



Analysis of Uric Acid Elevation

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ABSTRACT

Uric acid is a molecule that is produced following purine nucleotide metabolism. It is particularly synthesized in the liver and less often in other tissues. In normal concentrations, it is an antioxidant and a proinflammatory; however, if its serum concentration is over 7.0 mg/dL, it immediately crystalizes and precipitates, particularly in the vessel walls, soft tissues, joints, and renals. Several studies have demonstrated that there is a positive relationship between hyperuricemia and diseases such as metabolic syndrome, stroke, preeclampsia, hypertension, kidney diseases, cardiovascular diseases, and diabetes mellitus. Identification of the elevated uric acid concentration and early treatment of hyperuricemia may help in early diagnosis and treatment of diseases that are positively related to hyperuricemia. Thus, serum uric acid concentrations should be well examined during biochemical analyses of patients visiting the hospital. In this review, uric acid and its elevated concentrations were re-checked and its importance in health was emphasized. (*JAREM* 2016; 6: 74-7)

Keywords: Uric acid, hyperuricemia, analysis

INTRODUCTION

Uric acid is the final product of the catabolism of purine nucleotides in the body, namely guanylic acid, inosinic acid, adenylic acid, and adenosine triphosphate (Figure 1). It has endogenous and exogenous sources. The endogenous sources arise from tissues such as the liver, muscles, intestines, kidneys, and vascular endothelium (1, 2). The exogenous sources mostly originate from foods of animal origin and are also generated from fructose in fruit (1). It is composed of a heterocyclic structure having a molecular weight of 168 daltons. Its formula is $C_5H_4N_4O_3$ (7,9-dihydro-1H-purine-2,6,8 (3H)-trione). It is a weak acid with pKa of 5.8 at physiological pH. Hyperuricemia is generally a situation in which serum or plasma uric acid concentrations are higher than 7.0 mg/dL (3). Uric acid crystallizes and precipitates when its level is higher than 6.8 mg/dL. Although high levels of uric acid have become associated with gout, its importance in some other diseases is undeniable. Hyperuricemia is associated with hypertension, vascular diseases, renal diseases, and cardiovascular events. In addition, antioxidant and pro-inflammatory mechanisms of action come into question for uric acid (1). Although it has been reported that it clears toxic reactants at normal levels and protects tissue against oxidative stress (4), when there is oxidative stress, an increase in the level of serum uric acid (5) shows the state of the uric acid balance in the body. The purpose of this study was to evaluate and present the clinical significance of uric acid and the current perspective.

URIC ACID PATHOPHYSIOLOGY AND EFFECTS

Uric acid in serum is saturated at levels of 6.4–6.8 mg/dL in environmental conditions, and 7.0 mg/dL is its upper limit of solubility. When it exceeds this value, uric acid crystallizes and starts to precipitate. Uric acid suppresses the production of nitric oxide, which plays an influential role in glucose transport (6). It leads to renal vasoconstriction, systemic hypertension, tubulointersti-

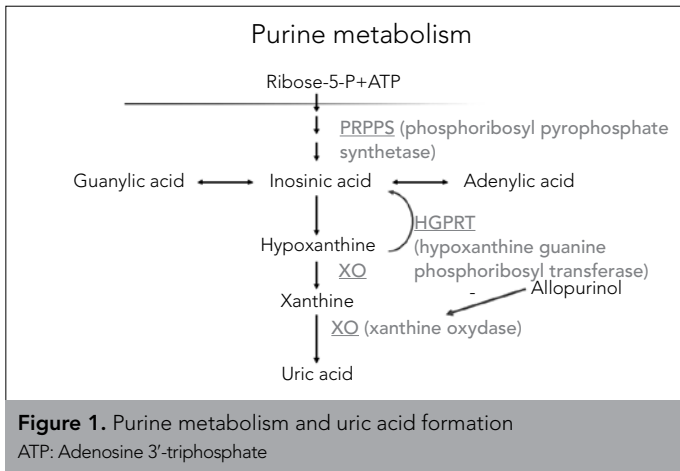
tial damage, a decrease in nitric oxide synthase production, and deterioration in afferent arteries (7-9). It suppresses nitric oxide bioactivity and insulin resistance via inflammatory factors and adipokines (10). It has been demonstrated to be correlated with blood glucose levels (7). It has been shown in a study by Şengül et al. (7) that HbA_{1c} , which reflects the long-term metabolism and elevated levels of glucose, is positively correlated with elevated uric acid levels in addition to elevated glucose levels.

Three urate transporters have been identified (1), namely URAT1/SLC22A12, GLUT9/SLC2A9, and ABCG2/BCRP, and these play important roles in the regulation of serum uric acid. Dysfunctions of these transporters also cause diseases. URAT1, which is encoded by SLC22A12, facilitates the reabsorption of uric acid in the proximal tubules (11). Dysfunctions of ABCG2 cause hyperuricemia and gout (12). GLUT9, which is encoded by SLC2A9 and is a member of the glucose transporter family, may be the major regulator of uric acid metabolism (13). SLC2A9 polymorphisms are associated with gout, coronary artery disease, and myocardial infarction (1). Fructose increases the level of uric acid. Defects in hypoxanthine–guanine phosphoribosyl transferase (HGPRT) lead to the accumulation of hypoxanthine and guanine and thus lead to increases in uric acid levels (1). In in vitro studies, uric acid induces growth factors secreted by monocytes and platelets and the gene expression of chemokines and stimulates the proliferation of vascular smooth muscle cells (14). Elevated uric acid levels cause increases in systemic cytokine production and tumor necrosis factor- α and local increases in chemokines, monocyte chemoattractant protein-1, and cyclooxygenase-2 in blood vessels (1).

EXCRETION OF URIC ACID

Two-thirds of the daily excretion of uric acid occurs via the kidneys and one-third via the gastrointestinal tract (1). Uric acid is thoroughly filtered through the glomerulus in normal and non-diabetic individuals and almost all of it is reabsorbed through the proximal





tubules (5). Almost all of the secretion of uric acid occurs in the S1 segment of the proximal tubule. Because uric acid is reabsorbed in the S2 segment of the proximal tubule, it is secreted in larger amounts. Reabsorption after secretion occurs in the more distal part of the proximal tubule and 10% of the filtered uric acid appears in the urine (1, 2). In the presence of hyperuricemia, accumulation of uric acid crystals occurs in the joints and kidneys (15).

CLINICAL SIGNIFICANCE

Hyperuricemia has been found to be associated with metabolic syndrome, stroke, pre-eclampsia, hypertension, and renal and cardiovascular diseases (7, 16). Studies in recent years have identified the relationship between gout and cardiovascular diseases (1). Unlike the relationship between chronic elevation of uric acid and the diseases described above, it is suggested that an acute increase in serum uric acid may have beneficial effects. According to studies, giving uric acid externally to those with normal levels of uric acid increases the plasma antioxidant capacity and restores endothelial function in those with type 1 diabetes and those who smoke regularly (17). Uric acid in humans neutralizes oxidative damage related to aging and atherosclerosis. The results of these studies show that uric acid may play a beneficial role in the protection of vascular function under both physiologically and pathologically difficult circumstances (1). High uric acid levels reduce the risk of Parkinson's disease and the risk of progression of the disease. The beneficial effects of uric acid are proposed to be due to its antioxidant effect (1).

KIDNEYS AND URIC ACID

An increase in uric acid levels is a common finding in renal failure (7). Although it was previously thought that hyperuricemia occurred as a result of a decrease in the excretion of uric acid in renal failure, it has now been reported that an increase in uric acid levels also causes kidney damage and plays an active role in the progression of the damage (18). After hyperuricemia occurs, if accompanied by diabetes, it facilitates the development of nephropathy (19). A decrease in glomerular filtration causes hyperuricemia, which is frequently observed in patients with chronic kidney disease (2, 20). The kidneys are responsible for the excretion of a large part of uric acid daily. More than 90% of all cases of hyperuricemia are caused by disorders of uric acid excretion (21). Uric acid crystals have the ability to adhere to the surface of renal epithelial cells (22). Thus,

an increased risk occurs of the formation of kidney stones and the glomerular filtration rate (GFR) decreases owing to this adhesion (23). It results in the development of both systolic and glomerular hypertension in relation to increased uric acid levels, increased renal vascular resistance, and decreased renal blood flow, and it can induce endothelial dysfunction and oxidative stress (1). Cortes et al. (24) reported a significant decrease in serum creatinine concentration and a significant increase in the calculated GFR as a result of a reduction in the serum uric acid level. It has been suggested in some studies that were recently conducted that owing to the treatment of hyperuricemia the onset of chronic renal failure can be prevented or delayed (25).

RELATIONSHIP WITH METABOLIC SYNDROME

Hyperuricemia has been found to be associated with metabolic syndrome (26-28). It has been emphasized that an increase in uric acid levels that is recognized early can be a sign of metabolic syndrome that may develop (29). An improvement has been shown in components of metabolic syndrome such as increases in blood pressure, hyperinsulinemia, weight gain, and high levels of serum triglycerides when an elevated uric acid level is reduced (30). When the body mass index (BMI) increases, the extent of hyperuricemia also increases. The increase in uric acid displays a parallelism with weight gain (16, 31). However, in most cases hyperuricemia is detected before hyperinsulinemia, obesity, and diabetes, so patients in whom an increased uric acid level is found should be followed very closely and therapy should be started early (7). There is a significant and positive relationship between waist circumference and BMI in men and serum uric acid levels (27, 32, 33). An increased uric acid level is an independent risk factor in metabolic syndrome (34). Nejatnami et al. (28) made the interpretation that an increased uric acid level was one of the risk factors of metabolic syndrome in the results of a study that they conducted. They expressed the opinion that hyperuricemia should be included as an additional component of metabolic syndrome. In the results of studies, body fat mass, especially torso fat mass, has been shown to be associated with serum uric acid levels. Hikita et al. (35) emphasized the close relationship between both visceral and total fat mass and increased uric acid levels.

DIABETES AND URIC ACID

There are studies reporting elevated uric acid levels in people with diabetes; on the other hand, there are studies reporting that uric acid levels are lower in people with diabetes compared with healthy people (19, 21, 36). Uric acid levels have been found to be lower in diabetic people with normal blood pressure and without any problems in terms of renal function (19). It is difficult to give an exact explanation of the rise in uric acid levels in diabetes; a reduction in production or an increase in excretion is suggested (36). The authors stated that uric acid levels decrease in diabetes and gave a description of increased uric acid clearance in diabetes; however, they are not able to clarify what the exact mechanism is (5, 19). Memişoğulları et al. (19) reported a decrease in uric acid levels; although they cannot explain the mechanism exactly, they have emphasized that the reduction in uric acid levels in diabetic people should not be considered to be associated with nephropathy alone and other mechanisms could also be involved. A positive correlation is seen between fasting blood glucose and

serum uric acid levels in people in whom blood glucose levels are not too high and when blood glucose exceeds a certain level [7 mmol/L], uric acid levels start to decrease (5). Glucose inhibits the reabsorption of uric acid in diabetic patients; the excretion of uric acid increases, but the exact mechanism is not known (5). Osmotic diuresis may be responsible for this mechanism (19).

RELATIONSHIP WITH CHOLESTEROL

It has been seen in a study that as HDL cholesterol levels decrease, uric acid levels increase (37). On the other hand, as VLDL cholesterol and triglyceride levels increase, the increase in uric acid levels displays a parallelism (37). In another study, no relationship was found between lipid and uric acid levels, but as triglyceride levels increased in analyses of subgroups, HDL cholesterol levels fell (7).

RELATIONSHIP BETWEEN SEX HORMONES AND URIC ACID

Giving testosterone externally leads to retention of water and sodium, hypertension, increased erythropoiesis, increased LDL levels, decreased HDL levels, elevated liver enzyme levels, obesity, the development of acne, and emotional and psychiatric problems (38). These effects vary depending on the testosterone dose (38). Estrogen replacement therapy in those who undergo male-to-female gender reassignment reduces serum uric acid concentrations and increases uric acid excretion in the urine (39). Considering the mechanisms underlying the increases in serum uric acid concentration induced by testosterone replacement therapy, it is possible that sex hormones affect serum uric acid concentrations by influencing renal uric acid excretion (38, 40-42). Testosterone and estradiol display inhibitory and enhancing effects, respectively, on the renal excretion of uric acid and this theory also explains the age and gender differences in serum uric acid levels (38). Muscle mass and uric acid levels display a positive correlation in those receiving testosterone therapy (38, 39). Transgender patients develop a muscular body owing to an increase in muscle mass after testosterone therapy and as a result of heavy exercise and muscle training. Increased muscle mass leads to an increase in purine and nucleic acids and thus an increase in the metabolism of ATP leads to the release of purine intermediates in muscle and induces an increase in serum uric acid levels (38).

HYPERURICEMIA AND HYPERTENSION

The increase in uric acid levels in hypertension may be due to the reduction in renal blood flow. A reduction in renal blood flow stimulates the reabsorption of uric acid (37, 43). Vascular damage at the micro level exists in hypertension. Tissue ischemia arises locally and when it occurs in the kidneys lactate develops in the proximal tubules and prevents the secretion of uric acid. In addition, the synthesis of uric acid also increases owing to ischemia (44). Moreover, uric acid itself also increases the arterial blood pressure (37). It has been shown in many studies that elevated uric acid levels are associated with hypertension (37, 45, 46). An increase of 1 mg/dL in uric acid levels in the blood has been calculated to correspond to an increase of 20 mg/dL in cholesterol levels in terms of the increase in the risk of cardiovascular diseases (45). However, although a positive relationship between hyperuricemia and hypertension was shown in several studies, Kalyon et al. (37) failed to determine a correlation with blood pressure in patients with

hyperuricemia. When the relationship between hyperuricemia and hypertension is investigated, the increase in renin levels, reduction in nitric oxide levels, interstitial inflammation and fibrosis, vasculopathy in afferent arterioles, increased ROS levels, vascular inflammation, and proliferation of vascular smooth muscle cells due to suppressed endothelial cell growth are the most important mechanisms that are put forward among the mechanisms of elevated blood pressure (7). Hyperuricemia is found in those with essential hypertension at a rate of 25–60% and in adolescents with essential hypertension at a rate of 90%. Reducing hyperuricemia causes a reduction in blood pressure (7, 11). In a study in which patients with hypertension in combination with elevated uric acid levels were excluded, a positive correlation was reported between both diastolic and systolic pressures and uric acid levels, even in the control group (19). Hypertension is also associated with renal vasoconstriction, which causes the retention of uric acid (47). In patients receiving diuretics and antihypertensive agents for the treatment of hypertension, it was reported that the levels of uric acid increased and hyperuricemia increased to a rate of 58% (48). High uric acid levels reduce renal blood flow and GFR (49). Endothelial dysfunction has been proposed as the reason for this (1).

CONCLUSION

Uric acid is a beneficial molecule for the body at normal levels. It has antioxidant and pro-inflammatory properties. It increases the secretion of growth factors and cytokines in *in vitro* studies. These positive effects give way to negative effects when the uric acid level is elevated. When serum uric acid levels exceed the threshold value [7.0 mg/dL], it rapidly crystallizes and precipitates in the joints, kidneys, and vessel walls. It is seen that it is closely associated with metabolic syndrome, stroke, pre-eclampsia, hypertension, kidney diseases, cardiovascular diseases, and diabetes. The early diagnosis and treatment of high uric acid levels are considered to be important in the fight against associated diseases. Therefore, uric acid levels should be checked in routine biochemical tests from youth onward in order to take early action against the related public health issues. The review of results should be carried out well along with the clinical findings.

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