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Received: 2 March 2023 | Revised: 8 May 2023 | Accepted: 19 May 2023

DOI: 10.1096/fj.202300393R

The FASEB Journal

REVIEW ARTICLE

Hyperuricemia: A key contributor to endothelial dysfunction in cardiovascular diseases

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Abstract

As an end product of purine metabolism, uric acid (UA) is a major endogenous antioxidant in humans. However, impaired UA synthesis and excretion can lead to hyperuricemia (HUA), which may in turn induce endothelial dysfunction

Abbreviations: •OH, hydroxyl radicals; ABCG2, ATP-binding cassette superfamily G member 2; ACS, acute coronary syndrome; ADMA, asymmetric dimethyl-L-arginine; Ang II, angiotensin II; APTT, activated partial thromboplastin time; ASC, apoptosis-associated speck-like protein containing a CARD; ATF, activating transcription factor; Ca^{2+}, calcium ions; CAD, coronary artery disease; CaM, calmodulin; CHOP, C/EBP homologous protein; CKD, chronic kidney disease; COX-2, cyclooxygenase-2; CVD, cardiovascular disease; DAMP, damage-associated molecular pattern; DDAH, dimethylarginine dimethylaminotransferase; EC, endothelial cell; ED, endothelial dysfunction; eIF2A, eukaryotic translation initiation factor 2; EndMT, endothelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; FAD, flavin adenine dinucleotide; FGF21, fibroblast growth factor 21; FMN, flavin mononucleotide; H_2O_2, hydrogen peroxide; HAEC, human aortic endothelial cell; HMGB1, high mobility group protein 1; HUA, hyperuricemia; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular cell adhesion molecule-1; IL, interleukin; IR, insulin resistance; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MEF2C, myocyte enhancer factor 2C; MPs, microparticles; MSU, monosodium urate; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NLRP3, nod-like receptor family pyrin domain-containing 3; NO, nitric oxide; NOX, NADPH oxidase; O_2, oxygen molecules; $O_2^{\cdot-}$, superoxide ions; $ONOO^-$, peroxynitrite; PAI-1, plasminogen activator inhibitor 1; PCA, procoagulant activity; PCI, percutaneous coronary intervention; PGE2, prostaglandin E2; PGI_2, prostaglandin I_2; PS, phosphatidylserine; PT, prothrombin time; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; SLC17A1/NPT1, novel putative transporter 1; SLC17A3/NPT4, novel putative transporter 4; SLC22A11/OAT4, organic anion transporter 4; SLC22A12/URAT1, urate transporter 1; SLC22A6/OAT1, organic anion transporter 1; SLC22A8/OAT3, organic anion transporter 3; SLC2A9/GLUT9, glucose transporter 9; SMC, smooth muscle cell; SREBP2, sterol regulatory element-binding protein 2; SUA, serum uric acid; T2DM, type 2 diabetes mellitus; TAZ, transcriptional coactivator with PDZ-binding motif; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TMEM16F, transmembrane protein 16F; TNF-α, tumor necrosis factor-alpha; t-PA, tissue plasminogen activator; TT, thrombin time; TXA_2, thromboxane A_2; UA, uric acid; UPR, unfolded protein response; VCAM-1, vascular cell adhesion molecule-1; XDH, xanthine dehydrogenase; XO, xanthine oxidase; XOR, xanthine oxidoreductase; YAP, Yes-associated protein.

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Funding information
Guangdong Medical College (GDMC), Grant/Award Number: 4SG21233G; MOST | National Natural Science Foundation of China (NSFC), Grant/Award Number: 81700269; Zhanjiang Science and Technology Bureau, Grant/Award Number: 2022E05011, 2022A01196, 2021A05158, 2021A05058, 2021A05056, 2020A01020, 2020A06003 and 2020A06004; Natural Science Foundation of Guangdong Province, Grant/Award Number: 2019A1515011925

(ED) and contribute to the pathogenesis of cardiovascular diseases (CVDs; e.g., atherosclerosis and hypertension). In this review, we discuss recent advances and novel insights into the effects exerted by HUA conditions in ED and related underlying mechanisms focusing on impaired UA metabolism, reduction in the synthesis and bioavailability of nitric oxide, endothelial cell injury, the endothelial-to-mesenchymal transition, insulin resistance, procoagulant activity, and acquisition of an inflammatory phenotype. We additionally discuss intervention strategies for HUA-induced ED and the paradoxical roles of UA in endothelial function. We summarize major conclusions and perspectives: the deleterious effects of HUA contribute to the initiation and progression of CVD-related ED. However, the treatment strategies (in addition to urate-lowering therapy) for increasing endothelial function are limited because the majority of literature on pharmacological and pathophysiological mechanisms underlying HUA-induced ED solely describes in vitro models. Therefore, a better understanding of the mechanisms involved in HUA-induced ED is critical to the development of novel therapies for preventing and treating CVD-HUA comorbidities.

KEYWORDS
atherosclerosis, cardiovascular diseases, endothelial dysfunction, hyperuricemia, uric acid metabolism

1 | INTRODUCTION

Cardiovascular disease (CVD) remains one of the leading causes of mortality in China and worldwide.[1] According to a 2021 China cardiovascular disease report, CVD accounted for more than 40% of all deaths in China in 2019.[2] To reduce the risk of CVD-related death and improve quality of life, many investigators have focused their studies on the pathogenesis and pathomechanism of CVD and searched for pharmacological targets against CVD, aiming to establish an optimal therapeutic strategy to combat CVD. Recently, increasing evidence has indicated that endothelial dysfunction (ED) plays an essential role in the pathogenesis of CVD, including hypertension, atherosclerosis, arterial dissection, coronary artery disease (CAD), heart failure, atrial fibrillation, and pulmonary hypertension.[3–9] Therefore, targeting ED may be a promising strategy for the prevention and treatment of CVD.[10]

In healthy endothelium tissues, a single layer of endothelial cells (ECs) is overlaid with glycocalyx. ECs line the lumen of blood vessels and perform key regulatory roles in vascular function and homeostasis.[11] ECs not only mediate oxygen and nutrient exchange between blood and perfused organs but also regulate vasoconstriction and vasodilation by synthetizing and releasing vasoactive factors, which include nitric oxide (NO), prostaglandin I_2 (PGI_2), endothelin-1 (ET-1), thromboxane A_2 (TXA_2), and angiotensin II (Ang II).[11] In addition, ECs inhibit platelet aggregation and inflammatory cell adhesion, preventing thrombosis and vascular inflammation.[12,13] In parallel, an intact endothelial barrier separates medial smooth muscle cells (SMCs) from blood to prevent excessive SMC proliferation.[14] In general, exposure to cardiovascular risk factors (e.g., smoking, hypertension, hyperlipidemia, hypercholesterolemia, diabetes, and hypoxia) increases the risk of developing ED.[15] As nonprofessional immune cells, ECs can be induced to produce proinflammatory factors and promote leukocyte recruitment and adhesion.[16] Once stimulated, ECs switch from the resting state to the activated state, which results in thrombosis, vascular inflammation, reduced NO release, and increased permeability, conditions that can eventually progress to ED.[17]

Uric acid (UA), a product of purine metabolism, is a major endogenous antioxidant in the body and regulates various biological processes.[18] For instance, UA has been shown to protect neurons, maintain blood pressure stability, increase bone density, and induce type 2 immunity.[19–22] However, with changes in human diet and lifestyle over the past few decades, the prevalence of hyperuricemia (HUA) has been increasing annually.[23,24] To date, HUA has become another major cardiovascular risk factor in addition to the traditional "three-high" diseases, which refer to hypertension, hyperlipidemia, and hyperglycemia. Specifically, increasing UA synthesis and/or decreased renal urate excretion can lead to HUA, which is defined as serum UA (SUA) levels >7 mg/dL (420 μmol/L)

in males and 6 mg/dL (360 μmol/L) in females.[25] HUA has been classified into symptomatic (e.g., gout and urolithiasis) and asymptomatic types based on clinical presentation. Most recent evidence supports the causal effect of HUA on CVD.[26–28] However, the contribution of soluble SUA to CVD risk for asymptomatic HUA is debated.[29–31] Inconsistent conclusion may be attributed to the differences in sample sizes, study designs, and potential confounders in experiments. Therefore, it is challenging to clinically determine a definitive association between HUA and CVD physiopathology. Considering importance of ED in CVD onset and progression, we discuss recent advances and novel insights into the precise mechanisms underlying the association between HUA and CVD-related ED.

2 | UA METABOLISM AND ED

In humans, UA is primarily metabolized from endogenous purine degradation, with the remainder derived from the decomposition and absorption of digested food (Figure 1).[18] In the liver, intestine, kidney, musculature, and vascular endothelium, purines are progressively transformed into hypoxanthine, xanthine, and UA by xanthine oxidoreductase (XOR) (Figure 1), which exists in two interconvertible forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO).[32] Despite acting on the same substrates, XDH and XO catalyze the formation of UA and reactive oxygen species (ROS; mainly superoxide ions [$O_2^{\cdot-}$] and hydrogen peroxide [H_2O_2]), respectively, the latter of which exerts dominant negative effects on redox balance.[33] In addition, XOR catalyzes the reduction of nitrate to nitrite and acts as a nitrite reductase to reduce nitrite to NO.[34] However, in response to oxidative stress stimuli, NO can react with $O_2^{\cdot-}$ to generate peroxynitrite ($ONOO^-$).[35] In the presence of transition metal ions, $O_2^{\cdot-}$ reacts with H_2O_2 to produce hydroxyl radicals (•OH).[36] These metabolic reactions indicate that an increase in UA synthesis may concomitantly lead to excessive oxidative stress and diminished NO bioavailability.

UA is excreted mainly via the kidney and gastrointestinal tract (Figure 1). At physiological pH (7.40), urate (the salt of UA) is the primary form of UA, and it is transported through the plasma membrane via transport proteins.[37] UA excretion is largely controlled by urate transporters expressed in epithelial cells that line kidney proximal tubules.[38] Among these transporters, SLC22A12/URAT1 (urate transporter 1), SLC2A9/GLUT9 (glucose transporter 9), and SLC22A11/OAT4 (organic anion transporter 4) mediate urate reabsorption, while SLC22A6/OAT1 (organic anion transporter 1), SLC22A8/OAT3 (organic anion transporter 3), SLC17A1/NPT1 (novel putative transporter 1), SLC17A3/NPT4 (novel putative transporter 4), and ABCG2 (ATP-binding cassette superfamily G member 2) are critical for urate secretion.[39] In addition to renal tubular epithelial cells, urate transporters are also expressed in ECs.[40] Moreover, high concentrations of UA treatments in human umbilical vein endothelial cells (HUVECs) increase GLUT9 expression while decrease the activity of ABCG2 (a UA efflux transporter),[41–43] resulting in intracellular UA and ROS accumulation, ultimately leading to inflammation and oxidative stress (Figure 1). In contrast, blocking UA transport into ECs through the action of the organic anion transporter inhibitor probenecid arrests ED progression.[44] This evidence suggests that controlling transporter-mediated cellular uptake and secretion of

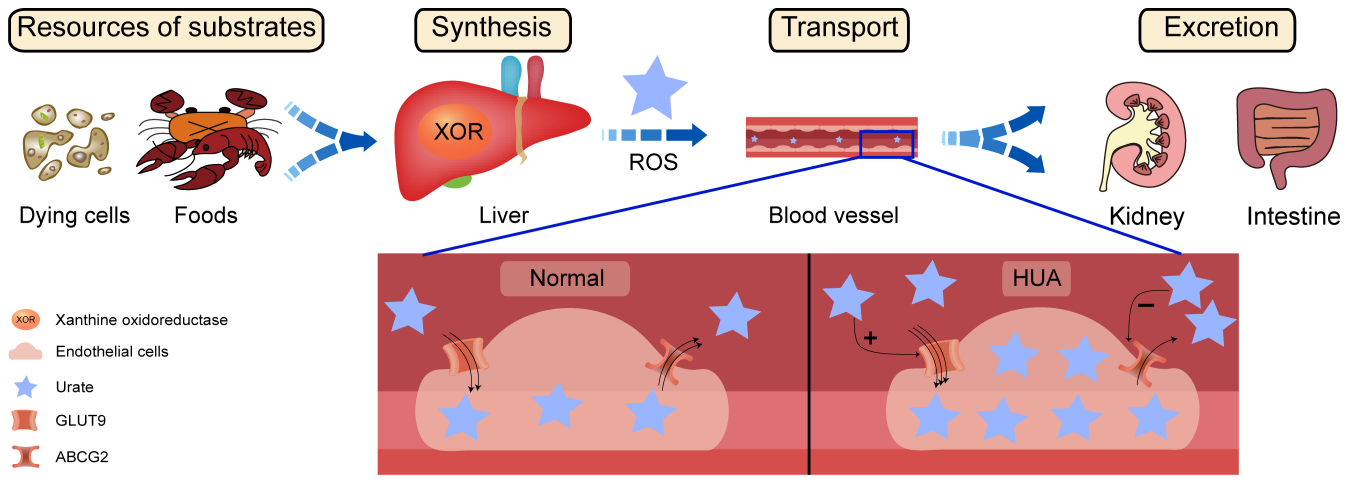

FIGURE 1 Uric acid metabolism and its effect on endothelial function. Uric acid originates from endogenous purines and digested food, and its synthesis is catalyzed by xanthine oxidoreductase, which also produces reactive oxygen species as byproducts. Endothelial cells can express urate transporters including GLUT9 and ABCG2, the function of which is impaired under hyperuricemic conditions. ABCG2, ATP-binding cassette superfamily G member 2; GLUT9, glucose transporter 9; HUA, hyperuricemia; ROS, reactive oxygen species.

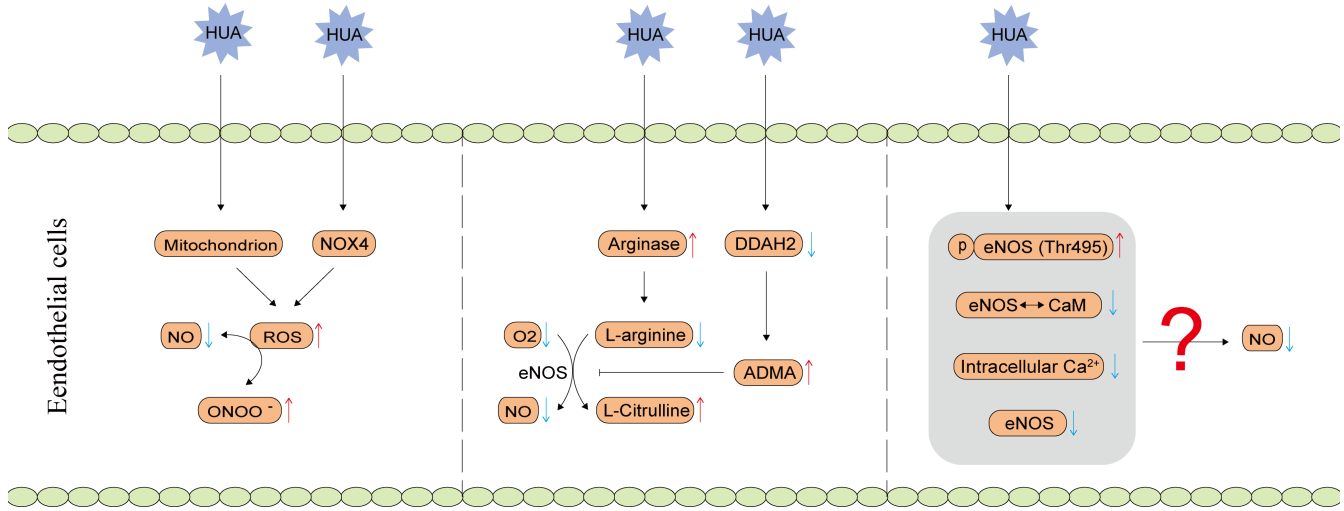

FIGURE 2 Decreased synthesis and bioavailability of endothelium-derived NO caused by hyperuricemia. Redox imbalance, reduced L-arginine supply, and eNOS inhibition contribute to decreasing NO production in the hyperuricemia context. ADMA, asymmetric dimethyl-L-arginine; CaM, calmodulin; Ca^{2+}, calcium ions; DDAH2, dimethylarginine dimethylaminotransferase 2; eNOS, endothelial nitric oxide synthase; HUA, hyperuricemia; NO, nitric oxide; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; $ONOO^-$, peroxynitrite; O_2, oxygen molecules; ROS, reactive oxygen species.

urate contribute to the mechanism governing the occurrence and progression of ED.

3 | MECHANISMS UNDERLYING HUA-INDUCED ED

3.1 | Decreased NO production

Decreased NO synthesis, release, and/or activity in ECs have been associated with the development of CVD.[45] NO, a highly reactive and gas diffusible free radical with potent vasodilatory, anti-inflammatory, and antioxidant properties, plays key roles in regulating vascular tone, angiogenesis, inflammatory cell adhesion, and platelet aggregation.[46] The biosynthesis of NO in ECs is catalyzed by endothelial nitric oxide synthase (eNOS).[47] Under normal conditions, eNOS dimer formation is highly dependent on the binding of calcium ions (Ca^{2+}) to calmodulin (CaM). In the presence of tetrahydrobiopterin, electrons from nicotinamide adenine dinucleotide phosphate (NADPH) are transferred to a heme prosthetic group through the actions of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) and subsequently catalyze L-arginine and oxygen molecules (O_2) to produce L-citrulline and NO.[48] However, in an uncoupled state, electrons are transferred directly from FAD and FMN to O_2 to generate $O_2^{\cdot-}$, which eventually binds with local NO to generate $ONOO^-$.[49] A high level of $ONOO^-$ is associated with the nitrosation or nitration of proteins, resulting in oxidative damage to cellular components.[50] Several mechanisms may contribute to HUA-induced decreases in endothelial NO production by promoting redox imbalance, reducing L-arginine supply, and inhibiting eNOS activity (Figure 2).

3.1.1 | Oxidative stress

Physiological concentrations of UA (in the normal value range) can inhibit ROS (including $O_2^{\cdot-}$, H_2O_2, and $ONOO^-$) in ECs.[51] In contrast, high UA concentrations (≥600 μmol/L) increase ROS production, largely through mitochondrial respiratory chain action.[51,52] Alternatively, NADPH oxidases (NOXs) contribute to HUA-induced ED, thus serving other major sources of ROS.[51,53] As membrane-bound enzyme complexes, NOXs reduce the conversion of O_2 to $O_2^{\cdot-}$ via the NADPH-dependent electron transport pathway.[54] To date, seven NOX isoforms have been identified and characterized: NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1, and DUOX2.[53] Therein, aldose reductase (AR)-mediated NOX4 activation reduces NO release in ECs exposed to high concentrations of UA in vitro or in vivo in association with ROS production.[51] Overall, high UA levels lead to mitochondrial dysfunction and NOX4 activation and hence promote ECs to generate excessive ROS, which react further with NO to produce $ONOO^-$, ultimately inducing ED. NOX4 has been shown to be a mediator of CVD in elderly hyperlipidemic mice, and its expression correlates with age and atherosclerosis severity in humans.[55] However, experiments with atherosclerotic animal models have demonstrated that endothelial NOX4 is atheroprotective.[56–58] Thus, a more in-depth investigation is necessary to determine whether or not NOX4 is involved in atherosclerosis under hyperuricemic conditions.

3.1.2 | Inadequate L-arginine supply

In addition to acting as a substrate for endogenous NO production, L-arginine can be cleaved by arginase to form urea and L-ornithine in the urea cycle (also termed the ornithine cycle).[59] High UA levels increase arginase activity in HUVECs and human pulmonary artery endothelial cells.[60,61] Moreover, a rat model of pulmonary hypertension with HUA exhibits a greater pressor response, which can be attenuated by arginase inhibitors.[61] As the natural homolog of L-arginine, asymmetric dimethyl-L-arginine (ADMA) mediates ED through the inhibition of eNOS activity. Under normal conditions, ADMA can be metabolized to the less-active by product citrulline via the actions of dimethylarginine dimethylaminotransferase (DDAH)-1 and DDAH-2.[62] However, the enzymatic activities of DDAHs are compromised in the ECs of CVD patients, leading to increased ADMA levels and impaired NO synthesis. Recently, Lee et al.[63] reported that high UA concentrations significantly increased the levels of ADMA in human aortic endothelial cells (HAECs) and the aorta of an $ApoE^{-/-}$ mouse model via the NOX/ROS pathway-mediated downregulation of DDAH-2, thereby reducing NO production and intracellular cGMP (a surrogate marker of NO production) level. The development of HUA leads to the inhibition of eNOS-catalyzed NO synthesis owing to the stimulation of arginase activity and ADMA production.

3.1.3 | Inhibition of eNOS activity

No consensus has been reached on the mechanism by which eNOS activity is inhibited in the HUA context. Park et al.[64] found that a high UA level impaired eNOS activity in HUVECs by inhibiting the interaction between eNOS and CaM without altering either the levels of intracellular calcium, CaM, and eNOS, or the phosphorylation of eNOS at three common activation sites (Ser1177, Thr495, and Ser114). These findings were partly supported by a report from Li et al.[65] indicating that a high UA level did not significantly change the concentrations of intracellular calcium, CaM, and eNOS or the phosphorylation rate of eNOS (Ser1177) in HUVECs. However, opposite outcomes were reported between both studies. Li et al.[65] indicated that at a high level, UA increased eNOS (Thr495) phosphorylation without influencing the interaction between eNOS and CaM. In addition, other studies demonstrated that UA at high levels induced the elevation of intracellular calcium level or the reduction in eNOS content in HUVECs in a dose- and time-dependent manner.[66,67] The contradictions among these observations may be results of different experimental conditions and differences in the execution of the study protocols. Therefore, further studies, especially with in vivo models, may be needed to clearly determine the effect and mechanism by which HUA alters eNOS activity.

3.2 | Stress-induced EC injury

Under pathophysiological conditions, the accumulation of misfolded proteins in the endoplasmic reticulum (ER) triggers signaling cascades in the unfolded protein response (UPR) to restore ER homeostasis.[68] However, prolonged UPR activation may induce cell death when the UPR cannot overcome the ER stress.[69] In HUVECs stimulated with high UA levels, ER stress was confirmed to be activated by oxidative stress, and this outcome was manifested by the increased expression of markers such as activating transcription factor 4 and 6 (ATF4 and ATF6), C/EBP homologous protein (CHOP), caspase-12, and eukaryotic translation initiation factor 2 (eIF2A).[65,70] Concomitantly, UA at a high level also promoted the expression of the nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, which included NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1.[70] These findings suggest that ER stress functions as a bridge between environmental stimulation and the cellular response in HUA-induced ED. Since caspase-12 and the NLRP3 inflammasome mediate apoptosis and pyroptosis, respectively, we speculate that both types of cell death contribute to HUA-induced EC injury. While EC injury disrupts the integrity of the vascular endothelium, EC proliferation and migration are essential for endothelial repair but may lead to intimal thickening.[71] High concentrations of UA have been implicated in the enhanced proliferation and attenuated migration of ECs,[72,73] indicating that HUA is associated with different stages of CVD.

3.3 | The endothelial-to-mesenchymal transition

The endothelial-to-mesenchymal transition (EndMT) contributes substantially to inflammation-induced fibrosis, which is an important link in the pathogenesis of atherosclerosis.[74–76] UA can induce the EndMT in HUVECs and hyperuricemic rats by promoting oxidative stress and glycocalyx shedding.[77] Disruption to the endothelial glycocalyx, which is associated with inflammation, can increase vascular permeability and promote leukocyte and platelet adhesion to ECs,[78–80] probably

playing an important role in atherosclerosis. Overall, HUA might drive the EndMT-mediated loss of endothelial function. To date, no studies have used atherosclerosis models to investigate the association of HUA with the EndMT.

3.4 | Endothelial insulin resistance

Insulin can stimulate ECs to release NO.[81] However, UA inhibits insulin-induced eNOS activation and NO production in ECs by impairing the PI3K/Akt and insulin signaling pathways, eventually leading to the development of insulin resistance (IR).[82,83] A meta-analysis supported this proposed mechanism, as SUA at an elevated level was found to be an independent predictor of vascular complications and mortality in type 2 diabetes mellitus (T2DM).[84] Moreover, the association between SUA and the development of diabetic vasculopathy has been sufficiently verified.[85,86]

3.5 | Procoagulant activity

The risk of deep vein thrombosis and pulmonary embolism increased by gout has been established.[87] HUA has been associated with increased risk of atherothrombotic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).[88] ECs exert both anticoagulant and antithrombotic effects, because they can secrete factors that mediate platelet aggregation and coagulation. However, when blood vessels are injured or exposed to proinflammatory cytokines, endothelial homeostasis is imbalanced, shifting toward procoagulant and prothrombotic effects.[89]

Cimmino et al.[90] reported that UA at high levels enhanced the procoagulant function of tissue factor (TF) and decreased the expression of its physiological inhibitor TFPI in HUVECs, leading to the acquisition of a prothrombotic phenotype. Similarly, a shorten activated partial thromboplastin time (APTT) and prothrombin time (PT), a prolonged thrombin time (TT), and increased levels of fibrinogen and D-dimer have been observed in the serum of a HUA mouse model.[91] These effects may have been partially due to myocyte enhancer factor 2C (MEF2C)-dependent nuclear factor kappa B (NF-κB) activation in ECs, which is regulated by let-7c and results in significant increases in the protein levels of plasminogen activator inhibitor 1 (PAI-1) and TF but marked reductions in tissue plasminogen activator (t-PA) expression.[91] In addition, endothelial microparticles (MPs) participate in the mechanism underlying HUA-induced coagulation. Yu et al.[67] demonstrated that UA at high levels can induce cytoskeletal structure disruption, transmembrane protein 16F (TMEM16F) activation, phosphatidylserine (PS) externalization, and MP shedding in HUVECs by increasing the levels of intracellular calcium and ROS. After MP shedding and PS externalization on ECs, binding sites are made available for the coagulation factors FXA and the prothrombinase complex, which activate the coagulation cascade, resulting in a marked increase in thrombin generation and enhanced endothelial procoagulant activity (PCA).[67] Collectively, these studies indicate that the interaction between ECs and coagulation-fibrinolytic systems is altered in HUA, increasing the risk of thromboembolic events. Therefore, HUA status needs to be considered in patients receiving antithrombotic therapies, including anticoagulants, antiplatelet agents, and thrombolytics.

3.6 | The inflammatory phenotype

The acquisition of the inflammatory phenotype by ECs in the atherosclerotic context leads to favorable conditions for leukocyte adhesion.[92] Activated ECs release inflammatory cytokines that attract lymphocytes and monocytes; simultaneously, enhanced expression of inflammatory adhesion molecules facilitates leukocyte adhesion and extravasation.[93] High UA treatment elevates the levels of proinflammatory factors, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-18, intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and monocyte chemoattractant protein-1 (MCP-1) in the supernatants of cultured ECs,[41,42,94–96] suggesting that HUA can drive the progression of endothelial inflammation, which further causes ED (Figure 3). The following signaling pathways are suggested to be involved in HUA-induced endothelial inflammation.

3.6.1 | NF-κB cascade

Elevated UA levels are damage-associated molecular patterns (DAMPs) that induce provoking NLRP3 inflammasome activation in ECs.[94,95] In this process, IL-1β and IL-18 are cleaved by activated caspase-1 and are then secreted into the extracellular space, amplifying the inflammatory response.[94,95] Subsequently, NF-κB plays a key regulatory role in the endothelial inflammatory response.[97] In addition, high mobility group protein 1 (HMGB1) combined with receptor for advanced glycation end products (RAGE) contributes to NF-κB activation in HUVECs treated with a high concentration of UA (Figure 3).[66] Together, these findings strongly support the suggestion that NF-κB is a

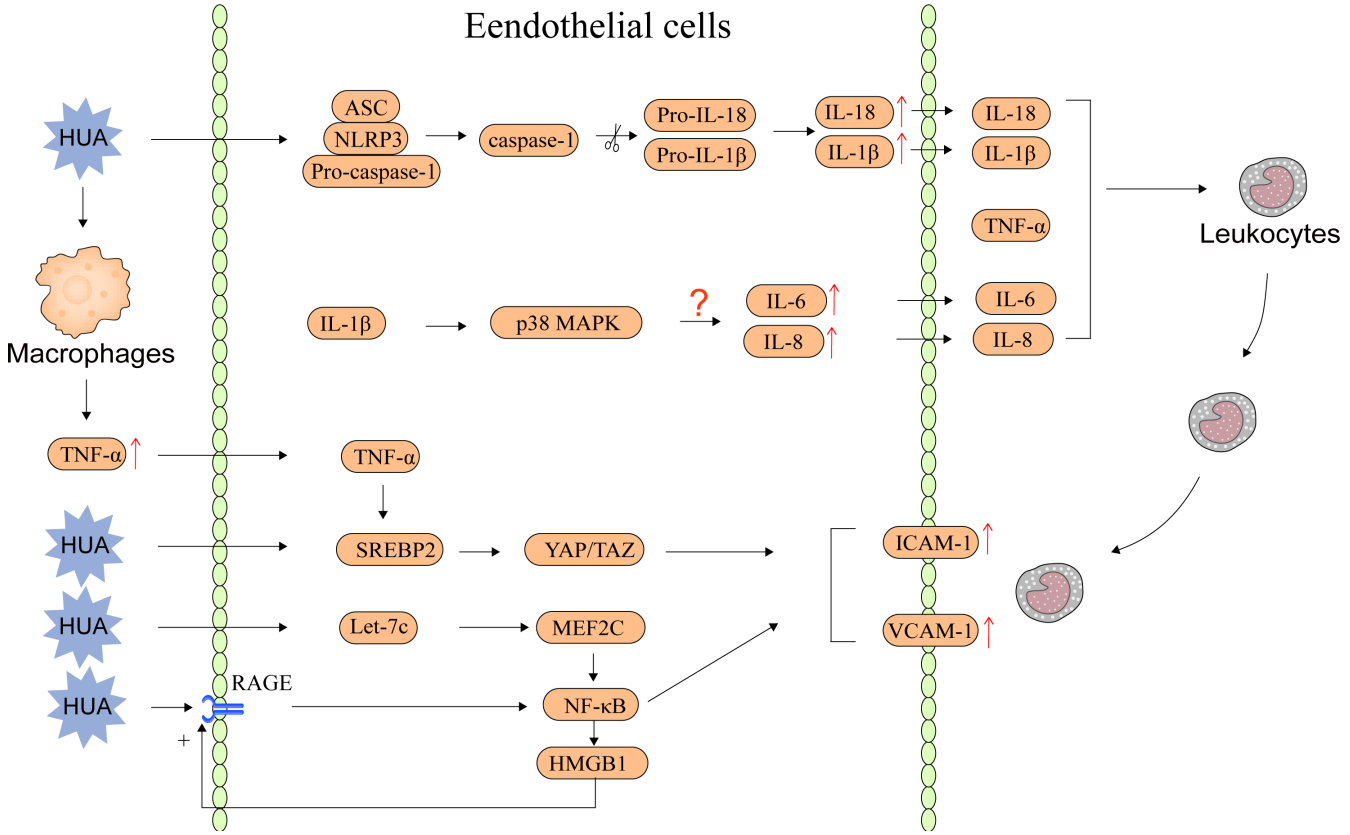

FIGURE 3 Hyperuricemia-induced endothelial inflammation. The NF-κB, MAPK, and Hippo pathways may be involved in the mechanism underlying the acquisition of the inflammatory phenotype in endothelial cells exposed to hyperuricemia. ASC, apoptosis-associated speck-like protein-containing a CARD; HMGB1, high mobility group protein 1; HUA, hyperuricemia; ICAM-1, intercellular cell adhesion molecule-1; IL, interleukin; MAPK, mitogen-activated protein kinase; MEF2C, myocyte enhancer factor 2C; NF-κB, nuclear factor kappa B; NLRP3, nod-like receptor family pyrin domain-containing 3; RAGE, receptor for advanced glycation endproducts; SREBP2, sterol regulatory element-bindingprotein2; TAZ, transcriptional coactivator with PDZ-binding motif; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1; YAP, Yes-associated protein.

potent target for HUA-induced endothelial inflammation. Indeed, NF-κB plays a crucial role in CVD, including atherosclerosis.[98] Further studies are required to investigate the pharmacological efficacy of targeting the NF-κB cascade in patients with CVD-HUA comorbidities.

3.6.2 | Mitogen-activated protein kinase signaling

Mitogen-activated protein kinase (MAPK) signaling composed of the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK pathways can be induced by various stimuli, including UA at high levels.[51,96] In addition to NF-κB, p38 has been suggested to be an important mediator of endothelial inflammation besides NF-κB.[99] Although the phosphorylation levels of p38 are markedly elevated in HUVECs treated with high levels of UA,[51] the precise regulatory relationships between p38 and HUA-induced endothelial inflammation and the mechanism by which p38 functions downstream remain to be explored (Figure 3).

3.6.3 | Hippo pathway

Physiologically, when the Hippo pathway is active, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are phosphorylated, ubiquitinated, and degraded by proteasomes.[100] In contrast, inhibition of the Hippo pathway promotes dephosphorylated YAP/TAZ entry into the nucleus, thus regulating cell proliferation, differentiation, tissue homeostasis, and organ morphogenesis.[101] Both soluble UA and monosodium urate (MSU) increase VCAM-1 and ICAM-1 expression in HUVECs via the sterol regulatory element-binding protein 2 (SREBP2) transactivation of YAP.[102] These findings have been confirmed with a mouse model of HUA.[102] Choi et al.[103] showed that TNF-α induced VCAM-1 expression in HUVECs via

the enhancement of YAP/TAZ activity, which was independent of NF-κB signaling. Importantly, YAP/TAZ has been confirmed to be involved in several CVDs, including atherosclerosis, myocardial infarction, and pulmonary hypertension.[104–106] These studies suggest that the Hippo pathway may be a novel interventional target in patients with HUA-related CVD presenting the endothelial inflammatory phenotype (Figure 3).

4 | INTERVENTION STRATEGIES

To date, urate-lowering agents such as allopurinol, febuxostat, and benzbromarone have been the standard treatments for HUA. However, the 2020 American College of Rheumatology guidelines for the management of gout do not recommend pharmacological treatments for CKD (chronic kidney disease)/CVD patients with asymptomatic HUA because the benefits of these urate-lowering agents may not outweigh the potential risk and cost of therapy.[107–109] Nonetheless, some studies have reported the effectiveness of pharmaceutical intervention for HUA-induced ED. For example, allopurinol, probenecid, and epalrestat have been demonstrated to partially abrogate the adverse effects of HUA on endothelial function (Table 1).[44,51,77,83,90,96,110] In addition, some natural and small-molecule compounds protected ECs in the HUA context (Table 1). Specifically, betulin attenuated HUA- or gout-induced EC inflammation via the inhibition of SREBP2.[102] Phloretin protected HUVECs against high UA-induced injury via the repression of inflammation and cellular UA uptake.[42] Treatment with mangiferin (a natural glucosyl xanthone) not only reduced the level of UA but also increased endothelial function by elevating the NO secretion rate in rats and HUVECs exposed to high levels of UA.[111] Either N-acetylcysteine or apocynin can increase NO bioavailability and reduce endothelial inflammation in high UA-treated HAECs.[63] Furthermore, miR-214 has been shown to alleviate apoptosis in UA-treated mouse aorta endothelial cells by targeting the COX-2 (cyclooxygenase-2)/PGE2 (prostaglandinE2) cascade.[112] α-Lipoic acid inhibited EC apoptosis and enhanced NO production in both in vitro and in vivo HUA models by attenuating oxidant stress and activating Akt signaling.[113] Fibroblast growth factor 21 (FGF21) attenuated ED induced by high levels of UA in HUVECs by activating Sirt1, which was manifested as the attenuation of oxidative stress, ER stress, and inflammation.[70] Collectively, although not an official recommendation, optimal pharmacological treatments might be an important approach to combat HUA-induced ED.

5 | PARADOX

To date, the majority of the literature indicates that HUA contributes to ED, although the findings are contradictory, possibly due to the cohorts of study subjects differing in age, race, sex, and treatment regimens.[114,115] Recently, a cross-sectional and retrospective study suggested independent association between HUA and hypertension only in men younger than 60 years of age.[30] However, a meta-analysis including 18 prospective cohorts demonstrated an association between HUA and a high risk of incident hypertension in young individuals

TABLE 1 Mechanism of action involved in pharmacologic interventions for hyperuricemia-induced endothelial dysfunction.

Publication	Agents	Mechanism of action
Liang et al.[44] Tassone et al.[83] Cimmino et al.[90] Yang et al.[96]	Probenecid	Anti-inflammation, anti-oxidation, and inhibiting uric acid reabsorption
Huang et al.[51]	Epalrestat	Anti-oxidation by inhibiting NADPH oxidase activity
Ko et al.[77] Lu et al.[110]	Allopurinol	Anti-inflammation and decreasing uric acid production
Zhao et al.[102]	Betulin	Anti-inflammation via inhibition of SREBP2
Liu et al.[42]	Phloretin	Anti-inflammation and lowering GLUT9-mediated uric acid uptake
Yang et al.[111]	Mangiferin	Lowering uric acid, anti-inflammation, and increasing NO production
Lee et al.[63]	N-acetylcysteine/apocynin	Anti-oxidation by scavenging reactive oxygen species
Yang et al.[112]	miR-214	Alleviating apoptosis by inhibiting COX-2/PGE2 cascade
Zou et al.[113]	α-Lipoic	Inhibiting oxidative stress and apoptosis by activating Akt pathway
Ouyang et al.[70]	FGF21	Attenuating stress responses and inflammation by activating Sirt1

and women.[116] Another meta-analysis of prospective cohort study data showed that the HUA-associated risk of CAD and all-cause mortality was greater in women than in men.[28] Similarly, a retrospective cross-sectional analysis revealed that the association between elevated SUA and ED was evident only in women.[117] These inconsistencies indicate that age and sex may impact the effects of UA on endothelial function. Notably, it has been reported that urate-lowering therapy failed to reduce the incidence of major adverse cardiovascular events.[31] Complicating the ability to make clear conclusions, UA at high levels has even been shown to reduce the risk of all-cause and cardiovascular mortality in hemodialysis patients by ameliorating indoxyl sulfate-induced ED.[118] In addition to HUA, hypouricemia is a potential risk factor for CVD.[119] These reports suggest that excessive overcorrection to lower the UA level may adversely influence the circulatory system. Therefore, revisiting the possible dual roles of UA in CVD might aid in the development of novel therapeutics for HUA-induced ED.

6 | CONCLUSIONS AND FUTURE DIRECTIONS

HUA-induced ED is associated with decreases in the synthesis and bioavailability of NO and increases in EC death, the EndMT, IR, PCA, and the rate of inflammatory phenotype acquisition (Figure 4). These impairments can lead to CVD. However, our understanding of the mechanisms underlying HUA-induced ED is limited for several reasons. First, the in vitro ED model exposed to high levels of UA was largely established with HUVECs, which may not closely represent ED in artery vessels. Second, very few in vivo studies have been performed; therefore, interpretation of the mechanisms underlying HUA-induced ED

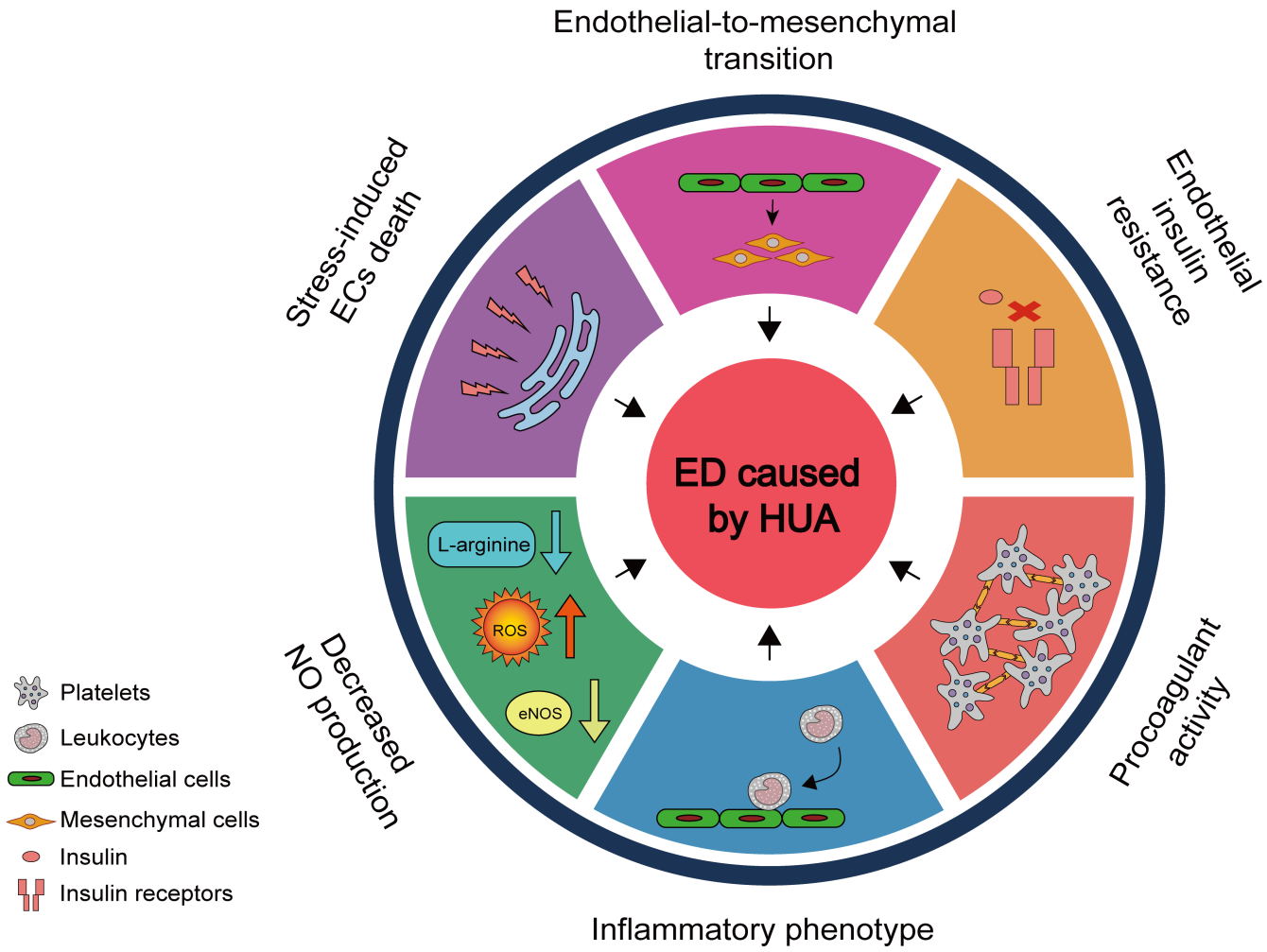

FIGURE 4 Diagram showing the mechanism by which hyperuricemia causes endothelial dysfunction. Decreases in NO production, and increases in endothelial cell death, the endothelial-to-mesenchymal transition, endothelial insulin resistance, procoagulant activity, and acquisition of an inflammatory phenotype are major manifestations of endothelial dysfunction caused by hyperuricemia. ED, endothelial dysfunction; eNOS, endothelial nitric oxide synthase; HUA, hyperuricemia; ROS, reactive oxygen species.

in relevant disease models has been challenging. Third, numerous confounding factors have limited HUA treatment in the clinic. For instance, age, sex, CKD, or another metabolic syndrome can interfere with the progression of HUA-associated cardiovascular comorbidities. Thus, further investigation into the mechanisms underlying the pathogenesis of HUA-induced ED is essential to develop novel and efficient therapies for the intervention of CVD with comorbid HUA.

AUTHOR CONTRIBUTIONS

Xin Wei and Yuan He conceived and designed the entire review and wrote the paper. Xin Wei and Mao Zhang assisted with the drawings. Shian Huang, Xiaozhong Lan, Jing Zheng, Hui Luo, Yuan He, and Wei Lei reviewed and edited the manuscript. All authors read and approved the manuscript.

ACKNOWLEDGMENTS

This work was supported by the Discipline Construction Project of Guangdong Medical University (4SG21233G), the National Natural Science Foundation of China (81700269), the Natural Science Foundation of Guangdong Province (2019A1515011925), the Key platform of Department of Education of Guangdong Province (2021LSYS007), and the Zhanjiang Science and Technology Development Special Funding Competitive Allocation Project (2022E05011, 2022A01196, 2021A05158, 2021A05058, 2021A05056, 2020A01020, 2020A06003, and 2020A06004).

DISCLOSURES

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Wei X, Zhang M, Huang S, et al. Hyperuricemia: A key contributor to endothelial dysfunction in cardiovascular diseases. *The FASEB Journal*. 2023;37:e23012. doi:10.1096/fj.202300393R