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Review of Concepts and Controversies of Uric Acid as Antioxidant and Pro-Oxidant

Ürik Asidin Antioksidan ve Pro-Oksidan Özellikleri ile İlgili Kavram ve Tartışmalarının Derlemesi

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ABSTRACT

Uric acid, the end product of purine catabolism in humans and is known for its crystal deposition at higher concentrations (>7 mg/dl) in gout. Less is known about its antioxidant property and the beneficial effects in various diseases. It is thought that high concentration of uric acid in humans is an evolutionary advantage and it is also hypothesized that high concentration of uric acid is to compensate the antioxidant capacity of ascorbic acid which is lost in humans during the course of evolution. In the extracelluar environment, uric acid can scavenge free radicals like hydroxyl radical, singlet oxygen and peroxynitrite radical therefore, it is considered as a powerful antioxidant. On the other hand uric acid depending upon the chemical milieu, changing its property and at times it acts as pro oxidant and is associated with the pathobiochemistry in developing various diseases like hypertension, cardio vascular diseases, ischemia reperfusion injury, diabetes mellitus, non alcoholic fatty liver disorders etc. In this review, we tried to summarize the evolutionary advantages of hyperuricaemia, effects of both antioxidant property and pro-oxidant nature of uric acid in various disease conditions.

Key words: Hyperuricaemia, antioxidant, pro-oxidant, paradox, beneficial effects of uric acid.

ÖZET

Ürik asit, insanlarda pürin metabolizmasının son ürünüdür, gutta kristallerinin yoğun olarak (>7

mg/dl) biriktiği bilinmektedir. İnsanlarda, yüksek konsantrasyonda ürik asitin evrimsel bir avantaj olduğu düşünülmektedir.Aynı zamanda, insanlarda yüksek ürik asit konsantrasyonunun; evrim sürecinde kaybolan askorbik asitin antioksidan kapasitesini telafi ettiği hipotezi ortaya atılmıştır. Hücre dışı ortamda, ürik asit; hidroksil, peroksinitrit ve tekil oksijen gibi serbest radikalleri uzaklaştırabilmektedir bu sebeple ürik asit güçlü bir antioksidan olarak düşünülmektedir. Öte yandan kimyasal ortamına bağlı olarak değişen özelliği ile ürik asit, zaman zaman pro-oksidan gibi davranır ve hipertansiyon, kalp damar hastalıkları, iskemi reperfüzyon hasarı, diyabet, ve alkolsüz yağlı karaciğer bozuklukları gibi çeşitli hastalıkların patokimyası ile ilişkilidir. Bu çalışmamızda, hiperüreseminin evrimsel avantajlarını ve çeşitli hastalık koşullarında, ürik asitin hem antioksidan özelliğinin hem de pro-oksidan doğasının etkilerini özetlemeye çalıştık.
Anahtar kelimeler: Hiperüresemi, antioksidan, pro-oksidan, paradoks, ürik astin faydalı etkileri.

Introduction

Uric acid (UA) is the end of purine catabolism and is excreted in urine of humans. It is a weak organic acid with a P_K of 5.75, and exists mainly as monosodium urate (MSU) at physiological P^H. In most mammals, uric acid is degraded further by the enzyme uricase. The pathway of purine catabolism is shortest among humans and great apes, because about 5–20 million years ago the activity of uricase gene was lost during hominoid evolution[1] Therefore uric acid is the final product in humans and great apes, which is excreted in urine, whereas in other mammals the final enzymatic product of purine degradation is allantoin and is excreted in the urine. As a consequence, humans and the great apes have to bear with higher uric acid levels (>2 mg/dl) compared with most mammals (< 2mg/dl) and they are more prone to hyperuricemia (>6.5 mg/dl).

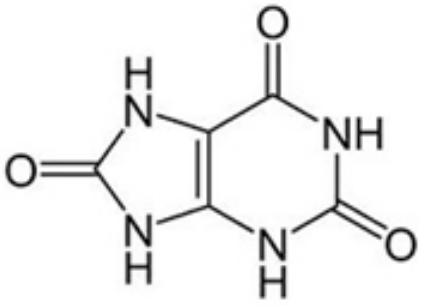
Many researchers do not consider uric acid as an antioxidant. They forget about the uric acid role and its importance as a protective antioxidant. Studies reported that uric acid is as effective as antioxidant ascorbate in humans. While doing the estimation of total antioxidant status in many diseased conditions, what we observe is researchers neglect the estimation of uric acid though it is proved to be a powerful antioxidant. It clearly suggests that many clinical researchers do not give much importance to very interesting compound uric acid. Less is known about the beneficial effects of uric acid. On the other hand uric acid also acts as pro oxidant in hydrophobic conditions. There is some controversy regarding uric acid acting as antioxidant and pro oxidant. With this background we made an attempt to discuss and

summarize the protective role of uric acid in various disease conditions as an antioxidant and harmful effects and also as risk factor for various diseases by acting as a pro-oxidant.

Uric Acid Chemistry and Its Formation

Uric acid is a heterocyclic organic compound with the formula $C_5H_4N_4O_3$ (2,6,8-trioxypurinne) (figure 1) and a molecular weight of 168 Daltons[2]. Uric acid is the final metabolic product of purine metabolism in humans. Many enzymes are involved in the conversion of the two purine nucleic acids, adenine and guanine, to uric acid. Initially, adenosine monophosphate (AMP) is converted to inosine by two different mechanisms; either first removing an amino group by AMP deaminase to form inosine monophosphate (IMP) followed by dephosphorylation with nucleotidase (NT) to form inosine, or by first removing a phosphate group by nucleotidase (NT) to form adenosine followed by deamination to form inosine. Guanine monophosphate (GMP) is converted to guanosine by nucleotidase (NT). The nucleosides, inosine and guanosine, are further converted to purine base, hypoxanthine and guanine, respectively, by purine nucleoside phosphorylase (PNP). Hypoxanthine is then oxidized to form xanthine by xanthine oxidase, and guanine is deaminated to form xanthine by guanine deaminase. Xanthine is again oxidized by xanthine oxidase to form the final product, uric acid (figure 2).

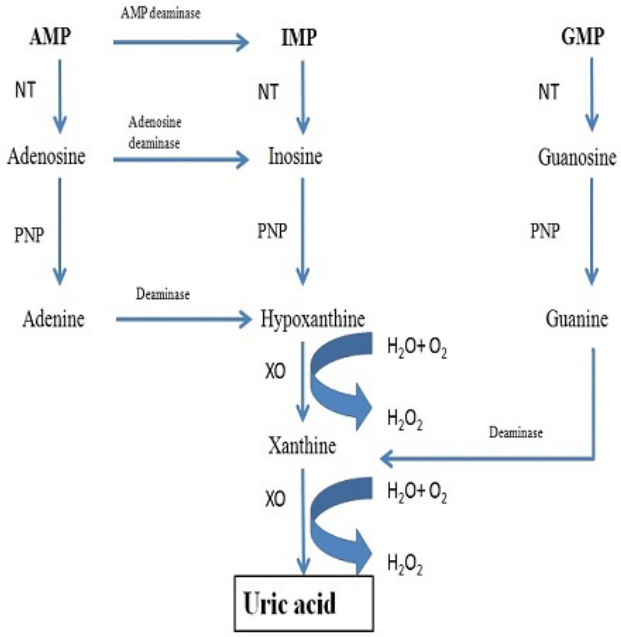
Figure 1: Biochemical structure of uric acid



Normal Range

The normal reference interval of uric acid in human blood is 1.5 to 6.0 mg/dl in women and 2.5 to 6.5 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)[2].

Figure 2: Steps in metabolism of purine degradation. AMP: adenosine monophoshate; IMP: inosine monophosphate; GMP: guanosine monophosphate; NT: nucleotidase; PNP: purine nucleoside phosphorylase; XO: xanthine oxidase.



Evolutionary Advantages of the Loss of Uricase

Several independent mutations in the uricase gene occurred during the evolution of hominids. These mutations have been interpreted as clear evidence of an important evolutionary advantage for the early primates that had increased UA[3,4,5]. As purine degradation is much less

complete in higher animals than in others, it is obvious that certain enzymes had been lost during animal evolution and it is assumed that it provided some evolutionary advantage[6].

On the other hand, if UA was a harmful/waste product, it would not explain how the kidneys recover 90% of filtered UA[7], instead of eliminating it. The evolution of hominids and the physiology of renal urate balance indicate that uric acid is something beneficial that we must retain instead of something harmful that has to be removed. These facts have led various authors to propose some hypotheses, on the evolutionary advantages of the loss of uricase and the subsequent increase in UA.

Since the discovery of antioxidant property of uric acid in 1981, it is believed that high blood levels of uric acid in humans carry an evolutionary advantage and thus protects cardiac, vascular, and neural cells from oxidative injury[3]. On the other hand, hyperuricemia even without crystal deposition and gout is strongly associated with cardiovascular disease, kidney disease, metabolic syndrome and hypertension, increasing the risk of mortality[8]. This dual nature of uric acid is creating a paradox among researchers whether uric acid is an antioxidant or an oxidant and raising a question is hyperuricaemia really an evolutionary advantage to humans?

Oxidative Stress

The oxygen consumed is utilized by mitochondria for oxidative phosphorylation and is reduced to water in the electron transport chain (ETC). A small fraction of it is not used for this purpose instead it is converted into free radicals – which are harmful for the body when present in excess. Free radicals are harmful for the body because they contain an unpaired electron in their structure. These oxygen particles with an unpaired electron are called as reactive oxygen species (ROS) and are proven to cause cell and tissue injury[9].

Oxidative stress, which is defined as an imbalance between the pro-oxidant reactive species and antioxidant molecules, both endogenous and exogenous, has been associated with many non-communicable diseases, such as obesity, insulin resistance[10] and diabetes[11], atherosclerosis[12,13], autoimmune diseases[14,15], neurodegenerative diseases[16,17], chronic renal disease[18,19], different malignancies[20,21], as well as in aging[22] as a physiological process.

Definition of Antioxidant

Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions by being oxidized themselves. So an antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules.

The antioxidant system can be weakened by a poor diet and a lack of nutrients, pathologic conditions or pharmacological intervention, including intake of certain medications.

Uric Acid as an Antioxidant

Initially, uric acid was considered as an inert waste product that crystallizes at high concentrations to form renal stones and provoke gouty arthritis. Subsequently, uric acid was recognized to be a powerful antioxidant that scavenges singlet oxygen, oxygen radicals, and peroxynitrite and chelates transition metals. Urate thus accounts for approximately half of the antioxidant capacity of human plasma, and its antioxidant properties are as powerful as that of ascorbic acid[23, 24, 25].

The protection system to prevent and repair the oxidative damage includes antioxidant enzymes like superoxide dismutase and glutathione peroxidase, free radical scavengers such as vitamin E and the ß-carotenes in the lipid portion of the cells, ascorbic acid and UA in the aqueous phase[23]. UA, being a powerful free radical scavenger as well as being able to act as chelator of metal ions, such as iron and copper, by converting them to poorly reactive forms, is one of the most important antioxidants in human biological fluids[9]. It is thought that UA contributes to more than 50% of the antioxidant capacity of blood[9,24]. For this reason, Ames et al., proposed[26] that the loss of uricase expression and the subsequent increase in UA levels had the evolutionary benefit of increasing antioxidant capacity, increasing the life expectancy of hominids and decreasing age-specific cancer rates. The loss of uricase could be associated with the previous loss of capacity to synthesize vitamin C[5, 25] which occurred 40–50 million years ago due to a mutation in L-gulono-lactone oxidase, in a period in which the primates of the epoch ate large quantities of vitamin C in their diet, so it was an inoffensive mutation[4, 5]. With a lower ingestion of vitamin C in later epochs and the subsequent loss of antioxidant capacity, could be compensated by the increase in uric acid concentration due to loss of uricase activity[5].

Protective (Antioxidant) Functions of Uric Acid

It has been hypothesized that the antioxidant properties of uric acid might be protective against aging, oxidative stress, and oxidative injury of cells, including cardiac, vascular, and neural cells (figure – 3). Therefore uric acid has some beneficial effects. Less is known about the beneficial effects of uric acid. Uric acid may function as a powerful antioxidant, and possibly one of the most important antioxidants in plasma[26-28]. Watanabe et al[23] has suggested that hyperuricemia maintains blood pressure during low salt intake environments, which may have provided a survival advantage during the course of primate evolution. Therefore, many researchers thought that hyperuricemia is an evolutionary advantage to humans developed due to the antioxidant properties of uric acid.

Urate (the soluble form of uric acid in the blood) can scavenge superoxide, hydroxyl radical, and singlet oxygen and can chelate transition metals. Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction[29]. Hink et al[30] reported that uric acid may also prevent the degradation of extracellular superoxide dismutase (SOD3), an enzyme critical in maintaining endothelial and vascular function. SOD3 is an extracellular enzyme that catalyzes the reaction of superoxide anion (O_2^{-}) to hydrogen peroxide (H_2O_2). The removal of super oxide anion (O_2^{-}) by SOD3 prevents the reaction and inactivation by O_2^{-} of the important endothelial vasodilator, nitric oxide (NO). SOD3, by removing O_2^{-}, Therefore helps to maintain NO levels and maintain endothelial function. Normally, SOD3 is inactivated in the presence of H_2O_2, suggesting a feedback inactivation of the enzyme. However, uric acid blocks SOD inactivation by H_2O_2 by regenerating SOD3 with the production of a urate radical[30]. This latter radical, although potentially a pro-oxidant, has been found to be markedly less reactive than classic oxidants and can be rapidly regenerated back to urate in the presence of ascorbate[31].

Ames et al[26] hypothesized that the uricase mutation occurred during early hominoid evolution because the antioxidant action of uric acid may have provided an evolutionary advantage and that this may account for the greater longevity of humans and the great apes compared with most other primates. The increase in serum uric acid in subjects with cardiovascular disease might therefore reflect a compensatory mechanism to counter the oxidative stress that occurs in these conditions[32].

Serum uric acid is considered as a useful biomarker for mortality in high-risk patients with acute coronary syndromes and heart failure and in patients with hypertension[33]. Despite emerging results on uric acid and its association with incident renal and cardiovascular outcomes, the beneficial role of reducing uric acid levels on cardiovascular risk, as well as on the progression of kidney diseases, is not established yet[34]. However, there is some evidence to suggest the potential beneficial effect of reducing uric acid levels in humans.

Uric Acid as Surrogate Marker

It is also reported that uric acid may play an important role in diagnosis, prognosis and therapy monitoring. Serum uric acid is a good indicator of the oxidative stress which is involved in development of cardiovascular disorders, obesity, impaired glucose tolerance, hypertension and hyperlipidemias. Hyperuricemia is not directly responsible for vascular injury and increased risk for cardiovascular or cerebrovascular disease but simply represents a surrogate marker for high levels of damaging oxidative stress associated with increased xanthine oxidase activity. Indeed, hyperuricaemia is a significant predictor of disease state and progression of chronic heart failure[35]. Uric acid is not only recognized as a marker of oxidative stress, it also has a protective role. As described earlier it acts an antioxidant which is involved in clinical investigations of therapy for cerebrovascular disorders in combination with the anticoagulants. The assessment of UA is widely available at low cost, which may be an advantage for widespread determination of this marker[35].

Uric Acid and Bone Mineral Density

Oxidative stress has been linked to osteoporosis. Serum uric acid, a strong endogenous antioxidant, has been associated with higher bone mineral density (BMD), lower bone turnover and lower prevalence of fractures in a large cross-sectional study of men. Recently, another cross-sectional study done in female subjects also revealed that uric acid has protective role in bone mineral density. A very recent study done by Makovey J et al., revealed that women with higher UA levels had significantly higher absolute BMD measures at all skeletal sites[36]. Therefore, higher serum UA levels appear to be protective for bone loss in peri- and postmenopausal women and this relationship is not affected by changes in body composition measures[36].

Uric Acid in Neurological Disorders

Uric acid is known to have powerful antioxidant effects capable of neutralizing large amounts of free radicals. The antioxidant activity of UA also occurs in the brain, being a protector for several diseases such as Parkinson's disease, Alzheimer's, multiple sclerosis and associated with a low level of uric acid. Uric acid possess beneficial role in some neurological disorders; the argument in support of this hypothesis results from the low levels found in patients with diverse neurological disorders. Higher concentration of UA is associated with lower risk of development of Parkinson's disease and a favorable effect at the disease progression mainly[37,38].

Recently, uric acid has been shown to play a role in innate immune responses to infection and other injury. However at this moment in time, the potential benefits of a relatively high level of uric acid are vastly outweighed by its adverse effects[2].

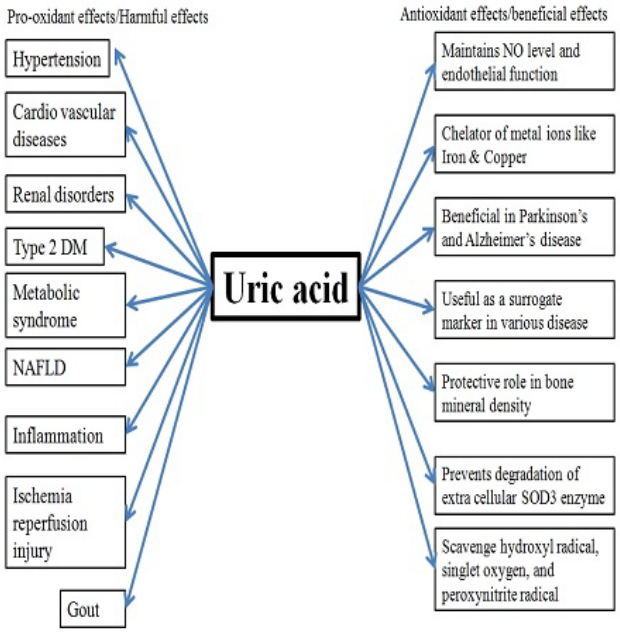
It is not clear, whether uric acid would be a causal factor or an antioxidant protective response against oxidative stress. While chronic high uric acid concentrations are associated to increased risk for coronary artery disease (CAD), acute elevations seem to provide antioxidant protection. Uric acid has a protective action in vitamins C and E with the stabilizing activities in these vitamins[39]. On the top of it, the presence of ascorbic acid in plasma is required for the antioxidant effect of uric acid.

Most authors do not consider uric acid as a detrimental factor to the body health, because of its antioxidant function. Available data suggest that uric acid acts not only as an antioxidant but depending on the chemical milieu, it may also act as pro oxidant. On one hand, in the extracellular environment, urate can scavenge hydroxyl radical, singlet oxygen, and peroxynitrite, especially when combined with ascorbic acid or thiols[35,39]. On the other hand, uric acid loses its antioxidant ability in the hydrophobic environment. Moreover, it can form free radicals either alone or in combination with peroxynitrite. Different mechanisms have been proposed as explanations of paradoxical associations of uric acid, but the role of uric acid as a causal, compensatory, or coincidental risk factor remains unclear. As there is tremendous complexity in these disorders, an unambiguous common pathogenic feature for all of them is an involvement of oxidative stress, conformational changes in proteins due to oxidative stress and lipids as well as redox-dependent low-grade inflammation[39].

Harmful Actions of Uric Acid

Growing epidemiological and clinical evidences suggest that hyperuricaemia might be a risk factor for cardiovascular disease, where enhanced oxidative stress plays an important pathophysiological role. The apparent paradox between protective and toxic effects of UA is supported by clinical evidence that antioxidant compounds may become pro-oxidant compounds in certain situations, particularly when they are present in blood at abnormally high levels. Hyperuricemia has detrimental effects for multiple organ systems. Uric acid is mainly known for its harmful effects such as gout and uric lithiasis, as well as its association with hypertension, renal disease, metabolic syndrome and, cardiovascular disease (figure – 3). It has also been hypothesized that hyperuricaemia might be involved in chronic heart failure and metabolic syndrome.

Figure 3: Shows harmful effects of uric acid when it acts as pro-oxidant and beneficial effects when it acts as antioxidant. DM: Diabetes Mellitus, NO: Nitric Oxide, NAFLD: Non alcoholic fatty liver disorder, SOD: superoxide dismutase.



Uric Acid in Hypertension and Cardiovascular Disorders

Hypertension is a multi-factorial process, prevalent in developed as well as in developing countries. These complex changes are consistent in the view that essential hypertension is associated with an abnormal level of antioxidant status. Some studies find that hyperuricemia can be predictive for the development of hypertension, renal disease, and cardiovascular disease despite controlling for associated risk factors. This raises the possibility that uric acid may have a pathogenic role in hypertension and cardiovascular disease[40].

High plasma uric acid levels are positively associated with increased incidences of hypertension in adults[41,42]. More specifically, plasma uric acid levels significantly predict diastolic hypertension, but not systolic hypertension[43,44]. This may be due to damage of small renal vessels by increased uric acid levels, which leads to irreversible salt sensitive hypertension. This salt sensitive hypertension persists regardless of uric acid levels[23]. However, this association decreases as patient's age increases and is not found in elderly patients[45-48]. When hypertension develops in the elderly, other pathophysiological mechanisms such as decreased arterial compliance may play a larger role in hypertension than hyperuricemia[48]. The association of hyperuricemia and hypertension can be found in babies with low birth weight. It is reported that low birth weight babies have an increased risk of hypertension at a later stage of life, and is associated with high levels of uric acid[49].

Hyperuricemia has also been established as an independent predictor of microalbuminuria[50] and renal dysfunction[51-53]. In healthy normotensive individuals, increased uric acid levels correlate with decreased kidney function. Both interstitial and vascular inflammation may also occur. Thus, high levels of uric acid can induce a vasoreactive hypertension, which can further develop into kidney-dependent hypertension[54].

Increased serum uric acid concentration is associated with variables elevation of which worsen cardiovascular prognosis, including blood pressure[55] body weight and plasma cholesterol, and with insulin resistance[42,56,57]. Nonetheless, large epidemiological studies that examined the possible direct relationships between serum UA and cardiovascular outcomes have produced inconsistent results[55,58-60]. For the preceding reasons, raised serum UA should not be considered an independent risk factor for cardiovascular disease or heart failure. Increased serum UA concentration may well be an innocent bystander associated with deleterious processes including increased reabsorption of filtered sodium in the proximal tubule of the

nephron[61] and insulin resistance, or it may constitute a compensatory response to oxidative stress[62].

Although several studies have found that higher UA is an independent risk factor for cardio vascular disorders (CVD) and mortality in subjects with cardiovascular risk profile. A negative prognostic factor for survival in heart failure patients is still controversial whether high uric acid is a compensatory attempt to counteract increased oxidative stress, an independent cause of CVD, or just a condition associated with other well-established risk factors such as hypertension, diabetes, and an accelerated clinical evolution of the disease[26-29]. Some authors suggested that high UA levels may promote the hypertensive organ damage, exerting a deleterious effect on endothelial function. However, these findings related to uric acid attributable to excess mortality risk is particularly evident in women, older persons, and subjects with pre-existing CVD[24, 45].

Uric Acid in Ischemia Reperfusion Injury

Reperfusion injury is the tissue damage caused when blood supply returns to the tissue after a period of ischemia or lack of oxygen. The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function. Reperfusion therapy is medical treatment that restores blood flow through blocked arteries, typically after a heart attack (myocardial infarction). Categories of reperfusion therapy thus include clot-busting (thrombolytic) drugs and procedures to open arteries with stents, or to graft arteries around blockages[63]. These interventions have become so central to the modern treatment of acute myocardial infarction[64,65].

In prolonged ischemia (60 minutes or more), hypoxanthine is formed as breakdown product of ATP metabolism. During prolonged ischemia the enzyme xanthine dehydrogenase is converted to xanthine oxidase as a result of the higher availability of oxygen. This enzyme uses molecular oxygen as its electron acceptor, leading to the generation of hydrogen peroxide and superoxide anion, toxic oxygen species that can be further metabolized to the highly reactive hydroxyl radical. Xanthine oxidase also produces uric acid, which may act as both a pro-oxidant and as a scavenger of reactive species such as peroxynitrite[63,66]. Excessive nitric oxide produced during reperfusion reacts with superoxide to produce the potent reactive species peroxynitrite. Such radicals and reactive oxygen species attack cell membrane lipids,

proteins, and glycosaminoglycans, causing further damage. They may also initiate specific biological processes by redox signaling.

Reperfusion of ischemic tissues is often associated with microvascular injury, particularly due to increased permeability of capillaries and arterioles that lead to an increase of diffusion and fluid filtration across the tissues. These "activated" endothelial cells produce more reactive oxygen species but less nitric oxide following reperfusion, and the imbalance results in a subsequent inflammatory response[66]. Further this process is aggravated by the formation of uric acid because of the increased activity of xanthine oxidase enzyme. The inflammatory response is partially responsible for the damage of reperfusion injury. White blood cells, carried to the area by the newly returning blood, release a host of inflammatory factors such as interleukins as well as free radicals in response to tissue damage[67]. The restored blood flow reintroduces oxygen within cells that damages cellular proteins, DNA, and the plasma membrane. Damage to the cell's membrane may in turn cause the release of more free radicals. Such reactive species may also act indirectly in redox signaling to turn on apoptosis. White blood cells may also bind to the endothelium of small capillaries, obstructing them and leading to more ischemia[67].

Uric Acid and Inflammation

The role of uric acid in the process of atherosclerosis and atherothrombosis is controversial. Epidemiological studies have recently shown that UA may be a risk factor for cardiovascular diseases and a negative prognostic marker for mortality in subjects with pre-existing heart failure. Researchers have suggested that the higher UA levels in subjects with CVD might be a compensatory response designed to counteract excessive oxidative stress[32]. This theory has a strong rationale in the biochemical characteristics of uric acid as anti-oxidant and is supported by pre-clinical studies performed *in vitro* and in experimental animals[9]. However, the role of UA in humans is still uncertain. A crude correlation between serum C-reactive protein and UA levels has been found in a German population-based survey[68], and a significant positive correlation between UA and inflammation was found in a small clinical series of heart failure patients[69,70]. Studies have demonstrated that after cellular death or injury, the degradation of nucleotides into UA serves as an endogenous 'danger signal' for the maturation and immunostimulatory action of dendritic cells[71]. In experimental studies, UA stimulates the release of chemokine monocyte chemoattractant protein-1[72] and interleukin-1 (TNF-a)

synthesis[73]. In spite of the evidence that UA might contribute to the development of human vascular disease and atherosclerosis through a pro-inflammatory pathway, the relationship between UA and inflammation has been little investigated.

Moreover, across the uric acid quintiles, it is reported that progressive increase in the percentage of subjects with abnormally high levels of IL-6 and CRP, which are considered solid markers of inflammation in clinical practice. These findings suggest that the relationship between UA and inflammatory markers is linear across the entire range of uric acid and that such a relationship may be clinically relevant even in subjects with UA within the normal range. However, the nature of such a relationship remains unknown. Actually, a significant linear trend was also detected within the uric acid 'normal range'. These findings suggest that UA is not only a marker of catabolic rate but also might be actively involved in systemic inflammation, which an important component of the causal pathway is leading to hypertension, vascular diseases, and renal failure[70–73].

Uric Acid and Type 2 Diabetes

It is has long been hypothesized that hyperuricemia might be a risk factor for the development of type 2 diabetes, but the casual association between hyperuricemia and type 2 diabetes remains controversial. Since elevated serum uric acid levels are often associated with established type 2 diabetes risk factors, such as alcohol consumption and metabolic syndrome, it is still unclear whether serum uric acid is merely a risk marker or an independent risk factor for diabetes[74].

Some researchers have proposed that hyperuricemia-induced oxidative stress represents a cause of the metabolic syndrome[75,76]. Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes[75, 77, 78].

Metabolic syndrome, type 2 diabetes, and atherosclerotic vascular disease are not only characterized by various established but also emerging risk factors, and interestingly, these three disorders have several risk factors in common. Very recently, several well-designed prospective studies[79-81] provided stronger evidence concerning the relationship between high serum uric acid level and the risk of type 2 diabetes. All these prospective studies adjusted for metabolic syndrome components to validate an independent association between uric acid and diabetes, which was not sufficiently demonstrated previously.

Several underlying mechanisms might be involved in the association between hyperuricemia and the development of type 2 diabetes. Hyperuricemia has been shown to induce endothelial dysfunction and to reduce the production of nitric oxide[40,82]. Nitric oxide reduction could lower insulin stimulated glucose intake in skeletal muscle, which contributes to insulin resistance and thus diabetes. In addition, hyperuricemia is associated with oxidative stress[8,83] which plays an important role in the pathogenesis of type 2 diabetes. These experimental evidence supports serum uric acid as a causal factor of diabetes.

Uric Acid and NAFLD

NAFLD is now considered a part of the metabolic syndrome, a clustering of cardiovascular disease risk factors closely associated with insulin resistance and many endocrine derangements including glucose homeostasis and central obesitiy[84 -87]. It has been reported that hyperuricemia is related to insulin resistance and associated conditions[88, 89] but its relationship with NAFLD is not well known. One recent study suggested that hyperuricemia was significantly associated with NAFLD, but the limitation of its cross-sectional study design did not permit a conclusive evaluation for its causal relationship[89]. Insulin resistance and hyperuricemia occur frequently in patients with NAFLD[90,91]. The close relationship between insulin resistance and hyperuricemia suggests that hyperuricemia can contribute to the development of NAFLD[91]. The mechanism which is involved in the association of NAFLD and hyperuricemia was also uncertain.

Conclusion

Uric acid can act as either antioxidant or pro-oxidant depending on its circumstances, especially on the availability of lipid hydro peroxides. From the available data it is evident that a rise in uric acid represents an attempted protective response by the host and also uric acid may function either as an antioxidant (primarily in plasma) or pro-oxidant (primarily within the cell). As uric acid is involved in a complex reaction with several oxidants and may have some protective effects under certain conditions. Uric acid is an antioxidant only in the hydrophilic environment, which is probably a major limitation of the antioxidant function of uric acid. Soluble uric acid can also mediate the generation of radicals and function as a pro-oxidant. These mechanisms by MSU or soluble uric acid found in gout may also contribute to the development of vascular diseases seen in patients with hyperuricemia. However, current

models of the pathophysiological mechanisms of uric acid are not yet fully sufficient to explain whether hyperuricaemia is really an evolutionary advantage for humans. Further research is needed to better understand the biological roles of uric acid, and identify its clear role in the pathophysiology of hyperuricemic related diseases.

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List of abbreviations used: UA – uric acid; MSU – monosodium urate; AMP - adenosine monophosphate; IMP - inosine monophosphate; NT – nucleotidase; GMP - Guanine monophosphate; PNP - purine nucleoside phosphorylase; ETC - electron transport chain; ROS - reactive oxygen species; SOD – superoxide dismutase; BMD - bone mineral density; CVD - cardio vascular disorders; NAFLD – non alcoholic fatty liver disease