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Review Article

URIC ACID: A MARKER OF INCREASED VARIOUS DISEASES AND RISKS

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ABSTRACT

Identifying the risk factor for the source of various diseases and disorders are essential for its early diagnosis and prevention. Serum uric acid (SUA) level has been suggested to be associated with various diseases including diabetes, cardiovascular diseases, hypertension, multiple sclerosis, hypothyroidism, obesity related factors, renal failure etc. Although elevated serum levels of uric acid in patients with various diseases or in those receiving maintenance of specific therapy like dialysis, the clinical impact of uric acid on mortality patients remain unknown. An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has been recognized for many years. Some studies also highlighted the elevated serum uric acid concentrations are also found in healthy offspring of the parents with heart diseases, indicating a possible casual relationship. However, increased serum uric acid level is also associated with possible confounding factors including elevated serum triglyceride, cholesterol concentrations, blood glucose, fasting and post carbohydrate plasma insulin concentrations, waist hip ratio and body mass index. Thus this review highlighted the importance of detecting raised uric acid in serum as a powerful risk marker for various diseases that cause mortality.

Keywords: Serum uric acid, Increased risk, Various diseases, Risk marker.

INTRODUCTION

The assessment of the independent prognostic value of serum uric acid is clinically relevant in the specific setting of essential hypertension; in which hyperuricemia is frequent and cardiovascular risk stratification is of utmost importance (Verdecchia *et al.,* 2000; Alderman *et al.,* 1999; Puig and Ruilope, 1999). Various studies indicated serum uric acid as a major marker of inflammation of various organs (Pravin *et al.,* 2013; Satoru *et al.,* 2009; Khan and Majumder, 2010; Hsu *et al.,* 2004; Weiner *et al.,* 2008; Homayounfar *et al.,* 2007; Taheraghdam *et al.,* 2013; Omar *et al*., 2007; Waring *et al.,* 2000). Raised serum uric acid concentrations are a powerful predictor of disease and poor outcome, although the underlying mechanisms remain unclear. Several potential explanations have been forward to explain the apparent association between hyperuricaemia and disease risk. Studies have demonstrated mechanisms by which uric acid could be directly injurious to the endothelium and to various organ functions. Parodoxically, uric acid elevation could be expected to confer protective anti oxidant effects, but these potential benefits may be obscured by detrimental effects elsewhere. The effects of raising or lowering serum uric acid on endothelial function, autonomic regulation and progression of

various organ specific inflammations require direct investigation, in order to understand a possible dual action in the system (Waring *et al.,* 2000). The understanding of the role of hyperuricaemia for individual patients allows a more rational approach to treatments that modify serum uric acid concentration.

BIOCHEMISTRY OF URIC ACID

Purines arise from metabolism of dietary and endogenous nucleic acids, and are degraded ultimately to uric acid in man, through the action of the enzyme xanthine oxidase. Uric acid is a week acid (pH 5.8), distributed throughout the extracellular fluid compartment as sodium urate, and cleared from the plasma by glomerular filtration. Around 90% of filtered uric acid is reabsorbed from the proximal renal tubule, while active secretion into the distal tubule by an ATPase dependent mechanism contributed to overall clearance (Waring *et al.,* 2000; Steele, 1999). Serum uric acid concentration within the population has a Gaussian distribution, with a typical reference range of 120-420 µmol/l. For an individual, urate concentration is determined by a combination of the rate of purine metabolism (both exogenous and endogenous) and the efficiency of renal clearance. This purine metabolism is influenced by diet and genetic factors regulating the cell turnover. Uric acid is sprangly soluble in aqueous media and persistent exposure to high serum levels predisposes to urate crystal deposition within soft tissues (Waring *et al.,* 2000; Emmerson, 1996). All species apart from man and higher apes express urate oxidase, an enzyme responsible for further metabolism of uric acid to allantoin-a more soluble waste product; prior to excretion. In man the urate oxidase gene located on chromosome 1 is not expressed due to two non-sense mutations. Loss of uric oxidase activity appears to have developed under evolutionary pressure suggesting that higher serum uric acid concentrations or reduced urate oxidase may confer the important advantages in man (Yeldandi *et al.,* 1992; Wu *et al.,* 1992). The biochemical pathway of the purine metabolism is depicted in Figure 1.

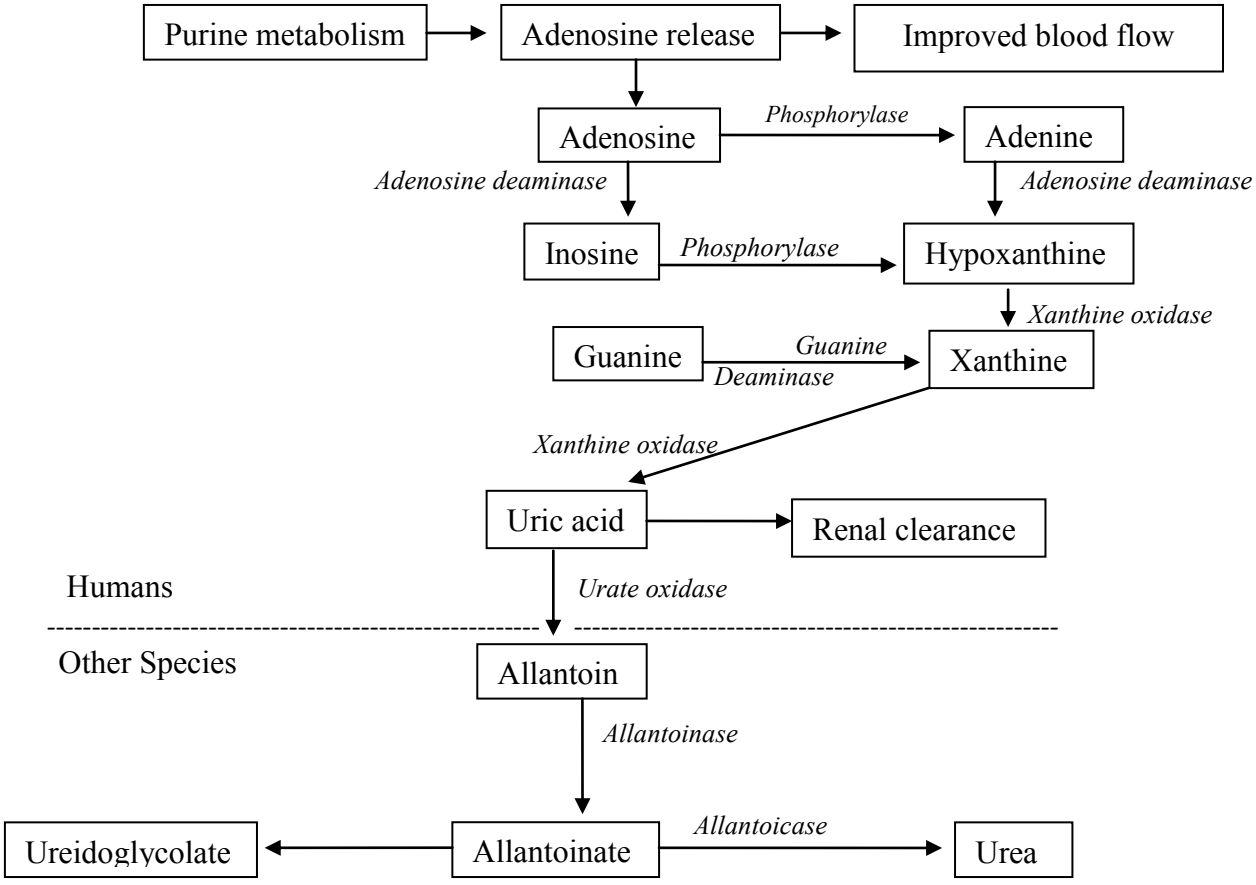

Figure 1: Uric acid as end product of purine metabolism in human and other species

URIC ACID AS A RISK FACTOR FOR CARDIOVASCULAR DISEASES

Adenosine is synthesized and released by cardiac and vascular myocytes. Binding to specific adenosine receptors causes relaxation of vascular smooth muscle and arteriolar vasodilatation. Adenosine makes a small contribution to normal resting vaxcular tone, since competitive antagonism at the adenosine receptor by methylxanthines such as theophylline, reduced blood flow response to ischaemia in the forearm vascular bed (Berne, 1980; Costa *et al.,* 1999). Cardiac and visceral ischaemia promote generation of adenosine, which may serve as an important regulatory mechanism for restoring blood flow and limiting the ischaemia. Adenosine synthesized locally by vascular smooth muscle in cardiac tissue in rapidly degraded by the endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low intracellular pH and negative membrane potential (Fredholm and Sollevi, 1986). Xanthine oxidase activity (Kroll *et al.,* 1992) and uric acid synthesis (Castelli *et al.,* 1995) are increased in vivo under ischaemic conditions and therefore elevated serum uric acid may act as a marker of underlying tissue ischaemia. In the human coronary circulation, hypoxia caused by transient coronary artery occlusion, leads to an increase in the local circulating concentration of uric acid. Study of tourniquet induced lower limb exsanguinations in patients undergoing surgery shows a fivefold increase in systemic vascular xanthine oxidase activity during reperfusion and a significant elevation of serum uric acid, which persists for atleast 2 hours (De Scheerder *et al.,* 1991; Mathru *et al.,* 1996; Anker *et al*., 1997). Thus, while uric acid appears to make a significant contribution to serum anti-oxidant capacity, it could also lead directly or indirectly to vascular injury. It is interesting to note that treatment of chronic cardiac failure patients with allopurinol restored endothelial function. Direct study of the actions of uric acid on endothelial function, platelet aggregation, vessel wall elasticity and autonomic cardiovascular regulation is required so that its effects on the cardiovascular system and in cardiovascular disease can be determined. Conflicting epidemiological data on the independent prognostic role of SUA might be accounted for by the complex interrelations between SUA and a variety of risk markers for CV disease, including male gender, blood pressure, and previous CV events. The Systolic Hypertension in the Elderly Program and the Chicago Studies (Levine *et al.,* 1989) included several individuals with previous CV events. Furthermore, the effect of diuretics on glucose and lipids, in addition to that on SUA, might lead to subtle interactions of potential prognostic value that could be difficult to control in a multivariate survival analysis (Modan *et al.,* 1987; Puig *et al.,* 1991; Frohlich, 1993).

PROGNOSTIC IMPORTANCE OF HYPERURICEMIA IN ACUTE MYOCARDIAL INFARCTION (AMI)

Several prospective studies have shown an association between baseline hyperuricemia and incident of coronary heart disease, cardiovascular disease and death. Eventhough these studies are highly remarkable in clinical studies, but none have evaluated an association between hyperuricemia and short term death after AMI. Uric acid production increases in AMI due to myocardial cell necrosis and destruction of adenosine triphosphate. The extensive myocardial infeaction and left ventricular dysfunction decrease cardiac output, renal blood flow and glomerular filtration rate leads to the reduction of uric acid excretion. Reduced tissue perfusion as a result of cardiogenic shock causes metabolic acidosis and increases lactate production, which competes with the secretion of uric acid in renal proximal tubules and decreases uric acid excretion. In patients with AMI, blood volume reduces as a result of perspiration, vomiting and thirsty mechanism disturbances, especially in old person, which increases uric acid reabsorption after secretion at renal tubules. So, SUA level could be one of the hemodynamic status indicator after AMI (Homayounfar *et al*., 2007; Brand *et al.,* 1985).

ASSOCIATION BETWEEN SERUM URIC ACID AND DIABETES

Identifying risk factors for the development of type 2 diabetes is essential for its early screening and prevention. SUA level has been suggested to be associated with risk of type 2 diabetes. Biologically, uric acid (UA) plays an important role in worsening of insulin resistance in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake. However, hyperinsulinemia as a consequence of insulin resistance causes an increase in SUA concentration by both reducing renal UA secretion and accumulating substrates for UA production (Khosla *et al.,* 2005; Galvan *et al.,* 1995; Fox, 1981). Therefore, it remains controversial whether SUA is independently associated with the development of type 2 diabetes.

URIC ACID AS A MARKER OF INSULIN RESISTANCE

Insulin resistance syndromes result in attenuation of insulin mediated glucose utilization and confer a substantial increase in cardiovascular risk, through activation of several pathways including the sympathetic nervous system. Elevated serum uric acid is consistent features of the insulin resistance syndromes, which are also characterized by elevated plasma insulin level (fasting and post-carbohydrate), blood glucose concentration and serum triglyceride concentration and raised body mass index and waist-hip ratio. Insulin has a physiological action on renal tubules, causing reduced sodium and uric acid clearance (Dobson, 1999; Agamah *et al.,* 1991; Muscelli *et al.,* 1996). Despite blunting of the action of insulin on glucose metabolism, sensitivity to the renal effects persists because plasma insulin concentration is characteristically elevated, hyperuricaemia may arise as a consequence of enhanced renal insulin activity.

Elevated serum uric acid concentrations predict subsequent development of diabetes mellitus and hypertension, even in the presence of normal creatinine clearance and plasma glucose concentrations and therefore may be a subtle, early marker of peripheral insulin resistance syndromes (Selby *et al.,* 1990; Muscelli *et al.,* 1996; DeFronzo, 1981; Perry *et al.,* 1995). Thus a link between elevated serum uric acid concentration and cardiovascular disease may arise through its non-casual relationship with insulin resistance syndromes, where cardiovascular risk is mediated by other factors.

URIC ACID LEVELS OF HYPOTHYROID PATIENTS

Uric acid was found significantly elevated in primary hypothyroidism. In some studies, serum uric acid level was found elevated in hypothyroid patients. The induced hypothyroid rabbits the serum uric acid level was found higher in hypothyroid condition than in euthyroid condition. In an epidemiological study in northern Finland in 1969, hyperuricemia was found in rural, urban and hospital admitted hypothyroid patients. In hypothyroidism the hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration (Karanikas *et al.,* 2004; Erickson *et al.,* 1994; Yokogoshi and Saito, 1996; Dariyerli *et al.,* 2003; Khan and Majumder, 2010). The serum creatinine concentration increases in hypothyroid patients due to reduction of glomerular filtration rate because of hemodynamic changes in severe hypothyroidism. Serum creatinine level may also be increased due to hypothyroid myopathy. In hypothyroidism, associated autoimmune diseases may also play role in modifying the underlying renal problem. Hypothyroidism, although rare, has been reported as a definite and authentic cause of rhabdomyolysis (Khan and Majumder, 2010; Karanikas *et al.,* 2004).

Hypothyroidism is associated with hyperuricemia. In comparison to the prevalence reported in the general population, a significant increase of both hyperuricemia and gout was found in the hypothyroid patients. In hypothyroidism the hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration. Many studies were done regarding the biochemical status of hypothyroid patients, including serum creatinine and uric acid levels (Giordana *et al.,* 2001; Karanikas *et al.,* 2004). Chronic kidney diseases also affect thyroid

function in many ways leading to decreased T_3 and T_4 (Khan and Majumder, 2010).

J SHAPED ASSOCIATION IN HAEMODIALYSIS PATIENTS

The kidneys excrete approximately two-thirds of the uric acid that is produced daily. For an individual, the serum uric acid concentration is determined largely by the rate of purine metabolism and the efficiency of renal clearance. Therefore, significant amounts of uric acid may accumulate in patients approaching end-stage renal disease (ESRD). The mean uric acid removal is ~1g per haemodialysis (HD) session, even with high-flux haemodialysers. Nevertheless, hyperuricaemia is still common in HD patients following HD therapy. Due to progressive loss of the glomerular filtration rate, patients with renal diseases or ESRD have decreased renal clearance of uric acid and higher serum uric acid levels than in the general population. Several large prospective cohort studies have demonstrated associations between serum uric acid levels and cardiovascular disease as well as all cause mortality in the general population (Sombolos *et al.,* 1997; Gertler *et al.,* 1951; Fang and Alderman, 2000; Hsu *et al.,* 2004).

URIC ACID AND CHRONIC KIDNEY DISEASE (CKD)

Uric acid may mediate aspects of the relationship between hypertension and kidney disease via renal vasoconstriction and systemic hypertension. Several studies reported an association between baseline uric acid and kidney function decline (Mazzali *et al.,* 2001; Kang *et al.,* 2002). Uric acid may be associated with CKD through the following mechanisms

- Uric acid may be directly toxic to the kidney
- Elevated uric acid may exacerbate other risk factors for kidney disease, specifically hypertension; or
- Uric acid may be a marker of the severity of other risk factors, including those attributable to or associated with diabetes and the metabolic syndrome.

In animal studies, mild hyperuricemia caused direct kidney toxicity, manifest by renal vasoconstriction and systemic hypertension as well as tubulointerstitial injury not accounted for by uric acid crystal deposition within the kidney. Uric acid may cause these conditions through inhibition of endothelial nitric oxide bioavailability, activation of the renin-angiotensin system, and/or direct effects on endothelial cells and vascular smooth muscle cells. Clinical support for this hypothesis is provided by data from the Health Professionals' Follow-up Study, which suggested that elevated serum uric acid is a risk factor for development of hypertension in younger men (Sanchez *et al.,* 2002; Crillo *et al.,* 2006; Weiner *et al.,* 2008).

The recognition of the biological mechanisms linking hyperuricemia to the development and progression of kidney disease is beyond the scope of this study. However, putative underlying mechanisms may include chronic inflammation, endothelial dysfunction, vascular smooth muscle proliferation, and impaired nitric oxide generation. Furthermore, experimental evidence suggests that hyperuricemia may exert adverse effects on oxidative metabolism, platelet adhesiveness, and aggregation. In animal models, elevated uric acid levels can lead to arteriolopathy of preglomerular vessels, impaired autoregulation, glomerular hypertension, as well as endothelial dysfunction. Kidney damage in hyperuricemic rats is not dependent on blood pressure and instead involves the renin-angiotensin and cyclooxygenase-2 systems (Mazzali *et al.*, 2001; Kang *et al.,* 2002; Lippi *et al.,* 2008; Hovind *et al.,* 2011).

ELEVATION OF SERUM URIC ACID WITH MULTIPLE SCLEROSIS (MS)

MS is a progressive neurologic disease where many factors may attribute to pathogenesis; the antioxidant effect of uric acid is well defined with this problem. The frequency of multiple sclerosis was more in women than men and the most prevalent age of onset is between 22 – 46 years. The serum uric acid level was not related to the severity of clinical score and recurrence rate. There was not any special gradient in diet, could

be attributed to MS. Despite the uric acid role in pathogenesis of MS based on many studies, there was not any relation of uric acid level with MS clinical severity or recurrence rate at least in 6 months period (Taheraghdam *et al.,* 2013).

OBESITY AND SERUM URIC ACID

Obesity has long been recognized as an associated factor with a variety of adverse health consequences; chiefly among them diabetes, hypertension, dyslipidaemia, increased cardiovascular events, and elevated serum uric acid. These patients are also more likely to present with silent disease and as a cluster of metabolic syndrome. The most commonly recognized risk factors in the metabolic syndrome are highly correlated with each other and are pre-summed to reflect common metabolic pathway and they interact to increase risk in a synergistic fashion. Furthermore, several epidemiological studies showed a positive association between obesity and hyperuricemia. Increases in serum uric acid concentration showed positive association with body mass index (BMI), waist hip ratio (WHR), Waist/thigh girth, and sub-scapula triceps skin fold ratios. The risk of gout was increased among men who had been overweight in adolescence. It has been suggested that other factors, such as muscle mass, may also play a role in producing high serum uric acid. Weight reduction has been associated with modest lowering of serum urate (Stern, 1995; Loenen *et al.,* 1990; Scott, 1977).

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