underlying hyperuricemic mechanism in majority of gout patients.[15-16]

Hyperuricemia is characterized by high uric acid level in the blood, causing deposition of urate crystals in the joints and kidneys a key risk factor for the development of gout, renal dysfunction, hypertension, hyperlipidemia, diabetes and obesity.[17-18] Various studies also have shown that hyperuricemia is associated with an increased risk for incident hypertension. Uric acid inhibits synthesis of the potent vasodilator nitric oxide, induces smooth muscle cell proliferation, and stimulates platelet-derived growth factor synthesis leading to arterial vasoconstriction. Soluble urate has been shown to directly stimulate the renin-angiotensin system in the kidney so it can induce renal interstitial and tubular inflammation causing hypertension.[19] There is increasing evidence, supporting hyperuricemia as a true risk factor of chronic kidney disease. An elevation in the serum urate concentration out of proportion to the degree of renal insufficiency has been defined when the serum uric acid level is more than 9 mg/dL if creatinine level is ≤1.5 mg/dL, more than 10 mg/dL if creatinine level is between 1.5-2.0 mg/dL, and more than 12 mg/dL with more advanced renal failure.[20,21] The association of uric acid with almost all

risk factors for Coronary Artery Disease/CAD (with smoking the only real exception) is very difficult to determine but many studies have linked hyperuricemia to numerous associations which are risk factors of CAD.[17]

Hyperuricemia occurs as a result of the increased uric acid production, the impaired renal uric acid excretion, or a combination of the two.[20,21] Asymptomatic hyperuricemia is a condition in which the serum urate concentration is elevated (>7 mg/dL in men or >6 mg/dL in women) but neither symptoms nor signs of urate crystal deposition have occurred.[17]

GOUT

Gout is the commonest cause of inflammatory arthritis in men than in women, five times, and its incidence is increasing.[22,23] Epidemiologic studies suggest that the overall disease burden of gout is substantial and growing. According to the European League Against Rheumatism (EULAR), the prevalence of symptomatic gout among the adult Western population is 1 to 2%, rising to 7% in those aged over 65 years.[23] It is a condition characterized by the deposition of monosodium urate crystals in the joints or soft tissue. Gouty arthritis (as an indicator of gout) is the most common form of arthritis in adults. The four phases of gout include asymptomatic hyperuricemia, acute gouty arthritis, inter-critical gout and chronic tophaceous gout. The peak incidence occurs in 30 to 50 years old.[24] Hyperuricemia is the most important risk factor.

The typical first manifestation of gout is an acute episode of monoarticular arthritis at the metatarsophalangeal joint of the large toe (podagra) that is very painful, starts at night, lasts around a week, and in many cases is self-limiting. The deposition of urate crystals in various tissues such as joints, connective tissue, and kidneys explains the chronic character of the gout. Almost 90% of patients who have suffered an attack of gout experience repeat episodes in 5 years. If the manifestation is atypical and serum urate normal, joint puncture to demonstrate the presence of crystals is highly desirable and the differential diagnosis in such a case includes septic arthritis.[25]

The identification of the risk factors for gout that are modifiable with available measures is an important first step in the prevention and management. Vitamin C, an essential micronutrient for humans, has been known become the potentially useful protective factors against hyperuricemia and gout.[26]

VITAMIN C

Vitamin C is a water-soluble vitamin, antioxidant, an essential micronutrient and an essential co-factor for collagen biosynthesis, carnitine and catecholamine metabolism, and dietary iron absorption. Humans are unable to synthesize vitamin C, so it is strictly obtained through dietary intake of fruits and vegetables. The biologic role of vitamin C is related to its reduced form, ascorbate. The best-known enzymatic function is probably as cofactor for the ferrous (Fe(II)) and 2-oxoglutarate dependent dioxygenases in collagen synthesis. These enzymes catalyze the hydroxylation of lysine and proline residues in unfolded procollagen chains, which are the building blocks of the triple-helical structure of mature, functional collagen. In nonenzymatic way, it is as water-soluble antioxidant that prevent oxidative damage by free radicals and reactive oxygen and nitrogen species. The highest concentrations of vitamin C are found in the brain, eye, and adrenal gland.[8,27]

Vitamin C absorption, tissue distribution, and excretion are tightly controlled by tissue specific. The absorption of vitamin C in human occurs in the buccal mucosa, stomach and the small intestine through passive diffusion and active transport system. Body ascorbate reaches a maximum of 20 mg/kg body weight, i.e. with a total pool size of about 1.5 gram, when ascorbate intake is increased from 30 to 180 mg/day. Above this level of intake, the excretion in the urine rises rapidly. Ascorbic acid can be found naturally in chemical forms of L-xylo-ascorbic acid and D-xylo-ascorbate. It is reversibly oxidized to L-dehydroascorbic acid on exposure to copper, heat or mildly alkaline conditions. Both L-ascorbic acid and L-dehydroascorbic acid are physiologically active forms of vitamin C.[28]

Many sources of vitamin C and 90% of the daily intake in the general population comes from these sources. The content varies between species, but citrus fruit, kiwi, mango, and vegetables such as broccoli, tomatoes, and peppers are all rich sources of vitamin C. Fish and milk also contain small amounts of it. There is a gradual decline in the amount of vitamin C as foods age.[27,28] The current recommended dietary daily allowance of vitamin C differs between gender dan ages. They are 75 mg/d for women and 90 mg/d for men.[27]

Many studies have shown health benefits of vitamin C include reduced susceptibility to and duration of the common cold, and reduced risk of cardiovascular disease, cancer, and other degenerative diseases, lowered blood pressure and cholesterol levels, helped thin the blood and protects it against oxidation, helped regulate nervous systems. With adequate intake, it was highly protective against stroke and heart attack.

As an antioxidant, it protects the body from the harmful effects of free radicals. Mega doses of vitamin C may, however, be toxic in diabetics with certain kidney disorders. Recent studies have shown that vitamin C concentration in the blood from rheumatoid arthritis patients are extremely low and that vitamin C may protect against further damage to inflamed joints. Vitamin C also increases the urinary excretion of uric acid.[28]

VITAMIN C AND HYPERURICEMIA

In population-based studies, the risk of gout steadily increases at successively higher levels of serum uric acid or hyperuricemia with a 10-fold increase in risk reported among those with serum urate levels of 9 mg/dl.[29] Medical therapy to prevent gout either act by reducing uric acid synthesis (xanthine oxidase inhibition) or via enhanced uric acid excretion (probenecid) but both classes carry significant side-effect profiles.[30] Dietary approaches provide an alternative and attractive management.[31] Recommendations to reduce consumption of high-protein foods to reduce purine intake, consume vegetable-based proteins, and lower alcohol consumption continue to play a critical role in disease management.[32] Supplementation with vitamin C has also been examined as an alternative dietary approach.[7]

Whether using or not using vitamin C supplementation in asymptomatic hyperuricemia is still debatable. Many studies did not recommend using urate-lowering therapy, yet it is shown to have beneficial effects. In 1952, relationship between the inhibition of xanthine oxidase and trace amount of ascorbic acid or vitamin C was first proposed, showed that the inhibition increased by the increased amount of vitamin C.[12] Berger et al, showed data suggest that total vitamin C intake of 500 mg/day or more found to reduce serum uric acid levels and has recently been linked to a reduced future risk of gout.[33] Huang et al, showed that total vitamin C intake of 500 mg/d or higher for 2 months is associated with a 0.6-0.7 mg/dL lower level of serum uric acid relative to those with intake <90 mg/d, in a randomized control study, by increasing the estimated glomerular filtration rate.[34,35] Choi et al, concluded that higher vitamin C intake is independently associated with a lower risk of gout in men and may be beneficial in the prevention of gout.[36] And Juraschek et al, also showed that in a meta-analysis of 13 randomized controlled trials, vitamin C supplementation significantly lowered serum uric acid level. Vitamin C at a dose of 500-1000 mg/day can also be used as an adjuvant to diet and exercise.[37] A Korean Multi-Rural Communities Cohort study showed that higher levels of dietary vitamin C intake, but not total vitamin C intake, are associated with a lower risk of hyperuricemia in both men and women.[38]

Firas et al, supplementation with 500 mg/day chewable vitamin C for 2 months significantly attenuated serum uric acid for hyperuricemic patients and insignificantly affected serum uric acid in gouty patients. The uselessness of vitamin C supplements on gouty patients could be associated to number of possible reasons. But when it was administered intravenously for a short-term at larger doses (infusion rates start with 0.25-1 gram, then increased and varied from 2.5 to 10 gram/minute) in patients with and without gout, it had significant increase in uric acid excretion in both study groups with no difference between them.[39] Patients with coronary artery disease, chronic kidney disease, and early onset hypertension with persistent hyperuricemia may likely to improve with urate-lowering therapy.[40,41] Biniaz et al, in their randomized controlled trial showed a significant negative relationship between vitamin C and serum uric acid levels in undergoing hemodialysis patients with 250 mg, three times per week for eight weeks, without in paired serum creatinine level.[42]

The upper limit of vitamin C ingestion per day has been stated by the US Food and Drug Administration to be below 2.0 gram/day in adults (age >19 years), as gastrointestinal effects such as diarrhea with doses over 1000 mg/day.[43] Taylor EN et al, showed total supplementation vitamin C intake seems to increase the risk of symptomatic nephrolithiasis.[44] Then, Ferraro et al, showed that supplementation of vitamin C intake of 1,000 mg/day or more by men was associated with a significant 19% increased risk of kidney stones compared with no intake, and was not associated in women.[45]

Although many studies reveal that vitamin C has beneficial effect, yet it is still debatable whether using or not using vitamin C supplementation in asymptomatic hyperuricemia. Mitch et al, showed that using mega dose of vitamin C, 4 or 12 gram, in divided doses had no effect on serum uric acid concentration or uric acid excretion and clearance by the kidney.[46] Harris et al, concluded that hyperuricemia do not require treatment, but need efforts to lower their urate levels by making changes in diet or lifestyle.[24] Dincer HE et al, stated that treatment of asymptomatic hyperuricemia is not necessary unless perhaps they have very high levels of uric acid or are otherwise at risk of complications.[47] Zhang et al, showed that asymptomatic hyperuricaemia is not considered to be an indication for urate-lowering therapy and in clinical practice.[48] Binoy JP et al, stated that lifestyle modification with diet and exercise is often enough to control asymptomatic hyperuricemia in majority, and pharmacotherapy is not needed.[49] Engel B et al, emphasized that in a person with normal renal function, asymptomatic hyperuricemia is not an indication for treatment to lower the serum uric acid level.[50] Author said that it was crucial to determine vitamin C dosage that need to lower uric acid in hyperuricemia because high levels can cause adverse effects.

CONCLUSION

Supplementation of vitamin C 500 mg/day for 2 months was showed effectively reduced serum uric acid in hyperuricemic patients, suggesting that vitamin C might be beneficial in the prevention and management of gout and other urate-related diseases. Giving small dose of vitamin C is not quite effective yet giving large dose of vitamin C also can cause adverse effects such as gastrointestinal discomfort, diarrhea, even form calcium oxalate kidney stone in some cases.

There has no recommendation to treat asymptomatic hyperuricemia but giving beneficial vitamin C

supplementation with exact dose in such periodic time has shown to be effective lowering serum uric acid level and prevent gout incidence. There are sufficient data today, to warrant well-designed clinical trials to determine urate-lowering therapies would be of benefit in the treatment or prevention of high urate-related diseases.

Yet, since genetic also play role in metabolism of uric acid and varies among people with underlying disease, authors need to carry out studies in each population setting for developing a comprehensive guideline to community. More studies are needed to support this conclusion.

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