Hypouricemia: Causes and clinical significance

presented by pejman pourshabanan

Recurrent Acute Kidney Injury Caused by Idiopathic Renal Hypouricemia:

The First Report from Iran with A Novel Mutation

A 27-year-old police officer was admitted to the hospital due to anorexia and a serum creatinine level of 18 mg/dL, after a "tug-ofwar" game. After one dialysis sessions per day over five days, his creatinine dropped to

1.3 mg/dL. Six months later, he developed bilateral flank pain and red discoloration of urine, following a 300- meter chase of a convict, and his creatinine level increased to 2.3 mg/dL, which was corrected with proper hydration alone.

Recurrent acute kidney injury can be due to hereditary renal hypouricemia, which should be considered among differential diagnoses for patients.

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Hypouricemia is a level of uric acid in blood serum that is below normal.

In humans, the normal range of this blood component has a lower threshold set variously in the range of 2 mg/dL to 4 mg/dL, while the upper threshold is 530 μmol/L (6 mg/dL) for women and 619 μmol/L (7 mg/dL) for men. Hypouricemia usually is benign and sometimes is a sign of a medical condition

Hypouricemia is arbitrarily defined as a serum urate concentration of less than 2 mg/dL (119 micromol/L). It is a fairly uncommon disorder, occurring in approximately 2 percent of hospitalized patients and less than 0.5 percent of the normal population.

REGULATION OF SERUM URATE LEVELS

Serum urate levels can be modulated by diverse physiologic conditions and neurohumoral factors.

Volume status and salt balance, in particular, have potent effects on circulating serum urate.

Experimentally, salt restriction causes significant hyperuricemia, which is reversed by salt loading .

Potential neurohumoral mediators include angiotensin-II and epinephrine, both of which can experimentally reduce the fractional excretion of urate in humans .

Clinically, volume depletion is associated with hyperuricemia, explaining in large part the association between diuretic use and gout .

The serum uric acid level depends on the balance between the production and excretion of uric acid. Healthy people maintain serum uric acid levels through the balance of uric acid production and excretion; imbalances can increase or decrease uric acid levels, causing hyperuricemia and hypouricemia.

In general, two-thirds of urate is excreted in the urine from the kidneys via the “renal excretion” pathway, whereas the remaining one-third is excreted via the “extra-renal excretion” pathway, such as intestinal excretion.

Uric acid is the end product of purine metabolism. Most uric acid circulates as the urate anion, and serum urate concentrations normally approach the theoretical limit of serum urate solubility.

Human tissues have a very limited ability to metabolize urate; thus, uric acid must be eliminated by the kidney and the gut to maintain urate homeostasis.

At physiological pH, uric acid is a weak acid with a pKa of 5.8. Uric acid exists primarily as urate, the salt of uric acid. The concentration of serum uric acid increases in tandem with uric acid crystal formation.

Urate is filtered by the glomeruli and reabsorbed by the proximal tubule with a normal fractional excretion of 10% .

Three urate transporters:

URAT1/SLC22A12,

GLUT9/SLC2A9, and

ATP-binding cassette subfamily G member 2 (ABCG2)/breast cancer resistance protein (BCRP)

URAT1 is a molecular target for uricosuric agents such as:

benzbromarone, probenecid, losartan, irbesartan, and dotinurad. These drugs inhibit the reabsorption of urate in the lumen of the proximal tubule.

GLUT9 is located in the basolateral membrane of proximal tubule. Urate taken up into proximal tubules is released on the vascular side by GLUT9. Mutations in GLUT9 have been reported to cause severe hypouricemia.

ABCG2/BCRP is an ATP-binding cassette (ABC) transporter:

The transporters are localized on the luminal side of small intestinal epithelial cells and in renal proximal tubules and are responsible for urate excretion in the stool and urine, respectively.

The major site of urate production is the liver, where it is produced by the degradation of dietary and endogenously synthesized purine compounds.

Dietary intake appears to provide a significant source of urate precursors, as a purine-free formula diet reduces urinary excretion of uric acid by approximately 40 percent.

Hypouricemia is common in vegetarians due to the low purine content of most vegetarian diets. Vegetarian diet has been found to result in mean serum uric acid values as low as 239 μ mol/L (2.7 mg/dL).

Transient hypouricemia sometimes is produced by total parenteral nutrition. Paradoxically, total parenteral nutrition may produce hypouricemia followed shortly by acute gout, a condition normally associated with hyperuricemia.

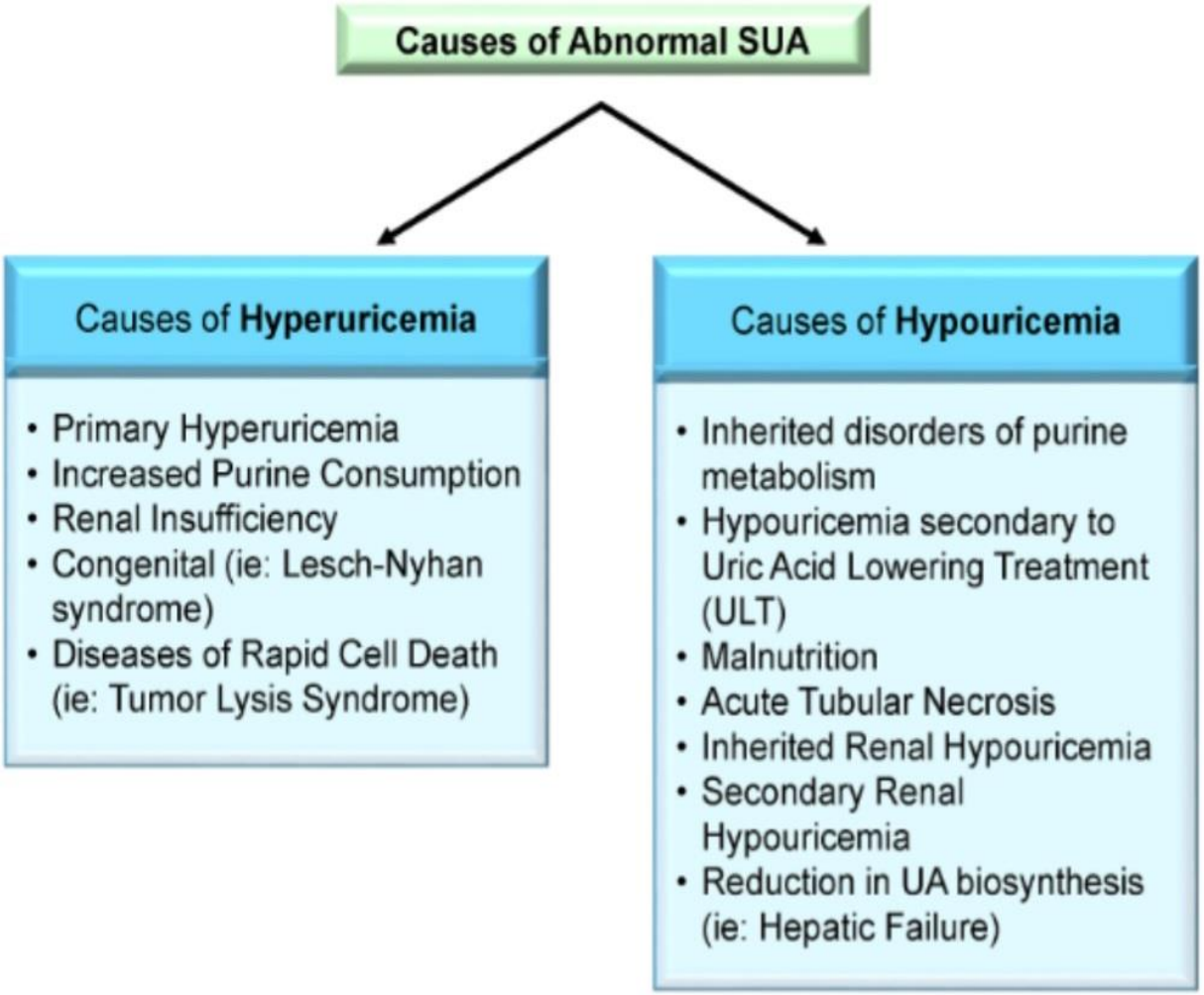


Fig. 1. Causes of Abnormal Serum Uric Acid (SUA). Both causes of abnormal high level of serum uric acid (hyperuricemia) and low level of serum uric acid level (hypouricemia) have primary and secondary etiologies as listed. The main cause of secondary hypouricemia is following uric acid lowering treatment (ULT).

Major kidney disorders that accompany altered serum uric acid levels:

Hyperuricemia

Chronic kidney disease (CKD)

Diabetes mellitus and diabetic kidney disease (DKD)

Autosomal dominant tubulointerstitial kidney disease (ADTKD)

Thiazide and loop diuretics

Cause of Hypouricemia

Major kidney disorders that accompany altered serum uric acid levels:

Hypouricemia

Renal hypouricemia type 1 and type 2
Fanconi syndrome: inherited or acquired
Coronavirus disease 2019 (COVID-19)
Hyponatremic disorders
Syndrome of inappropriate antidiuresis (SIAD)
Cerebral/renal salt wasting
Thiazide-induced hyponatremia

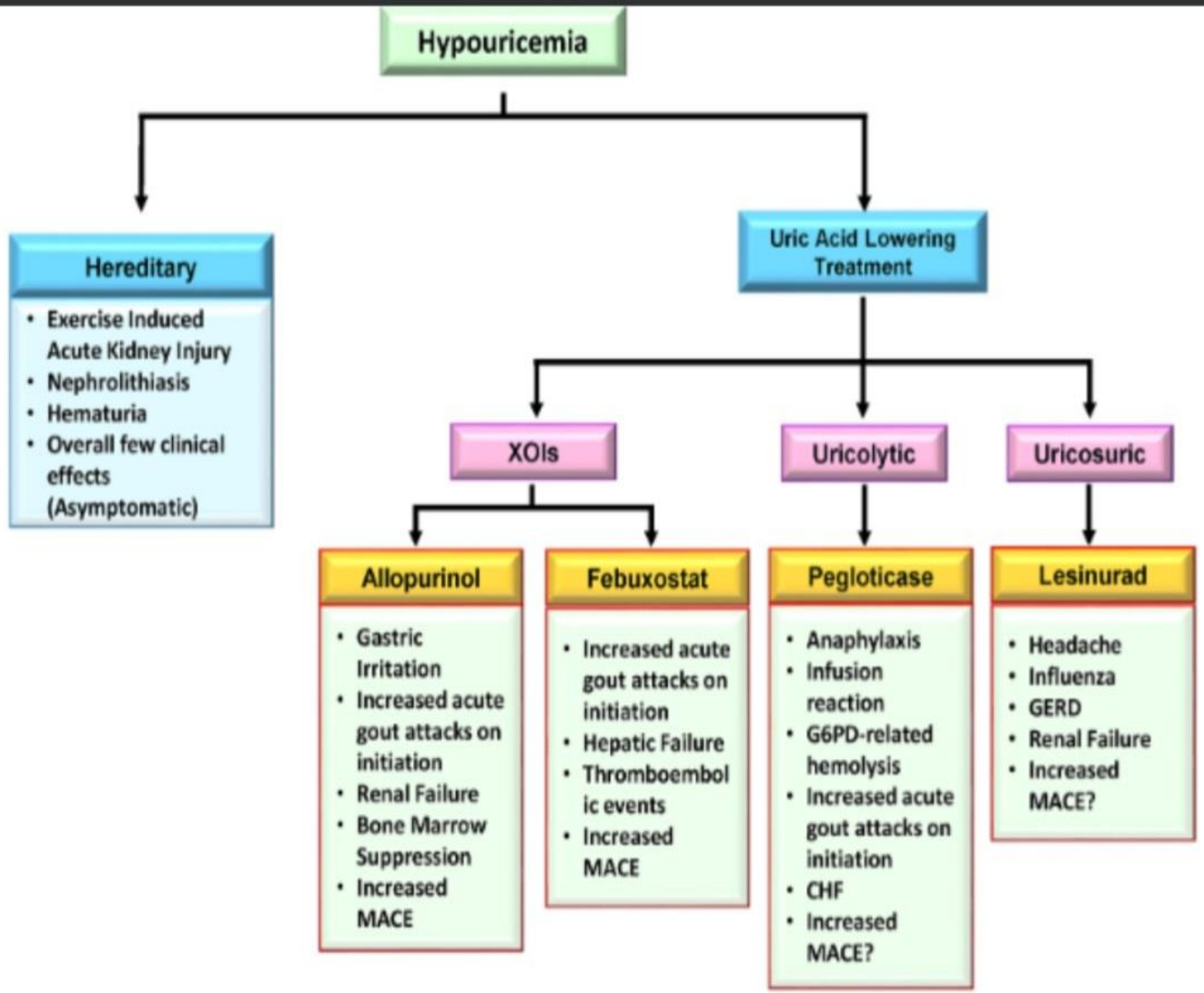


Fig. 2. Consequences of hypouricemia. Complications of both hereditary (primary) and ULT induced (secondary) hypouricemia have been listed. The most important of these is the ULT induced major adverse cardiovascular events (MACE).

Hypouricemia can be caused by decreased uric acid production, uric acid oxidation due to treatment with uricase, or enhanced urate excretion.

DECREASED PRODUCTION

Inherited disorders / Acquired disorders

DECREASED PRODUCTION

Decreased uric acid production can be caused by several rare inherited disorders of purine synthesis and catabolism and, more commonly, by acquired deficiency of xanthine oxidase due to allopurinol therapy or liver disease.

Urate production (ie, purine degradation):

involves the breakdown of the purine mononucleotides, guanylic acid (guanosine monophosphate, GMP), inosinic acid (inosine monophosphate, IMP), and adenylic acid (adenosine monophosphate, AMP),

ultimately into the purine bases guanine and hypoxanthine.

These last two compounds are then metabolized to xanthine. In the final step, which is catalyzed by the enzyme xanthine oxidase, xanthine is irreversibly oxidized to produce urate .

Urate is the end product of purine metabolism in humans because the human homolog of the mammalian uricase (urate oxidase) gene is structurally modified to an unexpressed (pseudogene) state.

By contrast, the vast majority of other mammalian species have extremely low serum urate levels (approximately 1 mg/dL; 60 micromol/L) because urate in these species is converted by uricase to allantoin, a highly soluble excretory product.

URIC ACID OXIDATION

Unlike most animal species, humans lack urate oxidase (uricase). Thus, in humans, uric acid is an end product of metabolism.

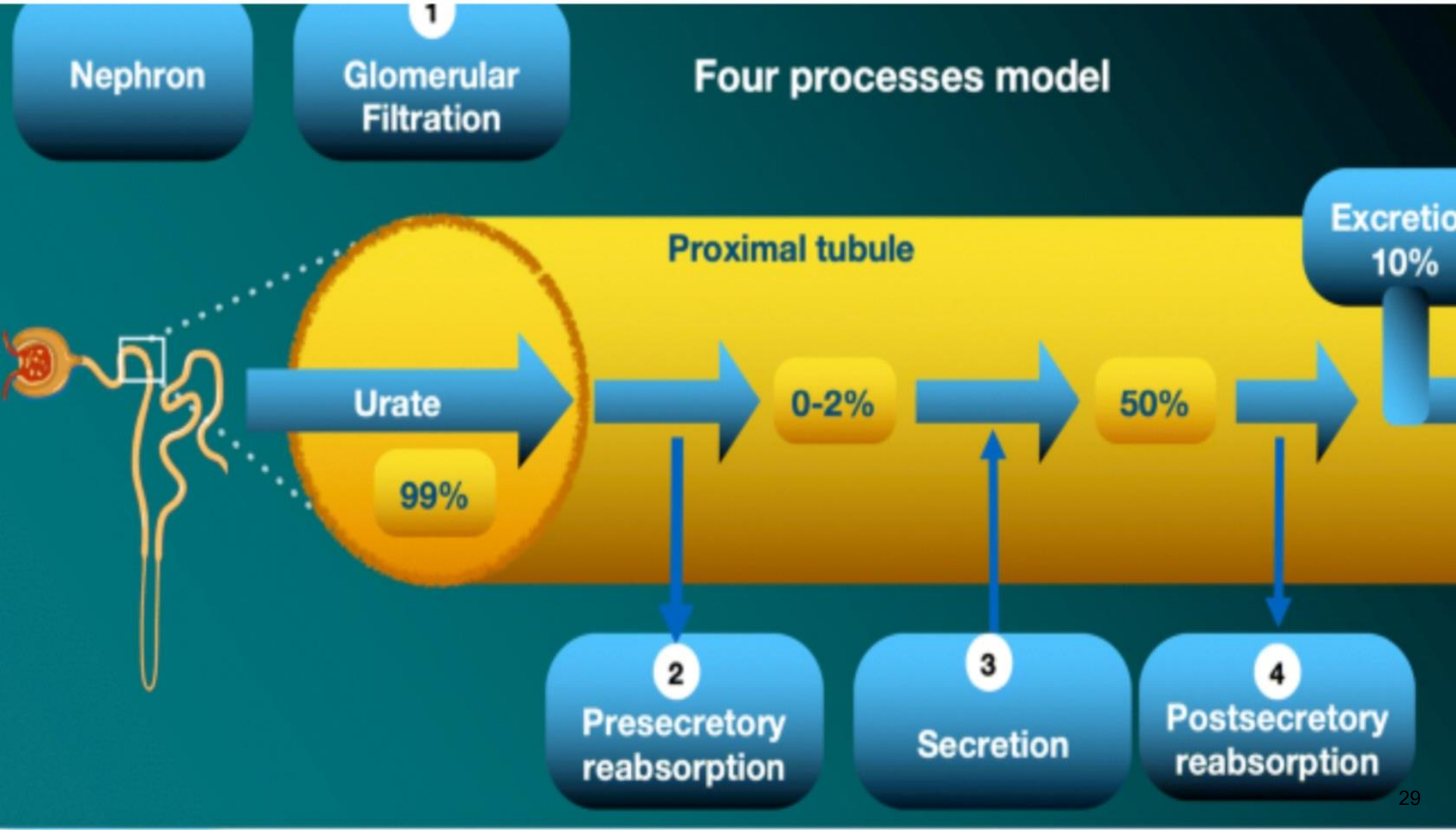
Derivatives of uricase (rasburicase), which catalyzes the oxidation of uric acid to allantoin, are widely used in the prevention and treatment of acute kidney injury (AKI) in tumor lysis syndrome.

A "PEGylated" rasburicase may be used in the management of refractory gout, causing profound hypouricemia.

Renal clearance of uric acid in normal adults is only 7 to 12 percent of the filtered load, indicating that, under usual circumstances, there is net tubular reabsorption of approximately 90 percent of filtered urate.

Urate handling involves glomerular filtration and urinary excretion, with separate tubular reabsorptive and secretory processes mediated by completely separate sets of transport mechanisms.

Increased urinary uric acid excretion



Renal hypouricemia caused by URAT1 or GLUT9 loss-of-function mutations is susceptible to exercise-induced AKI, probably because of an excessive urinary excretion of uric acid.

Hypouricemia derived from renal uric acid wasting is a component of Fanconi syndrome, which may be hereditary or acquired.

INCREASED URINARY EXCRETION

The frequency of nephrogenic hypouricemia due to a deficiency of URAT1 is high in Japan, accounting for most asymptomatic and persistent cases of hypouricemia. RHUC results in a high risk of exercise-induced acute kidney injury and urolithiasis.

INCREASED URINARY EXCRETION

Familial renal hypouricemia

Acquired disorders

- Fanconi syndrome
- Volume expansion
- Intracranial disease
- Acquired immunodeficiency syndrome
- Drugs
- Inflammation

INCREASED URINARY EXCRETION

Other:

- Pregnancy
- Total parenteral nutrition
- Malignancies, including Hodgkin lymphoma
- Diabetes mellitus; (it is likely that decreased urate reabsorption is a function of glucosuria in these patients)
- Amanita phalloides poisoning

Exercise-induced AKI is an important clinical presentation of renal hypouricemia.

It can be differentiated from rhabdomyolysis-associated AKI because of the absence of elevated creatinine kinase levels and myoglobinuria.

Interestingly, uric acid may function as an antioxidant in plasma and can act as a pro-oxidant within the cell .

In patients with hypouricemia, the antioxidant activity of uric acid is overwhelmed by the massive concentration of reactive oxygen species produced by exhaustive exercise.

Thus, the loss of antioxidant activity in plasma may lead to vascular constriction and endothelial damage, progressing to AKI.

Urine data are compatible with prerenal azotemia , and kidney function gradually improves with hydration. The characteristic computed tomography findings are patchy renal vasoconstriction or multiple patchy wedge-shaped delayed-contrast enhancements in the kidneys.

Two different aspects were viewed in the pathogenesis of renal injuries: a low serum uric acid level and a high urine uric acid level.

Drug-induced renal Fanconi syndrome can be explained by mitochondrial injury in the proximal tubule.

Hypouricemia is associated with proximal tubular injury in COVID-19 and is related to disease severity, including respiratory failure.

Among hyponatremic disorders, hypouricemia is a characteristic laboratory finding in SIAD, CSW/RSW, and thiazide-induced hyponatremia.

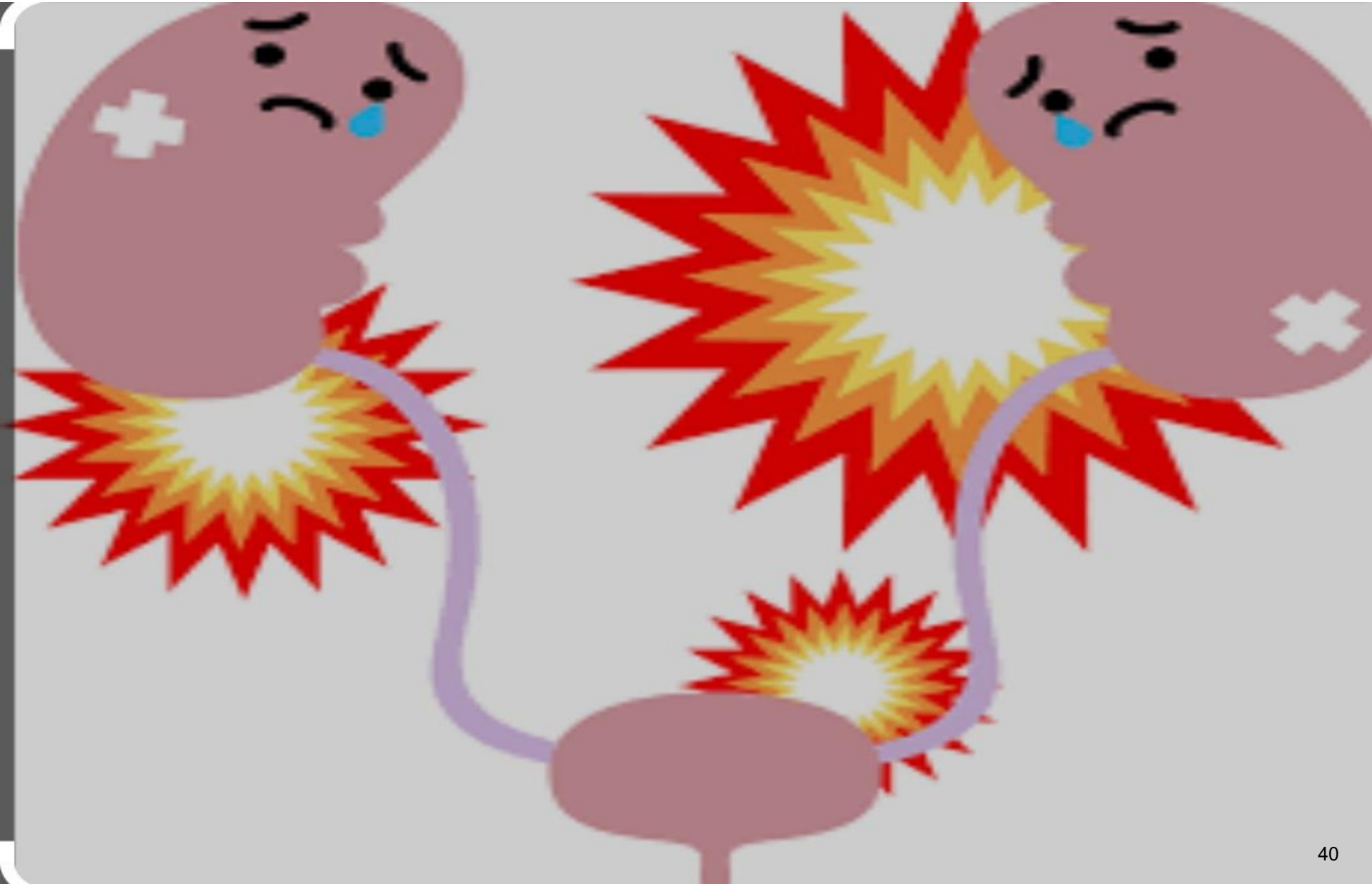
Expansion of the extracellular fluid volume, most commonly seen in patients receiving large volumes of intravenous fluids, those with primary polydipsia, and in the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Intracranial disease in association with renal sodium wasting and hyponatremia (cerebral salt-wasting).

Acquired immunodeficiency syndrome (AIDS), which may be related to intracranial disease and tends to correlate with disseminated disease and a poor prognosis.

Drugs, such as high-dose trimethoprim-sulfamethoxazole, high-dose salicylate, lesinurad, and losartan .

COMPLICATIONS



COMPLICATIONS

Three complications related to renal hypouricemia can occur: acute kidney injury (AKI), nephrolithiasis, and posterior reversible leukoencephalopathy syndrome (also called posterior reversible encephalopathy syndrome, or PRES).

Acute kidney injury

An increased incidence of AKI, often following exercise, has been described in patients with familial renal hypouricemia.

The largest reported experience comes from a review of 54 patients with renal hypouricemia, approximately 90 percent of whom were male .Episodes of AKI most often occurred after strenuous exercise, such as a short distance race.

The initial symptoms were severe loin or abdominal pain and nausea, which usually developed within 6 to 12 hours after exercise.

At presentation to medical care, the mean serum creatinine was 5.5 mg/dL (486 mmol/L), and the mean serum uric acid concentration was normal (4.4 mg/dL [262 micromol/L]), which was felt to be at least in part due to the kidney failure. After recovery, the serum uric acid fell to 0.7 mg/dL (42 micromol/L).

Recovery of kidney function occurred in all patients, although some required hemodialysis. At follow-up, 13 patients (24 percent) developed recurrent AKI. In some patients, repeated episodes of AKI may lead to chronic kidney disease.

Acute kidney injury

The majority of reported kidney biopsies in exercise-associated AKI in renal hypouricemia have demonstrated **ATN** **without** intratubular uric acid precipitation .

It is hypothesized that the reduction in circulating uric acid, which is a known antioxidant, impairs the ability of the kidney to cope with the increase in oxidative stress associated with strenuous exercise .

Acute kidney injury

Prolonged or intense exercise is also associated with an elevation in uric acid production, most likely due to muscle adenosine triphosphate (ATP) utilization.

The subsequent rise in adenosine diphosphate (ADP) leads to an increase in the production of hypoxanthine, which is then converted to uric acid in the liver, leading to increases in serum uric acid and uric acid excretion.

Volume depletion during exercise can lead to a reduction in urine volume, which might promote uric acid precipitation in the tubules. Uric acid precipitation in the tubules can also occur with other causes of an acute increase in uric acid excretion, including high-dose trimethoprim-sulfamethoxazole.

In a patient with renal hypouricemia and exercise-associated AKI, for example, both an acute increase in reactive oxygen species and a decreased antioxidant potential capacity were demonstrated soon after the initiation of exercise.

Consequently, many patients with a history of exercise-associated AKI are treated with oral vitamin C and vitamin E in an attempt to increase serum antioxidant capacity.

Uric acid stone formation

Patients with renal hypouricemia are at increased risk for nephrolithiasis .

In two series of 19 patients with familial renal hypouricemia, 5 (26 percent) had a history of kidney stones .

Most of these reports described uric acid stones and successful treatment with urinary alkalinization.

However, hyperuricosuria may predispose to calcium oxalate stones, which have also been described in patients with renal hypouricemia.

Reversible posterior leukoencephalopathy syndrome (PRES)

Reversible posterior leukoencephalopathy syndrome (also called posterior reversible encephalopathy syndrome, or PRES) was described in two patients with exercise-associated AKI due to renal hypouricemia, one with loss-of-function mutations in *SLC22A12/URAT1*, and the other with loss-of-function mutations in *SLC2A9/GLUT9*.

Many thanks for your attention