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HYPERURICEMIA: EMERGING COMORBIDITY OR SIMPLE PRECURSOR?

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Abstract

Hyperuricemia, characterized by elevated levels of uric acid in the blood, has garnered significant interest due to its increasing prevalence globally. This condition is often associated with dietary changes, such as increased consumption of sugary and alcoholic beverages, as well as a diet rich in purines. The consequences of hyperuricemia extend beyond gout, with established links to other pathologies such as metabolic syndrome, type 2 diabetes, hypertension, and renal insufficiency. This correlation raises the pivotal question of whether asymptomatic hyperuricemia should be treated. Managing hyperuricemia and its consequences involves hygienic and dietary approaches as well as specific treatments to lower uric acid levels in the blood. Advances in understanding the pathophysiology of gout and uric acid metabolism have led to the development of new therapeutic options. However, uncertainties persist regarding the optimal management of asymptomatic hyperuricemia, necessitating further research to determine relevant risk factors and the ideal timing to initiate urate-lowering therapy. This review explores the various aspects of hyperuricemia, from its clinical implications to its management strategies, providing a comprehensive overview of this increasingly concerning condition in the realm of health.

Keywords: Gout, Hyperuricemia, Consequence.

1. INTRODUCTION

Hyperuricemia is a common biochemical anomaly resulting from an excess production of uric acid and/or a defect in its renal elimination. Uric acid (UA) has antioxidant, pro-oxidant, and pro-inflammatory effects [1], and its elevation can negatively impact the functioning of certain organs. Several studies have shown that hyperuricemia contributes to renal and vascular damage, induces hypertension [2], and causes oxidative stress in blood vessels [3].

The past two decades have witnessed a significant increase in the frequency of comorbidities associated with hyperuricemia [4]. Hyperuricemia can either be a cause or a consequence of a comorbidity; however, the causal link between them is not fully established. What is established is that persistent hyperuricemia predisposes to gout development, becoming clinically symptomatic [3, 4]. The risk of developing gout depends on the degree and duration of hyperuricemia. Nevertheless, not all hyperuricemic individuals develop gout, reasons for which remain undetermined [4].

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2. DEFINITION OF HYPERURICEMIA

In the general population, serum uric acid levels are generally lower in women than in men, but both sexes follow Gaussian distributions [11], allowing for a statistical definition of hyperuricemia as a serum uric acid concentration exceeding two standard deviations from the mean [12].

Many researchers initially defined hyperuricemia as levels exceeding 70 mg/dL in men and 60 mg/dL in women, following the recommendations of the Rome Conference in 1963 [5]. However, definitions have evolved since then. Several articles now define the threshold for elevated serum uric acid levels differently, with lower thresholds for women than men, although these values vary between studies. Some publications define hyperuricemia starting at 77 mg/dL in men and 66 mg/dL in women [5, 6], while others use thresholds of 70 mg/dL in men and 57 mg/dL [5, 7] or even 60 mg/dL [5] in women, reflecting the variability in hyperuricemia definitions.

Some authors prefer to define hyperuricemia values similarly for both sexes: recent estimations in the United States used a threshold above 70 mg/dL [7], whereas in Italy [8], a similar study defined hyperuricemia as levels above 60 mg/dL.

Such discrepancies prevent us from relying on a statistical definition of hyperuricemia, particularly when considering threshold values for gout diagnosis or prevention, or when considering hyperuricemia as a risk factor for certain comorbidities.

Furthermore, automated colorimetric assays and uricase methods, the two main techniques for measuring UA levels [5, 9], yield slightly different results between sexes [9].

This definition, which sets higher normal values for men than women, is used in most laboratory reports, but significant variations exist among populations and age groups [5, 8]. It has been demonstrated that average uric acid levels in women increase after menopause [8].

It has also been shown that uric acid levels vary considerably over time in the same individual [10], further complicating the definition of normal uric acid levels. These levels also vary among ethnicities; for instance, in the United States, there are documented variations in average uric acid levels among different races [13], while in New Zealand, average uric acid levels are higher in Maori populations compared to those of European descent [14].

As it is known that gout depends on the crystallization of UA, a physicochemical definition of hyperuricemia, taking into account the plasma solubility threshold of UA, appears logical. From this perspective, there is no clear reason to differentiate between men and women. The challenge here lies in evaluating this saturation point.

The physicochemical definition is widely preferred over the statistical definition, which is based on the threshold value of uric acid solubility in the blood above which UA will crystallize; in the literature, this threshold is defined for uricemia exceeding 68 mg/dL (408

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µmol/L) or 70 mg/dL (420 µmol/L) [15]. However, the solubility limit of sodium urate is reached at 37°C for uricemia levels of 64 to 66 mg/dL (384–392 µmol/L) and at 35°C for uricemia of 60 mg/dL (360 µmol/L), the latter condition representing the estimated temperature at the big toe [15]. The solubility limit of uric acid appears to decrease with temperature, which may explain why gout mainly affects "cold" distal joints.

Microcrystals of sodium urate deposit in tissues, particularly on the cartilage surface, whose components can interfere with the crystallization process [17]. The threshold of 60 mg/dL (360 µmol/L) was adopted in the latest 2016 recommendations of the European League against Rheumatism (EULAR) to define hyperuricemia [16]. This value not only defines the level at which a patient may develop gout but also serves as the uricemia limit to assess the efficacy of urate-lowering treatment [18].

Thus, the lack of consensus in defining hyperuricemia extends to defining HUA due to the variability in the hyperuricemia threshold value and the consideration or not of ultrasound data [18]. Bardin and Richette described several stages and conditions before the onset of gout [5]: the first being the formation of sodium urate microcrystals, which requires specific conditions (pH, temperature, local joint factors that create a nidus for crystal formation, and chemical factors that promote or inhibit their formation) [5, 18].

Studies using ultrasound or dual-energy computed tomography (DECT) have shown signs of urate deposits in HUA comparable to those found in gout [6]. The presence of urate deposits in joint and periarticular areas is reported in 30 to 50% of patients with chronic asymptomatic hyperuricemia [18]. A new classification of progression towards gout has thus emerged with three different stages: asymptomatic hyperuricemia without urate deposits, asymptomatic uric acid crystal deposits, and symptomatic gout with urate deposits [5, 18].

Such deposits appear to remain asymptomatic for a long time before flare-ups occur, triggered by the mobilization of preformed crystals. Current knowledge suggests that hyperuricemia appears to be the primary, if not the sole, risk factor for gout. Furthermore, recent studies now support the view that hyperuricemia is an independent risk factor for renal and cardiovascular diseases [15].

3. HYPERURICEMIA AND ASSOCIATED PATHOLOGIES

To date, there is no conclusive study indicating that modulating uric acid levels decreases the risk of comorbidity association [19]. Consequently, there is no consensus on therapeutic approaches for these conditions in the context of hyperuricemia, and thus, urate-lowering therapies (ULT) are not indicated for these conditions. While other studies support the idea that chronic hyperuricemia is associated with an increased risk of comorbidities, and if actively reducing its levels proves protective, one might wonder if this will lead to a change in clinical practice toward increased monitoring of any hyperuricemia.

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However, it is unknown whether hyperuricemia is a causal factor in the development of these conditions, induced by the same risk factors, or if it is a consequence of these disorders manifesting. A recent review examining the evidence for the causality of hyperuricemia in gout concluded that the only solid evidence to date, based on both randomized clinical trials and/or Mendelian randomization, is for a causal role of hyperuricemia in gout and kidney stones [24].

Managing gout or hyperuricemia without considering comorbidities can only be an inadequate approach that does not address all of the patient's medical issues. Classical dietary recommendations for hyperuricemia or gout have focused solely on reducing purine intake, although individuals with hyperuricemia often maintain diets high in refined carbohydrates like fructose and saturated fats. These diets pose an increased risk of insulin resistance syndrome with major long-term consequences [19]. High serum insulin levels are known to reduce uric acid excretion [19] and sustain long-term hyperuricemia. It is therefore essential to develop appropriate guidelines that consider both hyperuricemia and comorbidities in every patient. For example, in patients with gout and hypertension, antihypertensive medications with uricosuric properties such as Losartan or Amlodipine might present a significantly higher benefit/risk ratio than diuretics [19].

If present, comorbidities must be recognized as potentially aggravating factors in the morbidity of patients with gout or hyperuricemia and must be adequately managed [19]. The presence of comorbidities in gout or hyperuricemia tends to affect women more than men, a trend found in several longitudinal cohort studies by sex [19]. Significant sex-specific differences in initial serum uric acid concentrations and possibly in uric acid metabolism [19] may explain stronger associations with several cardiovascular pathologies. Serum uric acid levels in men are approximately 10 mg/dL higher than in women in adulthood, although these levels increase around menopause [19]. Thus, the relative physiological impact of gout or a certain degree of hyperuricemia may be more significant in women than in men [19].

A Japanese study aimed to clarify the link between asymptomatic hyperuricemia and cardiometabolic disorders in subjects composed of Japanese adults aged 30 to 85 years, enrolled at the preventive medicine center of St. Luke International Hospital in Tokyo and available at the time of enrollment (2004) and five years later (2009) [20]. Subjects were excluded if they were overweight or obese, hypertensive, diabetic, or had dyslipidemia, a history of gout or medication-induced hyperuricemia, or if they had chronic kidney disease with an estimated glomerular filtration rate less than 60 mL/min/1.73 m2. Linear and logistic regression analyses were used to examine the relationship between hyperuricemia and the development of hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and overweight/obesity (unadjusted for age, smoking, alcohol consumption, estimated glomerular filtration rate, and body mass index). 5,899 subjects without comorbidities (mean age 47 ± 10 years, 1,864 men) were followed for five years. Hyperuricemia (defined in this study as >70 mg/dL in men and ≥60 mg/dL in women) was associated with increased cumulative incidence rates of hypertension (14.9% vs. 6.1%,

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p <0.001), dyslipidemia (23.1% vs. 15.5%, p <0.001), chronic kidney disease (19.0% vs. 10.7%, p <0.001), and overweight/obesity (8.9% vs. 3.0%, p <0.001), while diabetes mellitus (1.7% vs. 0.9%, p = 0.087) showed a trend without statistical significance [20].

An American study in the general population focused on the prevalence of comorbidities of hyperuricemia and gout and found that about 74% of American adults with gout also had hypertension, 71% had stage ≥2 chronic kidney disease, 53% were obese, 26% were diabetic, 24% had kidney stones, 14% had myocardial infarction, and 11% had heart failure. These prevalences were 2 to 3 times higher than those without gout. These associations tended to be stronger in women than in men. These results highlight the substantial and persistent presence of comorbidities in Americans with gout or hyperuricemia during the new millennium [19].

The various data regarding the link between hyperuricemia and different comorbidities will be detailed below.

- ***Type 2 Diabetes:***

Type 2 diabetes, with its continuously increasing incidence, is a significant public health issue that falls within the context of the metabolic syndrome [22]. Insulin resistance plays a central role in the pathophysiology of the metabolic syndrome [22]. In this context, hyperuricemia results from decreased uric acid clearance due to hyperinsulinemia, which stimulates UA tubular reabsorption and is improved by a low-calorie diet [22]. The development of sodium-glucose co-transporter 2 (SGLT2) inhibitors for diabetes treatment has reignited interest and debate about their role in diabetes and chronic kidney disease (CKD) [21]. SGLT2 inhibitors act through the kidneys independently of insulin to improve glycemic control but also reduce uric acid levels [21, 22]. It has been demonstrated that treatment with SGLT2 inhibitors contributes to decreasing plasma UA concentrations and increasing fractional excretion of uric acid (FEUA) [23]. The effect of SGLT2 inhibition on uric acid excretion is not clear, although effects on GLUT9 via glycosuria induction may contribute to higher levels of uric acid exchange across the apical membrane of tubular cells in the urine [21-22].

- ***Cardiovascular Disease:***

Clinical observations showing an association between elevated uric acid levels and hypertension are also confirmed in children and adolescents, where blood pressure values are significantly elevated (>95th percentile) in the presence of levels >55 mg/dL [25]. Moreover, regardless of the pharmacological mechanism (XO inhibitor and uricosuric), it has been shown that reducing uric acid levels lowers blood pressure early in hypertension in adolescents [26]. Finally, several studies have confirmed that individuals with high UA levels are at increased risk of hypertension, even if they otherwise appear to be in good health [27]. Experimental and clinical evidence suggests that deleterious effects of high uric acid levels in cardiovascular diseases can be observed at the vascular level. For example, it has been demonstrated that elevated uric acid levels are associated with a low-grade inflammatory state and vascular activation of the renin-

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angiotensin system [30]. Additionally, numerous studies have suggested that XO plays an important role in various forms of tissue and vascular damage, inflammatory diseases, and ischemic heart failure [31].

- ***Kidney Disease:***

It is well accepted that hyperuricemia is associated with microlithiasis pathologies affecting the urinary tract such as kidney stones. It has been demonstrated that elevated plasma uric acid levels are associated with an increased risk of kidney lesions due to renal vasoconstriction via an inflammatory phenomenon, endothelial dysfunction, and activation of the renin-angiotensin system [32]. A small Mendelian randomization study supports the hypothesis that hyperuricemia, induced by an instrumental variant of SLC2A9, may cause the progression of chronic kidney disease [21]. The kidneys play a major role in regulating serum uric acid levels due to significant manipulation of uric acid by proximal renal tubules; the debate persists as to whether hyperuricemia simply acts as an indicator of renal dysfunction or has a causal role. Consequently, numerous clinical data support the hypothesis that hyperuricemia is both a predictive factor for the onset of chronic kidney disease (CKD) and a modulator of the progression of acute kidney injuries and chronic kidney disease, the latter being increasingly recognized as a universal health problem [33]. However, other epidemiological studies have not shown a significant relationship between hyperuricemia and the progression of chronic nephropathy [33], so the debate is likely to continue.

4. CONCLUSION

Hyperuricemia is a current topic of interest due to its marked increase in prevalence worldwide, attributed to dietary changes favoring sugary and alcoholic beverages and a diet richer in purines. Hyperuricemia remains a precursor to gout and other comorbidities such as metabolic syndrome, diabetes mellitus, hypertension, and renal insufficiency. The adequate management of hyperuricemia sparks controversy but also attracts the attention of numerous scientific studies. Thus, a relevant question arises: should asymptomatic hyperuricemia be treated or not? One certainty remains, that even asymptomatic hyperuricemia is associated with increased incidence of cardiovascular events and renal impairments often accompanying it.

The management of hyperuricemia, like gout, involves lifestyle and dietary measures and sometimes urate-lowering treatments to reduce uric acid levels to the target recommended by major scientific societies in the field. Improvements in understanding the pathophysiology of gout as well as uric acid metabolism and renal pathways of reabsorption or secretion have enriched the therapeutic arsenal for gout. Several studies have focused on asymptomatic hyperuricemia, yet there are still areas of uncertainty in its proper management. Large-scale studies are necessary to assess risk factors that may warrant discussion of urate-lowering therapy in asymptomatic hyperuricemia and to determine the optimal timing to introduce such treatment to maximize its benefit-to-risk balance.

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Conflits of interest

The authors declare no conflicts of interest.

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