

## Clinical reviews

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# Hyperuricemia as a risk factor for cardiovascular disease: clinical review

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## Abstract

Cardiovascular diseases are one of the most important causes of morbidity and mortality worldwide. Several risk factors have been associated with the development of these pathologies. However, there is controversy about whether hyperuricemia is an independent risk factor for developing cardiovascular disease. To answer this question, we performed a recent literature review of relevant published material to assess the association of hyperuricemia with four major cardiovascular diseases: hypertension, coronary heart disease, heart failure and atrial fibrillation.

## Introduction

In the world, during the year 2008 there were 17.3 million deaths from cardiovascular disease and by 2030 they are expected to rise to 23 million deaths annually due to this cause [1].

Among the most important risk factors are sex, race, hypercholesterolemia, obesity, insulin resistance, consumption of tobacco, anxiety disorders or depression and inheritance. However, in recent years the possibility that hyperuricemia is an independent risk factor for development of cardiovascular disease has been considered [1],[2],[3].

The first time hyperuricemia was associated with cardiovascular diseases was in 1950 and since then, controversy has existed regarding the role of uric acid as an independent risk factor for the development of some of the more prevalent cardiovascular diseases such as hypertension, coronary heart disease, heart failure and atrial fibrillation [3],[4],[5].

With these antecedents, this work was proposed with the aim of conducting a literature review of the evidence published in recent years about clinical and

pathophysiological relationships of hyperuricemia with the most commonly cardiovascular diseases diagnosed in medical practice such as hypertension, heart disease, heart failure and atrial fibrillation.

## Methods

Search was performed through MEDLINE/PubMed for articles published between 2010 and 2016. Original articles, clinical reviews and meta-analysis, published in English were included. We did not taken into account letters to the editor, consensus articles or those not available in the full version.

Main search terms were "cardiovascular risk and uric acid"; "hypertension and uric acid"; "heart failure and uric acid"; "coronary disease and uric acid"; "atrial fibrillation and uric acid."

## Results

### Uric acid effect over the cardiovascular system

Uric acid is a weak organic acid resulting from the oxidation of xanthine and hypoxanthine due to the action of xanthine oxidoreductase enzyme [2]. In a physiological pH, it is a monosodium urate; when its concentration increases or its solubility decreases, the risk of becoming a deposit in

tissues or forming a structural part of some types of kidney stones growths [6].

Uric acid normal levels are 6 mg/dl in women and 7 mg/dl in men. However, these values may be influenced by factors such as: race (black people have lower concentration of uric acid than white people), sex (the level of uric acid is higher in men than in women), consumption of certain foods like red meat and seafood or alcohol intake [3],[4],[6],[7],[8].

Physiologically, uric acid has a dual effect because it acts as antioxidant at extracellular level and as a prooxidant intracellularly [4],[5],[7]. The prooxidant effect is mediated by the action of xanthine oxidase enzyme which induces the generation of reactive oxygen species, the release of proinflammatory cytokines and a decrease of nitric oxide synthesis by inactivation of the enzyme nitric oxide synthase which ultimately results in increased oxidative stress and apoptosis [1],[5],[8].

Hyperuricemia increases the activity of the renin-angiotensin-aldosterone system, especially in previously hypertensive and obese patients because hyperuricemia increases the levels of angiotensin II, a fact causing more vasoconstriction and finally produces hypertension [8],[9].

Furthermore, the increased activity of the renin-angiotensin-aldosterone system also is associated with an increased activation of the activated mitogen protein kinase leading to an increase of apoptosis of cardiac muscle fibers. Thus, hyperuricemia through this mechanism may contribute to the pathophysiological process of heart failure and atrial fibrillation [8],[10],[11].

Another aspect that has been linked to hyperuricemia is atherogenesis since uric acid acts in different stages of the atherosclerotic plaque formation. These effects can be produced by causing direct damage to the endothelial cell, by inducing a greater proliferation of smooth muscle or by provoking an increase of the lipid nucleus with a decrease in the concentration of fibrous tissue, which will generate a more unstable plate and with higher risk of rupture [7],[12],[13].

### **Hypertension**

High blood pressure is one of the most commonly diagnosed cardiovascular diseases and is responsible for approximately 1.5 million deaths per year [3],[4].

There are evidences linking hyperuricemia with increased risk of developing hypertension in populations with high intake of salt and in young people, however it is unclear whether this relationship is maintained in the general population [1],[4].

Two meta-analyses conducted on prospective studies found that people with hyperuricemia increased the risk of developing hypertension. This relationship was more relevant in African Americans and Asians [14]. It was also evidenced that people with hyperuricemia increased between 13% and 15% the risk of developing hypertension

for each mg/dl of uric acid above the normal value, RR 51.15 (95% CI: 1.06-1.26) [15].

Finally, a cohort study showed that even those whose uric acid levels were within normal range had a greater risk of developing hypertension. Risk increased in 66% for women, OR=1.76 (95% CI: 1.48 to 2.08) and in 54% for men OR=1.54 (95% CI: 1.27-1.87) [5].

On this base, we can consider that hyperuricemia as an independent risk factor for the development of hypertension although it is unclear whether the uric acid cutoff levels currently considered normal can accurately predict the risk of developing this disease.

### **Coronary disease**

Coronary heart disease is a leading cause of death from cardiovascular diseases worldwide [16]. In the United States of America in 2011 there were 375.295 deaths from this cause and it is estimated that each year 635.000 new cases are diagnosed [1],[13],[16].

In recent years, several studies were conducted in order to investigate whether hyperuricemia is a risk factor for development of coronary heart disease but the results are contradictory.

A cross-sectional study showed that in diabetic and hypertensive patients hyperuricemia was associated with increased risk of developing coronary heart disease, OR=1.77 (95% CI: 1.31-2.39) ( $p < 0.001$ ) [17]. In the same way, two meta-analyses show a modest but significant association between hyperuricemia and a new coronary event RR=1.67 (95% CI: 1.30-2.04) especially with an increase in the mortality by this cause in female patients RR=2.44 (95% CI: 1.69 - 3.54) [16],[18],[19].

However, several cohort studies and a meta-analysis with 11 randomized studies failed to demonstrate a significant association between these two pathologies. Neither these studies, showed that active treatment for hyperuricemia is associated with a decreased risk of developing new coronary events OR=0.966; (95% CI: 0.819-1.140); ( $p = 0.685$ ) [2],[20],[21],[22].

Another aspect evaluated by several studies was the relationship between hyperuricemia and the severity of coronary lesions evaluated by angiographic studies. In this context, four cross-sectional studies showed that patients with high levels of uric acid had a higher risk of complex coronary lesions or tri-arterial compromise, this being a stronger association in patients with uric acid levels equal or greater than 5.4mg/dl (74% sensitivity and 53% specificity) [8],[23],[24],[25].

Finally, based on these findings we can conclude that the evidence is contradictory regarding the hyperuricemia being an independent risk factor for developing coronary disease although there is evidence that elevated levels of uric acid could be linked with complex coronary disease.

### Heart failure

Approximately, 1% to 2% of cardiovascular deaths are due to heart failure [11],[26]. Several studies showed that hyperuricemia is associated with increased risk of altering various hemodynamic parameters such as: increasing pressure in the right atrium, increasing pulmonary capillary wedge pressure, increasing pulmonary systolic pressure and decreasing the cardiac index. However, no consensus exists in determining whether elevated uric acid levels are linked to an increased risk of clinical decompensation or an increased risk of developing heart failure [3],[26],[27],[28].

Retrospective and prospective studies, found that patients with hyperuricemia showed increased risk of developing heart failure with reduced ejection fraction and a higher risk to present clinical decompensation for this cause [3],[29],[30]. In addition, one meta-analysis showed that patients with heart failure with reduced ejection fraction and abnormal uric acid levels increased in 4% the mortality risk in relation to people with normal uric acid levels, HR=1.04 (95% CI: 1.02-1.06) [26].

Based on these antecedents, several studies were conducted to determine whether treatment of hyperuricemia was associated with a decreased risk of developing heart failure with reduced ejection fraction. Different studies found that patients with heart failure with reduced ejection fraction treated for hyperuricemia showed improvement in ejection fraction and brain natriuretic peptide levels [11],[27],[31],[32],[33]. However, one meta-analysis of 11 randomized trial failed to demonstrate that treatment of active hyperuricemia was associated with a lower risk of developing heart failure OR=1.407; (95% CI: 0.272-7.273) (p = 0.683) [22].

Another group of patients that were studied were those with acute heart failure and heart failure with preserved ejection fraction. [34],[35]. In both groups it was shown that in patients with elevated uric acid levels, there was an increased morbidity associated with heart failure [35],[36],[37]. However, in the group of patients with heart failure with preserved ejection fraction this association was only significant in female patients [11].

In conclusion, we can say that hyperuricemia is an independent risk factor for the development of heart failure and its presence is associated with increased mortality. However, there is no evidence to consider the active treatment of hyperuricemia as an alternative to reduce mortality or the number of complications associated with heart failure.

### Atrial fibrillation

Atrial fibrillation is the most frequently diagnosed arrhythmia in clinical practice and has greater impact on cardiovascular morbidity and mortality [38]. Among the risk factors associated with its development are: advanced age, male sex, history of hypertension, type 2 diabetes mellitus, heart failure or myocardial infarction [3],[38].

In recent years, several studies have evaluated whether hyperuricemia is an independent risk factor for developing atrial fibrillation in both the general population and in patients undergoing cardiac surgery or cryoablation procedures.

Regarding the first hypothesis, three studies (one cross-sectional and two cohort) showed that, compared with patients with normal uric acid levels, hyperuricemia was associated with increased risk of developing atrial fibrillation being more important the relationship in women (40%) than in men (17%) [38],[39],[40].

In relation to the second question, one study found that hyperuricemia is associated with increased risk of recurrence of atrial fibrillation after a cryoablation procedure HR=1.96, (95% CI: 1.49-2.59), (p <0.0001) being more frequent in patients with uric acid levels equal or greater than 6,37 mg/dl (sensitivity 85.7% and specificity of 83.7%) [41].

Another study, conducted in postoperative coronary surgery patients, showed that those patients previously diagnosed with hyperuricemia had an increased risk of developing atrial fibrillation after the surgical procedure OR=3.137 (95% CI: 1.873- 5.256) (p <0.05) (sensitivity 91.4%, specificity of 84.2% in patients with uric acid levels  $\geq$  6,55 mg/dl) [42].

With these precedents, we can conclude that there is insufficient evidence to consider hyperuricemia as an independent risk factor for development of atrial fibrillation.

On the other hand, there is evidence to determine that patients with high levels of uric acid have a higher risk of recurrence of atrial fibrillation after cryoablation process and of developing this type of arrhythmia after cardiac surgery.

### Conclusions and limitations

Based on this review, we can conclude that the evidence is insufficient to say that hyperuricemia is an independent risk factor for the development of some of the most common cardiovascular diseases such as hypertension, coronary heart disease, heart failure and atrial fibrillation.

Regarding the treatment of hyperuricemia, the impact that the urate-lowering agents could have on the incidence of cardiovascular diseases, taking them into account as a potential prevention strategy for the development of these diseases, should be further evaluated.

The major limitations of this study are that only references in English were included and that it was a non-systematic review with a short period of review time. Therefore it cannot be assured that all evidence concerning this matter was covered.

## Notes

### From the editor

The author originally submitted this article in Spanish and English. The *Journal* has not copyedited the English version.

### Conflicts of interest

The author completed the ICMJE conflicts of interest declaration form, translated to Spanish by *Medwave*, and declares not having received funding for the preparation of this report, not having any financial relationships with organizations that could have interests in the published article in the last three years, and not having other relations or activities that might influence the article's content. Forms can be requested to the responsible author or the editorial direction of the *Journal*.

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