Hyperuricemia, endothelial dysfunction and hypertension

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Abstract

The final product of purine bases degradation in humans, reptiles and other primates is uric acid. The serum level of uric acid can be influenced by diet, certain systemic pathologies and a decreased renal excretion. Xanthine oxidase (XO) catalyzes the formation of uric acid with generation of reactive oxygen species (ROS), being active in physiological stress and ischemia. Uric acid has an antioxidant role at the extracellular level, but also in certain biological fluids such as saliva. In the intracellular environment of endothelial cells it plays a prooxidant role in conditions of hyperuricemia, contributing to the decrease of nitric oxide (NO) level, leading to endothelial dysfunction and the development of hypertension. The purpose of this review is to present the synthesis and biological effects of uric acid, the effects of hyperuricemia on NO production, and the link between hyperuricemia, endothelial dysfunction and hypertension.

Keywords: uric acid, hyperuricemia, endothelial dysfunction, hypertension

INTRODUCTION

Purines play vital roles in the body - ATP (adenosine triphosphate) provides the energy needed to carry out intracellular reactions, while nitrogenous bases (adenine and guanine) are components of nucleic acids (DNA and RNA). The transformation of the mononucleotides AMP (adenosine monophosphate), GTP (guanine monophosphate), ITP (inosine monophosphate) involves several enzymatic steps to obtain hypoxanthine and its further oxidation to xanthine. Oxidation of hypoxanthine to xanthine and xanthine to uric acid is accomplished by two isoforms of xanthine oxidoreductase, xanthine dehydrogenase (XDH) and...
XO. The last isoform leads to the generation of ROS 
\( O_{2}^{-}, H_{2}O_{2}, O_{2}^{•−}, H_{2}O_{2} \), being activated in physiological 
stress and ischemia. XO oxidase is an enzyme present 
in a high concentration in the intestine and liver, con-
tains riboflavin, molybdenum and iron (1,2).

**URIC ACID SYNTHESIS**

Uric acid is the final product of purine catabolism in 
humans, birds, reptiles and other primates, which 
don’t contain the enzyme uricase. The serum uric acid 
level is influenced by diet, a diet rich in meat, fructose, 
alcohol, seafood and Na, which will increase its con-
centration. On the other part, consumption of vitamin 
C and coffee decrease uric acid level (2). The level of uric acid increases rapidly after fruc-
tose ingestion, fructokinase is activated, resulting in 
increments as high as 2 mg/dl within 1 h (3).

**BIOCHEMISTRY AND BIOLOGICAL ACTIONS 
OF URIC ACID**

Uric acid plays a dual role, antioxidant and pro-oxi-
dant. In the hydrophilic extracellular environment, the 
uric acid is antioxidant, neutralizes peroxynitrite rad-
cals \( \text{ONOO}^•− \) \( \text{ONOO}^•− \) and chelates metal ions (Fe, Cu, 
II), thus preventing the formation of new ROS such as 
hydroxyl radical \( \text{HO}^•− \) \( \text{HO}^•− \). By neutralizing \( \text{ONOO}^•− \) \( \text{ONOO}^•− \) radicals by uric acid, the enzymatic activity of 
endothelial nitric oxide synthetase (eNOS) is stabilized (4). Uric acid as an antioxidant cannot neutralize the 
superoxide anion \( \text{O}_{2}^{•−} \) \( \text{O}_{2}^{•−} \) and in the plasma needs vitamin C to exercise its antioxidant role (5). Uric acid 
presents a preventive role in the development of neu-
rodegenerative diseases such as dementia or bone 
metabolism by increasing bone mass and reducing 
bone turnover, involved in reducing vertebral fractures (6). In the oral cavity, uric acid is the most important 
antioxidant, achieving 85% of the total antioxidant ca-
pacity. Salivary uric acid levels are decreased in oral 
pathologies associated with oxidative stress (OS), such 
as periodontal disease, oral lichen planus and oral can-
cer (7-10). Unfortunately in the hydrophobic intracel-
lar environment, it plays a prooxidant role. The XO 
enzyme catalyzes the last two stages of purine catabo-
ism generating \( O_{2}^{•−} \) and \( H_{2}O_{2}, O_{2}^{•−} \) and \( H_{2}O_{2} \) (11-12). The 
intracellular prooxidant role of uric acid is mediated by 
a NADPH oxidase-dependent pathway. In several sys-
temic pathologies (diabetes, cardiovascular diseases, 
ischemic liver injury) plasma uric acid is a marker of 
oxidant damage (13-15).

**HYPERURICEMIA**

Hyperuricemia occurs when uric acid levels exceed 
339 μmols/l for premenopausal women and 416 
μmols/l for men and postmenopausal women, and 
urate crystals will be deposited in organs and tissues 
(16). This difference between the sexes is due to the 
effect of female sex hormones (17). At a concentration 
higher than 10 mg/dl (600 μmols/l) uric acid will be 
deposited in the joints and soft tissues. Uric acid can 
be oxidized to allantoin - a much more soluble com-
pound, by uricase (urate oxidase). Because of two 
truncating mutations in the uricase gene, which intro-
duce premature stop codon, the human species no 
longer synthesizes the uricase gene (18). Uric acid is a 
paradoxical biomolecule, in the intracellular environ-
ment of vascular smooth muscle cells (VSMC) and adi-
pocytes play prooxidant role. The negative effects of 
uric acid are manifested by decreased NO production, 
induces platelet aggregation and pro-inflammatory ac-
tivity (19).

Hyperuricemia is associated with many comorbidi-
ties, such as cardiovascular diseases, diabetes, dyslipi-
demia, metabolic syndrome, chronic kidney disease 
and obesity. Hypertension, atrial fibrillation, coronary 
atherosclerotic heart disease, heart failure are cardio-
vascular conditions associated with hyperuricemia 
(15,20).

Numerous factors can produce an increase of pu-
rines or uric acid synthesis, such as: clinical conditions 
(obesity and insulin resistance; cell turnover - haema-
tological disorders, malignant processes, severe prolif-
erative psoriasis; hypoxia, ischemic tissue; Down Syn-
drome), genetic disorders that lead to metabolic errors 
associated with enzymatic deficiencies (phosphoribo-
syl transferase deficiency; hyperactivity for phosphori-
bosylphosphate synthetase; glucozo-6-phosphatase), 
diet (excessive ingestion of purines, alcohol, fructose,
deficient B12, niacin), drugs or toxins (cytotoxic agents).

Moreover, urinary secretion can be decreased by several clinical conditions (renal failure, obesity, lactic acidosis, hyperparathyroidism, hypothyroidism, heart damage), genetic disorders (genetic polymorphism of genes that encodes urate transporters: GLUT9, URAT1), diet, alcohol, dehydration and ketoacidosis starvation, or by drugs or toxins (beta blockers, diuretics, laxative abuse, beryllium, calcineurin inhibitors, levodopa, low-dose salicylates, pyrazinamide, methoxyflurane) (21).

**HYPERURICEMIA AND NO**

Several mechanisms have been described so far by which hyperuricemia leads to decreased NO production in endothelial cells.

The increased uric acid level determines the decrease of NO production by generating ROS, with a central role belonging to XO. Studies on human umbilical endothelial cell lines conducted by Li et al., reported that hyperuricemia induces ROS formation and PKC (protein kinase C) signaling pathway activation and phosphorylation of Throneine 495 (Thr) from eNOS structure (22). Thr phosphorylation reduces the activity of the enzyme, Serine (Ser) phosphorylation, increases eNOS activity (22). eNOS phosphorylation at Thr due to OS reduces the interaction between enzyme and calmodulin and decreased NO production (23).

The second mechanism by which hyperuricemia reduces NO production is through two signaling pathways in which the insulin receptor is involved. Insulin binds to its specific receptor, leading to PI3K (phosphoinositid 3 kinase) or Akt (protein kinase B) signaling pathway activation, which promotes metabolic effects (cell growth and survival, glycogen metabolism). MAPK (mitogen-activated protein kinase) is also activated being involved in cell proliferation and differentiation, and gene expression. Insulin stimulates eNOS phosphorylation at Ser 1147, enhancing enzyme activity, but uric acid blocks this phosphorylation reaction (24). Elevated uric acid levels cause recruitment of the enzyme EN-PP1 (endonucleotide pyrophosphate/phosphodiesterase 1) at plasma membrane, of all insulin targeted tissues, and inhibit insulin receptor, affecting eNOS phosphorylation via PI3K/Akt signaling pathway (25).

In addition, uric acid stimulates through insulin receptor the gene expression for endothelin 1 (ET-1), the most important vasoconstrictor molecule, through MAPK / ERK (extracellular signal-regulated kinase) signaling pathways (26). Hyperuricemia inhibits vasodilation and stimulates vasoconstriction via insulin (25-27).

Also, NO is synthesized in endothelial cells by eNOS from L-arginine, which reaches the endothelial level via transmembrane transporter CAT (cation amino acid transporter). In pulmonary arterial endothelial cells, studies have shown that elevated uric acid levels enhance arginase activity, by attenuating cyclic GMP production, leading to arginine catabolism (23). Hyperuricemia reduces the uptake of arginine into endothelial cells (28).

Moreover, hyperuricemia enhanced activities for renin and angiotensin system (RAS). These findings were reported by clinical trials using laboratory animals (rabbits) (29). NO together with the RAS system maintain the normal function of blood vessels. NO relaxes VSMC, while RAS has vasoconstrictor action. Excess uric acid reacts with NO, leading to the formation of an unstable compound (nitrosouric acid), with 6 aminouracil formation in the end. 6 aminouracil will diminish NO role and enhance RAS activity in blood vessels (30). The renal epithelial sodium channel (ENaC) plays an important role in maintaining the Na balance, extracellular fluid volume, blood pressure, being responsible for the stage of limiting the rate of Na reabsorption. ENaC can be activated in conditions of hyperuricemia (31). Studies in rats with hyperuricemia, reported that α-, β- and γ-ENaC expressions were significantly increased, enhancing sodium ions absorption in the renal tubules and leading to increased blood volume and in the end to hypertension (31).

**HYPERURICEMIA AND ENDOTHELIAL DYSFUNCTION**

Endothelial dysfunction together with vascular stiffness are involved in the progression and development of cardiovascular and cardiorenal diseases. The mechanisms by which uric acid promotes cardiovascular damage are multiple, involving the existence of OS, reduced bioavailability of NO, inflammatory response and maladaptive cardiac, vascular, renal hepatic, and adipocyte immunity (3). There are two mechanisms by which hyperuricemia causes arterial stiffness: urate crystal mechanism and crystal-independent mechanism.

Hyperuricemia and uric acid crystal formation

- Decrease macrophage engulf crystal
- Decrease NLRP3 inflammasome activation
- Decrease IL-1β production
- Decrease Inflammation and collagen production
- Decrease Proliferation of smooth muscle

**FIGURE 2.** Urate crystal mechanism (adapted from 32). NLRP3 –nud-like receptor family protein

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Hyperuricemia
↓
Intracellular and mitochondrial OS
↓
eNos inhibition
↓
GLU9 (URATEv1) transport urate into vessels
↓
RAS stimulation
↓
Inflammation
↓
Vasocontraction
↓
Endothelium dysfunction
↓
Smooth muscle proliferation + endothelium dysfunction
↓
Arterial stiffness and Arteriosclerosis
↓
Hypertension

**FIGURE 3.** The independent-crystal mechanism (adapted from 32). URATv1 – voltage-driven urate efflux transporter 1

At endothelial level, uric acid crystals deposited, together with subendothelial lipids, will lead to vascular endothelial damage, inducing further vascular endothelial injury and finally atherosclerosis. Damage of endothelial cells will weaken their anticoagulant role, subendothelial collagen will be exposed to injury and will induce platelet aggregation and adhesion, promoting thrombus formation (33).

**HYPERURICEMIA AND HYPERTENSION**

According to cohort, cross-sectional and interventional studies conducted so far, hyperuricemia is an independent risk factor in hypertension. Hyperuricemia is present in hypertensive patients who are obese, diabetic, or have dyslipidemia, being involved in the production of atheroma plaque. Clinical studies have reported the association between hyperuricemia and atherosclerosis, with the presence of coronary artery calcifications, the decreased flow-mediated dilation, which indicates the vascular endothelial function and higher pulse wave velocity (32-36).

Hyperuricemia along with microalbuminuria is associated with prehypertensive patients. Uric acid levels greater than 5.5 mg/dl were observed in 90% of adolescents with essential hypertension, shared with healthy subjects and adolescents with secondary hypertension. Hyperuricemia was observed in 40-60% of untreated hypertensive patients (35,36). Animal studies have reported the association of hypertension with elevated uric acid levels that mediate renal vasoconstriction by reducing endothelial NO levels and activating RAS. Rats with hyperuricemia over time will develop essential hypertension and renal microvascular damage (37-39).

**CONCLUSIONS**

Uric acid is a biomolecule with a duplicative role that has an antioxidant role in the extracellular environment and prooxidant in the intracellular medium. Several clinical pathologies, genetics, diet, but also a decreased urinary excretion lead to hyperuricemia. Hyperuricemia conduces to decreased NO level, by involving OS and activating PKC signaling pathway, which will lead to decreased activity of the eNOS, involved in NO production from L-arginase. Increased serum uric acid levels reduce the entry of the amino acid arginine into endothelial cells, activates the RAS system, promoting endothelial dysfunction and hypertension. Decreasing uric acid levels will have beneficial effects on patient’s health.

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