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Review Article

Update on the epidemiology, genetics, and therapeutic options of hyperuricemia

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Abstract: Hyperuricemia may occur when there is an excess of uric acid in the blood. Hyperuricemia may result from increased production or decreased excretion of uric acid. Elevated uric acid levels are a risk factor for gout, and various risk factors, including some medications, alcohol consumption, kidney disease, high blood pressure, hypothyroidism, and pesticide exposure, as well as obesity, are associated with an elevated risk of hyperuricemia. Although the mechanisms underlying the pathogenesis of hyperuricemia are complex, previously reported studies have revealed that hyperuricemia is involved in a variety of biological processes and signaling pathways. In this review, we summarize common comorbidities related to hyperuricemia and describe an update of epidemiology, pathogenesis, and therapeutic options of hyperuricemia. This systematic review highlights the epidemiology and risk factors of hyperuricemia. Moreover, we discuss genetic studies on hyperuricemia to uncover current status and advances in the pathogenesis of hyperuricemia. Additionally, we conclude with a reflection on the underlying mechanisms of hyperuricemia and present the alternative drug strategies for the treatment of hyperuricemia to offer more effective clinical interventions.

Keywords: Hyperuricemia, epidemiology, genetics, mechanisms, treatment

Introduction

Uric acid, a nitrogenous component of urine, is a poorly soluble final product of protein and purine metabolism in humans. The level of serum uric acid maintained the balance between its production and excretion [1-3]. Uric acid is a by-product of amino acid metabolism, and the breakdown of amino acids produces uric acid in the liver. Moreover, the breakdown of purines releases uric acid in small quantities. Uric acid in human urine and the blood may form sharp crystals and bring about an increased risk of gout [3-6]. Hyperuricemia mainly caused by metabolic disorders of purine and closely associated with the increases in the risk of cardiovascular disease, kidney disease, diabetes, obesity can be congenital or acquired [7-9]. Hyperuricemia is the main factor that leads to long-term systemic inflammation in patients with gout [10]. Inflammatory reactions in patients with asymptomatic hyperuricemia induced by urate can contribute to the development of obesity, chronic kidney disease, diabetes mellitus, and hypertension [11]. Hyperuricemia may occur when there are high levels of uric acid in the blood due to excess production, or more commonly, inefficient excretion of uric acid. Defects in the key enzymes of purine metabolism lead to impaired purine utilization or enhanced purine oxidase activity. The increased reabsorption or decreased secretion of uric acid in proximal renal tubules results in a decrease in the rate of uric acid excretion. The regulation of the enzymes is responsible for uric acid breakdown and production. Multiple transport proteins related to uric acid transport are crucial in the treatment of hyperuricemia [12]. An absolute lack of comprehension of the mechanism is a limiting factor in the management of hyperuricemia. However, the cellular and molecular processes and its implications are still not completely elucidated. New insights towards understanding the mechanisms may provide more precise treatment options for hyperuricemia.

Epidemiology

Worldwide prevalence of hyperuricemia

In recent years, the disease burden of hyperuricemia is increasing, especially in high-income countries and economically developing world with a Western lifestyle [13, 14]. The prevalence and incidence of hyperuricemia substantially differ across geographical areas [15]. According to the data from the National Health and Nutrition Examination Survey (NHANES) 2007-2016, a nationally representative survey showed that the prevalence rates of hyperuricemia were 20.2% among men and 20.0% among women between 2015 to 2016 in the United States and the incidence of hyperuricemia remained stable in 2007-2016 [16].

The prevalence of hyperuricemia increases in both men (19.7% to 25.0%) and women (20.5% to 24.1%) from 2006 to 2014 in Ireland [17]. In the United States, an epidemiological survey has shown that the prevalence of hyperuricemia substantially increased from 19.1% (1988-1994 years) to 21.5% (2007-2008 years). The National Health and Nutrition Examination Survey (NHANES) 2007-2008 found a similar prevalence of hyperuricemia between women (21.6%) and men (21.2%) [15]. Most epidemiological studies show that the prevalence of hyperuricemia is generally higher in high-income countries than economically developing world [15, 17-20]. The reduction of hormone estrogen production in postmenopausal women can decrease the removal of urate from the body result in an increase in urate levels and an elevated risk of developing hyperuricemia [21].

Prevalence of hyperuricemia in China

China, as the largest developing country, is characterized by marked regional disparities and diverse populations [14, 18]. A national cross-sectional survey has shown that the prevalence of hyperuricemia was 8.4% (9.9% in men and 7.0% in women) among Chinese adults from 2009 to 2010 [14]. A systematic review and meta-analysis systematically have shown that the pooled prevalence of hyperuricemia was 13.3% in Mainland China from 2000 to 2014 [18]. According to a large-scale population-based survey, the overall crude prevalence of hyperuricemia of the elderly and middle-aged population in Tibet Autonomous Region is 1.83%, relatively lower than other places in China. The prevalence in men is 2.86%, whereas it is only 0.75% in women [22]. Additionally, the age-standardized prevalence rate of hyperuricemia in Henan rural population is 12.60% from July 2015 to September 2017, consistent with the primary meta-analysis (11.7%). The prevalence and risk of hyperuricemia increase significantly with age. Interestingly, the decreased prevalence of hyperuricemia is observed in older men, while the contradictory trend is found in women [23].

Risk factors

The levels of urate hinge on the dynamic balance between purine-rich foods intake, synthesis of urate within the body, the excretion of urate via urine or the gastrointestinal tract (**Figure 1**) [24]. Prospective epidemiologic studies have pointed to obesity, hypertension, metabolic syndrome, diuretic use, dietary factors, and chronic kidney disease as risk factors for gout and hyperuricemia [9, 25-29]. Recently, it turns out that iron overload can enhance serum uric acid levels, indicating a causal connection between hyperferritinaemia and hyperuricemia [30]. It is well known that chronic noncommunicable diseases, such as cardiovascular and rheumatic diseases, are associated with the development of hyperuricemia [31-33]. An onset sequence study revealed that hyperuricemia is an earlier-onset metabolic disorder than hypertriglyceridemia, diabetes mellitus, and hypertension [34]. The study of epidemiological aspects of hyperuricemia in Poland shows that doctors often underestimate the problem of hyperuricemia in patients with a high risk of cardiovascular disease [32]. Due to increased comorbidity, moderate hyperuricemia has associations with increased cardiovascular mortality [35]. A 5-year Japanese cohort study indicated that hyperuricemia is an independent risk factor for developing hypertension, especially in children and adolescents [36]. Uric acid associated with pro-inflammatory immune effects can not only contribute to microvascular injury within the intracellular environment but also conduce to increased blood pressure [37, 38]. Hyperuricemia or gout has relationships with a substantial comorbidity burden in patients with rheumatoid arthritis [35]. Previous scientific investigations make general refer-

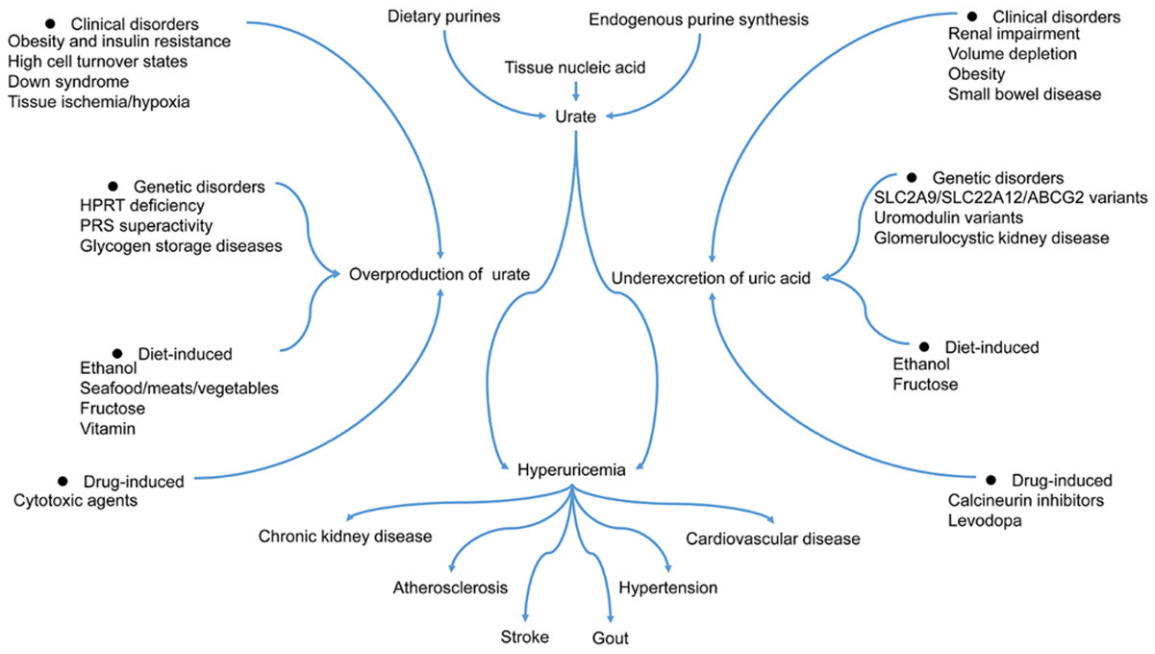

Figure 1. Mechanisms of hyperuricemia. HPRT, Hypoxanthine-guanine phosphoribosyltransferase; PRS, Phosphoribosylpyrophosphate synthetase.

ence to the relationship between excess serum uric acid and gout [39, 40]. Gout, a common rheumatic disease, characterized by the deposition of sodium monourate crystals in the periarticular joints, can mainly result from hyperuricemia [41]. Notably, some medicines used to treat chronic diseases have the side effects of elevated uric acid levels in the blood [24, 39, 42].

Some high-purine foods, such as beer, seafood, sugar-sweetened beverages, dried beans, and meat, can help raise serum uric acid levels. When purines break down to produce uric acid, it can cause hyperuricemia in some individuals [43-45]. However, there is limited information on the exact content of purines contained in foods mainly because several factors, such as food processing procedures, can affect its content. Some research suggests that purine-rich foods intake is closely associated with the prevalence of hyperuricemia. There was a direct and significant correlation between seafood intake and the prevalence of hyperuricemia, and an antagonistic relationship between soy food consumption and hyperuricemia among middle-aged Chinese men. Moreover, protein intake from animal or plant sources has the opposite contribution to the prevalence of hyperuricemia. Additionally, reducing the consumption of high-protein animal foods can help lower the levels of plasma uric acid [46]. The association between hyperuricemia and the intake of vitamin B12, vitamin B6, and folate among American adults was assessed according to the data from the National Health and Nutrition Examination Survey (NHANES) 2001-2014. The result revealed that the intakes of vitamin B12 and folate, but not vitamin B6, were associated with a reduced risk of hyperuricemia in males. The only intakes of food folate, folate, and total folate had associations with a lower risk of hyperuricemia in females [47].

According to a nationally representative survey, body mass index, alcohol use, Dietary Approaches to Stop Hypertension (DASH) diet, and diuretic use are modifiable risk factors, and they can be applied to illustrate the prevalence of hyperuricemia [48, 49]. Both endogenous and exogenous purine metabolism generates uric acid [42]. Previous studies capture much attention to fructose consumption because, during fructose metabolism, adenosine triphosphate (ATP) hydrolysis can generate adenosine diphosphate (ADP) and adenosine monophosphate (AMP), and the latter may stimulate the increase of serum uric acid concentrations and lead to hyperuricemia. Furthermore, fructose

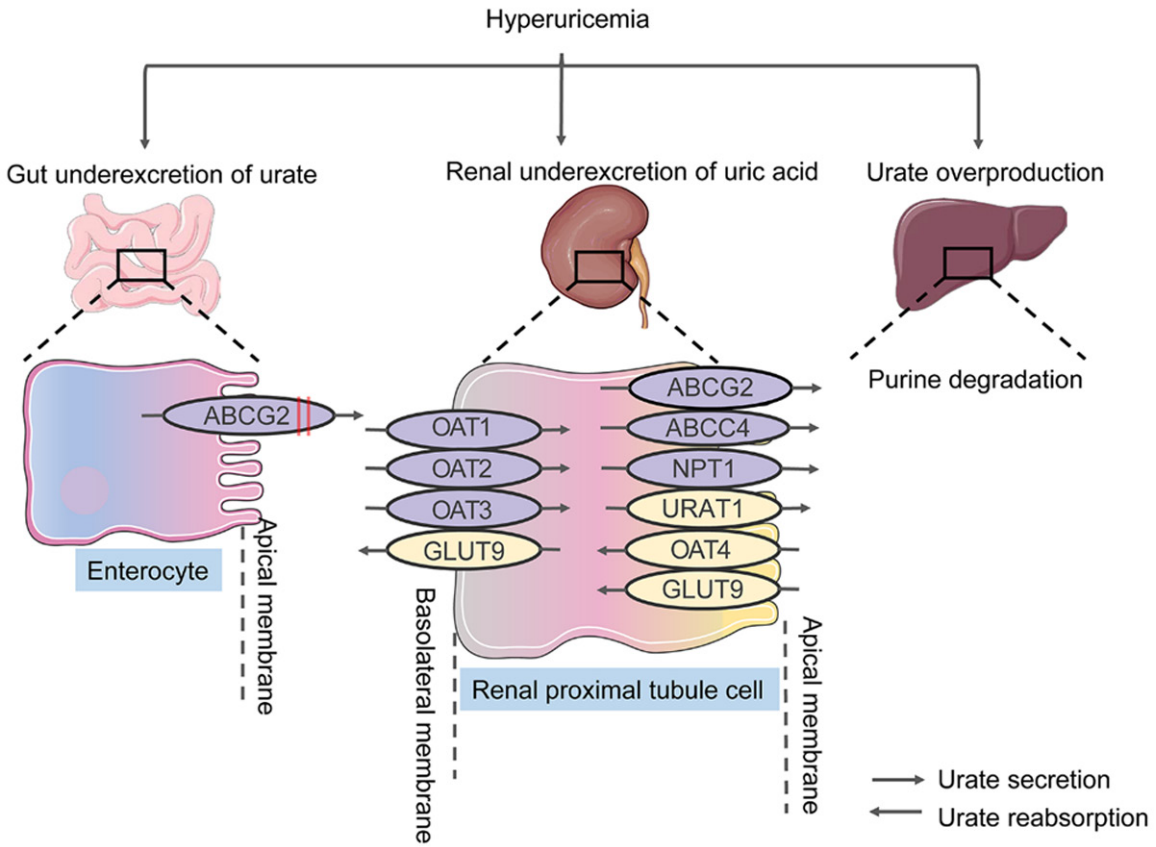

Figure 2. Urate transporters in humans. Overproduction and underexcretion of urate result in hyperuricemia. Underexcretion of urate occurs mainly in the proximal renal tubules. Urate overproduction in the liver and underexcretion of urate in the gut may lead to the occurrence of hyperuricemia. In the gut, Genetic variants in ABCG2 inhibit the excretion of urate and promote underexcretion. Numerous transmembrane transporters, such as ABCG2, URAT1, and GLUT9, have crucial roles in urate reuptake and secretion. OAT, organic anion transporter; NPT1, sodium-dependent phosphate cotransporter type 1; ABCG2, ABC transporter G family member 2; URAT1, urate anion exchanger 1; GLUT9, glucose transporter type 9; ABCC4, ATP-binding cassette sub-family C member 4.

intake can contribute to the biosynthesis of uric acid from amino acid precursors [50, 51]. Uric acid levels increase with the increase of body mass index (BMI), and obesity has an association with hyperuricemia. Additionally, hyperuricemia and obesity may ratchet up the likelihood of type 2 diabetes [52].

From the above, we can conclude that hyperuricemia is closely related to multiple risk factors. However, its pathophysiology has not yet been thoroughly investigated. We should pour enough attention to the adverse effects caused by hyperuricemia.

Genetics

Hyperuricemia, considered to result in a combination of environmental and genetic factors, is characterized by an excess of serum uric acid [53]. As shown in **Figure 2**, most uric acid disposal naturally occurs in the kidney. Insufficient excretion of urate in the kidney accounts for about 90% of individuals with hyperuricemia. Underexcretion associated with reduced glomerular filtration, impaired tubular secretion, and improved tubular reabsorption contributes to hyperuricemia. In the proximal tubular, URAT1 (uric acid transporter 1) manage uric acid reabsorption. Besides, multiple medications, extracellular fluid volume depletion, and organic acids facilitating transport lead to hyperuricemia. Furthermore, the kidney is held accountable for 60-65% of urate elimination associated with various transporters in the intestinal mucosa, salivary glands, and the proximal renal tubule. The filtered urate in the kidney via the glomerulus is mainly reabsorbed and secreted in the proximal tubule. Ultimately,

only 3-10% of the filtered urate is eliminated in the urine [54].

Uric acid, the end oxidation product of purine breakdown, is primarily excreted in the urine. It is clear that uric acid, a weak organic acid, circulates in the ionized shape of urate under normal physiologic conditions. The metabolism of purine chiefly happens in the liver, but it can occur in the tissues with a wide distribution of xanthine oxidase [3]. The excretion of uric acid from the kidney accounts for about two-thirds, and the remaining proportion of uric acid is mainly excreted into the intestine. Most uric acid is filtered in a free manner, with roughly 90% of the filtrate reabsorbed [55]. Enhanced cellular breakdown, endogenous purine production, and high-purine diets promote the production of urate, responsible for a small portion of hyperuricemia. High Purine Foods chiefly include some meats, some fish, seafood and shellfish, and alcoholic beverages, strengthening the levels of uric acid by lowering renal excretion. The higher phosphoribosylpyrophosphate (PRPP) synthetase activity, as well as hypoxanthine phosphoribosyltransferase (HPRT) deficiency, can not only improve endogenous purine production but also lead to uric acid overproduction and accumulation. Cell turnover or breakdown, such as tumor lysis, rhabdomyolysis, and hemolysis, can improve urate production. Ultimately, both environmental and physiological changes can influence the production of urate [56].

Patients who suffered from gout or hyperuricemia have elevated urate reabsorption in the proximal tubule. According to renal urate excretion, hyperuricemia is usually divided into urate overproduction type and underexcretion type. The urate reabsorption levels are driven by genetic variation in urate transporters or upstream regulators. Previous studies have confirmed that various genes are associated with hyperuricemia [57-59]. The great mass of the genes is involved in transporting urate, which is a byproduct of natural biochemical processes. Various hyperuricemia-associated genes regulate excretion or reabsorption of uric acid according to the body's needs. Some hyperuricemia-associated genes have relationships with the transport or breakdown of small molecules [57, 59, 60]. Researchers in mounting numbers tend to pay much attention to genetic studies, offering novel insights into the genetic effects on hyperuricemia. However, current research cannot fully account for the occurrence and progression of it. It is, therefore, crucial to conduct more extensive and intensive research on genetic studies.

Genome-wide association studies provide new perspectives on the genetic basis of hyperuricemia, which is dominated by loci containing urate transporters associated with urate excretion. Genome-wide association studies in hyperuricemia identify more genetic variants and delineate the pathogenesis of hyperuricemia, providing novel opportunities for underlying clinical translation [60]. A meta-analysis showed gout and asymptomatic hyperuricemia loci and reveal gout development by identifying the gout risk loci associated with crystal-induced inflammation [61, 62].

Previous research has revealed that various transporter genes have associations with serum uric acid levels, such as urate transporter 1 (URAT1), glucose transporter 9 (GLUT9), organic anion transporter 4 (OAT4), ATP-binding cassette transporter, subfamily G, member 2 (BCRP), and sodium-dependent phosphate cotransporter type 1 (NPT1). Among them, GLUT9 (SLC2A9) and BCRP (ABCG2) appear to have the most significant impact on urate levels [63].

GLUT9

GLUT9 (SLC2A9), encoding a member of the SLC2A facilitative glucose transporter family to maintain glucose homeostasis, has an essential role in urate transporter and reabsorption. The protein encoded by GLUT9 helps excrete urate into the urine or reabsorb urate into the bloodstream. GLUT9 variants can reduce the excretion of urate into the urine and enhance the reabsorption of uric acid into the bloodstream, leading to hyperuricemia [64]. The rs7442295 single nucleotide polymorphism in the SLC2A9 gene robustly associated with hyperuricemia, increased plasma uric acid levels, gout, and urate excretion has been proposed as a proxy measurement for uric acid. It has been used to explore its causal associations with ischaemic heart disease and blood pressure [51, 65]. Loss-of-function mutations in SLC2A9, interacting with the pore of the Glut9 urate transporter and the urate binding

pocket, decreased the expression of Glut9 and reduced the activity of Glut9 transport [66].

BCRP

BCRP (ABCG2), a member of the superfamily of ATP-binding cassette (ABC) transporters, is involved in the transport of several molecules across extra- and intra-cellular membranes. BCRP, an ATP-driven efflux pump in the apical membrane of the proximal tubule epithelial cells, excretes endogenous and exogenous substrates. BCRP dysfunction reduces the excretion of extra-renal urate, which is a significant contributor to hyperuricemia. Besides, the protein encoded by BCRP helps excrete urate into the gut, and it, therefore, can be removed from the body. Various functional variants of BCRP were identified and enhanced the risk of hyperuricemia and gout [67]. BCRP variants can reduce the excretion of urate into the gut, leading to hyperuricemia. Moreover, BCRP contributes to the clearance of urate in the gut [68, 69]. The BCRP 141K (rs2231142) variant contributes to hyperuricemia and has a role in the development of hyperuricemia to gout in Polynesian [70, 71]. Mutations in ABCG2 mediating the intestinal excretion of uric acid lead to hyperuricemia. In hereditary hemochromatosis patients, iron/heme overload enhances the activity of xanthine oxidase and accelerates the degradation of p53, causing the reduction of ABCG2 expression. In consequence, intestinal excretion of uric acid through ABCG2 is reduced and the production of uric acid is enhanced, leading to the accumulation of uric acid in tissue and serum and promoting the progression of hereditary hemochromatosis-associated arthritis [72].

URAT1

URAT1 (SLC22A12) as urate transporter gene to adjust and control blood urate levels is a disease-causing gene for renal hypouricemia type 1 [73, 74]. Glucocorticoids are crucial to maintaining uric acid homeostasis through the glucocorticoid receptor signaling pathway. Moreover, Glucocorticoids promote renal urate excretion via downregulating URAT1 in mouse kidney [75]. In a meta-analysis, the rs475688 polymorphism in SLC22A12 is associated with gout susceptibility and a significant association between hyperuricemia susceptibility and the rs3825016 polymorphism in SLC22A12 was observed [76]. The increased expression of ALPK1 reduced the expression of URAT1. The rs11726117 polymorphism in ALPK1 suppressed urate reuptake and reduced the risk of gout via SLC22A12 [77].

OAT4

OAT4 (SLC22A11), encoding an integral membrane protein, is associated with the sodium-independent transport and excretion of organic anions [51]. NPT1 (SLC17A1), a urate exporter, associated with the transport of phosphate into cells via Na (+) cotransport has crucial roles in the resorption of phosphate by the proximal tubule of the kidney [78].

OAT10

Organic anion transporter 10 (OAT10), also known as SLC22A13, encodes a urate reabsorption transporter protein on the apical side of the renal proximal tubular cells. OAT10 acts as a critical part of urate transport from urine to the blood and the dysfunctional variants of OAT10 reduce serum uric acid levels [79].

LDHD

Lactate Dehydrogenase D (LDHD) as a member of the D-isomer specific 2-hydroxyacid dehydrogenase family is involved in autosomal recessive gout with hyperuricemia and decreased excretion of uric acid. The mutations of LDHD result in the excessive production of blood D-lactate in exchange for uric acid reabsorption, eventually contributing to gout and hyperuricemia [80].

UMOD

Uromodulin encoded by UMOD is characterized as one of the most abundant proteins secreted in mammalian urine. Lower concentrations of urinary uromodulin associated with distal tubular cell damage are observed in individuals with UMOD-related diseases, such as familial juvenile hyperuricemic nephropathy (FJHN), renal disorders medullary cystic kidney disease-2 (MCKD2) and glomerulocystic kidney disease with hyperuricemia and isosthenuria (GCKDHI). Besides, uromodulin excretion in urine prevents urinary tract infections from uropathogenic bacteria. UMOD mutations impair uromodulin protein folding and accumulate mis-

folded proteins in the endoplasmic reticulum (ER) of renal tubular cells. The disruption of ER function contributes to hyperuricemia and tubulointerstitial nephritis [81, 82].

HPRT1

Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) encoded by hypoxanthine phosphoribosyltransferase 1 (HPRT1) is a transferase, which catalyzes the conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate. The catalytic reaction transfers the 5-phosphoribosyl group from 5-phosphoribosyl 1-pyrophosphate (PRPP) to the purine. HPRT1 exerts a vital part in purine nucleotide biosynthesis via the purine salvage pathway. HGPRT deficiency caused by HPRT1 mutation leads to elevated uric acid levels in the blood, which is associated with Kelley-Seegmiller syndrome, Lesch-Nyhan syndrome, and hyperuricemia [83, 84].

SARS2

The mitochondrial seryl-tRNA synthetase precursor, a member of the class II tRNA synthetase family, encoded by Seryl-TRNA Synthetase 2, Mitochondrial (SARS2), which catalyzes the ligation of Serine to tRNA (Ser) and is involved in selenocysteinyl-tRNA (sec) biosynthesis in mitochondria. Mutations in SARS2 have been identified in Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis syndrome (HUPRAS), which is a multi-system involvement disease including pulmonary hypertension, hyperuricemia, renal failure in infancy and alkalosis [85].

G6PC

Glucose-6-Phosphatase Catalytic Subunit (G6PC), a multi-subunit integral membrane protein of the endoplasmic reticulum, catalyzes the hydrolysis of D-glucose 6-phosphate to D-glucose and orthophosphate in the endoplasmic reticulum and is one of the critical enzymes in blood glucose homeostasis, exerting a critical part in the regulation of gluconeogenesis and glycogenolysis. Mutations in G6PC have been identified in Glycogen storage disease type I (GSD1), a metabolic disorder, is marked by hypoglycemia, hyperlipidemia, hyperuricemia, and lactic acidemia [86].

XDH

Xanthine Dehydrogenase (XDH), a member of the family of oxidoreductases, participates in the oxidative metabolism of purines, catalyzing the oxidation of hypoxanthine to xanthine and the oxidation of xanthine to uric acid. Sulfhydryl oxidation or proteolytic modification can convert xanthine dehydrogenase to xanthine oxidase. Xanthine dehydrogenase deficiency results in xanthinuria, leading to adult respiratory stress syndrome [87]. Downregulated XDH expression can reduce the levels of xanthine oxidoreductase, and it may be an underlying treatment for hyperuricemia [88, 89].

INS

Insulin (INS) encoded by INS is considered as an essential anabolic hormone in the metabolic process, participating in the control of carbohydrate and lipid metabolism. High levels of insulin in the blood hinder the production and secretion of glucose. As an anabolic hormone, it consolidates the conversion of small molecular substances in the blood into abundant molecular substances inside the cells. Low concentrations of insulin in the blood strengthen extensive catabolism. Insulin not only induces the change of cell permeability to fatty acids, amino acids, and monosaccharides, but also facilitates the synthesis of glycogen, the pentose phosphate cycle, and glycolysis in the liver. Insulin resistance may be a potential metabolic disturbance explaining the relationship among diverse elements of the metabolic syndrome associated with glucose intolerance, hyperlipidemia, hypertension, and obesity. Besides, hyperuricemia may be an underlying marker of insulin resistance [90, 91].

REN

REN encoding renin causes autosomal dominant tubulointerstitial kidney disease, REN-related (ADTKD-REN) characterized by low plasma renin activity, bland urinary sediment, decreased fractional excretion of urinary uric acid, hyperuricemia, and hypoproliferative anemia. Hyperuricemia is depicted in 80% of patients with ADTKD-REN beginning in childhood due to reduced renal excretion of uric acid [92, 93].

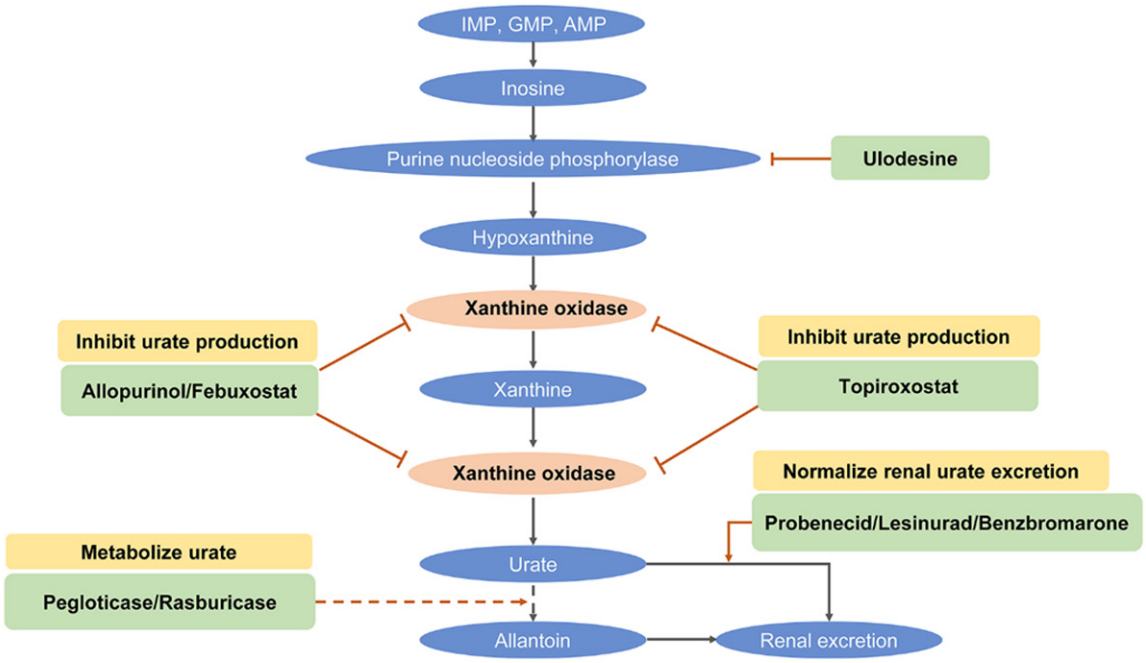

Figure 3. Mechanism of urate-lowering therapy for hyperuricemia. Numerous agents can be applied to inhibit urate production, promote renal urate excretion, and increase purine metabolism to allantoin.

GPATCH8

G-Patch Domain Containing 8 (GPATCH8), a member of the G-patch domain family, is encoded by GPATCH8. A potentially pathogenic mutation in GPATCH8 is a conceivable candidate for hyperuricemia [94].

Drugs for hyperuricemia

According to the clinical scenarios, hyperuricemia can be divided into asymptomatic or symptomatic hyperuricemia. Decreasing unnecessary costs and avoiding underlying side effects take precedence over taking medication in careful consideration of the interests of the asymptomatic hyperuricemia patients. There seems no need to carry medical therapy for a multitude of asymptomatic hyperuricemia patients. They accompany with an elevated serum urate level but never experience signs or symptoms of monosodium urate crystal deposition disease, such as nephrolithiasis, gout, and uric acid renal disease. Urate-lowering drugs are likely to appeal to the asymptomatic hyperuricemia patients subjected to cytolytic therapy for a malignant tumor to restrict tumor lysis syndrome. It is sufficient to change in lifestyles, such as exercise, dietary changes, and alcohol consumption, for asymptomatic hyperuricemia patients to decrease the levels of uric acid [95]. The clinical symptoms of symptomatic hyperuricemia can be gout, nephrolithiasis, and uric acid renal disease [39].

To effectively manage hyperuricemia, inhibiting uric acid synthesis and reabsorption, as well as facilitating the excretion of uric acid, can be alternative strategies. As shown in **Figure 3**, urate-lowering medications can be roughly divided into three main categories: reducing the synthesis of uric acid (xanthine oxidase inhibitors), enhancing the excretion of uric acid (URAT1 inhibitors), and regulating the metabolic hydrolysis of uric acid (uricase inhibitors). Xanthine oxidase inhibitors classified as purine analogs (including allopurinol) and non-purine analog agents (including febuxostat and topiroxostat) can lower endogenous uric acid production and further decrease the levels of uric acid [96, 97].

Allopurinol

Allopurinol, a purine-based competitive xanthine oxidase inhibitor, can be metabolized to alloxanthine, an inhibitor of xanthine oxidase enzyme. Both allopurinol and alloxanthine can restrain xanthine oxidase, converting hypoxanthine to xanthine and xanthine to uric acid.

Allopurinol promotes the secondary utilization of hypoxanthine and xanthine for the synthesis of nucleic acid and nucleotide by a metabolic reaction associated with hypoxanthine-guanine phosphoribosyltransferase (HGPRTase). This metabolic reaction accounts for an elevated level of nucleotide, which leads to feedback suppression of de novo synthesis of purine. Eventually, the reduced levels of urine and serum uric acid are responsible for a reduction in the incidence of hyperuricemia [98, 99]. Based on the data from the Taiwan National Health Insurance Research Database, a retrospective nationwide population-based study showed that allopurinol could cause hypersensitivity reactions in patients with asymptomatic hyperuricemia accompanied by cardiovascular or renal diseases [100].

Febuxostat

Febuxostat, a non-purine xanthine oxidase inhibitor, can reduce the levels of serum uric acid, but not restrain different enzymes associated with the metabolism and synthesis of pyrimidine and purine. The metabolism of Febuxostat is dependent on uridine diphosphate glucuronosyltransferase (UGT) enzymes (including UGT1A1, UGT1A3, UGT1A9, and UGT2B7), cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C8, and CYP2C9) and non-P450 enzymes [99, 101]. Based on US Medicare claims data (2008-2013), a cohort study on the assessment of cardiovascular risk in 99744 older medicare patients with gout showed that there was almost no difference in the risk of all-cause mortality, new-onset heart failure, myocardial infarction, coronary revascularization, or stroke between patients who used febuxostat compared with allopurinol initiators. Nevertheless, the risk of heart failure exacerbation was slightly lower in patients initiating febuxostat compared with allopurinol [102]. A randomized and controlled trial showed that treatment with febuxostat did not delay carotid atherosclerosis progression in Japanese patients with asymptomatic hyperuricemia and it did not support the use of febuxostat to delay the progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia [103].

Topiroxostat

Topiroxostat, a non-purine xanthine oxidase inhibitor, makes interaction with numerous amino acid residues in the solvent channel and bonds covalently to molybdenum (IV) ion, generating a hydroxylated 2-pyridine metabolite to inhibit xanthine oxidase. Additionally, Topiroxostat can restrain ATP-binding cassette transporter G2 (ABCG2), which is involved in the restoration of renal uric acid and uric acid secretion from the intestines [104].

Probenecid

Probenecid, a prototypical uricosuric agent, hinders the renal elimination of organic anions and impairs tubular urate reabsorption. Additionally, it can decrease the renal elimination of other drugs, and therefore it is a promising uric acid transporter 1 (URAT1) inhibitor for the treatment of renal impairment. Probenecid restrains the tubular urate reabsorption, facilitating urinary uric acid excretion, as well as reducing serum urate concentrations. Besides, Probenecid possibly decreases the binding of urate by plasma proteins and reduces uric acid secretion in the renal tubule [97, 105].

Lesinurad

Lesinurad, a common URAT1 inhibitor, restrains the levels of serum uric acid via the suppression of URAT1 and OAT4. URAT1, uric acid transporter, is associated with uric acid reabsorption from the renal tubule. Organic anion transporter 4 (OAT4), uric acid transporter, is linked with the sodium-independent transport and excretion of organic anions, involved in diuretic-induced hyperuricemia [98]. The administration of Lesinurad in combination with allopurinol causes a considerable reduction in serum concentrations of inflammatory cytokines, glutathione peroxidase, catalase, urea nitrogen, and uric acid in a hyperuricemic mouse model, ameliorating renal function of the hyperuricemic mice [106]. In vitro, lesinurad suppressing the activity of OAT4 and URAT1 but not GLUT9, OAT1, OAT3, or ABCG2 can reduce the levels of serum uric acid via restraint of urate transporters in the human kidney [107].

Rasburicase

Rasburicase, a recombinant uricase, catalyzes the conversion of uric acid to allantoin, which is a metabolite existing in an inactive and soluble form [108]. Rasburicase seems to have an advantage in the speedy correction of hyperuricemia compared with allopurinol. However, its

clinical benefit in cancer patients with tumor lysis syndrome (TLS) is still confusing, especially for patients with concurrent renal failure and hyperuricemia [109].

Conclusions

Hyperuricemia seems to be rising steadily in prevalence over the last decades. High uric acid concentrations are involved in the elevated risk of developing hyperuricemia. Hyperuricemia is a metabolic disease connected with Lesch-Nyhan syndrome and glycogen storage disease-ia. Substantial evidence suggests that hyperuricemia is an underlying risk factor for gout, and it can forecast the evolution of chronic kidney disease, obesity, diabetes, and hypertension. Although numerous studies have demonstrated close correlations between hyperuricemia and multiple comorbidities such as acute and chronic kidney disease, diabetes, metabolic syndrome, cardiovascular disease, hypertension, and dyslipidemia, it is currently unclear that there is a causal relationship between hyperuricemia and multiple comorbidities. Genetic characteristics provide novel perspectives on the physiology and pathophysiology of hyperuricemia. More importantly, genetic studies may provide more precision medicine for individuals. These are various approaches that help manage hyperuricemia. Nevertheless, patient and health-care provider education is the foundation of the successful treatment of hyperuricemia. As a general rule, it is not indispensable to treat most patients with asymptomatic hyperuricemia in the absence of kidney stones or gout. To effectively treat hyperuricemia, reducing the levels of uric acid is crucial, achieved by inhibiting uric acid synthesis and reabsorption, as well as facilitating the excretion of uric acid.

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Disclosure of conflict of interest

None.

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