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Uric Acid and Renal Function

Guilherme Ambrosio Albertoni, Fernanda Teixeira Borges and Nestor Schor
*Department of Medicine, Nephrology Division, Federal University of São Paulo
 (UNIFESP)
 Brazil*

1. Introduction

Since the discovery of hyperuricemia as the cause of gout in the early 1800s, hypertension, cardiovascular disease and kidney disease have also been related to increased serum uric acid (UA) levels in subsequent years (Nakagawa et al., 2006); patients with gout had a much higher prevalence of hypertension (25-50%), mild-to-moderate kidney disease (20-60%) (Kutzing & Firestein, 2008) and cardiovascular disease (90%) compared to the general population. However, conflicting results regarding the role of UA as the causative factor in diseases other than gouty arthritis resulted in a shift of interest away from UA. In recent years, uric acid regained the lost popularity due to new findings in a number of disease states including hypertension, renal disease, metabolic syndrome and many more (Feig et al., 2008).

Hyperuricemia arises from excess dietary purine or ethanol intake, decreased renal excretion of UA, or from tumor lyses in lymphoma, leukaemia, or solid tumours (Kutzing & Firestein, 2008). Finally, several drugs alter UA handling by the kidney, for example drug therapy with candesartan (Li et al., 2008) or both loop- and thiazide diuretics, all of which increase the net urate reabsorption (Suliman et al., 2006). In the majority of individuals, hyperuricemia will be asymptomatic, but as UA tends to precipitate in tissues and in other body fluids, persistent hyperuricemia may eventually lead to the accumulation of urate crystals in many places, resulting in either acute painful conditions, like gout/tophaceous gout/gouty arthritis, urolithiasis, or, in severe cases, like tumor lysis syndrome, in acute UA nephropathy (Riegersperger et al., 2011).

In recent years, increased fructose intake, particularly via sweetened beverages, started to attract more attention from the medical community. During the last two centuries, at least in the western world, dietary fructose intake dramatically increased, with corresponding increases in serum UA levels (Feig et al., 2008). The increase in fructose intake and hyperuricemia is now being associated to the development of metabolic syndrome.

Hyperuricemia is associated with an increased risk for developing CKD (Obermayr et al., 2008) and a risk factor for renal dysfunction in patients with rheumatoid arthritis (Daoussis et al., 2009). Retrospective data suggest an influence of hyperuricemia on graft loss after kidney transplantation (Haririan et al., 2010). A screening among 18,020 individuals with chronic kidney diseases (CKD) found a 20.6% prevalence of hyperuricemia. A cross-sectional study in individuals aged over 40 years found 10.5% prevalence of CKD, and among these, 26% were hyperuricemic (Shan et al., 2010). A

multi-center study of 2,145 consecutive patients with essential hypertension found a prevalence of hyperuricemia of 35% in males and 43% in females, and this was associated with elevated serum creatinine levels (Lin et al., 2010). A screening among 5,722 individuals found a 5.4% incidence of chronic kidney disease, and serum UA (sUA) correlated with serum creatinine levels (Chen et al., 2009). A cross-sectional study in 9,375 participants of a health-screening program found 14.5% hyperuricemic individuals (Kuo et al., 2010). A screening study found a higher incidence of end-stage renal disease among hyperuricemic women (Iseki et al., 2004), and a post-hoc analysis in 294 patients initiating renal replacement therapy found that half of these were hyperuricemic with a twofold increase in mortality when UA levels were ≥ 9.0 mg/dL (≥ 535 $\mu\text{mol/l}$) (Suliman et al., 2006).

2. Uric acid metabolism

UA is the end-product of purine nucleotide metabolism in humans. In contrast to many lower vertebrates, humans lack UA oxidase (uricase), an enzyme which further catalyses UA to allantoin, more soluble end product (Sautin & Johnson, 2008). Humans have higher serum UA levels when compared to other mammals due to the lack of uricase (Johnson et al., 2003). UA is primarily excreted via the urine. The balance between dietary intake, endogenous metabolism of purines and the urinary excretion rate of UA determines plasma UA levels (Kutzing & Firestein, 2008).

Almost all serum UA is present in the ionized form, monosodium urate, and only about 5% of urate is protein bound at physiological pH. The definition of hyperuricemia is currently arbitrary and varies from >6 mg/dL ($360\mu\text{mol/l}$) in women and >7 mg/dL ($416\mu\text{mol/l}$) in men, to ≥ 6.5 mg/dL ($387\mu\text{mol/l}$), or to >8.3 mg/dL ($494\mu\text{mol/l}$), regardless of gender. UA levels physiologically and gradually rise during the human lifetime; in female individuals, UA levels additionally rise after menopause (Hak et al., 2008).

Renal handling. Kidneys eliminate two-thirds, and the gastrointestinal tract eliminates one-third of the UA load. Urate is filtered completely at the renal glomerulus. However, the normal fractional excretion of UA is only 8% to 12%. Therefore, postglomerular reabsorption and secretion are the ultimate factors regulating the amount of UA excretion (Gutman et al., 1968; Steele et al., 1973). The proximal tubule is the site of UA reabsorption and secretion. Almost complete reabsorption of urate occurs at the S1 segment of the proximal tubule. However, in the S2 segment of the proximal tubule urate is secreted at a range greater than reabsorption via transporters URAT1, OAT1, -2, and -3, -4, and -10, the multi-drug resistance proteins ABCC4 and ABCG2, and the glucose transporters GLUT 9a and b, and others. Finally, post-secretory resorption occurs at a more distal site of the proximal tubule. Approximately 10% of the filtered urate appears in the urine (Shekarriz et al., 2002).

UA Chemistry. UA is a weak acid with 2 dissociation constants. Two factors contribute to UA solubility: UA concentration and solution pH. However, the solubility of UA in urine is primarily determined by urinary pH. The first pKa of UA is at a pH of 5.5, resulting in the loss of 1 proton from UA and the formation of anionic urate (Finlayson, 1974). The second pKa is 10.3, which has no physiological significance in humans. The supersaturation of urine with UA occurs when urinary pH is less than 5.5. In contrast, at a pH of more than 6.5 the majority of UA is in the form of anionic urate. The solubility of urate salts is affected by the relative concentrations of cations present in the urine. Increased urinary sodium

concentrations promote formation of the monosodium urate complex, which is more soluble than undissociated UA. Urine is frequently supersaturated with sodium urate but stones of this type are infrequent. However, supersaturation with sodium urate may contribute to calcium oxalate stone formation via heterogeneous nucleation.

UA pool. UA may be derived by endogenous or exogenous routes. The endogenous production of UA from purine synthesis, and tissue catabolism under normal circumstances, is relatively constant at 300 to 400mg per day. However, the exogenous pool varies significantly with diet. A diet rich in animal protein contributes significantly to the purine pool and subsequent UA formation by a series of enzymatic reaction involving xanthine oxidase as the final step.

Excretion. Renal excretion is the primary mode of UA clearance, accounting for two-thirds of its elimination. Intestine, skin, hair and nails account for the remaining one-third of UA excretion. In the intestine bacteria catabolise UA into carbon dioxide and ammonia, which are then eliminated as intestinal air or absorbed and excreted in the urine.

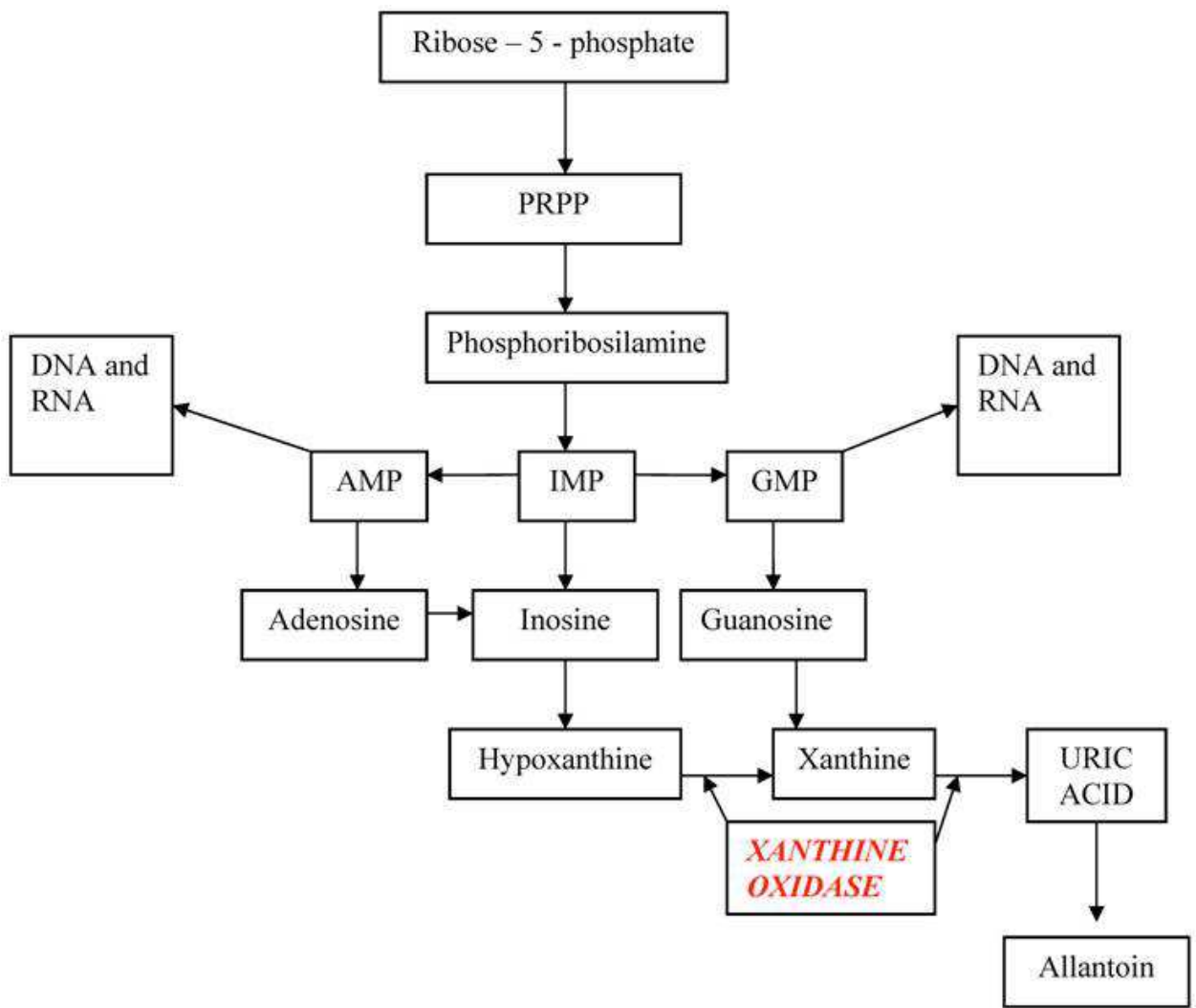


Fig. 1. Schematic representation of the metabolism of Uric Acid

3. Mechanisms of uric acid-induced hypertension

It is well established that when UA is deposited in tissues in the crystalline form, it initiates a proinflammatory state, as seen in gouty arthritis (Sanchez-Lozada et al., 2006). However, the precise pathogenetic role of soluble UA in the serum is somewhat less clear. Moreover, markedly elevated serum UA is clearly associated with gouty arthritis and nephrolithiasis, whereas the importance of subtle elevation in UA levels still remains to be established.

For many years, UA was regarded as a metabolically inert substance. However, several lines of evidence have demonstrated that soluble UA is a strong antioxidant (Ames et al., 1981).

Despite these well-recognized antioxidant effects, UA also behaves as a pro-oxidant and proinflammatory factor. A few points should be emphasized to better understand this apparent paradox. First, UA acts differently inside the cells or in the extracellular milieu, where it is present in soluble form. While being a potent antioxidant in extracellular fluid, UA exerts pro-oxidative effects once inside the cell (Sautin et al., 2007; Corry et al., 2008; Convento et al., 2011).

Second, one isoform of xanthine oxidoreductase – xanthine dehydrogenase – undergoes extensive phenotypic conversion to xanthine oxidase under local ischemic conditions. Unlike xanthine dehydrogenase, xanthine oxidase uses molecular oxygen instead of Nicotinamide Adenine Dinucleotide (NAD) as an electron acceptor (Glantzounis et al., 2005).

In addition to interference with free radical production, UA has some direct effects on endothelial and smooth muscle cells of the vascular wall, which ultimately lead to endothelial dysfunction (Mazzali et al., 2002). In endothelial cells, UA blocks nitric oxide (NO) release, inhibits endothelial proliferation and stimulates C-reactive protein production (Khosla et al., 2005). Several experimental studies also showed that UA can activate smooth muscle cells via activation of specific MAP kinases, nuclear transcription factors, stimulation of cyclooxygenase-2 (Cox-2), and various inflammatory mediators such as the tissue renin-angiotensin system (Corry et al., 2008; Watanabe et al., 2002; Kang et al., 2002). Recent evidence also suggests that hyperuricemia increased cellular proliferation, angiotensin II (AII) and endothelin-1 (ET-1) in human mesangial cells (Albertoni et al., 2010), which could contribute to reduce GFR.

In a landmark study by Mazzali et al., 2001 pharmacologically induced mild-to-moderate hyperuricemia via oxonic acid administration in rats resulted in the development of hypertension. Conversely, when UA elevation was treated with allopurinol or with a uricosuric agent, development of hypertension could be prevented. Other experimental studies show that at a concentration of 10 mg/dL UA significantly decreases the production of ET-1 in mesangial cells after 24h of treatment. This effect was blocked by Losartan (LOS), an AII receptor type 1 antagonist (Albertoni et al., 2010).

It is also possible that genetic polymorphisms of transporters or enzymes involved in UA metabolism affect blood pressure, especially in younger subjects. For example, hypertension has been associated with polymorphisms of xanthine oxidoreductase (Chaves et al., 2007).

4. Uric acid and acute renal failure

Uric acid, as the end-product of purine metabolism in humans, presents a clinical impact since it has a relative insolubility, particularly in the acidic environment of the distal nephron. As a result, states of enhanced purine catabolism increases the urate load on the kidney, leading to intrarenal precipitation. Major causes of increases on purine metabolism

are malignancies with rapid cell turnover, such as leukemia and lymphomas, and the added acceleration of cell lyses that occurs with chemotherapy and radiation. Serum urate levels rise rapidly, and acute renal failure occurs as a consequence of tubular deposition and obstruction of urate and uric acid. The keys to the diagnosis of acute uric acid nephropathy are the appropriate clinical settings as cell lyses increases, oliguria, marked hyperuricemia, and hyperuricosuria. A urinary uric acid-to-creatinine ratio greater than 1 helps to distinguish acute uric acid nephropathy from other catabolic forms of acute renal failure in which serum urate is elevated. Preventive treatment involves pharmacologic xanthine oxidase inhibition with allopurinol and alkaline diuresis. Occasionally, acute renal failure occurs despite allopurinol due to tubular precipitation of the metabolites precursors, such as xanthine, which accumulate with xanthine oxidase inhibition. Dialysis therapy may be required both to correct azotemia and to reduce the body burden of urate. Hemodialysis is preferred since it can achieve greater clearance than other dialysis modes. (Conger, 1990).

5. Uric acid and kidney disease

Association of UA with chronic kidney disease dates back to 1890s. Any functional decline which reduces glomerular filtration rates (GFR) and tubular reabsorption secondarily leads to UA elevation, but also the decrease in glomerular filtration rate can increase serum UA (Feig, 2009). To determine which comes first was the principal endeavor of UA researchers in the last two decades.

Experimental studies performed by Mazzali et al., 2002, demonstrated that hyperuricemic rats developed hypertension, afferent arteriopathy, glomerular hypertrophy, and increased glomerular pressure, tubulointerstitial damage and macrophage infiltration (Mazzali et al., 2002; Sanchez-Lozada et al., 2005; Nakagawa et al., 2003).

Several works analyzed the effects of UA in kidney cells and hyperuricemic animal models. Firstly, hyperuricemia induces endothelial dysfunction and inflammation (Yu et al., 2010, Khosla et al., 2005). UA has the ability to increase monocyte chemoattractant protein (MCP-1) in cultured vascular smooth muscle cells (Kanellis et al., 2003) and human proximal tubular epithelial cells (Cirillo et al., 2006). UA can induce the contraction (Albertoni, et al., 2010) and reactive oxygen species produced in mesangial cells (Convento et al., 2011).

6. Uric acid, metabolic syndrome and diabetes

The relationship between hyperuricemia, hypertension, and the metabolic syndrome has long been debated. Are the conditions different manifestations of a common underlying metabolic disorder? Is hyperuricemia in part responsible for hypertension? Recent evidences from animal studies and epidemiology suggest that hyperuricemia has a primary role in both hypertension and the metabolic syndrome. Rats that were made hyperuricemic rapidly developed hypertension through activation of the renin-angiotensin system, induction of endothelial dysfunction, and vascular smooth muscle proliferation. Lowering UA in these animals prevented this effect (Johnson et al., 2005). In a longitudinal study in children, there was a strong correlation between hyperuricemia and the subsequent development of hypertension (Feig et al., 2006). Recent epidemiological data suggest also that hyperuricemia is an independent risk factor for developing hypertension. In a group of subjects who did not have the metabolic syndrome, normotensive men with baseline hyperuricemia had 80% more risk of develop hypertension compared with those who did not have hyperuricemia (Krishnan

et al., 2007). Finally, the degree of hyperuricemia is strongly correlated with the prevalence of the metabolic syndrome (Yoo et al., 2005; Choi et al., 2007; Facchini et al., 1992).

Metabolic syndrome has many components which may independently mediate or lead to kidney damage, including increased inflammation (Calabro & Yeh, 2008), insulin resistance and endothelial dysfunction (Kim et al., 2006). Additionally, diets high in fructose constitute one of the major predisposing factors for the metabolic syndrome epidemic (Cirillo et al., 2006). Fructose is unique among sugars by its ability to rapidly deplete ATP, with resultant purine nucleotide degradation and eventual UA generation.

Experimental studies in rodents have suggested that UA may contribute to the development of the metabolic syndrome, hypertension, and kidney disease (Feig et al., 2008) and recently clinical studies focusing on UA and the development and progression of diabetic kidney disease have been published (Hovind et al., 2011). In the early report of the Modification of Diet in Renal Disease Study (Hunsicker et al., 1997), UA was not found to be an independent predictor for renal disease. Others large epidemiologic studies have revealed conflicting results in this respect. While the majority (Iseki et al., 2001; Domrongkitchaiporn et al., 2005; See et al., 2010; Chang et al., 2010; Obermayr et al., 2008) of these studies suggest an independent predictive role for UA in renal disease, others (Tomita et al., 2000; Sturm et al., 2008; Madero et al., 2009) argue against it.

Historically, the elevated level of UA observed in the metabolic syndrome has been attributed to hyperinsulinemia, since insulin reduces renal excretion of UA (Quinones et al., 1995).

Hyperuricemia, however, often precedes the development of hyperinsulinemia (Nakagawa et al., 2005; Carnethon et al., 2003), obesity (Masuo et al., 2003), and diabetes (Nakanishi et al., 2003; Dehghan et al., 2008; Chien et al., 2008). Hyperuricemia may also be present in the metabolic syndrome in people who are not overweight or obese.

The strongest evidence of a role for UA in the development of the metabolic syndrome has been from studies models showing that decreasing UA levels can prevent or reverse features of the metabolic syndrome (Nakagawa et al., 2006; Sanchez-Lozada et al., 2008; Reungjui et al., 2007). Two mechanisms have been suggested to explain how hyperuricemia might induce the metabolic syndrome. The first mechanism is related to the fact that glucose uptake in skeletal muscle depend in part on increases in blood flow mediated by the insulin-stimulated release of NO from endothelial cells. Features of the metabolic syndrome develop in mice lacking endothelial nitric oxide synthase (eNOS) (Cook et al., 2003). The observations that hyperuricemia can induce endothelial dysfunction in rats (Khosla et al., 2005) and that treatment with allopurinol can improve endothelial function in patients with hyperuricemia (Mercuro et al., 2004) would support this mechanism. The second mechanism concerns the inflammatory and oxidative changes UA induces in adipocytes (Sautin et al., 2007), a process that is key in causing the metabolic syndrome in obese mice (Furukawa et al., 2004).

The prevalence of diabetes, and for that matter the associated complications, has increased dramatically. Presently, diabetes is the leading cause of end-stage renal disease in the western world (United States Renal Data System, 2008). Although the progression of renal disease can be halted partially, diabetic nephropathy is still regarded as an irreversible and progressive disease (Parving et al., 2008).

Therefore, it has become increasingly essential to determine the pathophysiological mechanisms underlying the development and progression of diabetic nephropathy. Evidence is available of a complicated interaction between different contributors to the disease process. It is possible that genetic susceptibility, metabolic abnormalities,

hemodynamic changes, upregulated growth factors, and cytokines may all play a part in the development of diabetic glomerulopathy; however, the complex pathogenesis of development of diabetic nephropathy has not been fully clarified (Hovind et al., 2011).

Recently clinical studies focusing on UA, albuminuria and diabetic kidney disease have been published (Bonakdaran et al., 2011; Kim et al., 2010; Kuo et al., 2010). The new evidence suggests that UA could be a risk factor for the development of diabetic nephropathy; however, the significance of serum UA as pathogenic factor in the development of diabetic nephropathy is not yet fully clarified (Hovind et al., 2011).

7. Uric acid stones

A high concentration of urate and low pH are the determinants of UA stone formation. The prevalence of UA stones in the United States is estimated to be 5% to 10% (Gutman et al., 1968). Interestingly, these data originate from studies performed more than 30 years ago. Therefore, the current incidence of UA stones in the United States may be different. In a more recent study from Veterans Administration hospital stone analyses revealed that 12% of stones contained some UA component and 9.7% comprised pure UA (Mandel et al., 1989). Incidence also may vary with age. The incidence of UA stones was 11% in a geriatric population (Gentle et al., 1997). The frequency of UA stones also varies in different geographical locations within the United States. In southern states the incidence has been reported at 4% compared with 17% in Chicago (Riese et al., 1992). Other industrialized countries have wide variations in UA stone rates, with Germany reporting 17% to 25%, Sweden 4% and Israel up to 40% (Hesse et al., 1975; Scholz et al., 1979; Grenabo et al., 1985; Atsmon et al., 1963). Urate stones have frequently been reported in Iran and Pakistan. However, the majority of these stones are ammonium acid urate (Minon et al., 1983). These apparent geographical variations indicate that genetic, dietary and environmental factors may have an important role in the formation of UA stones.

Composition and different types of UA stones. UA stones can be classified based on crystalline composition as anhydrous uric acid, uric acid dehydrate, sodium acid urate monohydrate or ammonium acid urate (Halabe et al., 1994). The anhydrous form is thermodynamically the most stable crystal. The dehydrate form is unstable and undergoes dehydration to the anhydrous form. Uric acid dehydrate has been identified in 20% of UA calculi and may represent the entire component. Ammonium acid urate precipitation requires high urate and ammonium concentrations and occurs at a higher pH. Recently, a classification of UA stones based on their crystalline growth pattern has been suggested (Grases et al., 2000).

Mechanism of stone formation. UA stone formation requires supersaturation of urinary UA. Three factors contribute to the formation of these calculi: acidic urine, hyperuricemia and decreased urinary volume. One or more of these conditions may coexist in a specific patient and contribute to stone disease severity (Shekarraz et al., 2002).

Hyperuricosuria. Hyperuricosuria is defined as a mean 24-hour urinary UA excretion of more than 600 mg/24 hr in 2 of 3 collected samples (Pak et al., 1980). Hyperuricosuria may be associated with hyperuricemia, such as in primary gout, or may manifest as an isolated abnormality due to various factors such as diet or medications. The degree of hyperuricemia correlates with the incidence of UA stone formation. In patients with gout the incidence of UA stones was 23% in those with urinary UA levels less than 600 mg/24hr compared with

50% in those with UA levels greater than 1,000 mg/24 hr (Yu et al., 1967). In other study 11% of patients with UA excretion less than 300 mg/24 hr had UA stones (Hall et al., 1967; Katz et al., 1970). In patients with gout the rate of stone formation is higher when uricosuric drugs are administered.

Urinary pH. All conditions contributing to acidic urine promote uric acid stone formation. Urinary pH is abnormally low in a significant number of patients with gout and in idiopathic UA stone formers (Gutman et al., 1968; Yu et al., 1967; Zechner et al., 1982; Ito et al., 1995). Urinary alkalization is the cornerstone of medical management of UA stones. The concept of UA stone dissolution is not new. Shekarritz et al., 2002 observed impressive dissolution of large burden UA renal stones with oral alkalization. UA stone dissolution by oral alkalization is generally effective, with a reported success rate of 80% (Shekarritz et al., 2002). Continued alkalization will help prevent future stones, but in the treatment of gout, alkalization of urine (over pH 6.5) to maintain the solubility may precipitate calcium phosphate crystals (Meyer et al., 1990).

8. Gout

Gout is a disease of ancient origin and its association with UA stones has long been recognized. In 1683 London physician Thomas Sydenham, who suffered from renal stones, described the clinical features of gout. Michelangelo's special interest in anatomy and kidney function has been ascribed to his own urinary stone disease (Eknoyan et al., 2000).

Studies of the composition of urinary calculi were limited before the advent of modern chemistry. Gout is an inflammatory process initiated by tissue deposition of monosodium urate (MSU) crystals. A typical attack is an acute monoarthritis accompanied by classical signs of inflammation. However, inflammation can occur in any tissue in which MSU is deposited, as typified by tophaceous gout and by urate nephropathy due to renal medullary deposition of MSU crystals (So, 2008).

Multiple risk factors may interact and lead to development of gout:

Genetics – Monogenic disorders that result in overproduction of UA via enzyme defects in purine metabolism are extremely rare. Nevertheless, common primary gout in men often shows strong familial predisposition, although the genetic basis remains unknown. Twin studies have show high heritability for both UA renal clearance (60%) and UA: creatinine ratio (87%) and several susceptibility loci for this have been reported (Roddy et al., 2007).

Gender and age – Men have higher urate levels than women and an increased prevalence of gout at all ages, though less pronounced in older age. Estrogens have a uricosuric effect, making gout very rare in younger women. However, after the menopause, urate levels rise and gout becomes increasingly prevalent. Ageing is an important risk factor in both men and women, possibly due to multiple factors including: an increase in sUA levels (mainly due to reduced renal function); increased use of diuretics and others drugs that raise sUA; age-related changes in connective tissues, which may encourage crystal formation (Roddy et al., 2007).

Diet – Historically, gout has long been linked with a rich lifestyle involving excesses of meat and alcohol, but it is only recently that population studies have been undertaken to determine the risk associated with individual dietary components. Data from the large Health Professionals Follow-up Study (HPFS) have show that the relative risk of gout is higher in people who eat a high red meat diet: the relative risk of a first attack of gout associated with an additional daily portion of meat was 1.21 (95% CI 1.04, 1.41). Higher

consumption of seafood was associated with a lesser, but still significant, increase in risk. Diets high in purine-rich vegetables did not increase the risk, while diets high in low-fat dairy products were associated with reduced risk (relative risk with additional daily 0.79; 95% CI 0.71, 0.87) (Choi et al., 2004).

Alcohol – Some alcoholic drinks are rich in purines, notably beer which contains guanosine. Alcohol is thought to increase the risk of gout because the metabolism of ethanol to acetyl CoA leads to adenine nucleotide degradation, resulting in increased formation of adenosine monophosphate, a precursor of UA. Alcohol also raises the lactic acid level in blood, which inhibits UA excretion. In the HPFS, overall the higher the daily alcohol intake, the higher the risk of gout (Choi et al., 2004). However, differences in risk were observed with different alcoholic drinks. Beer had the greatest effect, probably because of its high purine content, then alcohol, whereas wine had no increased risk (Choi et al., 2004).

Drugs – Many drugs which either increase sUA levels (e.g. diuretics and pyrazinamide) or reduces sUA levels (e.g. uricosurics such as benzbromarone, sulphinpyrazone and vitamin C) effect these changes via interaction with urate transporters such as URAT1 (Anzai et al., 2005) and GLUT9 (Caulfield et al., 2008).

RENAL DISEASE AND GOUT – Gout frequently associates with kidney disease, each being a risk factor for the other. Primary kidney disease can lead to hyperuricemia and it has been suggested that the increasing prevalence of end-stage renal disease may be one cause of recent increases in gout (Roddy et al., 2007). Kidney damage secondary to gout is associated with urate crystals and microtophi in the interstitium and/or UA crystals within tubules. Evidence from animal studies suggests that hyperuricemia may accelerate chronic kidney disease, and several studies have demonstrated a significant and independent association between sUA levels and the progression of chronic kidney disease (Kang et al., 2002; Kang et al., 2005). A history of gout is an independent risk factor for urolithiasis in men (Kramer et al., 2003). The increased risk is not just for UA stones, but also for more common calcium phosphate stones. High urinary levels of UA increase the risk of stone formation and in gout patients, the higher the excretion of UA, the greater the risk of stone formation (Yu et al., 1967). However, the most important risk factor for UA stone formation is persistently acidic urine, favoring the precipitation of urate (Shekarritz et al., 2002). In patients with UA stones, a high urinary UA: creatinine ratio indicates overproduction of UA, which should prompt a search for an abnormality of purine metabolism.

9. Advances in therapy of hyperuricemia and gout

The treatment of hyperuricemia and gout remains a challenge even though we appear to have a number of effective drugs. Many clinicians recognize that our existing treatment choices are often limited in the routine clinical setting. Allopurinol, the most commonly used drug to treat hyperuricemia, can provoke severe allergic-type reactions and needs to be used with caution in renal failure. Fortunately, the incidence of these rare reactions is low, but skin rashes are frequently reported (Hung et al., 2005). Benzbromarone, a very effective uricosuric drug, was recently withdrawn from general distribution because of a number of cases of hepatic failure associated with its use. Other hypouricemic drugs are therefore needed. Recently, a new xanthine-oxidase inhibitor, febuxostat, underwent clinical trials and was shown to be as effective as allopurinol in reducing hyperuricemia (Becker et al., 2005). Febuxostat, unlike allopurinol, is not a purine analog and does not cross-react with allopurinol. In clinical trials, when administered at a daily dose of either 80 or 120 mg, it was

more effective than a 300 mg daily dose of allopurinol in achieving the target value of uricemia (less than 6 mg/dL or less than 360 $\mu\text{mol/L}$), a target that has been recommended in treatment guidelines for gout and hyperuricemia (Zhang et al., 2006).

10. Conclusion

It is becoming clear that the role of UA is no longer confined solely to gout and nephrolithiasis. Increasing evidence now points to a significant relation of UA to hypertension and renal disease. Moreover, recent studies have started to unveil the causal nature of this relationship in both hypertension and renal disease. Despite considerable progress, given the numerous confounders, more compelling evidence is needed before ultimately labelling UA as a causative factor in hypertension and renal disease. Persistently acidic urine resulting in supersaturation of UA is the only metabolic abnormality found in many patients with UA stones. Although the mechanism responsible for acidic urine in many patients remains unclear, urinary alkalization is the cornerstone of medical management and should be the primary mode of treatment in the absence of absolute indications for surgical intervention. Furthermore, prophylaxis with urinary alkalization using oral alkali prevents stone recurrence and associated morbidity. Hyperuricemia is the central risk factor for gout and is a key component of the metabolic syndrome, is also an independent risk factor for cardiovascular disease, although at present there is no evidence to support urate-lowering therapy for asymptomatic hyperuricemia. More studies in this exciting and provocative area of research are being conducted and published (Kanbay et al., 2007; 2010; Turgut et al., 2009).

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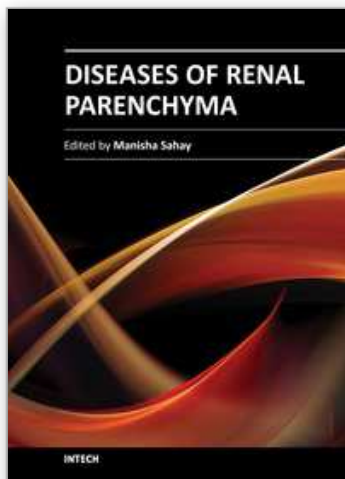
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Clinical nephrology is an evolving speciality in which the amount of information is growing daily. This book gives quick access to some important clinical conditions encountered in nephrology including the diseases of glomeruli, tubules and interstitium. It presents the latest information on pathophysiology, diagnosis and management of important diseases of renal parenchyma. The information is presented in a very user friendly and accessible manner while the treatment algorithms enable the reader to quickly access expert advice on arriving at the most appropriate treatment regimen. The book discusses the renal involvement in various systemic diseases including diabetes and autoimmune diseases. Diabetic nephropathy is fast becoming the commonest cause of end stage renal disease all over the globe and is discussed in this book. The editors believe that this book will be a valuable addition to the reader's library.

How to reference

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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