CHAPTER

61 Hyperuricemia, Gout, and the Kidney

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Uric acid is a weak acid trioxopurine with a molecular weight of 168 that is composed of a pyrimidine and imidazole substructure with oxygen molecules ($C_5H_4N_4O_3$). It is produced during the metabolism of purines, and specifically is generated by the degradation of xanthine by the enzyme xanthine oxidase or its isoform, xanthine dehydrogenase. In most mammals uric acid is oxidized to 5-hydroxyisourate by the hepatic enzyme, urate oxidase (uricase), which is then further hydrolyzed to allantoin.[1] However, during early hominoid evolution (12 to 20 million years ago) a series of mutations occurred, first affecting the promoter region and then the actual gene, eventually rendering uricase nonfunctional.[2,3] As a consequence, serum uric acid levels in humans are higher (3 to 15 mg per dL, 180 to 900 μM) and less regulatable than in most mammals (1 to 3 mg per dL, 60 to 180 μM).[4] Great apes (such as the chimpanzee, gorilla, and orangutan) share the same uricase mutation as humans, and lesser apes (gibbons and siamangs) have a different uricase mutation, but these apes have lower serum uric acid levels (2 to 4 mg per dL, 120 to 240 μM),[4] primarily due to diets relatively low in purines and fructose.

The most well-known consequence of an elevated uric acid in humans is the disease gout, due to the deposition of urate crystals in synovial joints, occasionally with tophi formation. However, there are also a number of renal manifestations associated with elevated uric acid, including the formation of uric acid kidney stones (urate nephrolithiasis), acute urate nephropathy (due to intratubular crystal formation with obstruction), and chronic urate ("gouty") nephropathy. The latter has been historically viewed as occurring as a consequence of interstitial urate crystal deposition with local inflammation; however, there is increasing evidence suggesting this entity may also result from crystal-independent effects of uric acid. There is also the entity of familial juvenile hyperuricemic nephropathy (FJHN), for which the gene responsible has been identified. Recent studies also suggest that uric acid may have a role in other renal diseases and may also have a direct role in mediating intrarenal vascular disease, hypertension, and even the metabolic syndrome. These are all discussed in subsequent text of this chapter.

URATE METABOLISM AND HOMEOSTASIS

Generation of Uric Acid

Uric acid is produced from metabolic conversion of either dietary or endogenous purines, primarily in the liver, muscle, and intestine (Fig. 61.1).[5] Uric acid can also be produced de novo from glycine, glutamine, and other precursors. The immediate precursor of uric acid is xanthine, which is degraded to uric acid by either xanthine oxidase, which generates superoxide anion in the process, or by its isoform, xanthine dehydrogenase, which generates the reduced form of nicotinamide-adenine dinucleotide. Both exogenous purines (such as is present in fatty meat, organ meats, and seafood) and endogenous purines are major sources of uric acid in humans. Approximately two thirds of total body urate is produced endogenously, whereas the remaining one third is accounted for by dietary purines. Purine-rich foods include beer and other alcoholic beverages, anchovies, sardines in oil, fish roes, herring, organ meat (liver, kidneys, sweetbreads), legumes (dried beans, peas), meat extracts, consommé, gravies, mushrooms, spinach, asparagus, and cauliflower.[6] In healthy men, the urate pool averages about 1,200 mg with a mean turnover rate of 700 mg per day.

Excretion of Uric Acid

The primary site of excretion of uric acid is the kidney, with normal urinary urate excretion in the range of 250 to 750 mg per day. Although urate (the form of uric acid at blood pH of 7.4) is freely filtered in the glomerulus, there is evidence that there is both reabsorption and secretion in the proximal tubule, and as a consequence the fractional urate excretion is only 8% to 10% in the normal adult because urate reabsorption dominates oversecretion in the kidney. Some adaptation occurs with renal disease, in which the fractional excretion will increase to the 10% to 20% range. In addition, uric acid is also removed by the gut, where uric acid is degraded by uricolytic bacteria, and this may account for one third of the elimination of uric acid in the setting of renal failure.

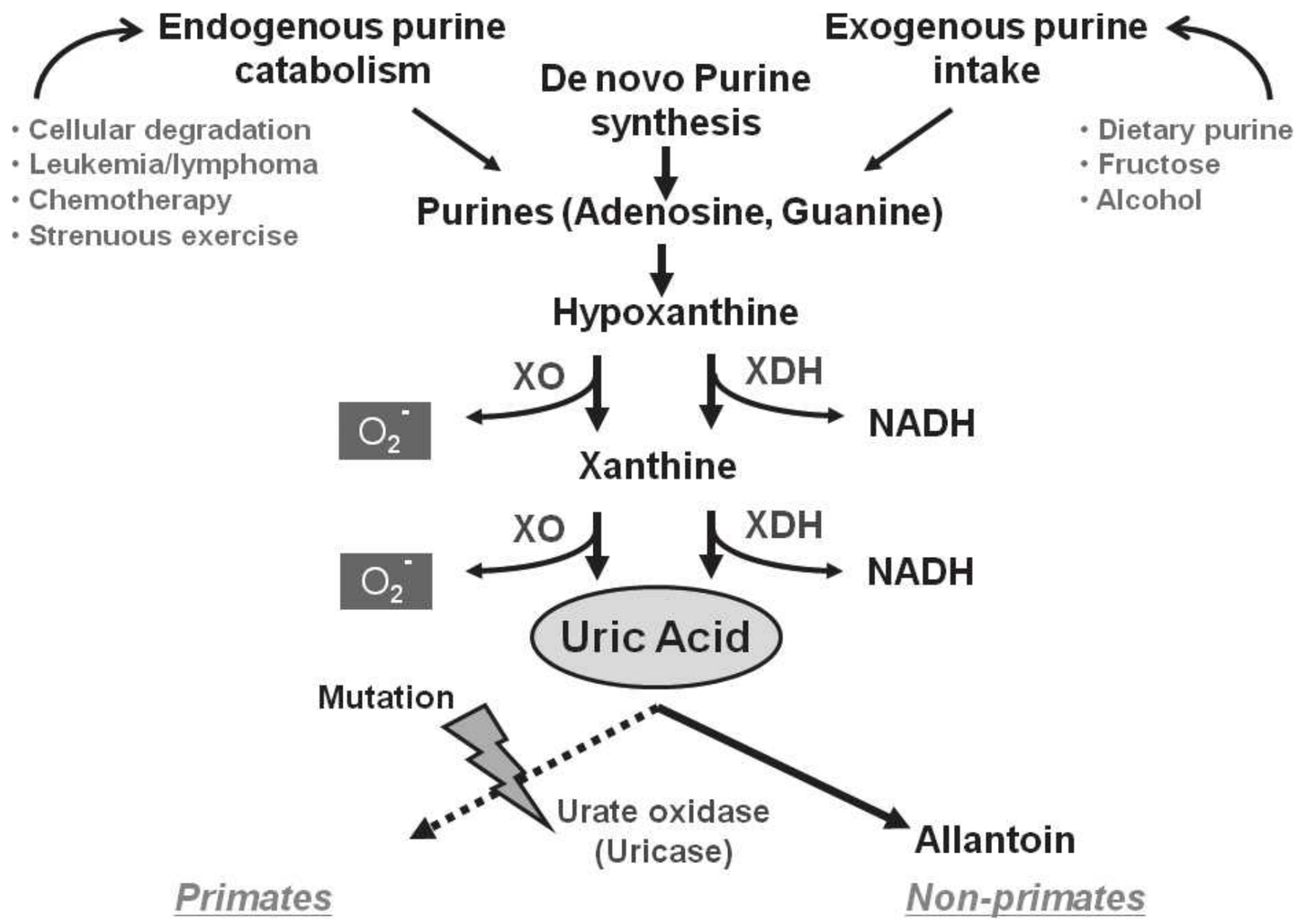

FIGURE 61.1 Urate metabolism.

The historic paradigm of uric acid excretion consists of a four-step model with glomerular filtration, followed by reabsorption, secretion, and postsecretory reabsorption, the latter three processes all occurring in the proximal convoluted tubule.[7,8] However, ideas of the handling of uric acid by the kidney have changed greatly during the last decades, with characterization and isolation of transporters and channels mainly or exclusively restricted to urate transport (Fig. 61.2).[9,10] Membrane vesicle studies have suggested the existence of two major mechanisms modulating urate reabsorption and secretion, consisting of a voltage-sensitive pathway and a urate/organic anion exchanger. Recently several of these transporters/channels have been identified. Organic anion transporters 1–10 (OAT1-10) and the urate transporter-1 (URAT-1) belong to the SLC22A gene family and accept a huge variety of chemically unrelated endogenous and exogenous organic anions including uric acid. Endou's group identified URAT-1, which is encoded by SLC22A12, as the major organic anion exchanger for uric acid on the apical (luminal brush border) side of the proximal tubular cell.[9] In the human kidney, urate is transported via URAT-1 across the apical membrane of proximal tubular cells, in exchange for anions being transported back into the tubular lumen to maintain electrical balance. URAT-1 has a high affinity for urate together with lactate, ketones, a-ketoglutarate, and related compounds. Pyrazinamide, probenecid, losartan, and benzbromarone all inhibit urate uptake in exchange for chloride at the luminal side of the cell by competition with the urate exchanger. OAT-4 exhibits 53% amino acid homology with URAT1.

Urate then moves across the basolateral membrane into the blood by other organic anion transporters, of which the most important is SLC2A9 (also known as GLUT9).[11,12] GLUT-9 is highly expressed in the kidney and liver. GLUT-9L (long isoform) is localized to basolateral membranes in proximal tubule epithelial cells, whereas the splice variant GLUT-9S (short isoform) localizes to apical membranes (Fig. 61.2).[13] Vitart et al.[14] showed that GLUT-9 transports urate and fructose, using a Xenopus oocyte expression system. GLUT-9 deficiency resulted in renal hypouricemia and is consistent with GLUT-9 being an efflux transporter of intracellular urate from the tubular cell to the interstitium/blood space.[15] Efflux transport of urate at basolateral membranes appears to depend principally on GLUT-9L whereas URAT-1 mainly acts as an influx transporter for urate at apical membranes.

OAT-4 and OAT-10 function as an organic anion/dicarboxylate exchanger and are responsible for the reabsorption of organic anions driven by an outwardly directed dicarboxylate gradient.[16] In addition, OAT1 and OAT3 may have a role in the transport of urate from the blood into the proximal tubule.[17,18]

Urate secretion appears to be mediated principally by a voltage-sensitive urate transporter, which is expressed ubiquitously and localizes to the apical side of the proximal tubule in the kidney. Genomewide association studies revealed the region which is related to serum urate concentration.[19] Recently, a novel human renal apical organic anion efflux transporter, called MRP4, has been identified.[20] MRP4 is a member of the ATP-binding cassette transporter family. It is proposed to mediate secretion of urate and other organic anions such as cAMP, cGMP, and methotrexate across the apical membrane of human renal proximal tubular cells. Human MRP4 is an ATP-dependent unidirectional efflux pump for urate with multiple allosteric substrate binding sites.[21] Renal sodium-dependent phosphate transport protein-1 (NPT-1),[22] which was first cloned as a phosphate transporter, is located in the proximal

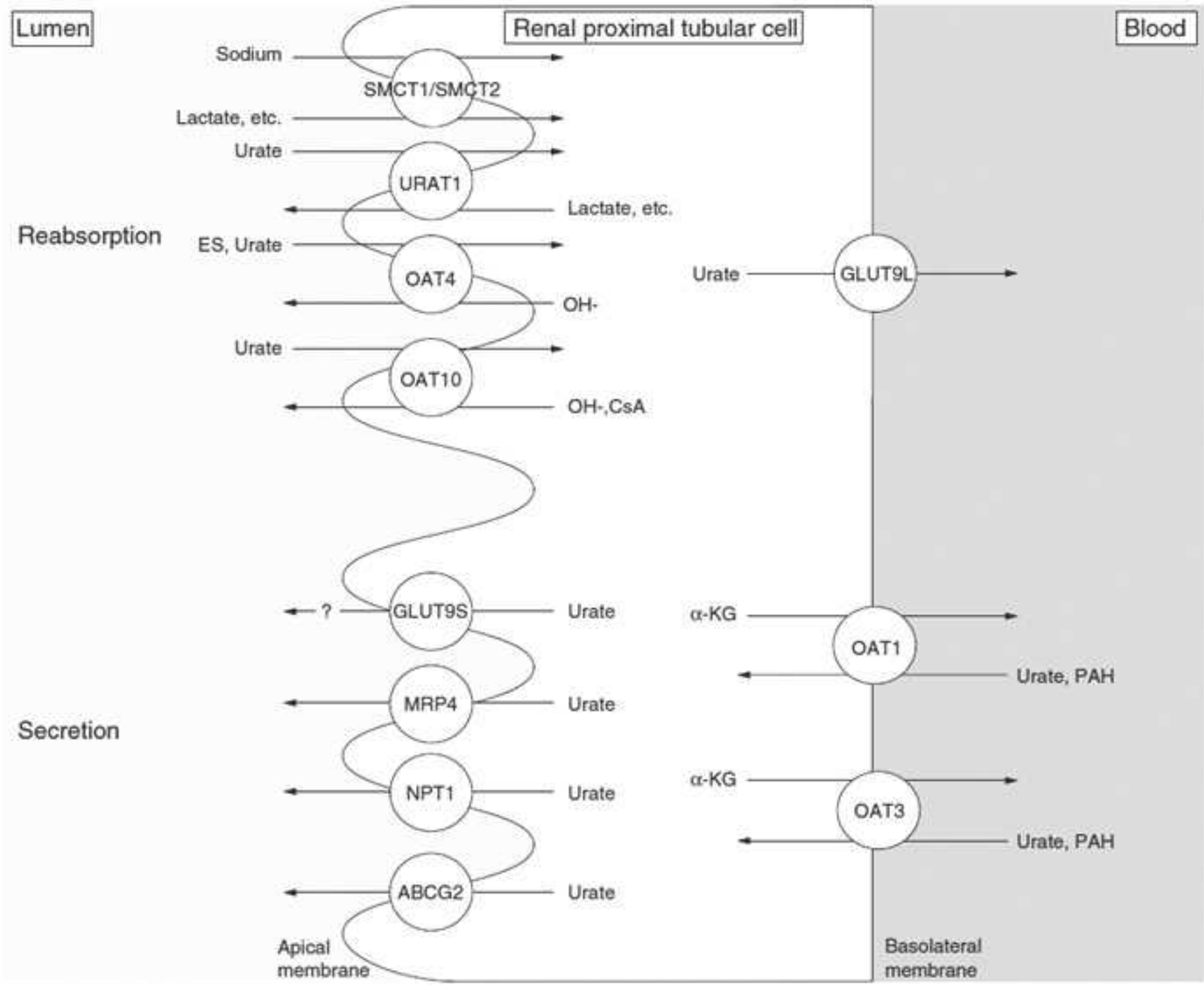

FIGURE 61.2 Urate transport. (From Ichida K. What lies behind serum urate concentration? Insights from genetic and genomic studies. *Genome Med*. 2009;1(12):118.)

convoluted renal tubule (Fig. 61.2). NPT1 mediates voltage-sensitive transport of organic anions, including urate, and is suggested to function as a urate secretor.[23] Another transporter located at the apical membrane of proximal tubules is ATP-binding cassette, sub-family G, member 2 (ABCG2). The ability of ABCG2 to transport urate was recently confirmed by measuring urate efflux from ABCG2-expressing Xenopus oocytes.[24]

Another gene involved in renal transport of urate is Tamm-Horsfall protein (THP), also known as uromodulin. THP is exclusively expressed and secreted by epithelial cells of the thick ascending limb, where it has been shown to have antibacterial effects. THP also co-localizes with the Na-K-2Cl transporter in lipid rafts in the apical cell membrane, suggesting a functional interaction.[25] Mutations in the human uromodulin gene have been identified in subjects with medullary cystic kidney disease type 2 and in patients with familial juvenile hyperuricemic nephropathy (see subsequent text).[26,27] It is not yet known how the THP mutation leads to hyperuricemia, as most evidence suggests that uric acid handling is restricted to the proximal tubule. However, there is some evidence that some urate secretion in the rat can occur distal to the proximal tubule.[28] Furthermore, there is also some evidence that the THP mutation may lead to sodium and water wasting, possibly resulting in stimulating urate reabsorption proximally (see following section on Familial Juvenile Hyperuricemic Nephropathy).

Causes of Hyper- and Hypouricemia

Hyperuricemia has been arbitrarily defined as >7.0 mg per dL in men and >6.5 mg per dL in women. "Normal" serum uric acid levels in the population appear to be rising throughout the last century, likely as a consequence of changes in diet, and mean levels in men in the United States are now in the 6.0 to 6.5 mg per dL range.[4] Uric acid levels tend to be higher in certain populations (e.g., African American and Pacific Islanders), with certain phenotypes (obesity, metabolic syndrome) and with special diets (meat eaters).[4] Uric acid also has a circadian variation, with the highest levels in the early morning.[29]

The serum urate concentration reflects the balance between urate production and elimination. Hyperuricemia may occur from excessive production of urate (overproduction) or decreased elimination (underexcretion), and frequently a combination of both processes occur in the same patient. Furthermore, uric acid levels may vary in the same

individual by as much as 1 to 2 mg per dL during the course of a day, due to the effects of diet and exercise.

Genetic mechanisms mediating hyperuricemia include overproduction due to mutations of two enzymes: hypoxanthine–guanine phosphoribosyltransferase (HGPRT) and phosphoribosyl pyrophosphate synthetase (PRPPS) (Table 61.1). Subjects with Lesch-Nyhan syndrome (due to a mutation of HGPRT on the X chromosome) present in childhood with neurologic manifestations (mental retardation, choreoathetosis, and dystonia) and have an increased risk for nephrolithiasis, renal failure, and gout. A partial deficiency of HGPRT may manifest later in life as recurrent gout and/or nephrolithiasis (partial HGPRT deficiency (Kelley-Seegmiller syndrome).[30] Other genetic mechanisms include subjects with the uromodulin mutation, who develop hyperuricemia (due to underexcretion) with early and progressive renal disease (see subsequent text). Certain populations such as indigenous peoples living in Oceania also have higher uric acid levels than Caucasian populations.[31] Finally, African Americans also have higher uric acid levels and a twofold higher incidence of gout compared to Caucasian or Asian populations[32]; however, this could also reflect diets higher in fructose-containing sugars (see subsequent text) rather than genetic mechanisms.

61.1 Major Causes of Hyperuricemia

- Genetic causes
  - Familial hyperuricemic nephropathy (mutation of uromodulin)
  - Lesch-Nyhan syndrome (HGPRT mutation)
  - Phosphoribosyl pyrophosphate synthetase mutation (PRPPS)
- Dietary causes
  - Diet high in purines (organ meats, shellfish, fatty meats)
  - Diet high in fructose (high fructose corn syrup, table sugar, honey)
  - Ethanol
  - Low salt diet
- Drugs
  - Thiazides
  - Loop diuretics
  - Calcineurin inhibitors (cyclosporine > tacrolimus)
  - Pyrazinamide
  - Low dose aspirin
- Volume depletion
- Hypoxia (systemic or tissue)
- Increased cell turnover (myeloproliferative disorders, polycythemia vera)
- Conditions associated with higher uric acid levels
- Renal failure
- Obesity metabolic syndrome
- Untreated hypertension
- African-American race
- Preeclampsia
- Vigorous exercise

Hyperuricemia may also result from diets high in purines, from ethanol, and from fructose. The effect of alcohol is in part related to increased urate synthesis, which is due to enhanced turnover of ATP during the conversion of acetate to acetyl-CoA as part of the metabolism of ethanol.[33] In addition, acute alcohol consumption causes lactate production, and because lactate is an antiuricosuric agent, it will reduce renal urate excretion and exacerbate hyperuricemia.[34] Fructose (a simple sugar present in sucrose, table sugar, high fructose corn syrup, honey, and fruits) can also induce a rapid rise in serum uric acid, due in part to its rapid phosphorylation in hepatocytes with the stimulation of AMP deaminase and ATP consumption.[35] Chronic fructose consumption also stimulates uric acid synthesis.[35] It has been proposed that the marked increase in fructose intake may have a role in the rising levels of serum uric acid and obesity worldwide.[36]

Uric acid may also be affected by exercise, with moderate exercise reducing urate levels (probably by increasing renal blood flow) and severe exercise causing a rise in uric acid (probably due to ATP consumption with adenosine and xanthine formation). Urate levels vary among gender, in that premenopausal women have lower uric acid, a fact attributed to the uricosuric effect of estrogen.[37] The mechanism may relate to gender effects on URAT-1 expression, as recent studies suggest that male mice have higher URAT-1 expression in their proximal tubules compared to female mice.[38] Androgens also increase xanthine oxidase levels that might contribute to the higher uric acid levels observed in men.[39] Uric acid also tends to increase in the setting of low blood volume and/or low salt diet (due to increased proximal reabsorption), and following the administration of catecholamines or angiotensin II (due to renal vasoconstriction resulting in increased reabsorption). Urate production also relates to body size and weight, so that larger persons produce more urate than those who are smaller. Hyperuricemia is particularly common in the obesity and metabolic syndrome (thought to be secondary to the effect of insulin to stimulate uric acid reabsorption)[40] and in untreated hypertension (thought to be due to reduced renal blood flow).[41] Thiazides also increase uric acid reabsorption by decreasing blood volume and via direct interaction with the organic anion exchanger.

Other drugs (cyclosporine, pyrazinamide, low dose aspirin) also increase uric acid, primarily by interfering with renal excretion. In addition, the generation of organic anions such as lactate, β-hydroxybutyrate, and others may interfere with urate secretion in the proximal tubule and cause a rise in serum uric acid. Chronic lead ingestion can also cause hyperuricemia by reducing urate excretion, whereas high concentrations tend to cause proximal tubular injury with no rise in uric acid.

Uric acid is also increased in the setting of tissue hypoxia[42] or with cell turnover.[43] With tissue hypoxia, ATP is consumed

and the isoform, xanthine oxidase, is induced, resulting in increased local uric acid concentrations. Uric acid levels are thus high in subjects with congestive heart failure, high altitude hypoxia, congenital cyanotic heart disease, and with obstructive sleep apnea. Uric acid levels are commonly elevated with certain malignancies, especially leukemias and lymphomas, and levels may sharply rise following chemotherapy (see acute urate nephropathy in the following text).[44] Finally, uric acid has a tendency to be elevated in polycythemia vera and other myeloproliferative disorders.[45]

In the setting of reduced renal function, the fractional excretion of urate increases but is not enough to fully compensate for the reduction in glomerular filtration rate (GFR), and as a consequence serum uric acid levels rise. Conversely, uric acid excretion via the gastrointestinal tract is also enhanced,[46] and therefore serum uric acid levels tend to be only mildly elevated in patients with chronic renal disease, and gout is relatively rare.

Low uric acid levels (levels <2.0 mg per dL) can occur via a variety of mechanisms, including with liver disease (due to decreased production), Fanconi syndrome (due to impaired proximal tubular function), and with diabetic glycosuria (due to proximal tubular dysfunction) (Table 61.2). Drugs such as probenecid, high-dose salicylates, sulfinpyrazone, benziodarone, benzbromarone, and losartan are all uricosuric, whereas allopurinol, febuxostat, and oxypurinol lower uric acid by blocking xanthine oxidase. Statins also lower uric acid,[47] and recombinant uricase (rasburicase) can markedly reduce serum uric acid and is approved for use in children with tumor lysis syndrome (in which marked hyperuricemia may develop).[48] There is also a hereditary hypouricemia syndrome that has been observed, and is particularly common in Japan, where it has been shown to be due to a mutation in the URAT-1 gene.[49] A similar hypouricemia syndrome has also been observed with mutations in SLC2A9.[50] These patients are particularly prone to develop acute renal failure following vigorous exercise, in which it is postulated to be due to massive uricosuria following ATP consumption in the muscle.

61.2 Major Causes of Hypouricemia

Liver disease
Fanconi syndrome
Diabetes (with glycosuria)
Inappropriate secretion of vasopressin
Familial hypouricemia (due to URAT1 mutation)
Total parenteral hyperalimentation
Medications with uricosuric property including aspirin (>2.0 g/day), X-ray contrast materials, ascorbic acid, calcitonin, outdated tetracycline, and glyceryl guaiacolate

URIC ACID AND RENAL DISEASE

In the following section, we discuss the major associations of uric acid with renal disease.

Acute Kidney Injury Associated with Hyperuricemia

Acute urate nephropathy is a form of acute renal failure that may occur when serum uric acid rapidly rises, such as in patients with malignancies following chemotherapy ("tumor lysis" syndrome).[44] Typically the patient has a hematologic malignancy in which rapid tumor lysis occurs, resulting in the release of DNA and RNA and their rapid metabolism to uric acid by the liver and other tissues. Serum uric acid levels may increase to greater than 14 mg per dL (>840 μM), resulting in a marked increase in urinary urate excretion that exceeds its solubility. Uric acid crystals form within the tubules, leading to obstruction and sometimes rupturing into the interstitium (Fig. 61.3). Monocytes and T cells are attracted to the site, and form giant cell reactions with tubular

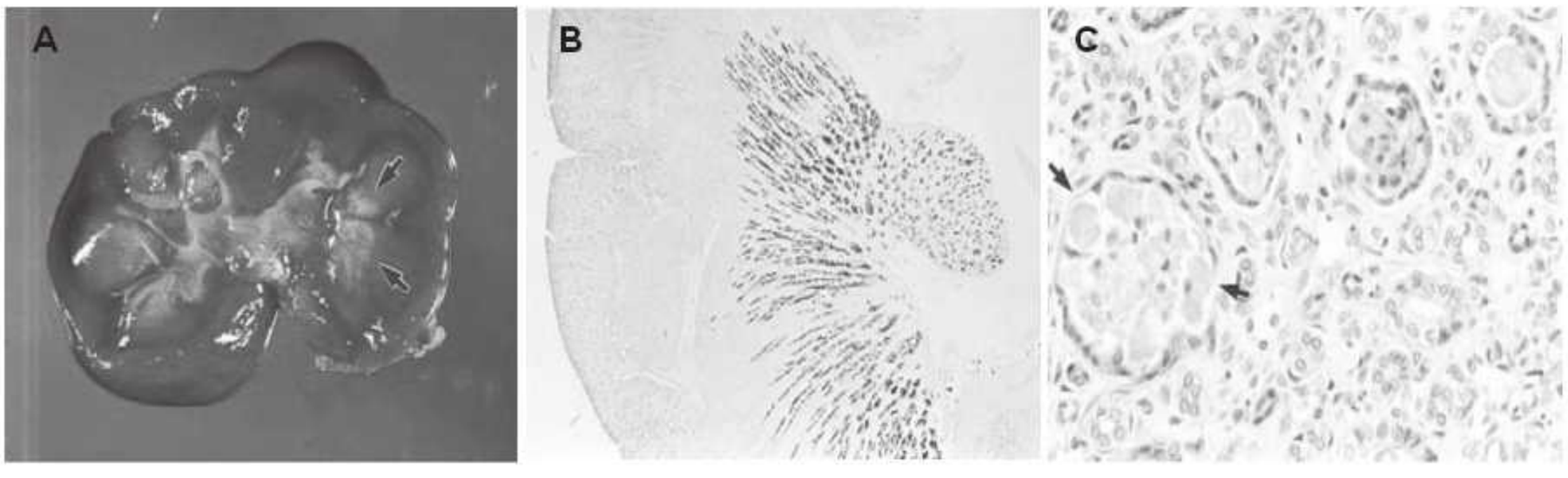

FIGURE 61.3 Pathology of acute uric acid nephropathy. **A:** Yellow/white streaks in the pyramids represent intratubular urate deposition (*arrows*). **B:** Intratubular urate deposition (Schultz stain, ×6). **C:** Urate precipitation in ducts of renal medulla with a denuded tubular basement membrane (*arrows*, H&E, ×125). (From Nickeleit V, Mihatsch MJ. Uric acid nephropathy and end-stage renal disease—review of a non-disease. *Nephrol Dial Transplant*. 1997;12(9):1832–1838.) (See Color Plate.)

proliferation and extracellular matrix deposition.[51] Diagnosis is facilitated by the characteristic clinical syndrome and with a urinary uric acid/urinary creatinine ratio of >1 mg per mg (or >0.66 mM/mM),[52] and by the presence of urate crystals in the urinary sediment. Historically, treatment consisted of forced alkaline diuresis (to facilitate solubilizing the urate) and large doses of xanthine oxidase inhibitors (typically allopurinol 300 to 600 mg per day). Recently, recombinant uricase (rasburicase) has become available, which can be administered intravenously and effectively lowers serum uric acid levels and corrects renal dysfunction more rapidly than allopurinol.[48] Dialysis can also be used to acutely lower the serum uric acid levels. The natural course is one similar to that for acute renal failure of any etiology with a period of oliguria, followed by partial or complete clinical recovery. However, some degree of residual renal injury/damage is common.

Hyperuricemia may also act as an independent risk factor for acute kidney injury in other settings such as following cardiovascular surgery or in association with the administration of nephrotoxic agents such as contrast or cisplatin.[53,54] Experimentally raising uric acid has also been shown to exacerbate acute kidney injury from cisplatin.[55] The mechanism is not due to crystals but rather appears to be secondary to the induction of local inflammation by uric acid. These observations have led to renewed interest that uric acid may be a potentially modifiable risk factor for preventing acute kidney injury.

Hyperuricemia as a Primary Cause of Chronic Kidney Disease

Hyperuricemia is common in subjects with chronic kidney disease. Some cases are due to specific entities, such as lead nephropathy or familial juvenile hyperuricemic nephropathy (discussed later). Uric acid is also retained with a reduction in GFR, so in many cases the rise in uric acid is likely secondary to chronic kidney disease (CKD). However, there remains the possibility that the uric acid may still have a role in modifying progression of renal disease.

Originally the entity of "gouty nephropathy" was attributed to the progressive renal disease seen commonly in subjects with gout. Natural history studies prior to the availability of uric acid–lowering drugs reported that as much as 25% of gouty subjects developed proteinuria, 50% developed renal insufficiency, and 10% to 25% developed end-stage renal disease (ESRD).[52,56] Histologic changes consist of arteriolosclerosis, glomerulosclerosis, and tubulointerstitial fibrosis, similar to the findings one observes in patients with hypertensive renal disease (nephrosclerosis) or with aging (Fig. 61.4).[56,57] In addition, subjects with chronic gout often have focal deposition of monosodium urate in interstitial areas, especially the outer

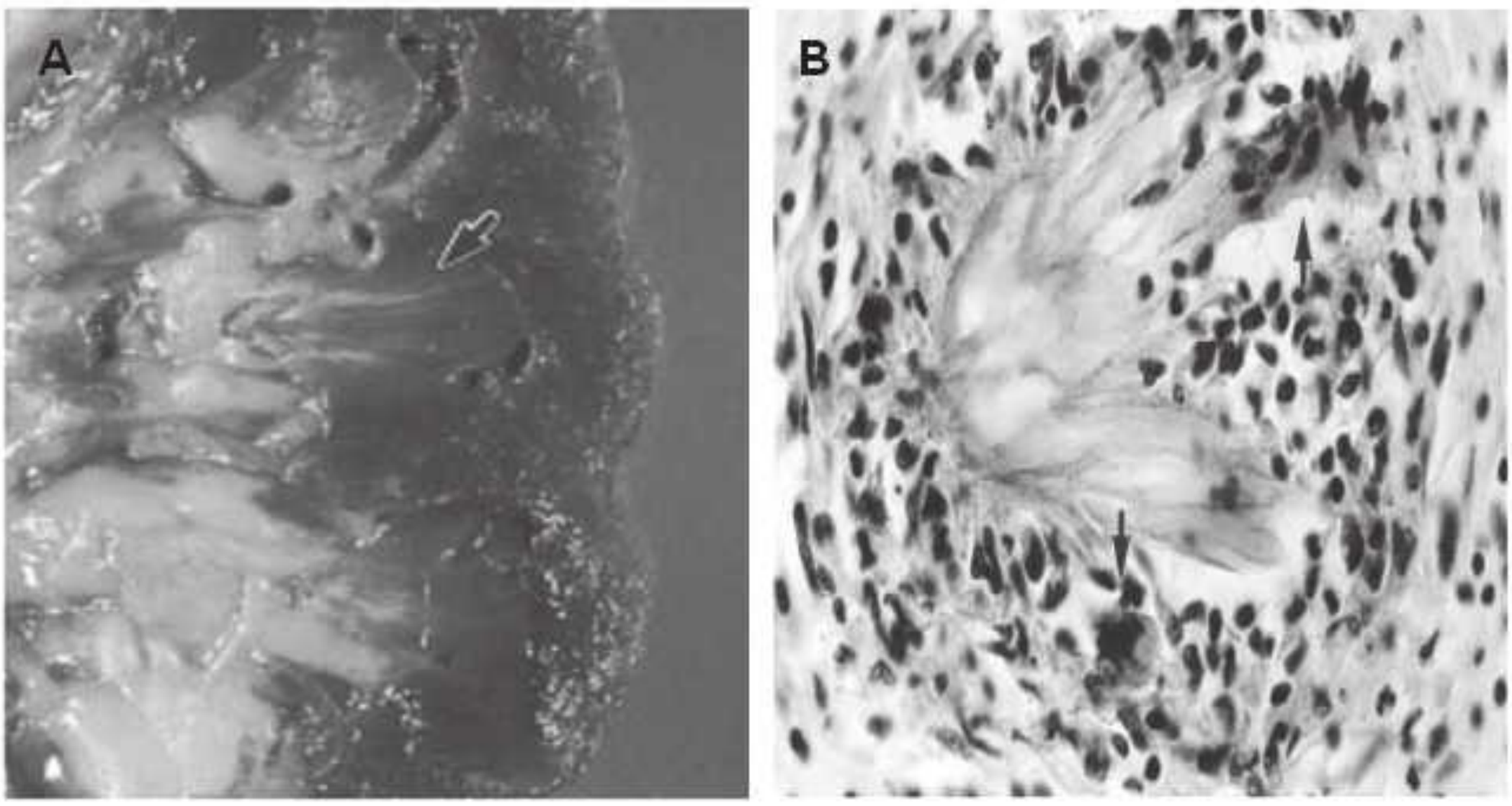

FIGURE 61.4 Pathology of chronic uric acid nephropathy. **A:** Gout tophi in renal pyramid (*arrow*) representing fibrosis and urate deposit. **B:** Typical gouty tophus in renal medulla surrounded by mononuclear inflammatory cells and giant cells (*arrow*, H&E, ×160). (From Nickeleit V, Mihatsch MJ. Uric acid nephropathy and end-stage renal disease—review of a non-disease. *Nephrol Dial Transplant*. 1997;12(9):1832–1838.)

medulla. Although intrarenal crystal deposition was originally thought to be mediating the renal injury,[57] this was later dispelled due to the focal deposition of crystals despite diffuse disease[58] and the fact that the renal disease was commonly associated with hypertension or aging, both conditions associated with the development of microvascular disease, glomerulosclerosis, and tubulointerstitial fibrosis.[59–61] Finally, although some studies suggested that lowering uric acid could improve the renal disease in gout,[62,63] other studies could not demonstrate any significant improvement of renal function with allopurinol.[64] Therefore, many authorities considered the term "gouty nephropathy" a misnomer, and concluded that uric acid had little to do with the renal disease present in these subjects.[65]

New Insights on the Entity of Primary Hyperuricemic Nephropathy

Renewed interest on the role of gout and/or asymptomatic hyperuricemia in CKD was sparked by the recognition that it seemed inappropriate to use the presence of hypertension to explain every case of renal insufficiency in the gouty patient, because most subjects with essential hypertension have relatively preserved renal function.[66] Another implicit assumption was that gouty nephropathy had to be due to crystal deposition, and the possibility that uric acid might mediate effects through crystal-independent mechanisms was not considered. Furthermore, the analysis also assumed that the presence of hypertension was a separate cause of renal disease and that it had to be independent of the uric acid. This led to a proposal to reinvestigate the role of uric acid in chronic renal disease.[66]

Subsequently numerous epidemiologic studies have shown that serum uric acid is an independent risk factor for developing CKD. In one Japanese study, hyperuricemia conferred a 10.8-fold increased risk in women and a 3.8-fold increased risk in men for the development of CKD compared to those with normal uric acid levels.[67] This higher relative risk in subjects with hyperuricemia was independent of age, body mass index, systolic blood pressure, total cholesterol, serum albumin, glucose, smoking, alcohol use, exercise habits, proteinuria, and hematuria. An elevated uric acid was also independently associated with a markedly increased risk of renal failure in another study of more than 49,000 male railroad workers.[68] A second insight came from experimental studies in which chronic mild hyperuricemia was induced in rats.[69,70] Because rats have functional uricase, the model of hyperuricemia was induced by administering the uricase inhibitor, oxonic acid, to the diet.[69,70] This resulted in serum uric acid levels that were only 1.5- to 3.0-fold greater than in the normal rat, levels which did not result in intratubular or interstitial urate crystal deposition. Over time, however, rats developed hypertension and progressive renal disease. Early in the course the rats developed arteriolar thickening and rarely hyalinosis of the preglomerular arterioles, often accompanied by glomerular hypertrophy.[70,71] Proteinuria appeared subsequently with the development of worsening vascular disease, glomerulosclerosis, and interstitial fibrosis.[70] The lesion was identical to that observed with nephrosclerosis of hypertension, with aging-associated glomerulosclerosis, and with gouty nephropathy, except for the absence of crystal deposition that had been observed in the latter condition. This led the authors to suggest that chronic hyperuricemia may cause renal disease and hypertension via a crystal-independent pathway.

Further studies showed that uric acid was able to induce endothelial dysfunction in vitro, and that it could inhibit endothelial release of nitric oxide, block endothelial cell proliferation, and induce senescence via an activation of the local renin-angiotensin system and an induction of oxidative stress.[72–74] Uric acid also stimulated vascular smooth muscle cell proliferation via uptake of urate into the cell with activation of MAP kinases, nuclear transcription factors (including NF-κB and AP-1), and inflammatory mediators (including monocyte chemoattractant protein-1 and C-reactive protein).[71–73,75,76] An induction of COX-2 with thromboxane production was also shown.[77] Uric acid can also inhibit tubular cell proliferation in vitro.[78] Hyperuricemic rats displayed evidence of endothelial dysfunction (with low serum nitrites reflecting low NO) and increased intrarenal renin expression.[69–72] The in vivo renal changes could be reversed by lowering uric acid with allopurinol. In addition, micropuncture studies performed on the hyperuricemic rats demonstrated that the rats developed glomerular hypertension with a reduction in renal plasma flow, both mechanisms that could lead to renal injury.[79,80]

Clinical Manifestations of Hyperuricemic Nephropathy

Most subjects with longstanding gout have asymptomatic renal involvement with either normal or only mild renal insufficiency, and with the majority having hypertension.[59–61] Renal blood flow is usually disproportionately low for the degree of renal insufficiency.[59–61,81] Fractional excretion of uric acid is usually less than 10%. Proteinuria occurs in the minority of cases and, when present, is usually in the nonnephrotic range. The urinary sediment is also usually benign. However, hypertension is frequent, occurring in 50% to 60% of subjects and increasing in prevalence as renal function worsens. Renal biopsy when performed may show chronic changes indistinguishable from chronic hypertensive nephropathy, with chronic glomerulosclerosis, tubulointerstitial fibrosis, and renal microvascular disease. Intrarenal crystals may occasionally be observed using ethanol fixed tissue with the De Galantha stain, but as discussed previously their presence or absence may not rule out a role for uric acid in the kidney disease. Nonetheless, a disproportionately elevated serum uric acid in relation to impaired renal function (such as a uric acid level of >9 mg per dL for a serum creatinine of <1.5 mg per dL, a uric acid of >10 mg per dL for a serum creatinine of 1.5 to 2.0 mg per dL, and a serum uric acid of >12 mg per dL when serum creatinine is >2.0 mg per dL) should make one consider the possibility that uric acid may have a role in the process.

Management of Primary Hyperuricemic Nephropathy

Historically hyperuricemic or gouty nephropathy was not thought to be due to gout, and hence management was focused on classical treatment strategies for CKD. The role of lowering uric acid still remains controversial in primary hyperuricemic nephropathy, and no definitive studies have been performed to resolve this important issue. Based on the experimental studies, it may be reasonable to lower serum uric acid in subjects with hyperuricemia, particularly in individuals in which it is markedly elevated (>10 mg per dL). In the setting of CKD most uricosuric agents are relatively ineffective, although some success with benziodarone has been reported in Europe.[82] The most effective way to lower uric acid chronically is with the use of xanthine oxidase inhibitors, but allopurinol can be associated rarely with the allopurinol hypersensitivity syndrome in which subjects develop a Stevens Johnson–like syndrome with fever, abnormal liver function tests, and worsening renal failure.[83] Recent studies suggest that subjects who develop the allopurinol hypersensitivity syndrome are usually HLA-B58 positive, and hence screening for HLA-B58 is recommended prior to initiating treatment.[84] In addition, high doses of allopurinol may lead to either xanthine or allopurinol intratubular crystal deposition and worsening of renal function. Thus, if allopurinol is to be used, one should start with 50 mg daily and then slowly increase the dose. The usual dose is 100 mg for each 30 mL per minute of GFR. An alternative choice is febuxostat, a non-purine-analogue inhibitor of xanthine oxidase; it may be preferential to allopurinol as there is no indication for dose adjustment in renal disease and to date it has not been associated with the hypersensitivity syndrome.[85] Finally, one should consider having the subject reduce ingestion of foods that can raise uric acid, such as foods with high-purine content, ethanol, and fructose.

Chronic Lead Nephropathy

Chronic lead ingestion may also lead to the triad of renal disease, hypertension, and hyperuricemia. In the 1800s some cases of lead nephropathy were observed in England where large amounts of fortified port wine that had been contaminated with lead was consumed. More recently chronic lead-induced renal disease has been observed in individuals exposed to lead as a consequence of working in or near foundries or individuals who drink moonshine prepared with lead distilling equipment.[86] Emmerson also reported a large number of subjects from Queensland who developed lead toxicity as a consequence of ingesting lead paint chips when they were children.[87] Some subjects provide no history of known exposure to lead, and in certain populations (such as in Taiwan), a substantial number of subjects with CKD may have low level lead toxicity.[88]

The etiology of lead nephropathy is complex. Experimentally lead-induced hypertension is observed only with low-dose ingestion of lead acetate, and this results in hypertension and mild renal injury that can be shown to be mediated by oxidants.[89] In contrast, high doses of lead cause proximal tubular injury with intranuclear inclusions, and a Fanconi-like picture in which serum uric acid levels are low and blood pressure is normal.[90] Acute lead toxicity in humans is also associated with development of Fanconi syndrome secondary to direct tubular toxicity.

Subjects present with hypertension, slowly progressive CKD, with hyperuricemia and/or gout (termed "saturnine" gout when it is secondary to lead). The renal excretion of uric acid is reduced, and this correlates with elevated blood lead levels.[91] The renal sediment is benign, similar to the findings observed with gouty nephropathy and/or arteriolosclerosis. Histologically, the renal lesion also appears like chronic hypertension, and is characterized by prominent vascular changes of arteriolosclerosis, often with variable degrees of glomerulosclerosis and tubulointerstitial fibrosis.[92] The strong association of lead intoxication with renal microvascular disease led Huchard, the French academician of the 1800s, to declare that lead intoxication was the second common cause of arteriolosclerosis.[93]

Diagnosis should be suspected when one observes hyperuricemia and/or gout in the presence of CKD and hypertension. Definitive diagnosis requires the EDTA challenge test. Ethylene diamine tetraacetic acid (EDTA, 1 gram) is administered intravenously and the total urinary lead excretion determined over the subsequent 72 hours. A urinary lead excretion over 600 μg per 72 hours is considered positive.[94] The differential diagnosis should include primary gouty nephropathy, familial juvenile hyperuricemic nephropathy (FJHN), and hyperuricemia accompanying other renal disorders.

Treatment consists of standard regimens for CKD of any etiology, ideally with the avoidance of drugs that can further raise serum uric acid levels (see previous section on treatment of gouty nephropathy). The role of lowering uric acid levels in this population is unknown. More recently, double-blind and prospective studies have shown that intravenous EDTA treatment can chelate the lead and improve renal function over time.[95] The dose used in the study consisted of 1 g calcium disodium EDTA in 200 mL of normal (0.9%) saline given over 2 hours on a weekly basis for 3 months with reassessment of lead burden, and if the urinary excretion continued to be greater than 600 μg per 72 hours, then the course was repeated.[95]

Familial Juvenile Hyperuricemic Nephropathy

A rare form of hereditary renal disease is familial juvenile hyperuricemic nephropathy (FJHN). This is an autosomal-dominant disorder typically present in children and/or young adults with slowly progressive CKD and marked hyperuricemia.[27,96,97] Renal histology shows glomerulosclerosis, tubulointerstitial fibrosis, and arteriolosclerosis, but urate crystal deposition is rare. Gout may or may not occur in the individual. A characteristic feature is a very low fractional

excretion of urate, typically < 5%.[96] Subjects often are normotensive initially, but hypertension is common as the CKD progresses. Hemodynamic studies have shown that there is severe renal vasoconstriction, with marked depression in renal plasma flow relative to the GFR.[97]

FJHN is due to a mutation in uromodulin, also known as the gene encoding the THP.[26] THP is produced only by the thick ascending limb tubular epithelial cells in the kidney, raising questions of how this mutation could result in hyperuricemia and renal failure. Interestingly, mutations in uromodulin have also been shown to be the cause of autosomal-dominant medullary cystic kidney disease type 2.[27] Indeed, a recent study also suggests that this latter entity is commonly associated with severe hyperuricemia and clinically mimics the phenotype of familial hyperuricemic nephropathy.[27] Therefore, these two conditions should be viewed as the same disease.

The pathogenesis of the renal injury remains unclear. Medullary cystic kidney disease is associated with salt wasting, but it remains uncertain if patients with FJHN also have a salt or water wasting defect. However, preliminary studies in such patients suggest that they have a defect in salt and water concentration, and this correlated inversely with the serum uric acid levels.[27] Mice with the uromodulin mutation also show a mild water and sodium wasting phenotype, and have evidence for upregulation of sodium transporters in their proximal tubules, as well as a relative defect in urinary urate excretion when factored for the sodium excretion.[98,99] This raises the possibility that the hyperuricemia in FJHN is due to increased proximal sodium and urate reabsorption secondary to renal salt loss. Moreover, the THP mutant mouse does not develop either hyperuricemia or renal disease. Again, it is tempting to speculate that this may be due to the presence of uricase in these mice that maintains serum uric acid within normal levels.

Diagnosis is suggested by a positive family history, the early onset of CKD in the setting of elevated uric acid levels (often >9 mg per dL), and by a fractional urinary urate excretion of <5%.[96] Confirmation is now possible by having leukocyte DNA analyzed for the mutation (available commercially by Athena Diagnostics [www.AthenaDiagnostics.com]).[100] Treatment is largely supportive. Controversy exists over whether lowering uric acid slows renal progression, but one group has suggested a benefit using this approach if treatment is started early.[96]

Hyperuricemia in Subjects with CKD of Other Etiologies

Patients with established renal diseases may also develop hyperuricemia, mainly in the setting of reduced renal clearance of uric acid associated with progressive decline of GFR. As discussed earlier, there is some retention of uric acid with CKD of other causes, despite compensatory increases in the fractional excretion of uric acid and an increase in enteric excretion in the gut.[46] Indeed, gouty arthritis is uncommon in CKD. This may relate to the fact that uric acid levels are often not that elevated and to the fact that uremia inhibits neutrophil chemotaxis and function,[101] and hence the inflammatory response may be partially subdued.

The role of uric acid in the progression of established CKD remains controversial (Table 61.3). Experimentally uric acid has been shown to be a risk factor for renal progression.[77] Hyperuricemic rats with CKD induced by surgical removal (remnant kidney model) show accelerated progression with worsening hypertension, proteinuria, renal function, and glomerulosclerosis. These hyperuricemic rats also developed severe preglomerular vascular disease, with vascular smooth muscle cell proliferation in the interlobular and afferent arterioles.[77] All of these changes could be reversed by allopurinol, and partially by benziodarone (a uricosuric drug used in Europe). Similarly, the lowering of uric acid in a model of type 2 diabetic renal disease was also associated with a reduction in albuminuria and less tubulointerstitial injury.[102]

There is also compelling evidence that hyperuricemia is an independent risk factor for CKD in the general population.[67,103] Hyperuricemia has also been reported to be an independent risk factor for renal disease progression in patients with glomerular diseases,[104–106] and in subjects with essential hypertension.[107] Subjects with type 1 diabetes who have higher serum uric acid levels are also at increased risk for the development of diabetic nephropathy.[108,109] To date only a few studies have examined if lowering uric acid can slow renal progression in subjects with CKD. Siu et al. randomly assigned 54 hyperuricemia CKD patients to allopurinol or placebo for 1 year. Allopurinol treatment resulted in a decrease in serum uric acid associated with a significant slowing of renal disease progression.[48] A recent randomized, prospective study in 113 CKD patients also found that allopurinol administration decreased C-reactive protein and slowed down the progression of CKD.[110] A small Iranian study also found that allopurinol could reduce proteinuria in type 2 diabetic subjects.[111]

Treatment Guideline of Hyperuricemia in CKD

Asymptomatic hyperuricemia in patients with CKD appears to be a risk factor for CKD, but larger studies are necessary before routine treatment should be recommended. Allopurinol and febuxostat are currently not indicated for treatment of CKD, and can be associated with toxicities.[112] Although screening for HLA-B58 appears to reduce the risk for allopurinol hypersensitivity syndrome,[84] more studies are needed to determine the safety and efficacy of uric acid lowering therapies in subjects with CKD.

Management of Hyperuricemia

Lifestyle modification with low purine diet and low fructose diets are the first option for treating hyperuricemia in CKD patients. Careful monitoring of nutritional status is necessary to avoid malnutrition. Dietary purines make a substantial

61.3 Epidemiology of Uric Acid and Chronic Kidney Disease

1st Author	Year	Subjects	Major Findings
Hsu	2009	177,570, USRDS	Higher uric acid quartile conferred 2.14-fold increased risk of ESRD over 25 years (+)
Obermayr	2008	21,457 Vienna Health Screening Project	Uric acid >7 mg/dL increased risk of CKD 1.74-fold in men, 3.12-fold in women (+)
Weiner	2008	13,338, ARIC	Each 1 mg/dL increase in uric acid increased risk of CKD 7%-11%
Iseki	2001	6403, Okinawa General Health	Uric acid >8 mg/dL increased CKD risk 3-fold in men and 10-fold in women (+)
Borges	2009	385, hypertensive women	Elevated uric acid associated with 2.63 fold increased risk of CKD in hypertensive women (+)
Chen, N	2009	2596, Ruijin Hospital, China	Linear correlation between uric acid and degree of CKD (+)
Chen, Y	2009	5722, Taipei University Hospital	Uric acid associated wtih prevalent CKD in elderly (+)
Park	2009	134, Yonsei University	Uric acid >7 mg/dL correlates with more rapid decline in residual renal function in peritoneal dialysis patients (+)
Sturm	2008	227, MMKD Study	Uric acid predicted progression of CKD only in unadjusted sample (+)
Chonchol	2007	5808, Cardiovascular Health Study	Uric acid strongly associated with prevalent but weakly with incident CKD (−)
See	2009	28,745, Chang Gung University	Uric acid >7.7 md/dL in men and >6.6 mg/dL in women only weakly associated with prevalent renal impairment (−)
Madero	2009	840, Instituto Nacional de Cariologia, Mexico	Patients with CKD 3-4 and uric acid correlates with death but not to ESRD (−)

+Supports the hypothesis that uric acid contributes to CKD progression.
−Does not support the hypothesis that uric acid contributes to CKD.
From Feig DI. Uric acid: a novel mediator and marker of risk in chronic kidney disease? Curr Opin Nephrol Hypertens. 2009;18(6):526–530.

contribution to serum uric acid levels, and a low purine diet can reduce serum uric acid levels by approximately 1 to 2 mg per dL.[113] Low fructose diets can also reduce uric acid and improve inflammatory markers and blood pressure in subjects with CKD.[114] In addition, the reduction of alcohol, and especially beer, is recommended to help lower uric acid levels.[115]

Medications that raise plasma uric acid levels, such as loop and thiazide diuretics, cyclosporine, aspirin (low dose), pyrazinamide, ethambutol, or nicotinic acid should also be discontinued if possible. In contrast, the angiotensin II receptor antagonist losartan has been reported to have a uricosuric effect[116] and the calcium channel blocker amlodipine increases uric acid clearance and reduces uric acid concentrations in comparison with perindopril.[117] In patients with primary hyperlipidemias, atorvastatin, but not simvastatin, has been shown to reduce uric acid concentrations.[118] Fenofibrate, but not other fibrates, has been shown to enhance renal uric acid clearance and reduce uric acid concentrations.[119] However, it should be noted that the fibrates have also been associated with an increase in serum urea and creatinine.[120] Sevelamer can also lower serum uric acid levels.[121] In summary, clinicians should carefully consider the therapeutic options for conditions associated with hyperuricemias such as hypertension and hyperlipidemia. In patients with difficult-to-control hyperuricemia, use of an agent that assists in reducing serum uric acid (or at least that does not increase serum uric acid) may be beneficial.

Antihyperuricemic Treatment: Old and New Drugs

Currently available options for reducing serum uric acid include either reducing uric acid production by the use of xanthine oxidase inhibitors (allopurinol) or increasing the renal excretion of uric acid through the use of uricosuric agents (probenecid, benzbromarone).

Allopurinol is the most commonly used hypouricemic agent because of its ability to lower serum uric acid regardless of the cause of hyperuricemia and the convenience of once daily dosing. It reduces the production of uric acid at its rate-limiting step through inhibition of xanthine oxidase. Allopurinol is rapidly metabolized to oxypurinol, which is responsible for most of the xanthine oxidase inhibition. The half-life of allopurinol is 1 to 2 hours, and that of oxypurinol is 18 to 30 hours in those with normal renal function, but its action is prolonged in CKD extending to a week in those with a creatinine clearance (CrCL) of <3 mL per minute.[122] Approximately 20% of patients experience side effects with allopurinol, with up to 5% ultimately discontinuing therapy.[123] The most serious side effect is a rare hypersensitivity syndrome, which results in fever, rash, eosinophilia, hepatitis, renal failure, and in some cases death. The exact mechanism of the allopurinol hypersensitivity syndrome is unclear, but it has been postulated to be related to elevated serum oxypurinol levels as well as to immunologic processes.[124]

Careful dosing of allopurinol is necessary in patients with renal impairment (Table 61.2).[112] However, such dosing regimens are often ineffective in controlling hyperuricemia and gout.[124] Furthermore, the ability of such dosing regimens to reduce allopurinol hypersensitivity syndrome remains unclear.[125] The net result is often undertreatment of a potentially curable disorder. Although there are multiple reports of clinicians using higher than recommended doses of allopurinol,[126] there is a lack of evidence as to the benefit of such therapy in controlling hyperuricemia.[125]

Uricosuric agents, such as probenecid and benzbromarone, lower serum uric acid by increasing renal uric acid excretion. One potential complication is the deposition of uric acid crystals within the kidney, which can result in urate nephropathy and/or the formation of uric acid stones. The risk of these complications can be reduced by gradual increases in drug dose, ensuring urine volume is ≥1,500 mL per day and maintaining an alkaline urine (pH 6.4 to 6.8). Probenecid was the first uricosuric drug available. Its use is limited as efficacy of probenecid declines as renal function declines, and it is ineffective when CrCL is <60 mL per minute. Probenecid is usually well tolerated at the recommended doses of 1 to 3 g per day. Of note, the uricosuric effect of probenecid is blocked by the simultaneous administration of aspirin.

Benzbromarone is a potent uricosuric agent, which lowers serum uric acid by inhibiting postsecretory tubular resorption of uric acid.[127] Low-dose benzbromarone (50 to 100 mg per day) has been reported to be more potent than 300 mg per day of allopurinol[82] and equipotent to 1 to 1.5 g per day of probenecid.[128] Benzbromarone appears to have only slightly impaired efficacy in patients with impaired renal function,[82] and in renal transplant recipients, it has been reported to be beneficial in patients with a CrCL >25 mL per minute. Benzbromarone therapy has also been associated with a faster tophus reduction than has allopurinol therapy.[129] Hepatic toxicity, rarely leading to death, has been reported in patients taking high doses of benzbromarone.[130] Benzbromarone is unavailable in the United States because of concerns over the potential for hepatotoxicity. However, in the largest series published there was no significant liver toxicity in 200 patients treated for a mean of 5 years with 75 to 125 mg per day of benzbromarone.[131] Benzbromarone remains a therapeutic option particularly for patients with significant renal impairment or with intolerance to allopurinol, or in transplant recipients who are taking azathioprine.

In the last few years, several new hypouricemic agents have emerged. One of them is febuxostat, a non-purine-selective inhibitor of xanthine oxidase. Unlike allopurinol, febuxostat does not resemble purines or pyrimidines structurally. In comparison to allopurinol, which only weakly inhibits the oxidized form of xanthine oxidase, febuxostat inhibits both the oxidized and reduced forms of xanthine oxidase.[132] Febuxostat has been shown to be safe and effective in lowering uric acid concentrations in randomized double-blind studies. Importantly, there is no need for dose adjustment in renal disease. In patients with normal (CrCL 80 mL/min/1.73 m^2), mild (CrCL 50–80 mL/min/1.73 m^2), moderate (CrCL 30–59 mL/min/1.73 m^2), or severe (CrCL 10–20 mL/min/1.73 m^2) impairment in renal function, 80 mg febuxostat daily for 7 days has been reported to be safe without requirement for dose adjustment.[133] General recommendations for the management of hyperuricemia in CKD patients are summarized in Table 61.3.[134]

Hyperuricemia in Renal Transplantation

Hyperuricemia commonly occurs following renal transplantation, and in particular has been associated with the use of cyclosporine, and to a lesser extent, tacrolimus.[135] Indeed, several studies suggest that hyperuricemia occurs in greater than 50% of subjects and gout develops in 10% to 15%.[135] The mechanism has been shown to be due to decreased renal excretion, driven in part by increased net tubular reabsorption as well as decreased glomerular filtration.[136]

Although the primary complication of hyperuricemia in renal transplant patients has classically been thought to be gout, again there has been recent concern that the rise in serum uric acid may contribute to the renal vasoconstriction and renal injury that occurs with chronic calcineurin inhibitors. Thus, Mazzali et al. reported that cyclosporine-treated rats developed mild hyperuricemia with the classic lesions of arteriolar hyalinosis and tubulointerstitial fibrosis, but this lesion was markedly exacerbated if uric acid levels were further increased by administering a uricase inhibitor.[137] Kobelt et al. also reported that allopurinol lowers blood pressure

and improves renal blood flow in rats administered cyclosporine,[138] and Assis et al. also demonstrated that allopurinol improved GFR (inulin clearances) in cyclosporine-treated rats.[139] Most notably, Neal et al. recently reported that allopurinol therapy lowered uric acid and improved renal function in liver transplant patients receiving cyclosporine.[140]

At this time insufficient evidence has been provided to recommend uric acid-lowering therapy in renal transplant subjects. However, if a subject has repeated episodes of gout, or if serum uric acid levels are excessively elevated (>9 mg per dL), we would consider pharmacologic therapy to lower uric acid. Because allopurinol interacts with azathioprine, the latter should be reduced to 25% to 50% of its original dose. In addition, we recommend initiating low doses of allopurinol (50 to 100 mg per day) with slow increases to minimize the risk for precipitating a gout attack (which is common on initiating allopurinol).

URIC ACID AND CARDIOVASCULAR DISEASE

In addition to its controversial role in renal disease, there has also been reawakened interest in the role of uric acid in cardiovascular disease, and in particular its role in hypertension. Although it had been known for over 100 years that hyperuricemic and/or gouty individuals are at increased risk for cardiovascular events and or mortality, this had historically been attributed to the fact that patients with gout frequently are obese or have other features associated with cardiovascular risk. Studies such as the Framingham analysis published in 1999 reported that this relationship of uric acid with cardiovascular disease was not independent when it was controlled for other accepted cardiovascular risk factors, such as hypertension, diuretic use, obesity, and renal disease.[141] Most societies concluded that there is insufficient evidence to support uric acid as a true cardiovascular risk factor.

However, recent studies have provided provocative data that uric acid may be a true risk factor for hypertension. Thus, a meta-analysis concluded that elevated serum uric acid is an independent risk factor for the development of hypertension.[142] Furthermore, an elevated serum uric acid is common in subjects with new onset hypertension. In one study of new onset hypertension in adolescents, 89% of subjects had a serum uric acid >5.5 mg per dL whereas this was not observed in any of 63 controls (including 22 subjects with white coat hypertension).[143] Furthermore, in a recent pilot study, treatment with allopurinol resulted in reduction in blood pressure in 30 adolescents with newly diagnosed hypertension.[144] Hyperuricemia has also been found to be an independent factor for mortality in subjects with normal renal function as well as in stage 3 and 4 CKD patients.[145,146] A recent prospective study in 294 newly diagnosed patients with CKD stage 5 followed for an average of 6 years revealed that subjects with markedly increased serum uric acid levels (≥9.0 mg per dL) had a twofold increased risk for mortality after adjusting for numerous comorbidities.[147] Although high uric acid levels were associated with lipid levels, calcium/phosphate metabolism, and levels of inflammation markers, an elevated uric acid level itself may represent a true risk factor for cardiovascular disease and mortality in CKD patients.[148] Few clinical studies have examined the effect of lowering uric acid on cardiovascular disease in subjects with CKD. However, in the randomized study by Goicoechea et al., the use of allopurinol was associated with a 70% reduction in cardiovascular events.[110]The mechanism by which uric acid may cause cardiovascular disease has been explored using both cell culture and animal models. It appears that uric acid must enter the endothelial and vascular smooth muscle cell via a specific organic anion exchanger, where it activates a variety of intracellular signaling molecules involved in inflammation and proliferation. In the endothelial cell there is a decrease in nitric oxide levels and an inhibition of endothelial proliferation, whereas in the vascular smooth muscle cell there is activation of proliferative and inflammatory pathways.[69–73,75,76] Local activation of the renin angiotensin system could also be shown.[73,75,76] Uric acid may also have direct effects on cardiac fibroblasts.[149] Experimental studies have further demonstrated that the mechanism by which uric acid causes hypertension is via a decrease in endothelial-derived nitric oxide, activation of the renin-angiotensin system, and the induction of preglomerular vascular disease. The latter may promote continued salt sensitivity even after the serum uric acid is corrected.[73]

URIC ACID AND METABOLIC SYNDROME

Hyperuricemia may also have a role in obesity and metabolic syndrome. A number of observational and cross-sectional studies showed an unequivocal association of high serum uric acid with metabolic syndrome.[150–153] Some reports have suggested that serum uric acid may be directly related to components of metabolic syndrome such as insulin resistance,[154] hypertension, abdominal adiposity,[155,156] and hypertriglyceridemia.[157] Hyperuricemia is also associated with increased risk of myocardial infarction and sudden cardiac death in patients with metabolic syndrome.[158] In a small prospective, open label study, Shelmadine et al.[159] demonstrated that 3 months administration of allopurinol in ESRD patients with gout led to significant reductions in serum uric acid levels and LDL cholesterol, although serum triglycerides increased. Ogino et al. also reported that lowering uric acid with benzbromarone can improve insulin resistance and markers of inflammation in subjects with congestive heart failure.[160] In addition, recent studies in which rats were fed fructose to induce metabolic syndrome found that lowering uric acid with allopurinol could significantly prevent the development of hypertension, hyperinsulinemia, hypertriglyceridemia, and obesity.[36]

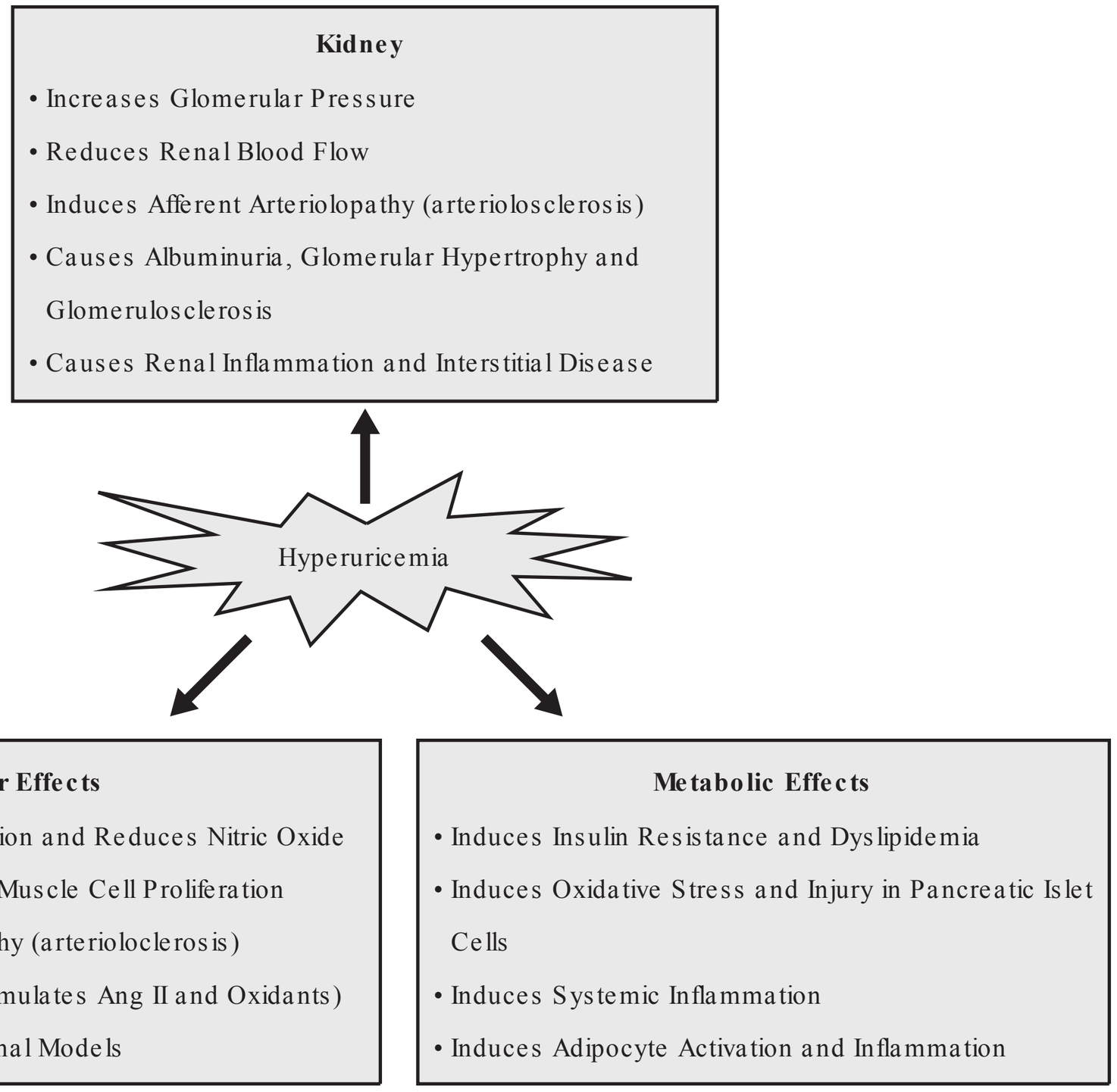

FIGURE 61.5 Proposed effects of uric acid on the kidney, vasculature, and metabolic state.

CONCLUSION

In conclusion, uric acid is emerging as a potential contributing factor to kidney disease, vascular disease, and metabolic disorders (Fig. 61.5). There is a strong relationship of uric acid with both acute and chronic kidney disease. Emerging evidence suggests that it may not only cause acute kidney injury as a consequence of crystal formation within the tubular lumina, but that both acute and chronic hyperuricemia may also cause renal disease via crystal-independent pathways. Indeed, uric acid may not only be a primary cause of chronic renal disease (gouty nephropathy), but could be a contributory factor in lead nephropathy, primary renal diseases, diabetic nephropathy, cyclosporine nephropathy, and the progression of CKD. Uric acid may also be an unrecognized contributor to cardiovascular risk as evidenced by recent studies linking it pathogenetically to hypertension and metabolic syndrome. An adequately powered randomized controlled trial is required to determine whether uric acid–lowering therapy prevents or ameliorates renal, cardiovascular, and metabolic diseases associated with hyperuricemia in order to better inform clinical practice and public health policy for the optimal management of hyperuricemia.

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