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Hyperuricemia as an Independent cardiovascular risk factor

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Abstract

Hyperuricemia (HU) is often underestimated as an important cardiovascular risk factor. A considerable number of epidemiological studies have shown the important role of HU and various cardiovascular disorders, chronic kidney disease, diabetes mellitus, metabolic syndrome, as well as cardiovascular mortality in general. Among the main mechanisms, that explain the role of uric acid in cardiovascular disease, we mention oxidative stress, systemic inflammation, endothelial dysfunction, as well as activation of the renin-angiotensin-aldosterone system. European and International guidelines recommends the treatment of HA with xanthine oxidase (XO) inhibitors, for a serum uric acid (SUA) level ≤6 mg/dl, while the treatment of asymptomatic HA remains one of the most discussed topics.

Keywords: cardiovascular, uric acid, allopurinol.

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INTRODUCTION

Uric acid is the end product of the endogenous and exogenous catabolism of mononucleotide purines, produced by the enzyme Xantine Oxidoreductase, which exists in two forms: Xanthine dehydrogenase and Xanthine oxidase (1). Uric acid is released under hypoxic conditions (2). The largest amount of SUA is produced in the liver and intestinal mucosa. About 2/3 of SUA are excreted by the kidneys, while 1/3 by the digestive tract.

Normal SUA are 3.4-7.2 mg/dl (men), and 2.4-6.1 mg/dl (woman) (3). HU is defined as SUA levels ≥6.0 mg/dL in women, and ≥ 7.0 mg/dL in men, which is caused as a result of overproduction or decreased uric acid excretion, known for many years as the main cause of gout. An important role in increasing SUA levels have genetic variations as well as foods such as meat, seafood, beer (4.5). Part of the population has a mutation in the protein responsible for the excretion of uric acid by the kidneys. Some of responsible genes have been identified: SLC2A9; ABCG2; SLC17A1; SLC22A11; SLC22A12; SLC16A9; GCKR; LRRC16A; and PDZK1 (6.7.8). SLC2A9 is known as a co-transporter of uric acid and fructose (9.10). Several epidemiological and genetic studies have shown the association between high SUA levels and the incidence of various cardiovascular diseases (11). Treatment of HU is recommended in all symptomatic patients. European guidelines recommends maintaining SUA levels ≤6 mg/dL in patients with chronic HU with urate deposits (12). Some studies, suggest that asymptomatic people, with HU should only be treated if the cardiovascular risk at 10 years is high, or if they have high SUA levels (> 8mg/dl). However, International guidelines recommends not treating asymptomatic HU other than the above conditions (5), although, asymptomatic HU has been proven to be an independent risk factor for various cardiometabolic diseases and cardiovascular disease (13). Debates, about the benefits of treating asymptomatic HU, persists as well as the effects regarding treating asymptomatic risk-free HU which need to be proven by further studies.

Causes of hyperuricemia

The prevalence of HU is increasing worldwide, mainly in higher income countries. This is a common laboratory finding with clinical significant implications. It is easily detected, but its mechanisms may not be clearly elucidated. About 45 diseases or categories of conditions, 20 drugs, and nine states of intoxication have been surveyed. HU can be a multifactorial genetic disorder or a discrete response to a specific stimulus. Some conditions have both increased production of uric acid as well as decreased renal outflow. For many patients, the underlying mechanisms have not yet been elucidated (14). Increased production of uric acid occurs in myeloproliferative diseases such as leukemia, lymphoblastoma, polycythemia, multiple myeloma, non-proliferative malignant neoplasms. Increased production of uric acid is

also found in tissue catabolism, necrosis or increased release of nucleotides, which occurs in hemolytic anemia, while receiving immunosuppressive therapy, myocardial or cerebral infarction, psoriasis. Increased de novo purine secretion is found in HGPRT (hypoxanthine guanine phosphoribosyl transferase) deficiency, increased PRPP synthetase (phosphoribosylpyrophosphate) activity, APRT deficiency (high adenine phosphoribosyl transferase) (14), meat, seafood, or foods rich in fructose, alcohol and salt are blamed for causing elevated SUA levels (1,15). Decreased uric acid secretion is found in chronic kidney disease, taking certain medications (eg: diuretics, salicylates, etc.), polycystic kidney disease, hypertension (14). Impairment of renal function in addition to being responsible for the increase of SUA level, some studies have shown that HU may precede the development of kidney injury (16.17). Increased SUA levels, may also be due to increased reabsorption or decreased acid excretion uric acid from the renal tubules, which occurs in situations such as hypothyroidism, metabolic acidosis, diabetes insipidus, or treatment with certain medications (eg, beta-blockers) (18).

Hyperuricemia and cardiovascular disease

HU has been shown to be a predictor factor of the development of hypertension, coronary heart disease, metabolic syndrome, chronic kidney disease, and type 2 diabetes mellitus (19.20.21.22.23). Furthermore, a few trials demonstrated that uric acid-lowering therapies can reduce blood pressure and insulin resistance and may exert nephroprotective effects (18.24).

The data obtained from a meta-analysis of 32 studies, concluded that HU increases the risk of developing heart failure, and the presence of which in patients diagnosed with heart failure is indicative of a poor prognosis of the disease (25). Furthermore, it has been observed that patients with hypertension and HU, have greater thickening of the intima-media of the carotid arteries, compared to patients with normal uric acid values (26). It has also been reported that the platelet count is higher in HU, which can affect the development of clots, thus leading to a reduction in coronary flow (27). Another mechanism between which uric acid reduces coronary flow, is among its effects on calcification of coronary arteries, thus classifying HU as an independent risk factor for coronary artery disease (28.29). High SUA levels have an important role in induction of crystallization of the vascular wall, which impairs smooth muscle function, thus leading to atherosclerosis through activation of the renin-angiotensin-aldosterone system. On the other hand uric acid may have anti-proliferative effects on the endothelium or may impair the nitric oxide production process (30). A large prospective cohort study, of 123,238 individuals conducted from 2006 to 2012, showed the association between HU and increased atrial fibrillation prevalence (31). A cohort study of 20,000 patients showing the association between SUA levels and all causes of

cardiovascular death, conducted at the URRAH (Uric Acid Right for Heart Health) study center in Italy determined a 5.6 mg/dl cut-off uric acid for the risk of cardiovascular mortality (32). Nevertheless, the association between SUA levels and cardiovascular disease remains partially unproven. Some mechanisms such as endothelial dysfunction, caused by HU, oxidative stress, and systemic inflammation, are common to other cardiovascular risk factors (18.24).

Treatment of hyperuricemia

In a systematic review of 24 guidance documents, 19 of them provided target levels for long-term SUA control, most of which recommended 6.0 mg/dL, except the South African guidelines, which recommended 5.0 mg/dL (5). Also, the Polish Society of Hypertension Guidelines 2019 recommend 5.0 mg/dL level for long-term SUA control (31). Still, the definition of HU varies greatly across clinical trials, making epidemiological reports somewhat inconsistent and difficult to compare. Guidelines recommend an initial dose of allopurinol 100 to 200 mg daily in mild cases, 300 to 600 mg daily in moderate cases, 700 to 900 mg daily in severe cases. The dose should be gradually titrated to achieve the desired SUA levels (33). In patients with chronic kidney disease the dose should be reduced to 100 mg per day in patients with chronic kidney disease stage IV-V. If allopurinol is used in dialysis patients, it should be administered at a 300–400 mg dose, immediately after dialysis, but without additional doses on other days (33).To rule out the toxic effects of allopurinol, guidelines recommend prior screening of HLA - B * 5801 especially in patients most at risk of developing a reaction to this drug (5.17.34).

The second line drug is another XO inhibitor, Febuxostat. Both drugs work by inhibiting XO activity, thereby reducing the production of xanthine uric acid, which is produced by purine catabolism. Febuxostat is recommended in patients who manifest intolerance to allopurinol and there is no need for dose reduction in patients with chronic kidney disease I-III. Febuxostat exerts strong inhibition of XO and has a stronger hypouricemic activity than the usual dose of allopurinol (35). However, preliminary results from a safety trial with febuxostat versus allopurinol, mainly based on a large-scale, randomized study design has suggested a modestly higher rate of cardiovascular events with febuxostat (36). Based on the preceding study's findings, treatment with febuxostat in patients at high cardiovascular risk has not been recommended (36). Allopurinol has been shown to have effects in reducing blood pressure and insulin resistance. Although high doses of allopurinol (≥ 300 mg/dL) have been associated with reduced risk of all causes of death (37.38), considering an optimal dose is one of the challenges of future studies.

Uricosuric drugs act on transporters of the proximal renal tubules, thereby reducing uric acid reabsorption. Lesinurad is a selective inhibitor of URAT1 and OAT 4 urate transporters; Probenecid and Benzbromarone inhibit only

URAT1 (15.34). In the CLEAR study, it was found that Lesinurad at a dose of 200 mg or 400 mg combined with allopurinol significantly reduced SUA levels, compared with patients treated with allopurinol alone (54.2%, 59.2%, and 27.9%, respectively, p <0.0001) (39). Probenecid can not be prescribed to patients with chronic kidney disease, while benzbromarone causes hepatotoxicity. SUA levels can be reduced by medications such as Pegloticase and Rasburicase, which are administered parenterally, but some individuals may develop anaphylactic reactions limiting their effectiveness (17.40).

Uric acid treatment target may still need to be reconsidered, especially since data from the URRAH study identified new cardiovascular thresholds and improved algorithms for assessing total cardiovascular risk. Still, there is a clear need for further evidence to support the treatment of asymptomatic HU, although a large body of evidence does show the beneficial effect of uric acid lowering therapy on cardiovascular results.

CONCLUSIONS

The prevalence of HU is steadily increasing worldwide. 1 in 5 patients suffers from HU, which is often underestimated as a risk factor for cardiovascular disease. Various epidemiological and genetic studies have shown the association between HU and various cardiovascular diseases, hypertension, diabetes mellitus, metabolic syndromes, heart failure, coronary artery disease, chronic kidney disease. Uric acid has been shown to be responsible for endothelial dysfunction, oxidative stress as well as local and systemic inflammation. Various guidelines recommended long-term treatment of HU, with a target serum uric acid level of ≤6 mg/dL. Data on the efficacy of treating asymptomatic HU and the benefits of cardiovascular disease are insufficient. This makes the challenge of the future, even more difficult for various studies, to clarify the role of SUA as an independent risk factor for cardiovascular disease, and the effectiveness of asymptomatic uric acid level reduction therapy in cardiovascular data.

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