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ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH GOUT AND ASYMPTOMATIC HYPERURICEMIA: AN INTEGRATIVE LITERATURE REVIEW

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Abstract

Introduction: Endothelial dysfunction is a key pathophysiological mechanism underlying cardiovascular disease and is characterized by reduced nitric oxide bioavailability, increased oxidative stress, and enhanced inflammatory activity. Growing scientific evidence suggests a relationship between endothelial dysfunction, gout, and asymptomatic hyperuricemia. While hyperuricemia has traditionally been viewed primarily as a precursor to gout, recent research indicates that elevated uric acid levels may independently contribute to vascular impairment. This integrative review aims to analyze the existing evidence regarding the relationship between endothelial dysfunction, gout, and asymptomatic hyperuricemia and to explore the potential mechanisms linking these conditions.

Methods: An integrative literature review was conducted using PubMed, CAPES Periodicals Portal, and IntraMed databases. The search included the descriptors “endothelial dysfunction,” “endothelial function,” “hyperuricemia,” and “gout,” combined using Boolean operators. Inclusion criteria comprised full-text studies published within the last 20 years in English, Portuguese, or Spanish that directly addressed the relationship between endothelial dysfunction and hyperuricemia or gout. After screening 369 identified articles by title, abstract, and full-text review, 18 studies were selected for analysis.

Results: The reviewed literature demonstrates a consistent association between elevated uric acid levels and endothelial dysfunction. Mechanisms identified include reduced nitric oxide bioavailability due to increased reactive oxygen species production, endothelial nitric oxide synthase (eNOS) uncoupling, activation of inflammatory pathways such as HMGB1/RAGE and NF-κB, disruption of the ADMA/DDAH pathway, mitochondrial calcium overload, and increased expression of pro-inflammatory cytokines and genes. Clinical and experimental studies also suggest that xanthine oxidase activity plays a central role in oxidative stress-mediated endothelial injury. While some uric acid-lowering therapies, such as allopurinol, show

improvement in endothelial function, results remain inconsistent across pharmacological interventions.

Conclusion: The current body of evidence supports a significant association between endothelial dysfunction, gout, and asymptomatic hyperuricemia, although the precise causal nature of this relationship remains unclear. Hyperuricemia appears to contribute to vascular injury through oxidative stress, inflammation, and nitric oxide pathway disruption. Given the rising global prevalence of hyperuricemia and gout, further clinical and mechanistic studies are necessary to clarify causality and guide preventive and therapeutic strategies aimed at reducing cardiovascular risk.

Keywords: *Endothelial dysfunction; Hyperuricemia; Gout; Nitric oxide; Oxidative stress.*

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Endothelial dysfunction in patients with gout and asymptomatic hyperuricemia: an integrative literature review

The innermost layer of capillaries and blood vessels can be described simply as a single layer of mesenchymal cells (Favero et al., 2014).

It represents an endocrine and metabolic organ which operates to preserve vascular equilibrium via regulated paracrine and autocrine signalling molecules triggered by mechanical, chemical and biological factors (Favero et al., 2014). Indeed, the endothelium is recognized for its critical role in various physiological processes, including regulating blood vessel elasticity, facilitating blood flow, mediating innate and acquired immune responses, and maintaining physiological equilibrium.

The endothelium can release a wide range of signalling molecules that regulate vascular function. These include vasodilatory agents such as nitric oxide (NO), endothelium-derived hyperpolarizing factors, and prostacyclin, as well as vasoconstrictive agents such as angiotensin II and endothelin-1. Additionally, the endothelium produces substances involved in blood clotting regulation, such as pro- and anticoagulant factors, and modulates inflammatory processes by secreting both pro-inflammatory and anti-inflammatory mediators. It also contributes to the balance of fibrinolytic and antifibrinolytic activity, alongside generating oxidative and antioxidative agents, among numerous other critical molecules (Favero et al., 2014; Maruhashi et al., 2018).

As a result, endothelial dysfunction disrupts regulatory mechanisms, increasing susceptibility to blood vessel narrowing, immune cell adhesion, clotting, free radical damage, blood clot formation, activation of the coagulation cascade, and inflammatory responses within the vascular wall (Favero et al., 2014).

Gout is a systemic tophaceous illness characterized by the accumulation of uric acid crystals in various tissues, with secondary inflammation in patients with hyperuricemia due to environmental and/or genetic factors (Martynov et al., 2022). This disease is characterized clinically by acute flare-ups of arthritis, usually involving one or a few joints, and by the formation of urinary stones. Another hallmark of the disease is the accumulation of large uric acid crystals, called tophi, mainly in the periarticular and subcutaneous tissues (Martins et al., 2016).

Several risk factors are associated with the development of gout, but the most well-known is hyperuricemia. However, it is crucial to note that although hyperuricemia is a major risk factor, gout may still develop in its absence.

Asymptomatic hyperuricemia refers to a condition where individuals exhibit elevated serum uric acid levels but do not show any clinical symptoms of related disorders. Uric acid, a byproduct of purine breakdown, is mainly eliminated from the body via renal excretion (Martins et al., 2016). Previously, hyperuricemia was defined as a uric acid level >420 μmol/L, based on the urate supersaturation point, where monosodium urate crystals begin to form. Currently, all national rheumatology societies, the European League Against Rheumatism, and the American College of Rheumatology recommend considering a blood urate level >360 μmol/L (6 mg/dL) as hyperuricemia (Martynov et al., 2022).

Hyperuricemic individuals have a greater chance of developing gout compared to normouricemic individuals and this progression is directly proportional to the level of uric acid (risk annual rate of 0.1% in men with a serum level below 7 mg/dL, 0.5% between 7 and 8.9 mg/dL and 4.9% at higher levels to 9 mg/dL) (Martins et al., 2016).

Based on this knowledge and the relatively high prevalence of hyperuricemia, estimated to range between 10 and 20% worldwide (Yip et al., 2020), as well as the significant prevalence of gout (around 1–4%, according to Singh and Gaffo, 2020), the possibility of a correlation between these factors has been theorized.

Therefore, in this study, through the review of various others, the evidence in the scientific field regarding the existence, nature and mechanisms of the relationship between endothelial dysfunction, gout and asymptomatic hyperuricemia was analyzed in order to explore whether the relationship exists, identify the factors that support it, and understand how they interact with each other.

Methodology

This is an integrative literature review guided by the following question: “What is the relationship between asymptomatic hyperuricemia, gout and endothelial dysfunction?” Research was conducted using articles from the PubMed, CAPES Periodicals Portal, and IntraMed databases. The searches were conducted with the descriptors “endothelial dysfunction”, “endothelial function”, “hyperuricemia” and “gout”. The Boolean expressions were “AND” and “OR” in different combinations.

The articles were selected under the following criteria: 1) Studies that address the selected descriptors and keywords; 2) Those which were obtained by accessing the full text, in the languages English, Portuguese, or Spanish; 3) Studies published in the last 20 years. As exclusion criteria, the following were used: 1) Studies that did not relate to endothelial dysfunction, gout and asymptomatic hyperuricemia; 2) Studies over 20 years old; 3) Studies in which endothelial dysfunction is not the main discussion, although it is addressed in the text.

Results

During bibliographic research using the terms “endothelial dysfunction”, “endothelial function”, “hyperuricemia” and “gout”, the terms were combined in pairs and trios, resulting in a total of 369 potential articles, highlighting that articles were duplicated across the different searches. Among the 369 articles, 311 were excluded by title screening, 28 by abstract reading and 12 were excluded by reading the full articles.18 articles were selected, and these are shown in Table 1 below, corresponding to a synthesis of the main theoretical references obtained in the bibliographic search of this study.

Table 1

Characteristics of studies related to endothelial dysfunction and gout and asymptomatic hyperuricemia: title, authors, year of publication and methodology.

Title	Author	Year of Publication	Methodology
Long-Term Effect of Febuxostat on Endothelial Function in Patients With Asymptomatic Hyperuricemia: A Sub-Analysis of the PRIZE Study.	Maruhashi et al.	2022	Sub-Analysis of the PRIZE Study.
Hyperuricemia Induces Endothelial Dysfunction and Accelerates Atherosclerosis by Disturbing the Asymmetric Dimethylarginine/Dimethylarginine Dimethy laminotransferase 2 Pathway.	Lee et al.	2021	Experimental Research.

Title	Author	Year of Publication	Methodology
Study of Endothelial Dysfunction by Flow Mediated Vasodilation in Individuals with Asymptomatic Hyperuricemia.	Shukla et al.	2021	Case Control Study.
Hyperuricemia and Endothelial Function: From Molecular Background to Clinical Perspectives.	Maruhashi et al.	2018	Literature Review.
Uric Acid Induces Endothelial Dysfunction by Activating the HMGB1/RAGE Signaling Pathway.	Cai et al.	2017	Experimental Research.
Effects of Allopurinol on Endothelial Function: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials.	Cicero et al.	2017	Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials.
The Role of Hyperuricemia on Vascular Endothelium Dysfunction.	Zhen & Gui	2017	Case-Control Study and *In Vitro* Experimental Research.
Uric Acid Enhances PKC-Dependent eNOS Phosphorylation and Mediates Cellular ER Stress: A Mechanism for Uric Acid-Induced Endothelial Dysfunction.	P. Li, et al.	2016	Experimental Research.

Title	Author	Year of Publication	Methodology
Xanthine Oxidoreductase in Atherosclerosis Pathogenesis: Not Only Oxidative Stress.	Battelli et al.	2014	Literature Review.
Uric Acid Modulates Vascular Endothelial Function Through the Down Regulation of Nitric Oxide Production.	Papežíková et al.	2013	Experimental Research.
Gout-Induced Endothelial Impairment: The role of SREBP2 Transactivation of YAP.	Zhao et al.	2012	Experimental Research.
Hyperuricemia Induces Endothelial Dysfunction Via Mitochondrial Na+/Ca2+ Exchanger-Mediated Mitochondrial Calcium Overload.	Hong et al.	2012	Experimental Research.
Association Between Endothelial Dysfunction and Hyperuricemia.	Ho et al.	2010	Cohort Study.
Hyperuricemia Is Associated With Increased C-Reactive Protein Concentrations in a Large Cohort of Unselected Outpatients.	Lippi et al.	2008	Cohort Study.
Associations Between Serum Uric Acid and Adipokines, Markers of Inflammation, And Endothelial Dysfunction.	Bo et al.	2008	Cohort Study.
Uric Acid and Inflammatory Markers.	Ruggiero et al.	2006	Cohort Study.
Uric Acid-Induced C-Reactive Protein Expression: Implication on	Kang et al.	2005	Experimental Research.

Title	Author	Year of Publication	Methodology
Cell Proliferation and Nitric Oxide Production of Human Vascular Cells.			
Hyperuricemia Induces Endothelial Dysfunction.	Khosla et al.	2005	Experimental Research.

Note: This table summarizes the characteristics of studies related to endothelial dysfunction, gout, and asymptomatic hyperuricemia, including the title, authors, year of publication, and methodology. The studies were selected from a bibliographic search using the terms "endothelial dysfunction," "endothelial function," "hyperuricemia," and "gout." A total of 369 potential articles were identified, of which 18 were included in this synthesis after screening by title, abstract, and full-text review.

Discussion

The current scientific evidence indicates a significant association among endothelial dysfunction, asymptomatic hyperuricemia, and gout. While this connection has been increasingly recognized in recent studies, the precise mechanisms and nature of this relationship remain incompletely understood. Emerging data suggest a causal link between these factors, supported by findings that hyperuricemia promotes endothelial damage and systemic inflammation. Nevertheless, despite these promising insights, establishing a definitive relationship requires further investigation, including both theoretical advances and practical clinical studies. A more robust, comprehensive framework is essential to fully elucidate the interplay among these conditions and their collective impact on vascular health.

This literature review explores and clarifies the intricate relationship between hyperuricemia and gout, with particular focus on their effects at the endothelial level. By examining existing research, this review aims to describe the potential pathways by which hyperuricemia may promote endothelial injury, ultimately leading to loss of vascular stability. Additionally, it highlights the need for future studies to address knowledge gaps and deepen understanding of the underlying mechanisms, as well as the importance of developing health strategies to reduce their impact.

Monosodium Urate and Endothelial Dysfunction: Enzyme Mechanism

Uric acid is produced by the oxidation of purine derivatives by the enzyme xanthine oxidase, which serves as the final product of purine breakdown. Xanthine oxidoreductase, a molybdenum-

dependent enzyme, facilitates the conversion of hypoxanthine into intermediate compounds, which are then transformed into urate during purine catabolism (Berry & Hare, 2004).

Xanthine oxidase (XO) and dehydrogenase (XD) are two physiological presentations of xanthine oxidoreductase. Under normal physiological conditions, xanthine oxidoreductase is primarily expressed as xanthine dehydrogenase by epithelial cells in tissues such as the liver and mammary gland. In humans, serum levels of this enzyme are typically low, reflecting its localized activity and tight regulation (Battelli et al., 2014).

In contrast, xanthine oxidase is a structurally altered form of the enzyme that undergoes changes after gene expression, becoming highly active under particular normal and abnormal biological states.

For instance, its expression and activity are significantly upregulated in hypoxic and ischemic conditions, where it contributes to oxidative stress and tissue damage (Maruhashi et al., 2018). This dual nature of xanthine oxidoreductase highlights its complex role in both normal metabolism and disease processes.

Although one form of xanthine oxidoreductase can be converted into the other, their functions are distinct and serve different roles in cellular processes. The transition of xanthine dehydrogenase to xanthine oxidase is facilitated by processes including the oxidation of sulfhydryl groups or partial proteolytic cleavage. This conversion is significant because xanthine oxidoreductase activity generates both oxidants and antioxidants, highlighting its dual role in cellular metabolism (Battelli et al., 2014).

Xanthine dehydrogenase primarily catalyzes the shift of hypoxanthine to xanthine and xanthine to urate, utilizing NAD+ as the primary and final electron acceptor. In contrast, molecular oxygen serves as the final electron acceptor for xanthine oxidase, generating reactive oxygen species (ROS). Hydrogen peroxide (H2O2) and superoxide anion (O2−) play a critical role in promoting oxidative stress and endothelial injury. The distinct electron acceptors and resulting products of these two forms underscore their differing contributions to cellular physiology and pathology (Battelli et al., 2014).

Uric Acid and Nitric Oxide (NO)

Nitric oxide, a vasodilator, is produced by endothelial cells (ECs) and acts as one of the main factors regulating endothelial function (Maruhashi et al., 2018). Therefore, reduced NO bioavailability is a key component in the evaluation of endothelial function.

In a scenario where the activity of xanthine oxidase is elevated, there is a corresponding rise in the levels of O2 −. Due to its strong affinity for nitric oxide (NO), this superoxide anion can react with NO, reducing its active concentration by promoting its degradation and inactivation. Simultaneously, this interaction enhances the production of peroxynitrite (ONOO−), a highly reactive oxidizing agent known to cause DNA injury, cellular death, and lipid oxidation (Maruhashi et al., 2018).

Following the rise in O2 −levels, a process known as endothelial NO synthase (eNOS) uncoupling also occurs. Peroxynitrite has the ability to oxidize the eNOS cofactor (specifically, converting tetrahydrobiopterin into its inactive form, trihydrobiopterin), resulting in a shortage of the essential cofactor. When insufficient levels of this cofactor are present, eNOS shifts from producing nitric oxide (NO) to generating superoxide (O2−), thereby sustaining and amplifying the cycle of these oxidative reactions (Maruhashi et al., 2018).

Besides that, a high level of uric acid decreases eNOS activity by increasing Thr495 phosphorylation via a protein kinase C-driven mechanism, diminishing eNOS binding to calmodulin (CaM) and its enzymatic efficiency, while also inducing endoplasmic reticulum stress (P. Li et al., 2016; Papežíková et al., 2013).

In vitro and animal studies reinforce the relationship between hyperuricemia and reduced bioavailability of NO. In an animal study using oxonic acid to induce high uric acid levels in rats, the increase in serum urate was associated with a reduction in nitrate and nitrite levels, an effect that was counteracted by allopurinol treatment at 1 and 7 days ($P<0.001$). Similarly, in a separate experiment using cultured bovine aortic endothelial cells, adding uric acid to the growth medium reduced nitric oxide (NO) levels generated in response to vascular endothelial growth factor (VEGF) (Khosla et al., 2005).

Research involving human umbilical vein endothelial cells (HUVECs) indicates that uric acid suppresses nitric oxide (NO) generation (Papežíková et al., 2013; Zhen & Gui, 2017). This process may occur through regulation of eNOS phosphorylation, enhancement of arginase function, and elevation of intracellular superoxide levels. Furthermore, the reduction in nitric oxide (NO) availability triggered by uric acid was validated by a decline in endothelium-dependent vasodilation observed at elevated uric acid concentrations (600 μM), while endothelium-independent vasodilation remained unaffected. These findings were demonstrated in an in vitro experiment utilizing isolated mouse aortic rings (Papežíková et al., 2013).

In addition to this analysis, an *in vitro* study (Kang et al., 2005) investigated the effect of uric acid on human vascular endothelial cells and found that uric acid significantly reduced NO availability.

Furthermore, measurements of endothelium-dependent flow-mediated vasodilation (FMD) and endothelium-independent nitroglycerin-mediated vasodilation, performed using high-resolution two-dimensional ultrasonographic imaging of the brachial artery, found an association between impaired FMD and asymptomatic hyperuricemic patients (Ho et al., 2010; Shukla et al., 2021; Zhen & Gui, 2017).

Uric Acid and Dimethylarginine/Dimethylaminotransferase 2 Pathway

Another indication of the influence of high urate levels on endothelial dysfunction is the disruption of the asymmetric dimethylarginine (ADMA) and dimethylarginine dimethylaminotransferases (DDAHs) system by excess uric acid, leading to endothelial cell dysfunction.

Asymmetric dimethylarginine (ADMA) is a naturally occurring inhibitor of endothelial nitric oxide synthase (eNOS), while the enzymes dimethylarginine dimethylaminotransferase (DDAH)-1 and DDAH-2 play a role in breaking down ADMA into citrulline, a less potent byproduct, within endothelial cells (Lee et al., 2021).

An *in vitro* experiment involving human aortic endothelial cells (HAECs) demonstrated that exposure to uric acid at clinically relevant concentrations (6 and 12 mg/dL) elevated intracellular ADMA levels while simultaneously decreasing DDAH-2 protein levels, without altering DDAH-1 expression (Lee et al., 2021). Besides this, these pathological concentrations led to reduced NO activity, increased monocyte adhesion to endothelial cells, increased ROS production, and significantly increased intracellular ADMA levels through NOX/ROS-dependent downregulation of DDAH-2 protein (Lee et al., 2021). Ultimately, these results culminated in endothelial cell dysfunction.

Uric Acid and Markers of Inflammation, C-Reactive Protein

The same *in vivo* study referenced earlier, conducted on human endothelial cells by Kang et al. (2005), showed that uric acid elevated C-reactive protein (CRP) expression in a dose-dependent manner. The study proposed that endothelial dysfunction induced by urate might be associated with increased CRP levels.

This idea is reinforced by the cohort study conducted by Lippi et al. (2008), in which cumulative data on serum uric acid and plasma high-sensitivity (hs)-CRP level concentrations were collected from 2103 subjects (961 men and 1142 women – years old range: 15 e 91y.o). The study demonstrated that plasma hs-CRP measurements, accounting for age, along with the proportion of participants with hs-CRP values exceeding 3 mg/L, were significantly elevated in individuals with hyperuricemia compared to those with serum uric acid concentrations within the normal range, observed in both male and female subjects.

At the same time, a connection between urate levels and other inflammatory markers, such as IL-6 and TNF-α, is also present. In a population-based study, elevated urate levels were associated with various inflammatory markers, including CRP and IL-6 (Ruggiero et al., 2006). Additionally, uric acid was shown to increase the expression of inflammatory cytokines in cultured human umbilical vein endothelial cells (Zhen & Gui, 2017).

Special attention should be given to the inflammatory cytokine called high mobility group chromosomal protein 1 (HMGB1). This signalling protein binds to the receptor for advanced glycation end products (RAGE), triggering oxidative damage and an inflammatory cascade, ultimately resulting in endothelial impairment. In research conducted by Cai et al. (2017) using human umbilical vein endothelial cells (HUVECs), elevated uric acid levels were shown to upregulate RAGE and HMGB1 expression and to increase HMGB1 secretion.

Not only that, but a high concentration of uric acid has been observed to activate NF-κB and signs of inflammation in HUVECs, and the blockade of RAGE mitigates endothelial injury and disrupts the HMGB1/RAGE signalling pathway triggered by elevated uric acid levels (Cai et al., 2017).

Uric Acid and Expression of Pro-Inflammatory Genes

As previously discussed, uric acid is linked to the expression of inflammatory markers. Going deep into this analysis, a link has been observed between endothelial cell dysfunction, elevated uric acid levels, specifically in individuals with gout, and the upregulation of pro-inflammatory genes. Zhao et al. (2021), in a detailed study, found that human umbilical vein endothelial cells treated with uric acid or monosodium urate showed activation of the Yes-Associated Protein (YAP) pathway, which was also associated with increased SREBP2 expression. YAP is an oncoprotein that activates the transcription of genes responsible for cell division and apoptosis,

and SREBP2 (Sterol regulatory element-binding protein 2) is a protein associated with endothelial cell inflammation.

In this same study, the researchers cultured endothelial cells in a medium supplemented with serum from gout patients, resulting in activation of the SREBP2 and YAP axes.

Therefore, the experiment provides a new perspective on the mechanism by which uric acid may be linked to endothelial dysfunction, which, in these cases, fits with the notion that it can increase pro-inflammatory signalling molecules.

Uric Acid and Adipokines

A cohort study conducted by Bo et al. (2008) showed an inverse correlation between serum uric acid and several inflammatory mediators, suggesting that the positive impact of adiponectin on endothelial cell activity may be diminished under conditions of elevated urate levels. Therefore, since adiponectin, an adipokine, through its anti-inflammatory, anti-fibrotic, and antioxidant effects, participates in regulating glucose levels, lipid metabolism, and insulin sensitivity, the suppression of its activity may suggest an impact on endothelial function.

Hyperuricemia, Endothelial Dysfunction and Mitochondrial Calcium Overload

It has already been established that elevated levels of uric acid can be associated with increased ROS production. At the same time, excessive calcium accumulation in mitochondria can stimulate the generation of reactive oxygen species within these organelles (Hong et al., 2012). Based on this notion, Hong et al. (2012) hypothesized that mitochondrial calcium signalling plays a role in endothelial impairment caused by elevated uric acid levels. To test this hypothesis, using the human umbilical vein endothelial cell line (HUVEC-C), the researchers demonstrated that when HUVEC-Cs were stimulated by uric acid buildup, excessive calcium accumulation in mitochondria via NCXmito was the key contributor to ROS secretion, leading to endothelial dysfunction.

Lowering Uric Acid Agents and Endothelial Dysfunction

As described, the relationship between endothelial dysfunction in gout-affected patients and asymptomatic hyperuricemia has been difficult to characterize, particularly with respect to whether it is causal or an effect.

A long-term treatment with allopurinol, a xanthine oxidase inhibitor, decreased plasma uric acid levels and improved endothelial function. This scenario is demonstrated in a rat study in which an induced increase in uric acid was associated with a reduction in serum nitrate and nitrite

levels, an unfavourable outcome that was counteracted by allopurinol treatment (Khosla et al., 2005). Similarly, a meta-analysis of 10 eligible randomized controlled trials involving 670 participants found a significant improvement in flow-mediated dilation following allopurinol administration (Cicero et al., 2018).

However, unlike allopurinol, Febuxostat, also a xanthine oxidase inhibitor, did not show similar results. In a study by Maruhashi et al. (2022), individuals with elevated uric acid levels were randomly assigned to either a febuxostat add-on therapy group or a non-pharmacological control group (hyperuricemia managed without medication). Of the 514 participants, endothelial function was evaluated in 41 subjects from the febuxostat group and 38 from the control group using brachial artery flow-mediated dilation (FMD) at study initiation and after 12 and/or 24 months of treatment. The results, as expected, showed a lowering in the uric level. However, no marked alteration in endothelial function was assessed by FMD during a 2-year study period in patients with asymptomatic hyperuricemia (Maruhashi et al., 2022).

Thus, these results contradict expectations, as the idea that blocking the enzyme xanthine oxidase, believed to participate in the development of endothelial injury in patients with hyperuricemia, would logically result in enhanced endothelial activity did not hold true. However, although studies involving uric acid-reducing agents generally do not corroborate this hypothesis, they also do not completely dismiss it, given that changes in endothelial dysfunction were neither positively nor negatively affected, leaving room for further analyses.

Impact of Gout and Hyperuricemia in The Public Health Field

From a public health perspective, hyperuricemia is a multifaceted factor. It is known that the global prevalence of hyperuricemia has been rising steadily each year. L. Li et al. (2020) bring up the correlation between the progressing prevalence of hyperuricemia cases in general, and especially in the western side of the world, which is also an economically developing side. A survey conducted by American researchers between 2011 and 2020 analyzed patterns in the prevalence of hyperuricemia and metabolic syndrome within the American population, also examining these associations across different racial and ethnic groups (Kuhns, 2024). As expected, the prevalence was higher across all ethnicities, with a greater emphasis on Hispanic and Asian groups, particularly younger individuals (Kuhns, 2024). In a similar case, national surveys indicate a hyperuricemia prevalence of 8.4% among Chinese adults (2009–2010), with higher rates in men (9.9%) than women (7.0%). Hyperuricemia prevalence generally increases

with age, though older men show a decline, while women exhibit an opposite trend (L. Li et al., 2020).

Regarding the burden of this disease under the sex-related trend, the worldwide occurrence of gout was observed to be approximately 3.26 times greater in men compared to women. In 2020, the global age-standardized prevalence rate was 1030.8 per 100,000 for males and 316.4 per 100,000 for females (GBD 2021 Gout Collaborators, 2024). Moreover, the prevalence of gout was noted to increase progressively with advancing age (GBD 2021 Gout Collaborators, 2024).

The burden of hyperuricemia, whether silent or not, also manifests in the ambulatory setting. A cross-sectional study conducted with 610 elderly patients with metabolic syndrome that investigated the relationship between elevated uric acid levels and metabolic syndrome-related factors in a diverse population in Salvador, Bahia, Brazil revealed significant associations between hyperuricemia, hypertension and hypertriglyceridemia, suggesting that hyperuricemia may be associated with metabolic and increased cardiovascular risk (Silva et al., 2021). Based on these results, the study recommends including uric acid measurement as a routine part of biochemical evaluations for patients with metabolic syndrome, as it requires treatment and monitoring. The study also calls for further prospective research to explore the underlying mechanisms of hyperuricemia in metabolic syndrome and its potential impact on cardiovascular risk, which could lead to new treatment options for minimizing complications from these conditions. Therefore, implementing secondary prevention actions through screening programs and primary prevention actions through health education programs are suggested strategies to minimize the burden of the disease.

With a higher prevalence of the disease, the financial burden associated with it also increases. As the number of affected individuals rises, so does the public cost of treatment, medication, sick leave, and early retirement, while the working-age population decreases, directly affecting the country’s economy.

Wertheimer et al. (2013) state that, among gout-affected American workers, on average, nearly 5 more days of absence per year are observed compared to their non-gout counterparts. The extra yearly healthcare expenses for an individual with gout are projected to surpass $3,000 when compared to those of individuals without gout. Although comorbid conditions linked to gout contribute to this heightened economic strain, the total annual expenditure associated with gout

in the United States is estimated to reach tens of billions of dollars, similar to the financial impact of other significant chronic diseases (Wertheimer et al., 2013).

For that reason, thinking about hyperuricemia, gout, and endothelial dysfunction is not only about considering their biochemical and biophysical aspects but also about translating their impact on patients and society into reality and using this understanding to guide the correlational study towards promoting health-promoting behaviours.

Conclusion

It is observed that, although discussed in the scientific field, it is still not possible to accurately determine the nature of the relationship, whether it is causal or effect, existing between the factors: endothelial dysfunction, gout and asymptomatic hyperuricemia.

Nonetheless, regarding the existence of this relationship itself, it is already possible to determine. After collecting and analyzing the numerous texts presented, it was noted that asymptomatic hyperuricemia, gout and endothelial dysfunction are interconnected. The factors by which one condition influences the other are theorized from different perspectives within the literature examined.

The influence of the high urate levels on the low bioavailability of nitric oxide levels, an important factor responsible for regulating the mechanism of the endothelial function, through the degradation and inactivation of NO, as well as through the process known as eNOS uncoupling, is evidence of greater prevalence obtained during the literature review conducted. The NO-reducing effect of elevated urate concentrations was observed in the vast majority of experiments.

In addition to the impact caused by the suppression of NO activity, further evidence of hyperuricemia's effects on the development of endothelial dysfunction can be observed when studying, for example, an increase in the level of factor of inflammation such as IL-6 , TNF-α, C-reactive protein, or an increase in the upregulation of pro-inflammatory-related gene, in the formation of reactive oxygen species and in the levels of adipokines or, even, when studying the disruption of the asymmetric dimethylarginine and dimethylarginine dimethyl aminotransferases system due to excess of uric acid, resulting in dysfunction of the endothelial cells.

Moreover, adopting a different approach, studies on long-term allopurinol treatment, a drug that reduces plasma uric acid levels and improves endothelial function, reinforce, once again, the existence of a connection between the factors studied.

Finally, based on the evidence of the relationship between the pathophysiological factors mentioned and knowing the growing prevalence profile of these factors in the general population, it is of utmost importance to adopt a health-promoting approach that directs research and health strategies to reduce the impact caused by patients affected by increased serum urate levels and gout, not only in the health sphere but also in the social and economic sphere.

References

1. Battelli, M. G., Polito, L., & Bolognesi, A. (2014). Xanthine oxidoreductase in atherosclerosis pathogenesis: Not only oxidative stress. *Atherosclerosis, 237*(2), 562–567. https://doi.org/10.1016/j.atherosclerosis.2014.10.006
2. Berry, C. E., & Hare, J. M. (2004). Xanthine oxidoreductase and cardiovascular disease: Molecular mechanisms and pathophysiological implications. *The Journal of Physiology, 555*(3), 589–606. https://doi.org/10.1113/jphysiol.2003.055913
3. Bo, S., Gambino, R., Durazzo, M., Ghione, F., Musso, G., Gentile, L., Cassader, M., Cavallo-Perin, P., & Pagano, G. (2008). Associations between serum uric acid and adipokines, markers of inflammation, and endothelial dysfunction. *Journal of Endocrinological Investigation, 31*(6), 499–504. https://doi.org/10.1007/BF03346397
4. Cai, W., Duan, X. M., Liu, Y., Yu, J., Tang, Y. L., Liu, Z. L., Jiang, S., Zhang, C. P., Liu, J. Y., & Xu, J. X. (2017). Uric acid induces endothelial dysfunction by activating the HMGB1/RAGE signaling pathway. *BioMed Research International, 2017*, 4391920. https://doi.org/10.1155/2017/4391920
5. Cicero, A. F. G., Pirro, M., Watts, G. F., Mikhailidis, D. P., Banach, M., & Sahebkar, A. (2018). Effects of allopurinol on endothelial function: A systematic review and meta-analysis of randomized placebo-controlled trials. *Drugs, 78*(1), 99–109. https://doi.org/10.1007/s40265-017-0839-5
6. Favero, G., Paganelli, C., Buffoli, B., Rodella, L. F., & Rezzani, R. (2014). Endothelium and its alterations in cardiovascular diseases: Lifestyle intervention. *BioMed Research International, 2014*, 801896. https://doi.org/10.1155/2014/801896
7. GBD 2021 Gout Collaborators. (2024). Global, regional, and national burden of gout, 1990–2020, and projections to 2050: A systematic analysis of the Global Burden of Disease Study 2021. *The Lancet Rheumatology, 6*(8), e507–e517. https://doi.org/10.1016/S2665-9913(24)00117-6
8. Ho, W. J., Tsai, W. P., Yu, K. H., Tsay, P. K., Wang, C. L., Hsu, T. S., & Kuo, C. T. (2010). Association between endothelial dysfunction and hyperuricaemia. *Rheumatology, 49*(10), 1929–1934. https://doi.org/10.1093/rheumatology/keq184
9. Hong, Q., Qi, K., Feng, Z., Huang, Z., Cui, S., Wang, L., Fu, B., Ding, R., Yang, J., Chen, X., & Wu, D. (2012). Hyperuricemia induces endothelial dysfunction via

mitochondrial Na+/Ca2+ exchanger-mediated mitochondrial calcium overload. *Cell Calcium, 51*(5), 402–410. https://doi.org/10.1016/j.ceca.2012.01.003

10. Kang, D. H., Park, S. K., Lee, I. K., & Johnson, R. J. (2005). Uric acid-induced C-reactive protein expression: Implication on cell proliferation and nitric oxide production of human vascular cells. *Journal of the American Society of Nephrology, 16*(12), 3553–3562. https://doi.org/10.1681/ASN.2005050572
11. Khosla, U. M., Zharikov, S., Finch, J. L., Nakagawa, T., Roncal, C., Mu, W., Krotova, K., Block, E. R., Prabhakar, S., & Johnson, R. J. (2005). Hyperuricemia induces endothelial dysfunction. *Kidney International, 67*(5), 1739–1742. https://doi.org/10.1111/j.1523-1755.2005.00273.x
12. Kuhns, L. (2024, April 30). Hyperuricemia prevalence shows upward trend among Hispanic populations in the US. *Rheumatology Advisor*. https://www.rheumatologyadvisor.com/news/hyperuricemia-prevalence-upward-trend-hispanic-populations-us/
13. Lee, T. S., Lu, T. M., Chen, C. H., Guo, B. C., & Hsu, C. P. (2021). Hyperuricemia induces endothelial dysfunction and accelerates atherosclerosis by disturbing the asymmetric dimethylarginine/dimethylarginine dimethylaminotransferase 2 pathway. *Redox Biology, 46*, 102108. https://doi.org/10.1016/j.redox.2021.102108
14. Li, L., Zhang, Y., & Zeng, C. (2020). Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. *American Journal of Translational Research, 12*(7), 3167–3181.
15. Li, P., Zhang, L., Zhang, M., Zhou, C., & Lin, N. (2016). Uric acid enhances PKC-dependent eNOS phosphorylation and mediates cellular ER stress: A mechanism for uric acid-induced endothelial dysfunction. *International Journal of Molecular Medicine, 37*(4), 989–997. https://doi.org/10.3892/ijmm.2016.2491
16. Lippi, G., Targher, G., Montagnana, M., Salvagno, G. L., & Guidi, G. C. (2008). Hyperuricaemia is associated with increased C-reactive protein concentrations in a large cohort of unselected outpatients. *Nutrition, Metabolism and Cardiovascular Diseases, 18*(8), e41–e42. https://doi.org/10.1016/j.numecd.2008.03.011
17. Maruhashi, T., Hisatome, I., Kihara, Y., & Higashi, Y. (2018). Hyperuricemia and endothelial function: From molecular background to clinical

perspectives. *Atherosclerosis, 278*, 226–231. https://doi.org/10.1016/j.atherosclerosis.2018.10.007

18. Maruhashi, T., Higashi, Y., Yoshida, H., Tanaka, A., Eguchi, K., Tomiyama, H., Kario, K., Kato, T., Oda, N., Thara, N., Oguri, M., Watada, H., & Node, K. (2022). Long-term effect of febuxostat on endothelial function in patients with asymptomatic hyperuricemia: A sub-analysis of the PRIZE study. *Frontiers in Cardiovascular Medicine, 9*, 882821. https://doi.org/10.3389/fcvm.2022.882821
19. Papežíková, I., Pekarová, M., Kolářová, H., Klinke, A., Lau, D., Baldus, S., Lojek, A., & Kubala, L. (2013). Uric acid modulates vascular endothelial function through the down regulation of nitric oxide production. *Free Radical Research, 47*(2), 82–88. https://doi.org/10.3109/10715762.2012.747677
20. Ruggiero, C., Cherubini, A., Ble, A., Bos, A. J., Maggio, M., Dixit, V. D., Lauretani, F., Bandinelli, S., Senin, U., & Ferrucci, L. (2006). Uric acid and inflammatory markers. *European Heart Journal, 27*(10), 1174–1181. https://doi.org/10.1093/eurheartj/ehi879
21. Shukla, V., Fatima, J., Varshney, A. R., Joshi, P., & Kugashiya, R. (2021). Study of endothelial dysfunction by flow-mediated vasodilation in individuals with asymptomatic hyperuricemia. *Journal of the Association of Physicians of India, 69*(2), 39–42.
22. Singh, J. A., & Gaffo, A. (2020). Gout epidemiology and comorbidities. *Seminars in Arthritis and Rheumatism, 50*(3S), S11–S16. https://doi.org/10.1016/j.semarthrit.2020.04.008
23. Wertheimer, A., Morlock, R., & Becker, M. A. (2013). A revised estimate of the burden of illness of gout. *Current Therapeutic Research, Clinical and Experimental, 75*, 1–4. https://doi.org/10.1016/j.curtheres.2013.04.003
24. Yip, K., Cohen, R. E., & Pillinger, M. H. (2020). Asymptomatic hyperuricemia: Is it really asymptomatic? *Current Opinion in Rheumatology, 32*(1), 71–79. https://doi.org/10.1097/BOR.0000000000000679
25. Zhao, Z., Zhao, Y., Zhang, Y., Shi, W., Li, X., Shyy, J. Y., He, M., & Wang, L. (2021). Gout-induced endothelial impairment: The role of SREBP2 transactivation of YAP. *The FASEB Journal, 35*(6), e21613. https://doi.org/10.1096/fj.202100337R

26. Zhen, H., & Gui, F. (2017). The role of hyperuricemia on vascular endothelium dysfunction. *Biomedical Reports, 7*(4), 325–330. https://doi.org/10.3892/br.2017.966

Tables

Table 1

Characteristics of studies related to endothelial dysfunction and gout and asymptomatic hyperuricemia: title, authors, year of publication and methodology.

Title	Author	Year of Publication	Methodology
Long-Term Effect of Febuxostat on Endothelial Function in Patients With Asymptomatic Hyperuricemia: A Sub-Analysis of the PRIZE Study.	Maruhashi et al.	2022	Sub-Analysis of the PRIZE Study.
Hyperuricemia Induces Endothelial Dysfunction and Accelerates Atherosclerosis by Disturbing the Asymmetric Dimethylarginine/Dimethylarginine Dimethylaminotransferase 2 Pathway.	Lee et al.	2021	Experimental Research.
Study of Endothelial Dysfunction by Flow Mediated Vasodilation in	Shukla et al.	2021	Case Control Study.

Title	Author	Year of Publication	Methodology
Individuals with Asymptomatic Hyperuricemia.			
Hyperuricemia and Endothelial Function: From Molecular Background to Clinical Perspectives.	Maruhashi et al.	2018	Literature Review.
Uric Acid Induces Endothelial Dysfunction by Activating the HMGB1/RAGE Signaling Pathway.	Cai et al.	2017	Experimental Research.
Effects of Allopurinol on Endothelial Function: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials.	Cicero et al.	2017	Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials.
The Role of Hyperuricemia on Vascular Endothelium Dysfunction.	Zhen & Gui	2017	Case-Control Study and *In Vitro*

Title	Author	Year of Publication	Methodology
			Experimental Research.
Uric Acid Enhances PKC-Dependent eNOS Phosphorylation and Mediates Cellular ER Stress: A Mechanism for Uric Acid-Induced Endothelial Dysfunction.	P. Li, et al.	2016	Experimental Research.
Xanthine Oxidoreductase in Atherosclerosis Pathogenesis: Not Only Oxidative Stress.	Battelli et al.	2014	Literature Review.
Uric Acid Modulates Vascular Endothelial Function Through the Down Regulation of Nitric Oxide Production.	Papežíková et al.	2013	Experimental Research.
Gout-Induced Endothelial Impairment: The role of SREBP2 Transactivation of YAP.	Zhao et al.	2012	Experimental Research.
Hyperuricemia Induces Endothelial Dysfunction Via Mitochondrial Na+/Ca2+ Exchanger-Mediated Mitochondrial Calcium Overload.	Hong et al.	2012	Experimental Research.

Title	Author	Year of Publication	Methodology
Association Between Endothelial Dysfunction and Hyperuricaemia.	Ho et al.	2010	Cohort Study.
Hyperuricemia Is Associated With Increased C-Reactive Protein Concentrations in a Large Cohort of Unselected Outpatients.	Lippi et al.	2008	Cohort Study.
Associations Between Serum Uric Acid and Adipokines, Markers of Inflammation, And Endothelial Dysfunction.	Bo et al.	2008	Cohort Study.
Uric Acid and Inflammatory Markers.	Ruggiero et al.	2006	Cohort Study.
Uric Acid-Induced C-Reactive Protein Expression: Implication on Cell Proliferation and Nitric Oxide Production of Human Vascular Cells.	Kang et al.	2005	Experimental Research.
Hyperuricemia Induces Endothelial Dysfunction.	Khosla et al.	2005	Experimental Research.

Note*: This table summarizes the characteristics of studies related to endothelial dysfunction, gout, and asymptomatic hyperuricemia, including the title, authors, year of publication, and*

methodology. The studies were selected from a bibliographic search using the terms "endothelial dysfunction," "endothelial function," "hyperuricemia," and "gout." A total of 369 potential articles were identified, of which 18 were included in this synthesis after screening by title, abstract, and full-text review.