

# Insights into the relationship between serum uric acid and pulmonary hypertension (Review)

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**Abstract.** Pulmonary hypertension (PH) is a progressive lethal disease, which is characterized by abnormal vascular remodeling and persistently elevated pulmonary artery pressure, eventually leading to right heart failure and even death. Although great progress has been made in treating PH, the mortality rate remains high. Metabolic disorders are one of the important hallmarks of PH. Obesity, lipids, glucose tolerance and insulin resistance are risk factors for numerous cardiovascular diseases and are often accompanied by a considerable increase in serum uric acid (SUA) concentrations. Uric acid (UA) is the end product of purine nucleotide metabolism and is closely related to cardiovascular diseases including PH. Hyperuricemia promotes the development and progression of PH through endothelial dysfunction, oxidative stress, inflammatory responses and activation of the renin-angiotensin system. In the present review, the advancements in knowledge about UA metabolism and PH, and the current understanding of the potential interactions and mechanisms of SUA in PH were systematically summarized, which may provide new insights into the pathogenesis of PH.

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## 1. Introduction

Pulmonary hypertension (PH) is a serious health problem that affects ~1% of the global population (1). In the United States and Europe, pulmonary arterial hypertension (PAH) is found in 15-50/million individuals (2). Among them, idiopathic, heritable and anorexigen-induced PH account for 52.6% of total PH cases, of which 6-10% of patients have a family history of PH (3,4). Furthermore, >70% of patients with PAH are women aged 20-40 years, and its incidence is twice as high as that in men (5-7). Although the advancement of medical treatments has improved the survival rate, the prognosis of PH is still poor, and its mortality rate remains high (8). The 5-year mortality rates of patients diagnosed with idiopathic pulmonary arterial hypertension (IPAH) or familial PH were 31.8 and 46.3%, respectively in China as of 2014 (9). Increasing evidence has shown that a variety of systemic metabolic derangements are associated with PH with a number of studies on this topic focused on the role of obesity, dyslipidemia, insulin resistance (IR), glucose intolerance and metabolic disorder in the progression of pulmonary circulation diseases (10-13). Hyperuricemia is an important metabolic syndrome and is closely associated with gout, coronary heart disease, hypertension, heart failure and atrial fibrillation through oxidative stress, endothelial

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dysfunction, inflammatory reactions and activation of the renin-angiotensin-aldosterone system (14-17). These conditions may directly lead to the occurrence or development of these diseases (18-25). Whether hyperuricemia is an independent risk factor of PH and how hyperuricemia promotes the occurrence of PH remains to be determined. To the best of our knowledge, there has been no systematic analysis of these issues to date. In the present review, the complex relationship between hyperuricemia and PH is focused on providing a novel viewpoint and strategy for the prevention and treatment of PH.

## 2. Search strategy

PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science ([webofscience.com/](https://www.webofscience.com/)) and Science Direct (<https://www.sciencedirect.com/>) databases were searched for PH and uric acid (UA; hyperuricemia) relevant studies and systematic reviews without language or time restrictions. The search subject terms included: Pulmonary hypertension, pulmonary arterial hypertension, IPAH, secondary PH, cardiovascular disease, UA, serum UA (SUA), hyperuricemia, metabolic, inflammatory responses, oxidative stress, renin-angiotensin system, endothelial dysfunction, smooth muscle cell proliferation. No artificial intelligence tools were used in the preparation of the reviews or manuscripts.

## 3. Pathophysiological basis of PH

PH is a chronic progressive disease, which is related to metabolic processes (26). PH is characterized by rising pulmonary artery pressure and vascular remodeling, which eventually lead to right heart failure and death (27). According to the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension, PH is defined on the basis of right heart catheterization hemodynamic assessment. Pre-capillary PH is defined as mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, pulmonary arterial wedge pressure (PAWP) <15 mmHg and pulmonary vascular resistance (PVR) >2 Wood units at rest. Postcapillary PH is defined as mPAP >20 mmHg and PAWP ≥15 mmHg at rest. Exercise PH is defined as an mPAP/cardiac output slope >3 mmHg/l/min between rest and exercise (28,29). Currently, the clinical classification of PH follows the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH (30,31) and the Proceedings of the 6th World Symposium on PH (32). PH is divided into five categories according to the etiology and hemodynamic parameters (33) as follows: i) PAH, including idiopathic and hereditary PH; ii) PH caused by left heart disease, including heart failure and valvular heart disease with a maintained or decreased ejection fraction; iii) PH caused by pulmonary diseases and/or hypoxia, including chronic obstructive pulmonary disease, interstitial lung disease and other pulmonary diseases with mixed restrictive and obstructive modes; iv) chronic thromboembolic PH and other pulmonary artery obstructions; and v) PH with unclear and/or multifactorial mechanisms, including blood and systemic disease (31,34). PH is not a disease isolated to pulmonary circulation but is considered a systemic disease associated with notable metabolic dysfunction (35). Among these, PH caused by left heart disease, lung disease and/or

hypoxia and connective tissue disease may be closely related to metabolic disorders of the pulmonary circulation (36-38). When pulmonary circulation metabolism is disordered, circulating metabolic substances can induce dysfunction of pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs), and stimulate excessive proliferation and anti-apoptosis of pulmonary vascular cells (26). These conditions eventually lead to pulmonary vascular remodeling and provide conditions for the development of PH (39,40). UA, which is one of the products of purine metabolism, can be affected in certain pathological states, resulting in abnormal UA concentrations in the pulmonary circulation. Although, increased UA in the pulmonary circulation deteriorates PH, the associated molecular mechanisms remain unclear (41). Before determining the effect of UA on PH, the sources, metabolic pathways and biological properties of UA need to be understood.

## 4. Metabolism and biological characteristics of UA

*Source and metabolism of UA.* UA can be derived exogenously and endogenously. Exogenous UA, which accounts for 20% of the total UA, originates from exogenous foods rich in purine compounds, nucleic acids and nucleoproteins, such as animal viscera, seafood, mushrooms, beans, wine and meat (42). Endogenous UA accounts for 80% of the total sources and is derived from purine products formed by the transformation, decomposition and metabolism of amino acids, phosphoribosyl and nucleic acids in the body (43,44).

There are numerous enzymes involved in the conversion of adenine and guanine to UA. Xanthine oxidase is the key rate-limiting enzyme in this process and it plays an important role in purine metabolism. Xanthine oxidase is involved in two important stages in the conversion of purines to UA: i) The conversion of hypoxanthine to xanthine; and ii) the conversion of xanthine to UA (45). Hypoxanthine nucleotides (inosine monophosphate) and guanine nucleotides are converted to xanthine by oxidation of xanthine oxidase-hypoxanthine and deamination of guanine by guanine deaminase (46). Finally, xanthine is further oxidized to UA by xanthine oxidase (46-48). In most mammals, uricase further oxidizes UA to allantoin, but humans cannot convert UA into allantoin, which is more soluble owing to the lack of uricase (Fig. 1) (49-51). Therefore, human purine catabolism ends in the UA stage.

The metabolism of SUA *in vivo* requires an important transporter called human urate transporter 1 (URAT1), which is encoded by the gene, *SLC22A12* (52). It is expressed in the mural membrane of proximal renal tubular cells (53,54). Human URAT1 acts as a urate/anion exchanger and is involved in the reabsorption of urate in the kidneys (55). At a physiological pH, UA mainly exists in the form of urate (46). Reportedly, ~70% of UA is metabolized in the kidney, and after filtration by the glomerulus, more than 90% of UA is reabsorbed and secreted by the renal tubules, with ~10% excreted in the urine (46,56). In addition, ~30% of UA is metabolized in the intestine (42). Adenosine triphosphate binding cassette transporter 2, which is another urate transporter, is widely expressed on the surface of intestinal lumen cells and plays a major role in intestinal excretion (Fig. 2) (57-60). Therefore, UA excretion occurs mainly in the kidneys and intestines.

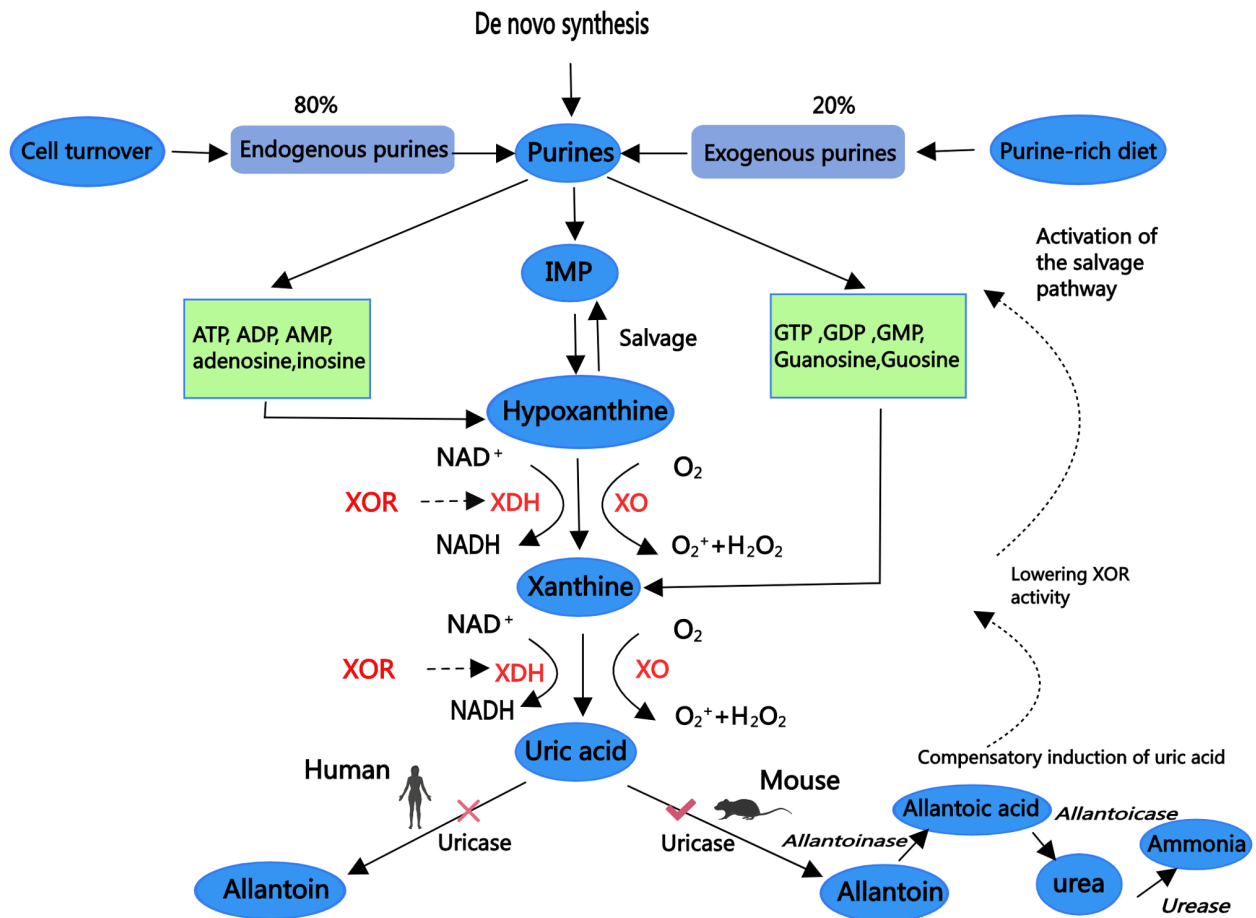


Figure 1. Sources and metabolism of UA. Endogenous and exogenous purines are metabolized to UA by XO through the *de novo* and remedial synthesis pathways of purines. Purine metabolism terminates at the UA stage owing to the absence of uricase in the human body. However, rodents have the enzyme allantoinase, which metabolizes UA into the more soluble allantoin, and further breaks it down into urea and ammonia. XO, xanthine oxidase; UA, uric acid; IMP, inosine monophosphate; XDH, xanthine dehydrogenase; XOR, xanthine oxidoreductase.

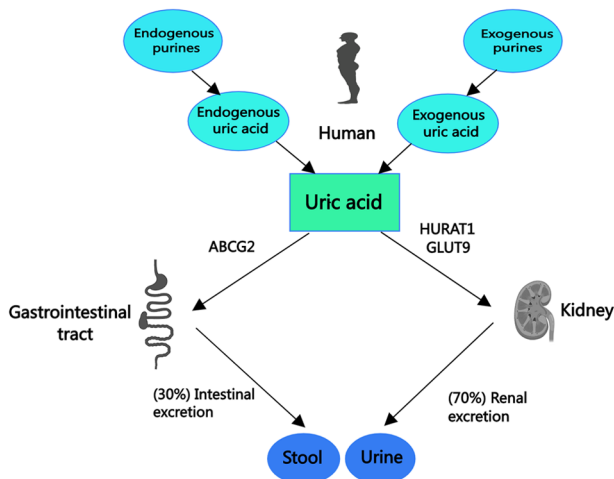


Figure 2. Excretion routes of UA. Endogenous and exogenous purines are ultimately synthesized into UA through a variety of metabolic pathways. A total of 30% of the body's UA is excreted through the intestines and 70% in the kidneys. UA, uric acid; ABCG2, ATP-binding cassette superfamily G member 2; HURAT1 human uric acid transporter 1; GLUT1, glucose transporter 1.

Normal SUA concentrations are 89-357  $\mu\text{mol/l}$  (1.5-6.0 mg/dl) in women and 149-417  $\mu\text{mol/l}$  (2.5-7.0 mg/dl)

in men (46). However, impaired purine metabolism in the body, such as excessive purine food intake and disease (e.g., obesity, diabetes and tumor), can lead to increased UA production and/or decreased excretion, which further results in an increase in SUA concentrations and even hyperuricemia (61). Hyperuricemia is usually defined as an SUA concentration  $>417 \mu\text{mol/l}$  (7.0 mg/dl) in men and postmenopausal women, or  $\geq 357 \mu\text{mol/l}$  (6.0 mg/dl) in premenopausal women with a normal purine diet (46). When the average SUA concentration in humans is higher than its solubility limit of  $405 \mu\text{mol/l}$  (6.8 mg/dl), urate crystals are formed and deposited in the kidneys, tissues and joints (62), leading to renal calculi, gout and other diseases (e.g., gouty arthritis).

The variability of SUA concentrations is multifactorial, and it is also affected by genetic and non-genetic factors (63). Genome-wide association studies have shown that the polymorphism and mutations of genes encoding SLC22A12, SLC2A9 and adenosine triphosphate binding cassette transporter 2 are related to hyperuricemia (64). In addition, the transporters URAT1, glucose transporter 9 (GLUT9) and breast cancer resistance protein are associated with hyperuricemia and gout (64-67). The concentration of UA is influenced by non-genetic factors, mostly caused by excessive intake and decreased excretion.

**Physiological characteristics of UA.** Biologically, UA can have not only pro-oxidative but also anti-oxidative properties (68-72). UA has antioxidant effects under physiological conditions. The antioxidant mechanism of UA is mainly driven by the fact that UA is an oxygen radical scavenger, scavenging superoxide anions, hydroxyl groups, singlet oxygen and other reactive substances *in vivo* (73,74). This protects the cardiovascular system from oxidative stress damage. UA acts as a pro-oxidant in states with high levels of UA or low levels of other antioxidants (68). The oxidative effects of UA mainly manifest in mediating the immune response after cell injury (75), increasing pro-inflammatory immune activation (76) and promoting low-density lipoprotein oxidation (77), the proliferation of smooth muscle cells and activation and the adhesion of platelets (78). In the presence of  $\text{Cu}^{2+}$  in the *in vitro* environment, UA is susceptible to antioxidant-oxidant interconversion (79,80). In addition, UA can react with other oxidants ( $\text{ONOO}^-$ ,  $\text{OH}^-$ ) and form pro-oxidants, which participate in lipid metabolism and cause a chain reaction of lipophilic radical oxidation (81,82). Therefore, UA exerts oxidative and antioxidant effects at different concentrations (83,84). In cardiovascular disease, UA is considered a 'double-edged sword' with beneficial and detrimental effects on cardiovascular disease (17,85). So, is there a similar association between UA and PH?

## 5. Interaction of UA and PH

**PH affects the level of UA metabolism.** Hyperuricemia is commonly found in patients with secondary PH. Patients with PH and hemolytic diseases, such as thalassemia (86), sickle cell anemia (87), spherocytosis (88) and paroxysmal sleep hemoglobinuria (89,90), can develop erythrocyte lysis, adenosine deaminase release (91), tissue and organ hypoxia, reduced oxygen-carrying capacity and increased UA metabolism (92). In patients with PH and metabolic syndrome (93), hyperinsulinemia enhances the reabsorption of urate in the proximal tubules and UA concentrations increase (94). Inflammation, hypoxia and endothelial damage caused by connective tissue disease-related PH, such as systemic sclerosis, systemic lupus erythematosus and Sjogren's syndrome, also play an important role in the increase in UA concentrations (95). After inflammation is activated, the release of cytokines promotes pulmonary artery vessel remodeling and cell proliferation, resulting in insufficient lung perfusion, tissue ischemia and hypoxia (96,97). These findings suggest that patients with secondary PH are closely associated with abnormal UA metabolism, and the SUA concentration reflects the severity of the illness to a certain extent. Therefore, UA may be useful as a potential biological marker of PH and may be able to be applied to the clinical setting and therefore, the importance of the application of UA in clinical treatment is discussed in the present review.

**UA as a potential biomarker of PH.** The relationship between SUA and IPAH was first discovered in 1999 (98). Nagaya *et al* (98) found that patients with IPAH have considerably elevated SUA concentrations and the degree of SUA increase was positively correlated with the severity of New York Heart Association (NYHA) classification (99), negatively

correlated with cardiac output, positively correlated with total pulmonary resistance, and correlated with the severity of IPAH, which was also an independent risk factor for poor prognosis of IPAH (98). The logarithm of SUA concentration was closely related to MPAP and right atrial pressure (100-102). When SUA concentrations are  $>339 \mu\text{mol/l}$  (5.7 mg/dl), SUA concentrations predict right ventricular dysfunction in patients with IPAH (102,103). Baseline hyperuricemia and high variability in SUA concentrations at the first follow-up are strongly associated with 5-year mortality in patients with IPAH (104). Elevated SUA concentrations shorten the survival of patients with IPAH, whereas low SUA concentrations improve survival and delay clinical deterioration (105). Therefore, in the long term, high SUA concentrations may be a good predictor of survival in patients with IPAH. Close monitoring of UA concentrations may be useful in assessing the disease severity, clinical prognosis of patients with PH and early detection of patients at high risk of death from IPAH.

Similar to IPAH, UA has high clinical value in connective tissue disease-associated PH. In patients with PH secondary to systemic sclerosis, elevated SUA concentrations are negatively correlated with the 6-min walk test distance and linearly correlated with pulmonary artery pressure (106-109). Serum uric acid concentrations were significantly elevated in patients with systemic lupus erythematosus (SLE) secondary to PH and were significantly correlated with plasma NT-pro-B natriuretic peptide (NT-pro-BNP) levels and resting pulmonary systolic pressure (sPAP), as well as responding to the severity of SLE disease (110). When SUA is above the critical concentration of 6.5 mg/dl, the incidence of PH in patients with SLE can be reasonably and accurately predicted. Therefore, SUA concentrations can be used as an alternative marker to screen for PH in patients with SLE (111). When the baseline SUA concentration is  $\geq 416 \mu\text{mol/l}$  (7 mg/dl), future development of PH secondary to SLE can be predicted (112). A multifactorial analysis showed that high UA concentrations were not only associated with all-cause mortality from disease but also strongly associated with death from PH and thus, UA concentrations may serve as an independent predictor of survival in patients with connective tissue-related PH (113). Therefore, dynamic observation of SUA concentrations may be useful for assessing the severity of the condition and serve as a predictor of prognosis in connective tissue disease-associated PH.

In conclusion, UA is not only a marker of metabolism but also a representative independent risk factor and predictor of PH. The aforementioned evidence suggests that UA is closely associated with PH (114-117). However, the specific mechanisms involved in hyperuricemia promoting the development and progression of PH is unclear. In the present review, the effects of high UA concentrations on PH and the molecular mechanisms of the effects of high UA concentrations on endothelial cells, smooth muscle cells and renin-angiotensin system (RAS) activation are described.

## 6. Hyperuricemia promotes the development of PH

Hyperuricemia can mediate the development of cardiovascular disease by inducing endothelial dysfunction, oxidative stress, inflammatory responses and activation of the RAS (Fig. 3) (118-122). On a pathophysiological basis, UA also

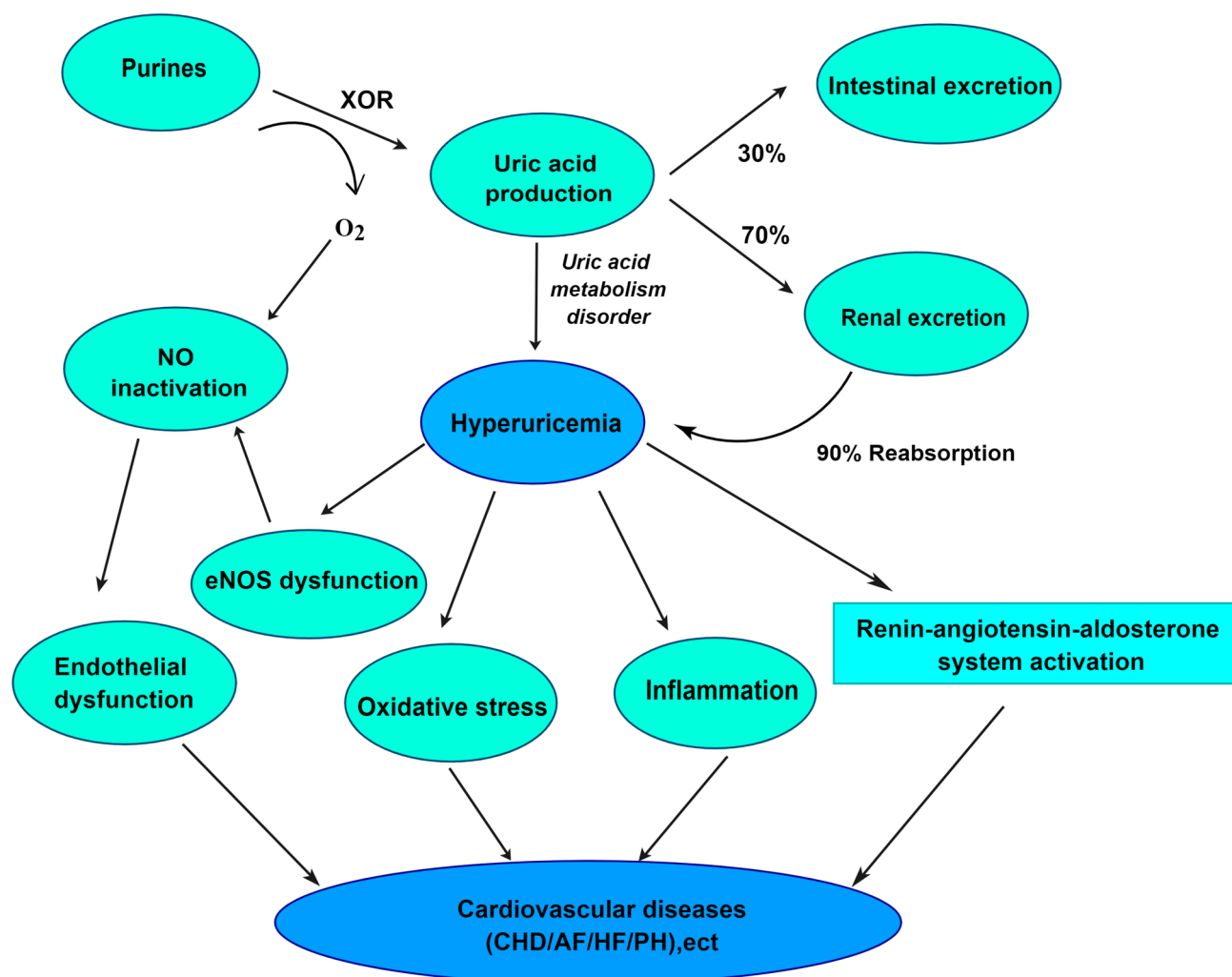


Figure 3. High UA affects the development of cardiovascular disease through endothelial dysfunction, oxidative stress, inflammation and activation of the RAS system. Disturbances in UA metabolism can cause hyperuricemia, which affects the development and progression of cardiovascular diseases through endothelial dysfunction, oxidative stress, inflammation and activation of the RAS system. Pre-capillary PH: mPAP >20 mmHg, PAWP <15 mmHg and PVR >2 Wood units at rest. Post-capillary PH: mPAP >20 mmHg and PAWP ≥15 mmHg at rest. PH, pulmonary hypertension; CHD, coronary heart disease; AF, atrial fibrillation; HF, heart failure; RAS, renin-angiotensin system; UA, uric acid; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; NO, nitric oxide; eNOS, endothelial NO synthase; XOR, xanthine oxidoreductase.

induces pulmonary vascular endothelial dysfunction and promotes the transformation of smooth muscle cell proliferation (123,124), thereby possibly promoting the development of PH. The series of molecular mechanisms whereby UA affects the course of PH through a series of molecular mechanisms are described in the present review.

**UA induces endothelial dysfunction.** Endothelial cells are in direct contact with blood flow and act as a permeability barrier to maintain the exchange between the tissues of the vessel wall and blood (125,126). Furthermore, endothelial cells secrete vasoactive substances and cytokines, which also play an important role in regulating vasoconstriction, vascular inflammation, platelet aggregation and adhesion (127). Therefore, the integrity of endothelial function plays a major role in maintaining cardiovascular homeostasis.

Endothelial dysfunction is one of the main pathological features of PH (128-130). Numerous studies have shown that hyperuricemia causes endothelial dysfunction and may play an important role in the vascular remodeling of PH (131).

However, the specific mechanisms by which UA affects endothelial dysfunction are not fully understood.

Nitric oxide (NO) is an endothelium-derived relaxing factor and it regulates vascular tension, inhibits platelet activation and causes intimal hyperplasia (132). High UA concentrations are hypothesized to result in endothelial dysfunction by affecting the production of NO, which may contribute to PH (133). UA may affect the formation of NO in two ways. Firstly, UA can be directly oxidized with NO to form superoxide anion, which consumes high levels of NO. Secondly, there are various pathways by which UA inhibits NO production which are described in the present review.

Endothelial NO synthase (eNOS) is a key enzyme for NO synthesis in endothelial cells. This enzyme catalyzes the hydrolysis of L-arginine to produce NO (134). UA can enter endothelial cells through URAT1 on the cell membrane (135), inducing intracellular reactive oxygen species production, endoplasmic reticulum stress and protein kinase C activation (136). Activated protein kinase C inactivates the inhibitory site of eNOS, Thr495, by phosphorylating it and rendering it

unable to bind calmodulin and catalyzes NO synthesis (136). In addition to regulating glucose homeostasis, insulin activates the signal of phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt), which promotes the activation of eNOS phosphorylation and NO production, thus inducing vasodilation (137). Hyperuricemia antagonizes insulin receptor substrates and blocks insulin-dependent eNOS phosphorylation in the PI3K/Akt/eNOS pathway, thereby inhibiting NO production (137,138). Elevated UA concentrations in patients with metabolic syndrome (MS) can trigger endothelial dysfunction by decreasing endothelial NO bioavailability, while reduced NO production in this pathway may be associated with hyperinsulinemia and insulin resistance (IR) (139), which lead to increased monocyte adhesion and impaired cellular energy metabolism (140,141). However, allopurinol may restore the effect of insulin on NO production and vasodilation by reducing SUA concentrations, thereby improving the associated clinical symptoms (142,143).

UA also increases the expression of the inflammatory cytokines interleukin-6 and interleukin-8, tumor necrosis factor- $\alpha$  and miR-155 by activating nuclear factor- $\kappa$ B (NF- $\kappa$ B) (144,145). Overexpression of miR-155 leads to decreased eNOS stability, reduced NO production and endothelial dysfunction (146). By contrast, the use of NF- $\kappa$ B inhibitor II can prevent the UA-induced decrease in NO and the inflammatory reaction (145). Furthermore, arginase competes with eNOS to bind L-arginine and catalyze its hydrolysis to ornithine and urea (147). However, UA reduces NO production in endothelial cells by increasing arginase activity and promoting competition between arginine and eNOS for L-arginine (41,147). Mitochondrial damage is also a major feature of endothelial dysfunction. UA can trigger mitochondrial calcium overload and reactive oxygen species production by activating the mitochondrial Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (148). This process can inhibit the tricarboxylic acid cycle and damage mitochondrial DNA, thus leading to endothelial dysfunction (149). These findings suggest that UA induces reduced NO production and vascular endothelial dysfunction, which in turn causes abnormal pulmonary vasoconstriction and provides a pathophysiological basis for the development of PH.

*UA promotes smooth muscle cell proliferation.* UA can enter vascular smooth muscle cells (VSMCs) via URAT1 (SLC22A12, a member of the organic anion transporter superfamily) (150,151), stimulating specific mitogen-activated protein kinases (MAPKs), ERK 1/2 and p38 MAPK (152,153). This stimulation induces cyclooxygenase-2 production and local coagulation, promotes platelet-derived growth factor (PDGF)-A and PDGF-C chain secretion and upregulates PDGF-A receptor mRNA expression, promotes VSMC proliferation, increases cell survival and reduces apoptosis (123,153-159). However, angiotensin II (Ang II) type I receptor inhibits UA-induced activation of p38 MAPK and ERK 1/2, thereby blocking the proliferative pathway of VSMCs (153,160). In addition, UA may also regulate the proliferation of smooth muscle cells by inducing inflammatory responses and activation of the chemokine monocyte chemoattractant protein 1, transcription factor activator protein-1, NF- $\kappa$ B and inflammasome NOD-like receptor protein 3 (153,161,162). Xanthine oxidase and URAT1 were

up-regulated in remodeled pulmonary artery walls in patients of IPAH, monocrotaline (MCT) and Sugen-hypoxia rats, increasing intracellular UA production, which promotes the proliferation of pulmonary artery smooth muscle cells, leading to further deterioration of PH (163). Thus, UA promotes smooth muscle cell proliferation and may play an important role in vascular remodeling in PH.

*Activation of the RAS by UA aggravates pulmonary artery pressure.* The RAS is an important and complex endocrine system in the body. It not only plays an important role in regulating blood pressure and maintaining extracellular fluid homeostasis, but also affects the normal development of the cardiovascular system and maintains homeostasis of cardiovascular function (164). Several studies have shown that elevated SUA concentrations may be associated with activation of the RAS (121,161,165-168). In animal studies, high UA concentrations inhibited NOS-1 activity in glomerular dense plaques, downregulated NO production and activated the RAS (157,160,169-171), leading to elevated blood pressure. These findings are consistent with human studies suggesting that UA activates the RAS to mediate an elevation in blood pressure (172,173). Usually, the activation of RAS begins with the decrease of blood flow through renal artery (174). The production of angiotensin peptides is first initiated by the synthesis and processing of prorenin in juxtaglomerular cells neighboring the renal glomerulus with subsequent proteolytic cleavage of the signal peptide, intracellular sorting of prorenin to dense-core secretory vesicles, and cleavage of the prosegment, producing catalytically active renin that is secreted in the systemic circulation (164,175,176). Renin hydrolyzes angiotensinogen secreted by the liver to produce angiotensin I (Ang I) (177). In PAECs, Ang I is cleaved to Ang II by angiotensin-converting enzyme (178). In the mechanism of high UA-induced endothelial dysfunction, excess UA can be rapidly taken up by vascular smooth muscle cells, and intracellular UA upregulates angiotensinogen mRNA expression, thereby promoting Ang II production and Ang II type 1 receptor (main effector peptide of RAS) expression (179). These findings suggest that UA upregulates Ang II expression, activates the RAS system, produces oxidative stress, and leads to endothelial cell senescence and apoptosis (179,180). Ang II, which is a pleiotropic endocrine and paracrine hormone, upregulates vasopressin released by the central nervous system and induces VSMC contraction in the pulmonary circulation and systemic arterial and venous circulation (176,181). In addition, Ang II stimulates the release of aldosterone, which stimulates mineralocorticoid receptors in PAECs, inducing hypertrophy of PSMCs and pulmonary artery vascular remodeling (182-185). However, the vascular remodeling effects caused by UA and Ang II stimulation of VSMC proliferation and hypertrophy is inhibited by losartan [an angiotensin receptor blocker (ARB)] and captopril [an angiotensin-converting enzyme inhibitor (ACEI)] (157,186). Ang II also promotes vasoconstriction, proliferation, inflammation and fibrosis in the pulmonary vascular system and lung parenchyma by stimulating ANG II type 1 receptor (187,188). All of these studies suggest that UA mediates the relationship between the RAS and PH, promoting pulmonary vascular remodeling, enhancing



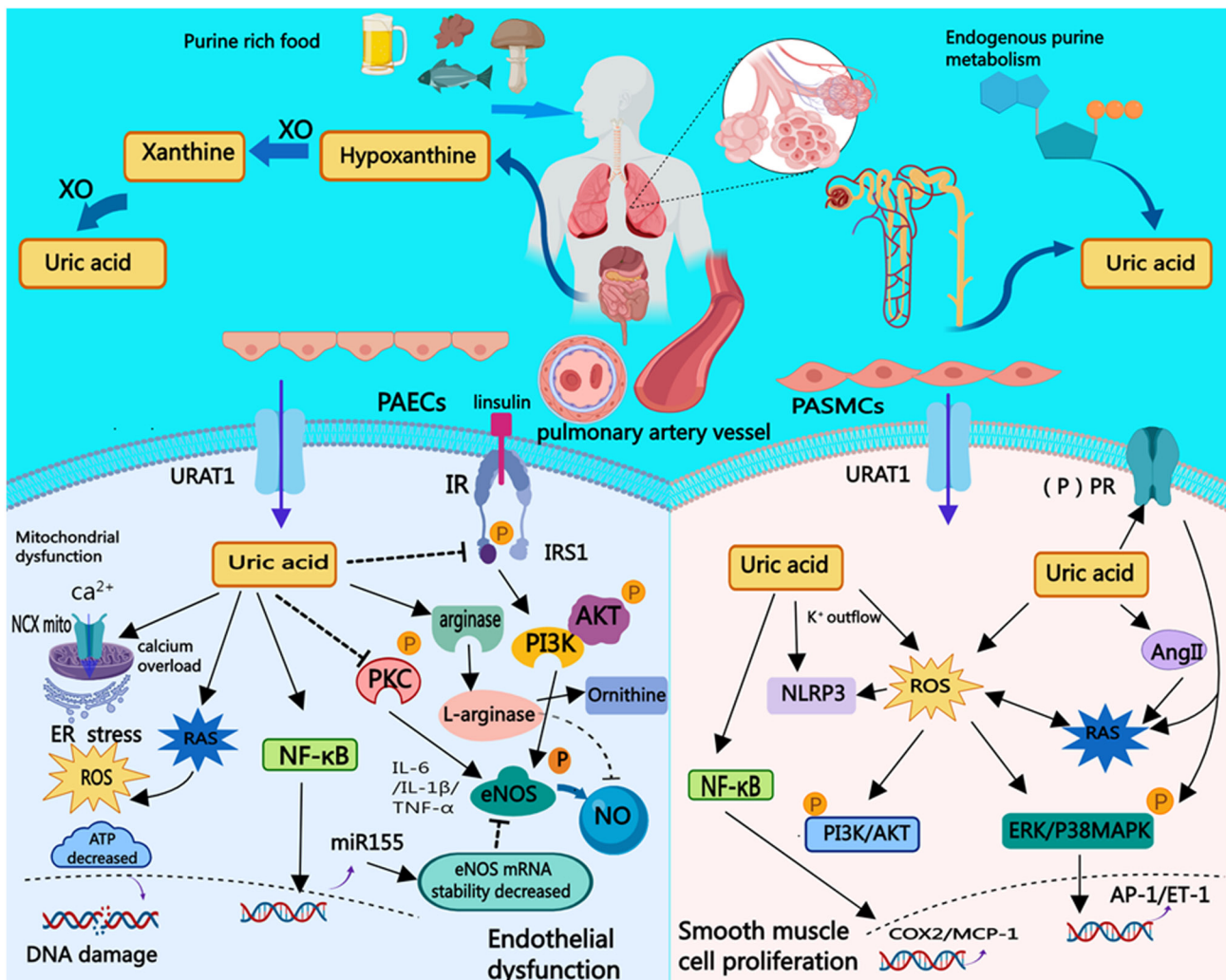


Figure 4. Investigation of the molecular mechanisms of the potential association between high UA concentrations and PAECs and PAMCs. After entering endothelial cells, UA induces the production of ROS, activates mitochondria to trigger calcium overload and affects NOS activity or stability through various pathways. The activation of these pathways causes reduced NO production and an inflammatory response, which leads to endothelial dysfunction and abnormal pulmonary vascular constriction. UA can also directly act on smooth muscle cells, promoting smooth muscle cell proliferation. NO, nitric oxide; PAECs, pulmonary artery endothelial cells; PAMCs, pulmonary arterial smooth muscle cells; XO, xanthine oxidase; RAS, renin-angiotensin system; URAT1, urate transport protein 1; GLUT-9, glucose transporter-9; NLRP3, NOD-like receptor protein 3; eNOS, endothelial NO synthase; NCX mito, mitochondrial Na<sup>+</sup>/Ca<sup>2+</sup> exchanger; NF-κB, nuclear factor-κB; PKC, protein kinase C; ER, endoplasmic reticulum; ROS, reactive oxygen species; IR, insulin receptor; IRS1, insulin receptor substrate 1; MCP-1, monocyte chemoattractant protein 1; (P)PR, renin (pro)receptor.

pulmonary vasoconstriction and ultimately exacerbating the progression of PH.

## 7. Potential mechanisms by which PH affects UA concentrations

PH affects UA concentrations in two main ways. First, an elevation in SUA concentrations in patients with PH is mainly due to tissue ischemia/hypoxia and oxidative stress (30,189,190). When oxygen metabolism is abnormal in the body, tissue ischemia or hypoxia and oxidative stress can lead to elevated UA concentrations (191,192). For example, PH is associated with chronic heart failure and chronic obstructive pulmonary disease, tissue hypoxia, increased anaerobic metabolism, decreased adenosine triphosphate synthesis and accelerated purine degradation, leading to increased uric acid production (193-195). In addition, patients with heart failure are often associated with renal insufficiency or even renal failure, which

can reduce UA excretion and lead to increased UA concentrations (196). As SUA concentrations rise, free radicals released by xanthine oxidase may activate inflammatory cells (197). When UA concentrations exceed the threshold, hyperuricemia enhances intracellular urate accumulation via down-regulation of cell-surface BCRP/ABCG2 expression in vascular endothelial cells (198), leading to endothelial dysfunction, leukocyte recruitment, cytokine release, and stimulation of activation and proliferation of VSMCs, as well as vasoconstriction and diastolic dysfunction (199) and ultimately, exacerbates tissue hypoxia (200). Moreover, hyperuricemia is involved in oxidative metabolism, platelet adhesion, blood rheology and platelet aggregation (201,202). These processes can increase platelet adhesion and make patients with PH more susceptible to pulmonary vascular thrombosis (203). Hypoxia also leads to impaired pulmonary vascular perfusion, and the release of additional cytokines further accelerates vascular remodeling and fibrosis (191,204,205). The effect of the use of drugs, such

as diuretics in the setting of heart failure, on UA concentrations should not be overlooked. Borghi *et al* (206) reported that diuretics, thiazides and aspirin may increase SUA concentrations. When PH is combined with underlying diseases, such as renal insufficiency, hypermetabolic syndrome, obesity, hyperlipidemia, hypertension, coronary artery disease and diabetes mellitus, it can also result in hyperuricemia (11,93,131). These diseases mainly cause dysfunction of UA excretion/increased UA synthesis (199). Additionally, the use of clinical medications in these conditions can interfere with UA concentrations. Examples of these medications include calcium channel blockers (e.g., amlodipine and cilnidipine) (207), angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril and ramipril) (208,209), angiotensin-converting enzyme II receptor antagonists (e.g., losartan) (210), lipid-lowering agents (e.g., atorvastatin, simvastatin, ezetimibe and fenofibrate) (211), weight loss medications (e.g., orlistat) (212) and hypoglycemic agents (e.g., metformin) (213). Additionally, sodium glucose transporter protein 2 reduces UA concentrations (214,215). Therefore, PH with hypoxia leads to elevated UA concentrations. However, UA, as a risk marker, exacerbates the severity of PH and increases the risk of death due to PH.

## 8. Protective effect of UA-lowering drugs on PH

Currently, UA-lowering drugs mainly include the following categories: i) Drugs that inhibit UA production (xanthine oxidase inhibitors, such as allopurinol and febuxostat) (216,217); ii) drugs that promote UA excretion (drugs that inhibit the production of the UA reabsorption proteins URAT1 and GLUT9, such as benzbromarone and probenecid) (218,219); iii) drugs that promote UA catabolism (UA enzymes, such as rasburicase and pegloticase) (220,221); and iv) antihypertensive drugs (ACEIs such as enalapril, and ARBs such as irbesartan and losartan) (208,210). Based on the role of UA in PH, some of these drugs (e.g., allopurinol and benzbromarone) have been shown to reduce SUA concentrations and has a certain protective effects against arterial hypertension (163,222-224). Therefore, lowering SUA concentration has the potential to serve as a target for the treatment of PH.

## 9. Conclusions and prospects

Increasing evidence has shown that UA is inextricably associated with PH and may serve as a circulating marker of PH (189) (Fig. 4). UA may be involved in PH by mediating inflammatory responses, oxidative stress, RAS activation and endothelial dysfunction (131). PH leads to tissue ischemia/hypoxia and oxidative stress, and impaired UA metabolism, which lead to an increase in SUA concentrations (225,226). However, the causal relationship between UA and PH is not completely clear. Hyperuricemia may be considered a risk factor/independent risk factor for PH and a predictor of disease onset, progression and prognosis (115,116,227), but whether SUA can be used as a circulating marker for PH needs to be validated by additional clinical and basic research. In addition, to determine whether lowering SUA concentrations improves the clinical symptoms of PH, further investigation and clinical studies are required.

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## Availability of data and materials

Not applicable.

## Authors' contributions

YZ and WL conceived and designed the entire review and wrote the paper. YZ assisted with the figures. MC, JZ, YH, HL, XS and WL reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References

- Hoepfer MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, Jing ZC and Gibbs JS: A global view of pulmonary hypertension. *Lancet Respir Med* 4: 306-322, 2016.
- Beshay S, Sahay S and Humbert M: Evaluation and management of pulmonary arterial hypertension. *Respir Med* 171, 106099, 2020.
- Morrell NW, Aldred MA, Chung WK, Elliott CG, Nichols WC, Soubrier F, Trembath RC and Loyd JE: Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J* 53: 1801899, 2019.
- Levine DJ: Pulmonary arterial hypertension: Updates in epidemiology and evaluation of patients. *Am J Manag Care* 27 (3 Suppl), S35-S41, 2021.
- Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, *et al*: Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 107: 216-223, 1987.
- Girerd B, Montani D, Eyries M, Yaici A, Sztrymf B, Coulet F, Sitbon O, Simonneau G, Soubrier F and Humbert M: Absence of influence of gender and BMPR2 mutation type on clinical phenotypes of pulmonary arterial hypertension. *Respir Res* 11: 73, 2010.
- Ventetuolo CE, Praestgaard A, Palevsky HI, Klinger JR, Halpern SD and Kawut SM: Sex and haemodynamics in pulmonary arterial hypertension. *Eur Respir J* 43: 523-530, 2014.



8. Jing ZC, Xu XQ, Han ZY, Wu Y, Deng KW, Wang H, Wang ZW, Cheng XS, Xu B, Hu SS, *et al*: Registry and survival study in chinese patients with idiopathic and familial pulmonary arterial hypertension. *Chest* 132: 373-379, 2007.
9. Xu X, Sun M, Jiang X, Zhang R, Zhao Q, Wang Y, Sun K, Wang X, Peng F, Zheng L, *et al*: Comparison of clinical characteristics and survival on patients with idiopathic pulmonary arterial hypertension and familial pulmonary arterial hypertension during conventional therapy era and targeted therapy era. *Zhonghua Xin Xue Guan Bing Za Zhi* 42: 465-468, 2014 (In Chinese).
10. Hansmann G, Wagner RA, Schellong S, Perez VA, Urashima T, Wang L, Sheikh AY, Suen RS, Stewart DJ and Rabinovitch M: Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. *Circulation* 115: 1275-1284, 2007.
11. Zamanian RT, Hansmann G, Snook S, Lilienfeld D, Rappaport KM, Reaven GM, Rabinovitch M and Doyle RL: Insulin resistance in pulmonary arterial hypertension. *Eur Respir J* 33: 318-324, 2009.
12. Fessel JP, Hamid R, Wittmann BM, Robinson LJ, Blackwell T, Tada Y, Tanabe N, Tatsumi K, Hemnes AR and West JD: Metabolomic analysis of bone morphogenetic protein receptor type 2 mutations in human pulmonary endothelium reveals widespread metabolic reprogramming. *Pulm Circ* 2: 201-213, 2012.
13. Zare E, Kafshbani P, Chenaghloou M, Noori M, Ghaemmaghami Z, Amin A, Taghavi S and Naderi N: Prognostic significance of insulin resistance in pulmonary hypertension. *ESC Heart Fail* 9: 318-326, 2022.
14. Feig DI, Kang DH and Johnson RJ: Uric acid and cardiovascular risk. *N Engl J Med* 359: 1811-1821, 2008.
15. Gagliardi AC, Miname MH and Santos RD: Uric acid: A marker of increased cardiovascular risk. *Atherosclerosis* 202: 11-17, 2009.
16. Borghi C and Cicero AFG: Serum uric acid and acute coronary syndrome: Is there a role for functional markers of residual cardiovascular risk. *Int J Cardiol* 250: 62-63, 2018.
17. Ndrepepa G: Uric acid and cardiovascular disease. *Clin Chim Acta* 484: 150-163, 2018.
18. Krishnan E, Kwok CK, Schumacher HR and Kuller L: Hyperuricemia and incidence of hypertension among men without metabolic syndrome. *Hypertension* 49: 298-303, 2007.
19. Brodov Y, Behar S, Boyko V and Chouraqui P: Effect of the metabolic syndrome and hyperuricemia on outcome in patients with coronary artery disease (from the Bezafibrate Infarction Prevention Study). *Am J Cardiol* 106: 1717-1720, 2010.
20. Galassi FM and Borghi C: A brief history of uric acid: From gout to cardiovascular risk factor. *Eur J Intern Med* 26: 373, 2015.
21. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W and Tang Z: Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. *Sci Rep* 6: 19520, 2016.
22. Kuwabara M, Niwa K, Nishihara S, Nishi Y, Takahashi O, Kario K, Yamamoto K, Yamashita T and Hisatome I: Hyperuricemia is an independent competing risk factor for atrial fibrillation. *Int J Cardiol* 231, 137-142, 2017.
23. Sanchez-Lozada LG, Rodriguez-Iturbe B, Kelley EE, Nakagawa T, Madero M, Feig DI, Borghi C, Piani F, Cara-Fuentes G, Bjornstad P, *et al*: Uric acid and hypertension: An update with recommendations. *Am J Hypertens* 33: 583-594, 2020.
24. Si K, Wei C, Xu L, Zhou Y, Lv W, Dong B, Wang Z, Huang Y, Wang Y and Chen Y: Hyperuricemia and the Risk of Heart Failure: Pathophysiology and Therapeutic Implications. *Front Endocrinol (Lausanne)* 12: 770815, 2021.
25. Wang X, Hou Y, Wang X, Li Z, Wang X, Li H, Shang L, Zhou J, Zhang Y, Ren M and Zhang Y: Relationship between serum uric acid levels and different types of atrial fibrillation: An updated meta-analysis. *Nutr Metab Cardiovasc Dis* 31: 2756-2765, 2021.
26. Gomes MT, Bai Y, Potje SR, Zhang L, Lockett AD and Machado RF: Signal transduction during metabolic and inflammatory reprogramming in pulmonary vascular remodeling. *Int J Mol Sci* 23: 2410, 2022.
27. Perera FP, Rauh V, Whyatt RM, Tang D, Tsai WY, Bernert JT, Tu YH, Andrews H, Barr DB, Camann DE, *et al*: A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. *Neurotoxicology* 26: 573-587, 2005.
28. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, *et al*: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 43: 3618-3731, 2022.
29. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, *et al*: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 61: 2200879, 2023.
30. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, *et al*: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 46: 903-975, 2015.
31. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, *et al*: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 37: 67-119, 2016.
32. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, *et al*: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 54 (1 Suppl): S43-S54, 2009.
33. Gelzinis TA: Pulmonary Hypertension in 2021: Part I-Definition, Classification, Pathophysiology, and Presentation. *J Cardiothorac Vasc Anesth* 36: 1552-1564, 2022.
34. Badesch DB, Champion HC, Gomez Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ and Torbicki A: Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 54 (1 Suppl): S55-S66, 2009.
35. Assad TR and Hemnes AR: Metabolic dysfunction in pulmonary arterial hypertension. *Curr Hypertens Rep* 17: 20, 2015.
36. Satoh T, Wang L, Espinosa-Diez C, Wang B, Hahn SA, Noda K, Rochon ER, Dent MR, Levine AR, Baust JJ, *et al*: Metabolic Syndrome Mediates ROS-miR-193b-NFYA-Dependent down-regulation of soluble guanylate cyclase and contributes to exercise-induced pulmonary hypertension in heart failure with preserved ejection fraction. *Circulation* 144: 615-637, 2021.
37. Nicolls MR and Voelkel NF: Hypoxia and the lung: Beyond hypoxic vasoconstriction. *Antioxid Redox Signal* 9: 741-743, 2007.
38. Langleben D, Orfanos SE, Giovinazzo M, Hirsch A, Baron M, Senécal JL, Armaganidis A and Catravas JD: Pulmonary capillary endothelial metabolic dysfunction: Severity in pulmonary arterial hypertension related to connective tissue disease versus idiopathic pulmonary arterial hypertension. *Arthritis Rheum* 58: 1156-1164, 2008.
39. Jones PL, Cowan KN and Rabinovitch M: Tenascin-C, proliferation and subendothelial fibronectin in progressive pulmonary vascular disease. *Am J Pathol* 150: 1349-1360, 1997.
40. Stacher E, Graham BB, Hunt JM, Gandjeva A, Groshong SD, McLaughlin VV, Jessup M, Grizzle WE, Aldred MA, Cool CD and Tudor RM: Modern age pathology of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 186: 261-272, 2012.
41. Watanabe T, Ishikawa M, Abe K, Ishikawa T, Imakiire S, Masaki K, Hosokawa K, Fukuuchi T, Kaneko K, Ohtsubo T, *et al*: Increased Lung Uric Acid Deteriorates Pulmonary Arterial Hypertension. *J Am Heart Assoc* 10: e022712, 2021.
42. Lippi G, Montagnana M, Franchini M, Favaloro EJ and Targher G: The paradoxical relationship between serum uric acid and cardiovascular disease. *Clin Chim Acta* 392: 1-7, 2008.
43. Yamaoka T and Itakura M: Metabolism of purine nucleotides and the production of uric acid. *Nihon Rinsho* 54: 3188-3194, 1996 (In Japanese).
44. El Ridi R and Tallima H: Physiological functions and pathogenic potential of uric acid: A review. *J Adv Res* 8: 487-493, 2017.
45. Benn CL, Dua P, Gurrell R, Loudon P, Pike A, Storer RI and Vangjeli C: Physiology of hyperuricemia and urate-lowering treatments. *Front Med (Lausanne)* 5: 160, 2018.
46. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C and Mollace V: Regulation of uric acid metabolism and excretion. *Int J Cardiol* 213: 8-14, 2016.

47. Chaudhary K, Malhotra K, Sowers J and Aroor A: Uric Acid-key ingredient in the recipe for cardiorenal metabolic syndrome. *Cardiorenal Med* 3: 208-220, 2013.
48. Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A and Checherita IA: Uric acid and oxidative stress-relationship with cardiovascular, metabolic, and renal impairment. *Int J Mol Sci* 23: 3188, 2022.
49. Sánchez-Lozada LG, Nakagawa T, Kang DH, Feig DI, Franco M, Johnson RJ and Herrera-Acosta J: Hormonal and cytokine effects of uric acid. *Curr Opin Nephrol Hypertens* 15: 30-33, 2006.
50. Chen C, Lü JM and Yao Q: Hyperuricemia-Related Diseases and Xanthine Oxidoreductase (XOR) Inhibitors: An Overview. *Med Sci Monit* 22: 2501-2512, 2016.
51. Furuhashi M: New insights into purine metabolism in metabolic diseases: Role of xanthine oxidoreductase activity. *Am J Physiol Endocrinol Metab* 319: E827-E834, 2020.
52. Shima Y, Teruya K and Ohta H: Association between intronic SNP in urate-anion exchanger gene, SLC22A12, and serum uric acid levels in Japanese. *Life Sci* 79: 2234-2237, 2006.
53. Caulfield MJ, Munroe PB, O'Neill D, Witkowska K, Charchar FJ, Doblado M, Evans S, Eyheramendy S, Onipinla A, Howard P, *et al*: SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* 5: e197, 2008.
54. Wright AF, Rudan I, Hastie ND and Campbell H: A 'complexity' of urate transporters. *Kidney Int* 78: 446-452, 2010.
55. Ma Q, Fang L, Su R, Ma L, Xie G and Cheng Y: Uric acid stones, clinical manifestations and therapeutic considerations. *Postgrad Med J* 94: 458-462, 2018.
56. Lipkowitz MS: Regulation of uric acid excretion by the kidney. *Curr Rheumatol Rep* 14: 179-188, 2012.
57. Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, Yamanashi Y, Kasuga H, Nakashima H, Nakamura T, *et al*: Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun* 3: 764, 2012.
58. Eckenstaler R and Benndorf RA: The Role of ABCG2 in the pathogenesis of primary hyperuricemia and Gout-An Update. *Int J Mol Sci* 22: 6678, 2021.
59. Homolya L: Medically Important Alterations in Transport Function and Trafficking of ABCG2. *Int J Mol Sci* 22: 2786, 2021.
60. Ohashi Y, Toyoda M, Saito N, Koizumi M, Kanai G, Komaba H, Kimura M, Wada T, Takahashi H, Takahashi Y, *et al*: Evaluation of ABCG2-mediated extra-renal urate excretion in hemodialysis patients. *Sci Rep* 13: 93, 2023.
61. Su J, Wei Y, Liu M, Liu T, Li J, Ji Y and Liang J: Anti-hyperuricemic and nephroprotective effects of *Rhizoma Dioscoreae septemlobae* extracts and its main component dioscin via regulation of mOAT1, mURAT1 and mOCT2 in hypertensive mice. *Arch Pharm Res* 37: 1336-1344, 2014.
62. Wu XH, Zhang J, Wang SQ, Yang VC, Anderson S and Zhang YW: Riparoside B and timosaponin J, two steroidal glycosides from *Smilax riparia*, resist to hyperuricemia based on URAT1 in hyperuricemic mice. *Phytomedicine* 21: 1196-1201, 2014.
63. Nath SD, Voruganti VS, Arar NH, Thameem F, Lopez-Alvarenga JC, Bauer R, Blangero J, MacCluer JW, Comuzzie AG and Abboud HE: Genome scan for determinants of serum uric acid variability. *J Am Soc Nephrol* 18: 3156-3163, 2007.
64. Anzai N, Jutabha P, Amonpatumrat-Takahashi S and Sakurai H: Recent advances in renal urate transport: Characterization of candidate transporters indicated by genome-wide association studies. *Clin Exp Nephrol* 16: 89-95, 2012.
65. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A and Witteman JC: High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care* 31: 361-362, 2008.
66. Okada Y, Sim X, Go MJ, Wu JY, Gu D, Takeuchi F, Takahashi A, Maeda S, Tsunoda T, Chen P, *et al*: Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. *Nat Genet* 44: 904-909, 2012.
67. Major TJ, Dalbeth N, Stahl EA and Merriman TR: An update on the genetics of hyperuricaemia and gout. *Nat Rev Rheumatol* 14: 341-353, 2018.
68. Sautin YY and Johnson RJ: Uric acid: The oxidant-antioxidant paradox. *Nucleosides Nucleotides Nucleic Acids* 27: 608-619, 2008.
69. Jakše B, Jakše B, Pajek M and Pajek J: Uric acid and plant-based nutrition. *Nutrients* 11: 1736, 2019.
70. Shi Y, Chen W, Jalal D, Li Z, Chen W, Mao H, Yang Q, Johnson RJ and Yu X: Clinical outcome of hyperuricemia in IgA nephropathy: A retrospective cohort study and randomized controlled trial. *Kidney Blood Press Res* 35: 153-160, 2012.
71. Joosten LAB, Crişan TO, Bjornstad P and Johnson RJ: Asymptomatic hyperuricaemia: A silent activator of the innate immune system. *Nat Rev Rheumatol* 16: 75-86, 2020.
72. Miao Y, Ottenbros SA, Laverman GD, Brenner BM, Cooper ME, Parving HH, Grobbee DE, Shahinfar S, de Zeeuw D and Lambers Heerspink HJ: Effect of a reduction in uric acid on renal outcomes during losartan treatment: A post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. *Hypertension* 58: 2-7, 2011.
73. Ames BN, Cathcart R, Schwiers E and Hochstein P: Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. *Proc Natl Acad Sci USA* 78: 6858-6862, 1981.
74. Zou H, Wang H, Liu T, Li X, Zhu X and Wang Z: Protective role of  $\alpha$ -lipoic acid in hyperuricemia-induced endothelial dysfunction. *Exp Ther Med* 13: 3047-3054, 2017.
75. Shi Y, Evans JE and Rock KL: Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature* 425: 516-521, 2003.
76. Netea MG, Kullberg BJ, Blok WL, Netea RT and van der Meer JW: The role of hyperuricemia in the increased cytokine production after lipopolysaccharide challenge in neutropenic mice. *Blood* 89: 577-582, 1997.
77. Bagnati M, Perugini C, Cau C, Bordone R, Albano E and Bellomo G: When and why a water-soluble antioxidant becomes pro-oxidant during copper-induced low-density lipoprotein oxidation: A study using uric acid. *Biochem J* 340 (Pt 1): 143-152, 1999.
78. Kang DH, Park SK, Lee IK and Johnson RJ: Uric acid-induced C-reactive protein expression: Implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol* 16: 3553-3562, 2005.
79. Patterson RA, Horsley ET and Leake DS: Prooxidant and anti-oxidant properties of human serum ultrafiltrates toward LDL: Important role of uric acid. *J Lipid Res* 44: 512-521, 2003.
80. Samocha-Bonet D, Lichtenberg D and Pinchuk I: Kinetic studies of copper-induced oxidation of urate, ascorbate and their mixtures. *J Inorg Biochem* 99: 1963-1972, 2005.
81. Sautin YY, Nakagawa T, Zharikov S and Johnson RJ: Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol* 293: C584-C596, 2007.
82. Zhang JX, Zhang YP, Wu QN and Chen B: Uric acid induces oxidative stress via an activation of the renin-angiotensin system in 3T3-L1 adipocytes. *Endocrine* 48: 135-142, 2015.
83. Wang JG, Staessen JA, Fagard RH, Birkenh  ger WH, Gong L and Liu L: Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. *Hypertension* 37: 1069-1074, 2001.
84. Kuzkaya N, Weissmann N, Harrison DG and Dikalov S: Interactions of peroxynitrite with uric acid in the presence of ascorbate and thiols: Implications for uncoupling endothelial nitric oxide synthase. *Biochem Pharmacol* 70: 343-354, 2005.
85. Nagahama K, Inoue T, Iseki K, Touma T, Kinjo K, Ohya Y and Takishita S: Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. *Hypertens Res* 27: 835-841, 2004.
86. Morris CR, Kuypers FA, Kato GJ, Lavrishia L, Larkin S, Singer T and Vichinsky EP: Hemolysis-associated pulmonary hypertension in thalassemia. *Ann N Y Acad Sci* 1054: 481-485, 2005.
87. Castro O, Hoque M and Brown BD: Pulmonary hypertension in sickle cell disease: Cardiac catheterization results and survival. *Blood* 101: 1257-1261, 2003.
88. Verresen D, De Backer W, Van Meerbeeck J, Neetens I, Van Marck E and Vermeire P: Spherocytosis and pulmonary hypertension coincidental occurrence or causal relationship. *Eur Respir J* 4: 629-631, 1991.
89. Heller PG, Grinberg AR, Lencioni M, Molina MM and Roncoroni AJ: Pulmonary hypertension in paroxysmal nocturnal hemoglobinuria. *Chest* 102: 642-643, 1992.
90. Devallet B, Mullier F, Chatelain B, Dogn   JM and Chatelain C: Pathophysiology, diagnosis, and treatment of paroxysmal nocturnal hemoglobinuria: A review. *Eur J Haematol* 95: 190-198, 2015.

91. Tofovic SP, Jackson EK and Rafikova O: Adenosine deaminase-adenosine pathway in hemolysis-associated pulmonary hypertension. *Med Hypotheses* 72: 713-719, 2009.
92. Cerqueira BA, Boas WV, Zanette AD, Reis MG and Goncalves MS: Increased concentrations of IL-18 and uric acid in sickle cell anemia: Contribution of hemolysis, endothelial activation and the inflammasome. *Cytokine* 56: 471-476, 2011.
93. Robbins IM, Newman JH, Johnson RF, Hemnes AR, Fremont RD, Piana RN, Zhao DX and Byrne DW: Association of the metabolic syndrome with pulmonary venous hypertension. *Chest* 136: 31-36, 2009.
94. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D and Ferrannini E: Effect of insulin on uric acid excretion in humans. *Am J Physiol* 268 (1 Pt 1), E1-E5, 1995.
95. Gashouta MA, Humbert M and Hassoun PM: Update in systemic sclerosis-associated pulmonary arterial hypertension. *Presse Med* 43 (10 Pt 2): e293-e304, 2014.
96. Kherbeck N, Tamby MC, Bussone G, Dib H, Perros F, Humbert M and Mouthon L: The role of inflammation and autoimmunity in the pathophysiology of pulmonary arterial hypertension. *Clin Rev Allergy Immunol* 44: 31-38, 2013.
97. Ferreira NS, Tostes RC, Paradis P and Schiffrin EL: Aldosterone, inflammation, immune system, and hypertension. *Am J Hypertens* 34: 15-27, 2021.
98. Nagaya N, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, Yamagishi M, Kunieda T and Miyatake K: Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med* 160: 487-492, 1999.
99. Editorial: Major changes made by Criteria Committee of the New York Heart Association. *Circulation* 49: 390, 1974.
100. Voelkel MA, Wynne KM, Badesch DB, Groves BM and Voelkel NF: Hyperuricemia in severe pulmonary hypertension. *Chest* 117: 19-24, 2000.
101. Li ZN, He JG, Liu ZH, Gu Q, Ni XH, Cheng XS and Xiong CM: Relationship between serum uric acid levels and patient conditions and prognosis in idiopathic pulmonary arterial hypertension. *Zhonghua Yi Xue Za Zhi* 92: 3261-3264, 2012 (In Chinese).
102. Zhang CY, Ma LL, & Wang LX: Relationship between serum uric acid levels and ventricular function in patients with idiopathic pulmonary hypertension. *Exp Clin Cardiol* 18: e37-3e9, 2013.
103. Seyyedi SR, Malekmohammad M, Chitsazan M, Behzadnia N, Sadr M, Hashemian SM and Sharif-Kashani B: Relationship between Serum Uric Acid Levels and the Severity of Pulmonary Hypertension. *Tanaffos* 16: 283-288, 2017.
104. Yan L, Huang Z, Zhao Z, Zhao Q, Tang Y, Zhang Y, Li X, Duan A, Luo Q and Liu Z: The Prognostic Impact of Serum Uric Acid on Disease Severity and 5-Year mortality in patients with idiopathic pulmonary artery hypertension. *Front Med (Lausanne)* 9: 805415, 2022.
105. Dhaun N, Vachieri JL, Benza RL, Naeije R, Hwang LJ, Liu X, Teal S and Webb DJ: Endothelin antagonism and uric acid levels in pulmonary arterial hypertension: Clinical associations. *J Heart Lung Transplant* 33: 521-527, 2014.
106. Dimitroulas T, Giannakoulas G, Dimitroula H, Sfetsios T, Parcharidou D, Karvounis H and Settas L: Significance of serum uric acid in pulmonary hypertension due to systemic sclerosis: A pilot study. *Rheumatol Int* 31: 263-267, 2011.
107. Denton CP: Systemic sclerosis: From pathogenesis to targeted therapy. *Clin Exp Rheumatol* 33 (4 Suppl 92): S3-S7, 2015.
108. Gigante A, Barbano B, Barilaro G, Quarta S, Gasperini ML, Di Mario F, Romaniello A, Amoroso A, Cianci R and Rosato E: Serum uric acid as a marker of microvascular damage in systemic sclerosis patients. *Microvasc Res* 106: 39-43, 2016.
109. Pagkopoulou E, Soulaïdopoulos S, Triantafyllidou E, Malliari A, Kitas GD, Garyfallos A and Dimitroulas T: Association Between Uric Acid and Worsening Peripheral Microangiopathy in Systemic Sclerosis. *Front Med (Lausanne)* 8: 806925, 2021.
110. Aghdashi M, Behnemoon M, Mahmoodi Rad J and Rabiepour M: Evaluation of serum uric acid level in systemic lupus erythematosus patients with normal and high pulmonary arterial hypertension. *Biomedicine (Taipei)* 8: 16, 2018.
111. Kim KJ, Baek IW, Park YJ, Yoon CH, Kim WU and Cho CS: High levels of uric acid in systemic lupus erythematosus is associated with pulmonary hypertension. *Int J Rheum Dis* 18: 524-532, 2015.
112. Castillo-Martínez D, Marroquín-Fabián E, Lozada-Navarro AC, Mora-Ramírez M, Juárez M, Sánchez-Muñoz F, Vargas-Barrón J, Sandoval J and Amezcua-Guerra LM: Levels of uric acid may predict the future development of pulmonary hypertension in systemic lupus erythematosus: A seven-year follow-up study. *Lupus* 25: 61-66, 2016.
113. Njamen W, Iesaki T, Iwama Y, Takasaki Y and Daida H: Serum uric acid as a prognostic predictor in pulmonary arterial hypertension with connective tissue disease. *Int Heart J* 48: 523-532, 2007.
114. Luo DL, Zhang CJ, Huang YG, Huang T and Li HZ: Serum uric acid is associated with disease severity and an important predictor for clinical outcome in patients with pulmonary hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi* 45: 496-500, 2017 (In Chinese).
115. Simpson CE, Damico RL, Hummers L, Khair RM, Kolb TM, Hassoun PM and Mathai SC: Serum uric acid as a marker of disease risk, severity, and survival in systemic sclerosis-related pulmonary arterial hypertension. *Pulm Circ* 9: 2045894019859477, 2019.
116. Uk Kang T, Park KY, Kim HJ, Ahn HS, Yim SY and Jun JB: Association of hyperuricemia and pulmonary hypertension: A systematic review and meta-analysis. *Mod Rheumatol* 29: 1031-1041, 2019.
117. Hong JW, Noh JH and Kim DJ: Association between serum uric acid and spirometric pulmonary function in Korean adults: The 2016 Korea National Health and Nutrition Examination Survey. *PLoS One* 15: e0240987, 2020.
118. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J and Mazzali M: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease. *Hypertension* 41: 1183-1190, 2003.
119. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S and Johnson RJ: Hyperuricemia induces endothelial dysfunction. *Kidney Int* 67: 1739-1742, 2005.
120. O'Riordan E, Chen J, Brodsky SV, Smirnova I, Li H and Goligorsky MS: Endothelial cell dysfunction: The syndrome in making. *Kidney Int* 67: 1654-1658, 2005.
121. van Thiel BS, van der Pluijm I, te Riet L, Essers J and Danser AH: The renin-angiotensin system and its involvement in vascular disease. *Eur J Pharmacol* 763(Pt A): 3-14, 2015.
122. Podkowińska A and Formanowicz D: Chronic kidney disease as oxidative stress- and inflammatory-mediated cardiovascular disease. *Antioxidants (Basel)* 9: 752, 2020.
123. Rao GN, Corson MA and Berk BC: Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. *J Biol Chem* 266: 8604-8608, 1991.
124. Kanbay M, Segal M, Afsar B, Kang DH, Rodriguez-Iturbe B and Johnson RJ: The role of uric acid in the pathogenesis of human cardiovascular disease. *Heart* 99: 759-766, 2013.
125. Potente M, Gerhardt H and Carmeliet P: Basic and therapeutic aspects of angiogenesis. *Cell* 146: 873-887, 2011.
126. Eelen G, Treps L, Li X and Carmeliet P: Basic and therapeutic aspects of angiogenesis updated. *Circ Res* 127: 310-329, 2020.
127. Krüger-Genge A, Blocki A, Franke RP and Jung F: Vascular endothelial cell biology: An update. *Int J Mol Sci* 20: 4411, 2019.
128. Dai Z, Zhu MM, Peng Y, Jin H, Machireddy N, Qian Z, Zhang X and Zhao YY: Endothelial and smooth muscle cell interaction via FoxM1 signaling mediates vascular remodeling and pulmonary hypertension. *Am J Respir Crit Care Med* 198: 788-802, 2018.
129. Evans CE, Cober ND, Dai Z, Stewart DJ and Zhao YY: Endothelial cells in the pathogenesis of pulmonary arterial hypertension. *Eur Respir J* 58: 2003957, 2021.
130. Liu B, Peng Y, Yi D, Machireddy N, Dong D, Ramirez K, Dai J, Vanderpool R, Zhu MM, Dai Z and Zhao YY: Endothelial PHD2 deficiency induces nitrate stress via suppression of caveolin-1 in pulmonary hypertension. *Eur Respir J* 60: 2102643, 2022.
131. Zharikov SI, Swenson ER, Lanasa M, Block ER, Patel JM and Johnson RJ: Could uric acid be a modifiable risk factor in subjects with pulmonary hypertension? *Med Hypotheses* 74: 1069-1074, 2010.
132. Komaszko K, Zalewska R, Mariak Z and Wiśniewska RJ: Biosynthesis of nitric oxide and its function in organism. *Klin Ocna* 108: 99-102, 2006 (In Polish).
133. Gersch C, Palii SP, Kim KM, Angerhofer A, Johnson RJ and Henderson GN: Inactivation of nitric oxide by uric acid. *Nucleosides Nucleotides Nucleic Acids* 27: 967-978, 2008.

134. Förstermann U: Janus-faced role of endothelial NO synthase in vascular disease: Uncoupling of oxygen reduction from NO synthesis and its pharmacological reversal. *Biol Chem* 387: 1521-1533, 2006.
135. Mishima M, Hamada T, Maharani N, Ikeda N, Onohara T, Notsu T, Ninomiya H, Miyazaki S, Mizuta E, Sugihara S, *et al*: Effects of Uric Acid on the NO Production of HUVECs and its Restoration by Urate Lowering Agents. *Drug Res (Stuttg)* 66: 270-274, 2016.
136. Li P, Zhang L, Zhang M, Zhou C and Lin N: Uric acid enhances PKC-dependent eNOS phosphorylation and mediates cellular ER stress: A mechanism for uric acid-induced endothelial dysfunction. *Int J Mol Med* 37: 989-997, 2016.
137. Choi YJ, Yoon Y, Lee KY, Hien TT, Kang KW, Kim KC, Lee J, Lee MY, Lee SM, Kang DH and Lee BH: Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. *FASEB J* 28: 3197-3204, 2014.
138. Bahadoran Z, Mirmiran P, Kashfi K and Ghasemi A: Hyperuricemia-induced endothelial insulin resistance: The nitric oxide connection. *Pflugers Arch* 474: 83-98, 2022.
139. Roy D, Perreault M and Marette A: Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO dependent. *Am J Physiol* 274: E692-E699, 1998.
140. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, *et al*: A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 290: F625-F631, 2006.
141. Lee TS, Lu TM, Chen CH, Guo BC and Hsu CP: Hyperuricemia induces endothelial dysfunction and accelerates atherosclerosis by disturbing the asymmetric dimethylarginine/dimethylarginine dimethylaminotransferase 2 pathway. *Redox Biol* 46: 102108, 2021.
142. Deedwania PC: Mechanisms of endothelial dysfunction in the metabolic syndrome. *Curr Diab Rep* 3: 289-292, 2003.
143. Yu W and Cheng JD: Uric acid and cardiovascular disease: An update from molecular mechanism to clinical perspective. *Front Pharmacol* 11: 582680, 2020.
144. Lee KS, Kim J, Kwak SN, Lee KS, Lee DK, Ha KS, Won MH, Jeoung D, Lee H, Kwon YG and Kim YM: Functional role of NF- $\kappa$ B in expression of human endothelial nitric oxide synthase. *Biochem Biophys Res Commun* 448: 101-107, 2014.
145. Zhen H and Gui F: The role of hyperuricemia on vascular endothelium dysfunction. *Biomed Rep* 7: 325-330, 2017.
146. Zhang X, Hong Q, Hou K, Wang Y, Wu D and Chen X: High concentration uric acid regulates endothelial function via miR-155. *Nan Fang Yi Ke Da Xue Xue Bao* 33: 1141-1145, 2013 (In Chinese).
147. Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER and Patel J: Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am J Physiol Cell Physiol* 295: C1183-C1190, 2008.
148. Hong Q, Qi K, Feng Z, Huang Z, Cui S, Wang L, Fu B, Ding R, Yang J, Chen X and Wu D: Hyperuricemia induces endothelial dysfunction via mitochondrial Na<sup>+</sup>/Ca<sup>2+</sup> exchanger-mediated mitochondrial calcium overload. *Cell Calcium* 51: 402-410, 2012.
149. Sánchez-Lozada LG, Lanaspa MA, Cristóbal-García M, García-Arroyo F, Soto V, Cruz-Robles D, Nakagawa T, Yu MA, Kang DH and Johnson RJ: Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. *Nephron Exp Nephrol* 121: e71-e78, 2012.
150. Kang DH, Han L, Ouyang X, Kahn AM, Kanellis J, Li P, Feng L, Nakagawa T, Watanabe S, Hosoyamada M, *et al*: Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol* 25: 425-433, 2005.
151. Price KL, Sautin YY, Long DA, Zhang L, Miyazaki H, Mu W, Endou H and Johnson RJ: Human vascular smooth muscle cells express a urate transporter. *J Am Soc Nephrol* 17: 1791-1795, 2006.
152. Oğuz N, Kırça M, Çetin A and Yeşilkaya A: Effect of uric acid on inflammatory COX-2 and ROS pathways in vascular smooth muscle cells. *J Recept Signal Transduct Res* 37: 500-505, 2017.
153. Kırça M, Oğuz N, Çetin A, Uzuner F and Yeşilkaya A: Uric acid stimulates proliferative pathways in vascular smooth muscle cells through the activation of p38 MAPK, p44/42 MAPK and PDGFR $\beta$ . *J Recept Signal Transduct Res* 37: 167-173, 2017.
154. Bowen-Pope DF, Ross R and Seifert RA: Locally acting growth factors for vascular smooth muscle cells: Endogenous synthesis and release from platelets. *Circulation* 72: 735-740, 1985.
155. Berk BC: Vascular smooth muscle growth: Autocrine growth mechanisms. *Physiol Rev* 81: 999-1030, 2001.
156. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R and Johnson RJ: A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 13: 2888-2897, 2002.
157. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, *et al*: Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 282: F991-F997, 2002.
158. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, Mazzali M and Johnson RJ: Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 40: 355-360, 2002.
159. Doğru S, Yaşar E and Yeşilkaya A: Uric acid can enhance MAPK pathway-mediated proliferation in rat primary vascular smooth muscle cells via controlling of mitochondria and caspase-dependent cell death. *J Recept Signal Transduct Res* 42: 293-301, 2022.
160. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH and Aristimuno GG: Serum uric acid in essential hypertension: An indicator of renal vascular involvement. *Ann Intern Med* 93: 817-821, 1980.
161. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L and Johnson RJ: Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 41: 1287-1293, 2003.
162. Li H, Qian F, Liu H and Zhang Z: Elevated Uric Acid Levels Promote Vascular Smooth Muscle Cells (VSMC) Proliferation via an Nod-Like Receptor Protein 3 (NLRP3)-Inflammasome-Dependent Mechanism. *Med Sci Monit* 25: 8457-8464, 2019.
163. Savale L, Akagi S, Tu L, Cumont A, Thuillet R, Phan C, Le Vely B, Berrebeh N, Huertas A, Jais X, *et al*: Serum and pulmonary uric acid in pulmonary arterial hypertension. *Eur Respir J* 58: 2000332, 2021.
164. Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, Scalia R and Eguchi S: Angiotensin II Signal Transduction: An update on mechanisms of physiology and pathophysiology. *Physiol Rev* 98: 1627-1738, 2018.
165. Satou R, Penrose H and Navar LG: Inflammation as a Regulator of the Renin-Angiotensin System and Blood Pressure. *Curr Hypertens Rep* 20: 100, 2018.
166. Saxena T, Ali AO and Saxena M: Pathophysiology of essential hypertension: An update. *Expert Rev Cardiovasc Ther* 16: 879-887, 2018.
167. Wang XD, Liu J, Zhang YC, Wang Y, Wang Y and Ma D: Correlation between the elevated uric acid levels and circulating renin-angiotensin-aldosterone system activation in patients with atrial fibrillation. *Cardiovasc Diagn Ther* 11: 50-55, 2021.
168. Sanakityayan H, Rao PD, Shelke V, Kulkarni YA, Mulay SR and Gaikwad AB: Endoplasmic reticulum stress and renin-angiotensin system crosstalk in endothelial dysfunction. *Curr Mol Pharmacol* 16: 139-146, 2023.
169. Saito I, Saruta T, Kondo K, Nakamura R, Oguro T, Yamagami K, Ozawa Y and Kato E: Serum uric acid and the renin-angiotensin system in hypertension. *J Am Geriatr Soc* 26: 241-247, 1978.
170. Cappuccio FP, Iacone R and Strazzullo P: Serum uric acid and proximal sodium excretion: An independent association in man (the Olivetti Study). *J Hypertens (Suppl 9)*: S280-S281, 1991.
171. Welch WJ, Wilcox CS and Thomson SC: Nitric oxide and tubuloglomerular feedback. *Semin Nephrol* 19: 251-262, 1999.
172. Perlstein TS, Gumieniak O, Hopkins PN, Murphey LJ, Brown NJ, Williams GH, Hollenberg NK and Fisher ND: Uric acid and the state of the intrarenal renin-angiotensin system in humans. *Kidney Int* 66: 1465-1470, 2004.
173. Feig DI, Kang DH, Nakagawa T, Mazzali M and Johnson RJ: Uric acid and hypertension. *Curr Hypertens Rep* 8: 111-115, 2006.
174. Brewster UC and Perazella MA: The renin-angiotensin-aldosterone system and the kidney: Effects on kidney disease. *Am J Med* 116: 263-272, 2004.
175. Sparks MA, Crowley SD, Gurley SB, Mirotso M and Coffman TM: Classical Renin-Angiotensin system in kidney physiology. *Compr Physiol* 4: 1201-1228, 2014.



176. Nehme A, Zouein FA, Zayeri ZD and Zibara K: An Update on the Tissue Renin Angiotensin System and Its Role in Physiology and Pathology. *J Cardiovasc Dev Dis* 6: 14, 2019.
177. Laghlam D, Jozwiak M and Nguyen LS: Renin-Angiotensin-Aldosterone System and Immunomodulation: A State-of-the-Art Review. *Cells* 10: 1767, 2021.
178. Bernstein KE, Khan Z, Giani JF, Cao DY, Bernstein EA and Shen XZ: Angiotensin-converting enzyme in innate and adaptive immunity. *Nat Rev Nephrol* 14: 325-336, 2018.
179. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H and Tuck ML: Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens* 26: 269-275, 2008.
180. Yu MA, Sánchez-Lozada LG, Johnson RJ and Kang DH: Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens* 28: 1234-1242, 2010.
181. Basso N and Terragno NA: History about the discovery of the renin-angiotensin system. *Hypertension* 38: 1246-1249, 2001.
182. Lipworth BJ and Dagg KD: Vasoconstrictor effects of angiotensin II on the pulmonary vascular bed. *Chest* 105: 1360-1364, 1994.
183. Orte C, Polak JM, Haworth SG, Yacoub MH and Morrell NW: Expression of pulmonary vascular angiotensin-converting enzyme in primary and secondary plexiform pulmonary hypertension. *J Pathol* 192: 379-384, 2000.
184. Abraham WT, Raynolds MV, Badesch DB, Wynne KM, Groves BM, Roden RL, Robertson AD, Lowes BD, Zisman LS, Voelkel NF, *et al*: Angiotensin-converting enzyme DD genotype in patients with primary pulmonary hypertension: Increased frequency and association with preserved haemodynamics. *J Renin Angiotensin Aldosterone Syst* 4: 27-30, 2003.
185. Chung WK, Deng L, Carroll JS, Mallory N, Diamond B, Rosenzweig EB, Barst RJ and Morse JH: Polymorphism in the angiotensin II type 1 receptor (AGTR1) is associated with age at diagnosis in pulmonary arterial hypertension. *J Heart Lung Transplant* 28: 373-379, 2009.
186. Berk BC and Rao GN: Angiotensin II-induced vascular smooth muscle cell hypertrophy: PDGF A-chain mediates the increase in cell size. *J Cell Physiol* 154: 368-380, 1993.
187. Morrell NW, Atochina EN, Morris KG, Danilov SM and Stenmark KR: Angiotensin converting enzyme expression is increased in small pulmonary arteries of rats with hypoxia-induced pulmonary hypertension. *J Clin Invest* 96: 1823-1833, 1995.
188. de Man FS, Tu L, Handoko ML, Rain S, Ruiter G, François C, Schalij I, Dorfmueller P, Simonneau G, Fadel E, *et al*: Dysregulated renin-angiotensin-aldosterone system contributes to pulmonary arterial hypertension. *Am J Respir Crit Care Med* 186: 780-789, 2012.
189. Pezzuto B, Badagliacca R, Poscia R, Ghio S, D'Alto M, Vitulo P, Mulè M, Albera C, Volterrani M, Fedele F and Vizza CD: Circulating biomarkers in pulmonary arterial hypertension: Update and future direction. *J Heart Lung Transplant* 34: 282-305, 2015.
190. Foris V, Kovacs G, Tscherner M, Olschewski A and Olschewski H: Biomarkers in pulmonary hypertension: What do we know?. *Chest* 144: 274-283, 2013.
191. Ozanturk E, Ucar ZZ, Varol Y, Koca H, Demir AU, Kalenci D, Halilcolar H and Ozacar R: Urinary uric acid excretion as an indicator of severe hypoxia and mortality in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. *Rev Port Pneumol* (2006) 22: 18-26, 2016.
192. Deng S, Zhu T, Wang C, Gu X, Zhang J, Lu Q, Yang Y and Ma X: Analysis of Correlation Between Serum Hypoxia-Inducible Factor-1 $\alpha$ , Uric Acid, and Inflammatory Factor Levels and Lung Function in Patients with AECOPD. *Altern Ther Health Med* AT8122: Aug 11, 2023 (Epub ahead of print).
193. Leyva F, Anker S, Swan JW, Godslund IF, Wingrove CS, Chua TP, Stevenson JC and Coats AJ: Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *Eur Heart J* 18: 858-865, 1997.
194. Horodinschi RN, Bratu OG, Dediu GN, Pantea Stoian A, Motofei I and Diaconu CC: Heart failure and chronic obstructive pulmonary disease: A review. *Acta Cardiol* 75: 97-104, 2020.
195. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, *et al*: Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 53: 1801914, 2019.
196. Kaufman M and Guglin M: Uric acid in heart failure: A biomarker or therapeutic target?. *Heart Fail Rev* 18: 177-186, 2013.
197. Richette P, Frazier A and Bardin T: Impact of anti-inflammatory therapies, xanthine oxidase inhibitors and other urate-lowering therapies on cardiovascular diseases in gout. *Curr Opin Rheumatol* 27: 170-174, 2015.
198. Komori H, Yamada K and Tamai I: Hyperuricemia enhances intracellular urate accumulation via down-regulation of cell-surface BCRP/ABCG2 expression in vascular endothelial cells. *Biochim Biophys Acta Biomembr* 1860: 973-980, 2018.
199. Yanai H, Adachi H, Hakoshima M and Katsuyama H: Molecular biological and clinical understanding of the pathophysiology and treatments of hyperuricemia and its association with metabolic syndrome, cardiovascular diseases and chronic kidney disease. *Int J Mol Sci* 22: 9221, 2021.
200. Lokmic Z, Musyoka J, Hewitson TD and Darby IA: Hypoxia and hypoxia signaling in tissue repair and fibrosis. *Int Rev Cell Mol Biol* 296: 139-185, 2012.
201. Alderman M and Aiyer KJ: Uric acid: Role in cardiovascular disease and effects of losartan. *Curr Med Res Opin* 20: 369-379, 2004.
202. Cai H and Harrison DG: Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. *Circ Res* 87: 840-844, 2000.
203. Țăpoi L, Șalaru DL, Sascău R and Stătescu C: Uric Acid-An emergent risk marker for thrombosis?. *J Clin Med* 10: 2062, 2021.
204. Schober A: Chemokines in vascular dysfunction and remodeling. *Arterioscler Thromb Vasc Biol* 28: 1950-1959, 2008.
205. Voelkel NF, Mizuno S and Bogaard HJ: The role of hypoxia in pulmonary vascular diseases: A perspective. *Am J Physiol Lung Cell Mol Physiol* 304: L457-L465, 2013.
206. Borghi C, Verardi FM, Pareo I, Bentivenga C and Cicero AF: Hyperuricemia and cardiovascular disease risk. *Expert Rev Cardiovasc Ther* 12: 1219-1225, 2014.
207. Das A, Kumar P, Kumari A, Chandra S, Gari M, Singh N and Dey D: Effects of cilnidipine on heart rate and uric acid metabolism in patients with essential hypertension. *Cardiol Res* 7: 167-172, 2016.
208. Qin X, Li Y, He M, Tang G, Yin D, Liang M, Wang B, Nie J, Huo Y, Xu X and Hou FF: Folic acid therapy reduces serum uric acid in hypertensive patients: A substudy of the China Stroke Primary Prevention Trial (CSPPT). *Am J Clin Nutr* 105: 882-889, 2017.
209. Chida R, Hisauchi I, Toyoda S, Kikuchi M, Komatsu T, Hori Y, Nakahara S, Sakai Y, Inoue T and Taguchi I: Impact of irbesartan, an angiotensin receptor blocker, on uric acid level and oxidative stress in high-risk hypertension patients. *Hypertens Res* 38: 765-769, 2015.
210. Kim EJ, Song WH, Lee JU, Shin MS, Lee S, Kim BO, Hong KS, Han SW, Park CG and Seo HS: Efficacy of losartan and carvedilol on central hemodynamics in hypertensives: a prospective, randomized, open, blinded end point, multicenter study. *Hypertens Res* 37: 50-56, 2014.
211. Newman CB: Safety of statins and nonstatins for treatment of dyslipidemia. *Endocrinol Metab Clin North Am* 51: 655-679, 2022.
212. Noori S, Mirzababaei A, Amini MR, Clark CCT and Mirzaei K: Effect of orlistat on serum uric acid level in adults: A systematic review and meta-analysis of randomised controlled trials. *Int J Clin Pract* 75: e14674, 2021.
213. Zhang G, Ma Y, Xi D, Rao Z, Sun X and Wu X: Effect of high uric acid on the disposition of metformin: in vivo and in vitro studies. *Biopharm Drug Dispos* 40: 3-11, 2019.
214. Katsiki N, Karagiannis A, Athyros VG and Mikhailidis DP: Hyperuricaemia: More than just a cause of gout. *J Cardiovasc Med (Hagerstown)* 14: 397-402, 2013.
215. Thomas MC: Renal effects of dapagliflozin in patients with type 2 diabetes. *Ther Adv Endocrinol Metab* 5: 53-61, 2014.
216. George J, Carr E, Davies J, Belch JJ and Struthers A: High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 114: 2508-2516, 2006.
217. Tani S, Nagao K and Hirayama A: Effect of febuxostat, a xanthine oxidase inhibitor, on cardiovascular risk in hyperuricemic patients with hypertension: A prospective, open-label, pilot study. *Clin Drug Investig* 35: 823-831, 2015.



218. Lin HC, Daimon M, Wang CH, Ho Y, Uang YS, Chiang SJ and Wang LH: Allopurinol, benzbromarone and risk of coronary heart disease in gout patients: A population-based study. *Int J Cardiol* 233: 85-90, 2017.
219. Kim SC, Neogi T, Kang EH, Liu J, Desai RJ, Zhang M and Solomon DH: Cardiovascular risks of probenecid versus allopurinol in older patients with gout. *J Am Coll Cardiol* 71: 994-1004, 2018.
220. Moss JD, Wu M, Axelrod DM and Kwiatkowski DM: Rasburicase versus intravenous allopurinol for non-malignancy-associated acute hyperuricemia in paediatric cardiology patients. *Cardiol Young* 29: 1160-1164, 2019.
221. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, Vázquez-Mellado J, White WB, Lipsky PE, Horowitz Z, *et al*: Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: Two randomized controlled trials. *JAMA* 306: 711-720, 2011.
222. Theilmann AL and Ormiston ML: Repurposing benzbromarone for pulmonary arterial hypertension: Can channelling the past deliver the therapy of the future?. *Eur Respir J* 53: 1900583, 2019.
223. Liu-Shiu-Cheong PSK, Lipworth BJ, Weir-McCall JR, Houston JG and Struthers AD: Allopurinol in patients with pulmonary hypertension associated with chronic lung disease. *Int J Chron Obstruct Pulmon Dis* 15: 2015-2024, 2020.
224. Gokcen T, Inci K, Inci EE, Sevgen O and Serdar U: Allopurinol treatment reduced vascular remodeling and improved vascular functions in monocrotaline-induced pulmonary hypertensive rats. *Pulm Pharmacol Ther* 77: 102166, 2022.
225. De Scheerder IK, van de Kraay AM, Lamers JM, Koster JF, de Jong JW and Serruys PW: Myocardial malondialdehyde and uric acid release after short-lasting coronary occlusions during coronary angioplasty: Potential mechanisms for free radical generation. *Am J Cardiol* 68: 392-395, 1991.
226. Friedl HP, Till GO, Trentz O and Ward PA: Role of oxygen radicals in tourniquet-related ischemia-reperfusion injury of human patients. *Klin Wochenschr* 69: 1109-1112, 1991.
227. Many A, Hubel CA and Roberts JM: Hyperuricemia and xanthine oxidase in preeclampsia, revisited. *Am J Obstet Gynecol* 174 (1 Pt 1): 288-291, 1996.



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