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The Impact of Uric Acid on Human Health: Beyond Gout and Kidney Stones

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Abstract

In most primates, including humans, uric acid (UA) is the end product of purine metabolism due to the loss of hepatic uricase activity during evolution. This loss resulted in higher serum urate concentrations (3.5–7.5 mg/dL) than normally observed in other mammals (0.05–2 mg/dL). About 70% of the daily urate burden is eliminated via the kidneys and the remainder via the intestines, where gut bacteria break it down. Urate is freely filtered through the glomerular capillaries, and most of the filtered urate is reabsorbed so that only an amount equivalent to about 10% of the filtered load is excreted in the urine. Virtually all of the renal urate reabsorption takes place in proximal convoluted tubules. Many transport proteins connected with urate have been identified. However, the best studied are URAT1 and GLUT9, which function in concert to translocate urate from the proximal tubule lumen to the peritubular fluid, the first in the apical membrane and the second in the basolateral membrane. Genetic mutations, as well as drugs that alter the function of these transporters, can affect urate homeostasis resulting in abnormal serum levels, which may, in turn, be involved in the pathogenesis of chronic metabolic and inflammatory diseases, including most features of the metabolic syndrome, hypertension, cardiovascular disease, and chronic kidney disease. Several mechanisms are thought to provide the link between urate and these disorders, including reactive oxygen species (oxidative stress) and both acute and chronic inflammation. This mini-review summarizes the basic human biology of UA and its association with and potential involvement in developing chronic diseases beyond gout and nephrolithiasis.

Keywords

- Uric acid
- metabolism
- hyperuricemia
- pathogenesis of disease
- oxidative stress
- chronic inflammation
- insulin resistance
- essential hypertension
- chronic kidney disease

Introduction

Uric acid (UA/urate; 2,6,8-trihydroxy purine, C5H4N4O3; Mwt 168 dalton), which is a metabolic end product, was first found in kidney stones in 1776[1] and later was identified in normal human urine and was given its current name.[2] However, some 750 years earlier, the disease UA is most associated with gout was described in great detail by Avicennia (Ibn Sina; 980–1037 AD) in his famous encyclopedic work, the Canon of Medicine, published in 1025 AD. In these volumes, Avicennia described gout's clinical features (excruciating joint pain, redness, and swelling) and its potential complications, including kidney stones. He also advised to help alleviate these symptoms and hinted at the presence in

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the circulation of a toxic substance as a potential causative agent.

Presently most clinical aspects of gout, including prevention and treatment, are pretty well-defined. However, while our current knowledge about the impact of UA on human health, in general, has expanded enormously in the past several decades, our understanding of most aspects of its involvement in the pathophysiology of human diseases still needs to be completed.

Uric Acid Metabolism

In humans, UA is the end-product of the oxidative breakdown of purine nucleotides. There are two sources of purines: (1) senescent cells and the breakdown of their nucleic acids; and (2)diet: purine-rich food, urate molecules, and dietary fructose. In mammals except for primates, UA is further oxidized in the liver by UA oxidase (uricase), converting it to allantoin. Unlike UA, allantoin is a nontoxic, highly soluble substance easily eliminated in the urine. During evolution, most primates, including humans, lost the ability to oxidize UA due to the loss of uricase activity. As a consequence, UA became the terminal waste product of purine metabolism.

Purines (adenine, inosine, and guanine) are nucleic bases derived from the nucleotides adenylate (AMP) and guanylate (GMP) breakdown and are produced endogenously and derived from dietary sources. Red meat (beef, lamb, etc.) and organ meat (e.g., liver and kidney) are particularly rich in purines, and so is seafood (tuna, sardines, shrimp, etc.). Purines are also found in alcoholic drinks, especially beer. Vegetables (asparagus, cauliflower, brussel sprout, etc.) contain much lower amounts of purines than animal sources. Purines can also be generated in the course of fructose metabolism. Therefore, fructose-rich food tends to promote endogenous UA production. Also, prolonged hyperglycemia can, via the polyol pathway, stimulate endogenous fructose production and its subsequent metabolism, increasing the production of purines and UA. Evidence is mounting that the negative influence of fructose on metabolic health is due primarily to its ability to cause ATP depletion, nucleotide turnover, and UA production.[3,4] The liver is responsible for most (>80%) of UA production. At the same time, the small intestine makes a more minor but significant contribution (►**Fig. 1**).

The metabolic pathway from nucleotides to UA involves several enzymatic reactions starting with nucleotidase and the conversion of the AMP and GMP to the nucleosides adenosine and guanosine. A specific phosphorylase converts guanosine to guanine, while adenosine must first be deaminated to inosine before it is converted to hypoxanthine by nucleotide phosphorylase. The remaining two reactions are catalyzed by xanthine oxidoreductase (XOR), which is made up of xanthine dehydrogenase (XDH) and xanthine oxidase (XO). XDH converts hypoxanthine to xanthine, while XO catalyzes the final step converting xanthine to UA (►**Fig. 2**). XOR is expressed in the liver and the intestine. When released into the plasma, it is converted to XO. The two drugs used to lower serum urate levels, allopurinol, and febuxostat, are both inhibitors of OX.

The enzymatic activity of XOR is particularly elevated in the liver, intestine, and vascular endothelium. Furthermore,

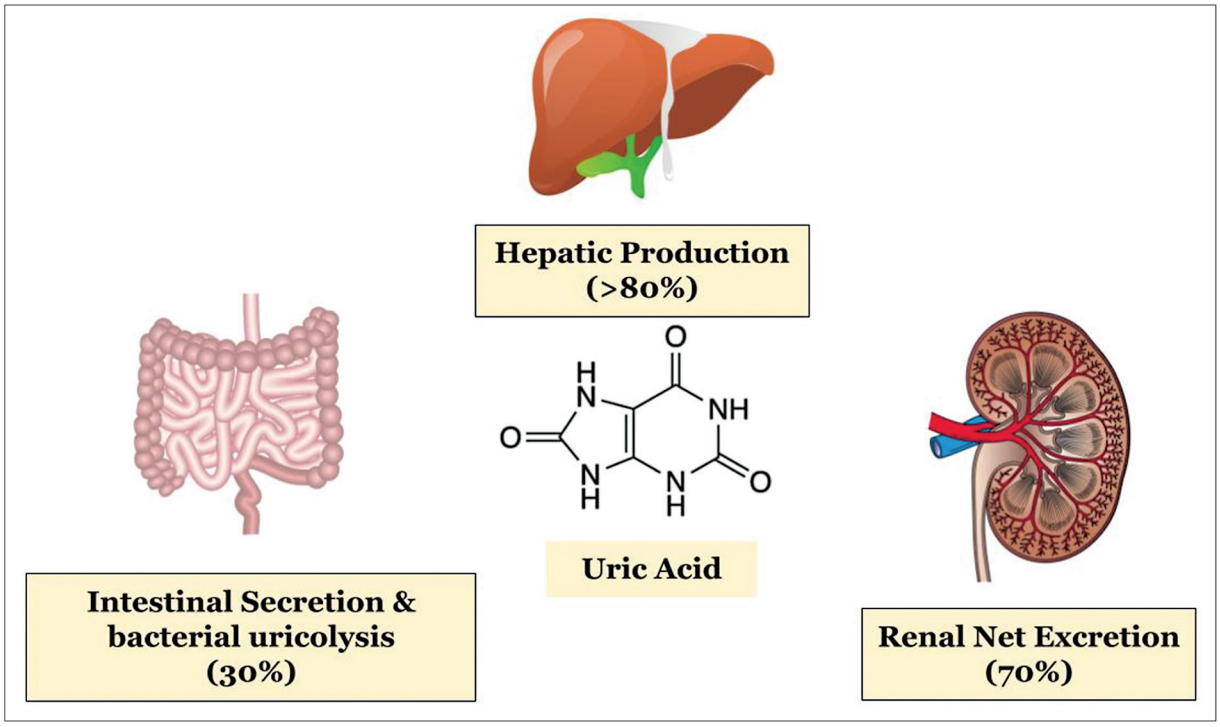

Fig. 1 Production and elimination of uric acid. The liver produces most of it, but the intestine contributes significantly to its production (<20 %). The kidneys eliminate nearly 70% of the daily uric acid production. The intestine is responsible for eliminating about 30%. In the intestine, uric acid is broken down by the resident bacteria (urinalysis).

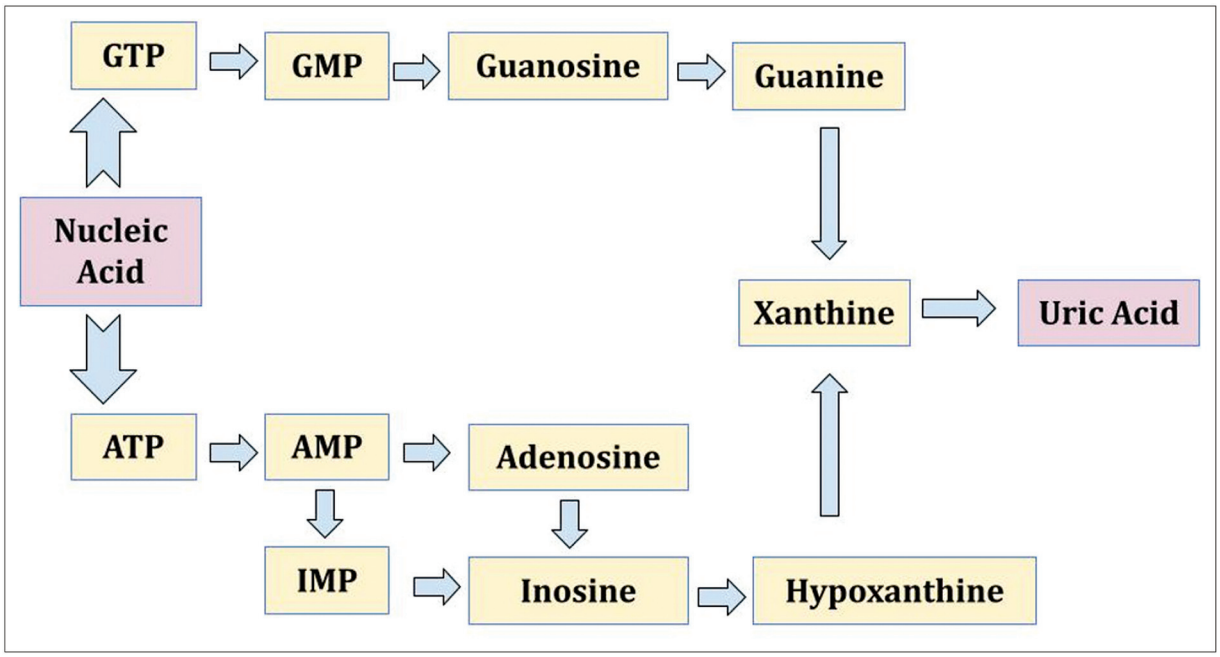

Fig. 2 The purine nucleotide pathway: the sequence of enzymatic reactions breaking nucleotides into uric acid. The key enzyme in this pathway is xanthine oxidase catalyzing the final step. Here is a list of the reactions and the corresponding enzymes:

A. From Guanosine Triphosphate (GTP) to uric acid:
1. GTP to guanosine diphosphate (GDP): Nucleoside Triphosphate Diphospho-hydrolase (NTPDase)
2. GDP to guanosine monophosphate (GMP): Nucleoside Diphosphate Kinase (NDPK)
3. GMP to guanosine: 5′-nucleotidase
4. Guanosine to guanine: Purine Nucleoside Phosphorylase (PNP)
5. Guanine to xanthine: Guanine Deaminase (aka, guanase)
6. Xanthine to uric acid: Xanthine oxidase

B. From Adenosine Triphosphate (ATP) to uric acid:
1. ATP to adenosine diphosphate (ADP): Nucleoside Triphosphate Diphospho-hydrolase (NTPDase).
2. ADP to adenosine monophosphate (AMP): Nucleoside Diphosphate Kinase (NDPK)
3. AMP to adenosine: 5′-nucleotidase
4. Adenosine to inosine: Adenosine Deaminase (ADA)
5. Inosine to hypoxanthine: Purine Nucleoside Phosphorylase (PNP)
6. Hypoxanthine to xanthine: Xanthine Dehydrogenase (XDH)
7. Xanthine to uric acid: Xanthine Oxidase (XO)

the reactions catalyzed by the XOR enzymes are accompanied by the production of two major reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), and the free radical superoxide anion ($O_2^{\bullet -}$). Thus, the potential for oxidative stress is particularly elevated in these tissues. These observations lend support to the suggestion that oxidative stress and the accompanying inflammation and mitochondrial and endothelial dysfunctions may explain the association between elevated UA and several chronic conditions, including chronic inflammation, metabolic syndrome, cardiovascular disease (CVD), hypertension (HTN), and chronic kidney disease (CKD). These associations and related mechanisms will be expanded further below.

The Renal Handling of Uric Acid

UA is a weak acid with two dissociable protons. In other words, it is a diprotic acid with two pKa values: at 37°C, $pKa_1 = 5.35$, and $pKa_2 = 10.3$. Consequently, at the normal pH of extracellular fluid (ECF) of 7.4, over 99% of UA in the ECF exists as the anion urate. This percentage drops dramatically in the renal tubular fluid, especially in the distal tubules and collecting ducts, as the medium becomes more acidic. As the urine pH falls, more filtered urate becomes the undissociated form of UA, which is markedly less soluble in water than urate. Therefore, the lower the urine pH, the greater the tendency for UA to precipitate, forming kidney stones. UA begins to crystallize when the pH falls below 5.75. In plasma, under physiological conditions (37°C; pH 7.4), the solubility of urate is several times higher than that of the undissociated form of UA, but both solubilities are relatively low (approximately 400 vs. 75 mg/dL). Thus, in the case of severe hyperuricemia (serum levels $>$ 7.5 mg/dL or $>$450 micromoles/L), both urate and UA tend to precipitate, the first as urate crystals in the joints and the second mostly as kidney stones. Gout typically emerges when the serum urate level exceeds 6.8 mg/dL (360 µmol/L), and its prevalence rises with increases in serum urate above this threshold. Thus, hyperuricemia is defined as serum urate concentration $>$6.8 mg/dL.

UA homeostasis depends on the balance between its production and elimination rates. Its production (often

referred to as load or burden) is dictated primarily by the rate of purine catabolism, which may vary from one individual to another but is relatively constant for each individual. Thus, UA balance depends primarily on its elimination rate. The kidneys eliminate approximately two-thirds, while the gastrointestinal tract eliminates one-third of the daily UA load. Under normal conditions (pH = 7.4; 37°C), virtually all of the UA in the circulation exists as urate anions, and over 95% of the circulating urate exists free (not bound to plasma proteins), and the remainder (<5%) is bound almost exclusively to albumin.[5] Therefore, virtually all the urate in the plasma is freely filterable at the glomerulus level. As the tubular fluid flows along the renal tubules, urate ions are transported in both absorptive and secretory directions, with the balance determining the amount that is ultimately excreted in the urine, thereby regulating its level in circulation. The renal handling of urate is a complex process involving multiple transporters located in the proximal tubules' luminal and antiluminal aspects. Regulation of these transporters is critical for maintaining homeostasis and preventing the development of hyperuricemia and associated disorders.

Given the relatively high pH in the ultrafiltrate, most of the UA in the proximal tubule fluid exists as the urate anion, as is the case in plasma. Current evidence indicates that most urate transport (both reabsorption and secretion) takes place almost exclusively in the proximal tubule, with almost all of the reabsorption occurring in the early (S1) segment and secretion in the more distal (S2) segment of the proximal tubule. However, there is also the suggestion that both reabsorption and secretion may co-occur in the same segment. The concept of postsecretory reabsorption occurring in the late proximal tubule is becoming increasingly questionable for lack of convincing evidence.[6] The net result of the activity of the various transporters is that only about 10% of the filtered urate ends up in the urine, with the remaining 90% reabsorbed back into the circulation.

Urate transport in the proximal tubule is best described as a tertiary active transport process driven ultimately by the active reabsorption of Na^+. The process begins with the Na^+/K^+-ATPase activity in the basolateral membrane generating the Na^+ gradient across the cell membrane (primary active transport). This gradient drives many Na^+-coupled organic anion transporters (secondary active transport) in the apical (aka luminal or brush-border) membrane. These transporters, in turn, provide the driving force for urate reabsorption. The primary transporter responsible for translocating urate anions across the apical membrane (lumen ⇨ cell interior) is the urate-anion exchanger (URAT1), which mediates the exchange of urate for organic monocarboxylate anions such as lactate. On the basolateral side, GLUT9 is the primary transporter responsible for transferring the urate anions from the cell interior to the peritubular fluid (ICF ⇨ ISF). BCRP (encoded by ABCG2), an essential apical transporter, carries the urate anion in a secretory direction (ICF ⇨ lumen). Genetic variations can affect the transport activity of BCRP and, consequently, urate levels in the body fluids. Specific variants of the BCRP gene have been associated with an increased risk of gout, while others have been linked to a reduced risk.[7] At least half a dozen additional transport proteins have been identified, including OAT4 and OAT10, but they appear to play a minor role in urate homeostasis. Rare genetic mutations that result in the inactivation of URAT1 can lead to a dramatic drop in renal urate reabsorption and a corresponding rise in its fractional excretion (from the normal level of about 10% to as high as 90%), resulting in marked hypo-uricemia (serum urate ⍂ 1 mg/dL). GLUT9 (encoded by SLC2A9) is a member of a large and widely distributed family of proteins dedicated to transporting hexoses such as glucose and fructose.[8] It is expressed in many tissues but mainly in the kidney, liver, and intestine. Despite its name, GLUT9 is not known to participate significantly in glucose transport. It is almost exclusively dedicated to transporting urate anions and fructose to a lesser extent. Loss-of-function mutation in SLC2A9 leads to a marked drop in urate reabsorption, a marked increase in its secretion, and a dramatic drop in serum level, as observed in some cases of familial hypo-uricemia.[9]

The Role of Uric Acid in the Pathogenesis of Disease

The functional significance of UA beyond its role in purine catabolism has been debated for decades and remains uncertain. However, the association between hyperuricemia and human diseases has been recognized since the 1800s.[2]

The normal range of serum UA (or urate) level in adults can vary slightly depending on the laboratory and the method used for the measurement. However, the generally accepted normal range in adult males is 3.4 to 7.2 mg/dL, while for adult females, 2.4 to 6.0 mg/dL. It is important to note that, like glucose, UA levels can fluctuate throughout the day, influenced by diet, medication, and medical conditions. The review defines relative hyperuricemia as a serum UA level >6.4 mg/dL and severe hyperuricemia as a UA level >7.0 mg/dL.

Elevated serum UA level is commonly observed in patients with metabolic syndrome. It is widely accepted as a significant risk factor for gout, kidney stones, HTN, non-alcoholic fatty liver disease (NAFLD), CKD, and CVD.

From a pure chemical standpoint, at least in the extracellular environment, UA may be regarded as an antioxidant. At relatively low levels (<6 mg/dL), UA is thought to exert a protective antioxidant effect, particularly in the plasma and interstitial fluid. It is believed to account for nearly half the antioxidant capacity in the plasma. This property has given rise to an evolutionary perspective. It is believed that primates, including homo sapiens, had gradually lost the ability to break down UA due to a series of genetic mutations that ultimately led to the complete loss of uricase (UA oxidase) activity. The uricase mutations occurred after and perhaps as a compensatory adaptation to the loss of another key enzyme, L-gluconolactone oxidase, that is responsible for the ability to synthesize ascorbic acid (vitamin C) endogenously, a potent antioxidant.[10,11] Because UA is a significantly weaker antioxidant than vitamin C, much higher concentrations of UA would be required to compensate for the

absence of endogenous vitamin C. This was achieved by losing uricase activity and the resultant buildup of UA levels in body fluids. Although this narrative sounds plausible, it still needs more definitive evidence.

Further, it is now well established that under certain conditions in the intracellular environment, UA acts as a prooxidant agent.[12] Thus, UA is best thought of as a redox agent, acting as an antioxidant under certain conditions and as prooxidant under a different set of conditions. A rise in serum UA level is often observed together with oxidative stress and chronic low-grade inflammation, conditions that are, in turn, linked to multiple chronic diseases other than gout and nephrolithiasis. These include CVD, HTN, CKD, and most features of the metabolic syndrome (obesity, insulin resistance, etc.)[13,14] The association of hyperuricemia with these disorders has been documented in both children and adults.

Uric Acid and Oxidative Stress

Oxidative stress occurs when the production of ROS overwhelms the body's antioxidant defenses, leading to an excess of ROS that can cause damage to cellular components such as DNA, proteins, and lipids. ROS are highly reactive molecules generated during normal metabolic processes but can also be produced in response to environmental stressors such as radiation, toxins, or infections.[15,16] ROS are highly unstable, powerful oxidizing agents. They can, over time, damage tissues, causing inflammation, cell dysfunction or cell death, and disease. UA increases ROS production and, at the same time, limits the body's antioxidant defenses. $O_2^{\bullet -}$ is produced during purine metabolism and UA production. It is also formed through an autooxidative process when UA is exposed to XO. While XDH uses NAD^+ to oxidize substrates producing NADH, XO oxidizes substrates using O2 and producing H_2O_2 plus the $O_2^{\bullet -}$. The activity of XO is enhanced by NADPH oxidase (NOX), a powerful ROS-generating complex of multiple enzymes that catalyze the transfer of electrons from NADPH to oxygen, producing $O_2^{\bullet -}$:

$$NADPH + 2\ O_2 \rightarrow NADP^+ + 2\ O_2^{\bullet -} + H^+$$

The NOX enzymes can also catalyze the dismutation of the $O_2^{\bullet -}$, generating H_2O_2: $2\ O_2^{\bullet -} + 2\ H^+ \rightarrow H_2O_2 + O_2$. The H_2O_2 thus generated can react with the ferrous ion (Fe^{++}) to produce other ROS such as the hydroxyl radicals ($OH^{\bullet}$):

$H_2O_2 + Fe^{++} \rightarrow OH^{\bullet} + OH^- + Fe^{+++}$. Both $O_2^{\bullet -}$ and H_2O_2 are powerful oxidizing agents produced in several hot spots in the cell, including the mitochondria and the endoplasmic reticulum (ER). ROS and associated oxidative stress can damage lysosomes impairing their function (the breakdown of cellular waste and recycling of cellular components), resulting in the accumulation of cellular debris.

In the endothelial cells of blood vessels, XO is the predominant form of XOR, and through the production of ROS, it is thought to promote inflammation and the formation of atherosclerotic plaques.[17] UA increases mitochondrial ROS production and oxidative stress, which can promote mitochondrial dysfunction and can also interfere with protein folding in the ER triggering the unfolded protein response.[18] Besides promoting ROS production, UA impairs the body's antioxidant defenses by inhibiting superoxide dismutase and glutathione peroxidase. Also, UA tends to stimulate the production of specific cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNFα), that activate inflammatory pathways, further promoting ROS generation and developing inflammatory diseases. Further, UA promotes hepatic fat accumulation via the ROS/JNK/AP-1 pathway,[19] leading to NAFLD and metabolic syndrome.

Uric Acid and Inflammation

The exact mechanism by which UA causes inflammation has yet to be understood entirely. However, when the hyperuricemia is severe enough to trigger gout and/or kidney stones, urate crystals activate the immune system and trigger the release of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α. These cytokines promote the influx of immune cells like neutrophils and macrophages to the site of tissue injury, triggering an inflammatory response. The NLRP3 inflammasome, which stimulates the production of proinflammatory cytokines, is thought to mediate the activation of the immune system. UA can bind to and activate the NLRP3 inflammasome, leading to the release of cytokines, which then trigger inflammation.[20,21] More recent findings suggest that the activation of the NLRP3 inflammasome may be triggered at levels of UA well below the threshold of hyperuricemia.

UA can also trigger inflammation by activating the toll-like receptors (TLRs), protein macromolecules that play a vital role in the immune system's response to pathogens. However, endogenous ligands can also activate these receptors, such as UA.[22,23] Activation of TLRs can lead to the production of proinflammatory cytokines and the recruitment of immune cells to the site of inflammation.

In addition, a significant bridge between UA and inflammation is provided by oxygen radicals. The ROS produced during UA metabolism can trigger several signaling pathways promoting inflammation in various body parts, thereby promoting the development of inflammatory disorders, including CVD and metabolic syndrome.

Uric Acid and Insulin Resistance

Chronically elevated UA level is linked to obesity and metabolic syndrome, a cluster of biochemical and clinical abnormalities including abdominal obesity, HTN, elevated triglyceride level, low high-density lipoprotein, and elevated fasting blood glucose level.[24–26] It is mainly associated with insulin resistance, a condition in which the cells do not respond adequately to insulin, leading to persistently high blood glucose levels. Thus, with environmental exposure, individual lifestyle habits, and genetic predisposition, elevated UA is considered a significant risk factor for developing obesity, fatty liver, insulin resistance, and type 2 diabetes (T2D). While the exact mechanism by which UA contributes

to the development of insulin resistance is not entirely understood, several possible pathways have been proposed, including inflammation, oxidative stress, and endothelial dysfunction. Also, UA can directly interfere with the insulin receptor and downstream signaling molecules, leading to impaired glucose uptake and metabolism. The inflammatory response triggered by relative hyperuricemia can impair insulin signaling. Oxidative stress caused by ROS can cause oxidative damage to cellular components, including proteins, impairing the insulin signaling pathway, and contributing to insulin resistance. Endothelial dysfunction can cause a drop in nitric oxide (NO) production reducing blood flow to insulin-sensitive tissues, further exacerbating insulin resistance.[26]

Uric Acid and Essential (Primary) Hypertension

Studies in humans have documented elevated serum UA levels years before the onset of HTN, obesity, T2D, and CKD.[4] Pilot studies under various conditions showed improvement in blood pressure following reductions in serum urate levels.[24] A recent study in a Chinese hospitalized population demonstrated a dose–response relationship between serum urate level and HTN.[27] Cross-sectional studies and clinical trials in children with essential HTN showed a close association between elevated UA and new-onset essential HTN. Further, lowering UA levels with allopurinol or febuxostat appears to lower BP, at least in some patients.[28]

Several mechanisms through which UA may induce HTN have been proposed mainly based on laboratory studies involving mostly rodents or isolated cells. (1) Endothelial dysfunction: elevated serum urate can interfere with NO generation reducing its bioavailability. This may increase oxidative stress, vascular endothelial cell dysfunction, vasoconstriction, and elevated blood pressure.[29,30] (2) Renal vasoconstriction: UA may directly cause renal vasoconstriction, reducing renal blood flow and contributing to the activation of the renin-angiotensin-aldosterone system (RAAS). This can lead to increased sodium retention, ECF volume expansion, and ultimately, HTN.[31](3) Activation of the renin-angiotensin system: UA may directly stimulate the production of renin and angiotensin II, which can lead to renal vasoconstriction, sodium retention, and HTN.[32] (4) Inflammation: the inflammation associated with high serum urate can lead to vascular damage, arterial stiffness, and, ultimately, HTN.[33]

Uric Acid and Chronic Kidney Disease

CKD is when the kidneys gradually lose function over time. CKD is a common and serious health problem affecting millions of people worldwide. Many factors can contribute to the development of CKD, including high blood pressure, diabetes, and other medical conditions. Recent studies have suggested that UA may also play a role in the development and progression of CKD.[34,35] Like the case of HTN, several mechanisms are thought to mediate the role of UA in the progression of CKD. Elevated serum urate level can trigger an inflammatory response in renal tissue leading to the release of proinflammatory cytokines and chemokines, causing renal injury and promoting fibrosis. UA-induced tubular damage and interstitial fibrosis can lead to a decline in kidney function. This process is associated with activating the renin-angiotensin system and increased expression of inflammatory markers. While the inflammatory response is easily triggered by the tissue injury caused by the accumulation of urate crystals, there are also crystal-independent mechanisms, such as activation of the renin-angiotensin system, increased oxidative stress, and endothelial dysfunction. In addition to its effects on the tubules, UA may also contribute to CKD through its effects on the blood vessels in the kidneys. UA has been shown to impair endothelial function and promote oxidative stress, which can contribute to the development of atherosclerosis and other vascular diseases. These processes can lead to vasoconstriction of the renal blood vessels, glomerular HTN, reduced renal blood flow, and a decline in kidney function. Ultimately this leads to the kidney's inability to process the ultrafiltrate, regulate the composition of body fluids, and excrete waste products, leading to a buildup of toxins in the body and the development of CKD. Finally, some studies have suggested that the main contribution of UA to the development and progression of CKD is through its effects on inflammation and fibrosis, which are processes involved in the development of kidney damage. As stated above, UA has been shown to promote the production of pro-inflammatory cytokines and the activation of the RAAS, both of which can contribute to renal inflammation and fibrosis. Inhibiting XOR activity with allopurinol and febuxostat can reduce UA production and ROS generation, slowing CKD progression and improving kidney function.[36,37]

Conclusions

UA is no longer regarded solely as the culprit behind the excruciating pains of gout and kidney stones. Due to its ability to induce oxidative stress and trigger inflammation, it is now being investigated as a potentially critical risk factor for several chronic diseases, including obesity, insulin resistance, T2D, NAFLD, HTN, CKD, and CVD. The kidney is responsible for excreting over 70% of the daily load of UA. The remainder is secreted into the intestine, where the gut bacteria degrade it. Virtually all urate reabsorption occurs in the early segment of the proximal tubule (S1), and URAT1 and GLUT9 are the principal transport proteins responsible for their reabsorption. Some secretory activity also occurs in the proximal tubules, carried out by the BCRP transporter in the apical membrane.

Typically, the net result of the various transport activities is that the amount of UA excreted in the urine is equivalent to about 10% of the filtered load. UA transporters are subject to genetic variations, which can affect their circulating level and may lead to reduced elimination and the development of diseases, including gout. Drugs are currently being used to treat symptomatic and asymptomatic hyperuricemia to

reduce the burden of chronic diseases. Most of these treatments are still experimental, and further clinical trials are needed. Rare mutations can also lead to enhanced elimination via the kidneys and/or the small intestine and the development of hypouricemia.

Compliance with Ethical Principles
No ethical approval is required for the review article type of study.

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Conflict of Interest
None declared.

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