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HYPERURICEMIA - AS A PATHOGENETIC AND INDEPENDENT RISK FACTOR IN RELATION TO THE METABOLIC SYNDROME

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Abstract

Introduction: *The Metabolic Syndrome is considered at present as one of the most important causes of mortality and morbidity at world level. Even if the uric acid is not part of any definition of the Metabolic Syndrome, the actual studies have shown strong associations between uric acid concentration and the Metabolic Syndrome or its components, the role of Uric Acid within the Metabolic Syndrome (MS) being increasingly investigated.* ***Aims:*** *We have analyzed recently published data that show the importance of hyperuricemia in MS, Cardiovascular Diseases, Chronic Kidney Disease.* ***Conclusions:*** *Uric Acid (UA) is a central player in MS progression and in cardiorenal pathology, which is why a multidisciplinary approach and a correct treatment are required, in order to obtain multiple benefits and, possibly, in the future, new therapeutic guidelines in approaching MS.*

key words: *Uric acid, metabolic syndrome, type 2 diabetes mellitus, arterial hypertension, chronic kidney disease*

Introduction

In today's society, we are witnessing, at world level, a constant increase in the number of subjects with obesity, cardiovascular disease and diabetes mellitus, with the Metabolic Syndrome (MS) requiring special attention, while still being the subject of many controversies.

The metabolic syndrome (MS) has been defined in numerous instances according to the criteria of the National Cholesterol Education Program (NCEP), also called the Adult Treatment Panel III (ATP III) [1]. In 2009, international scientific organizations proposed a consensual description, so that MS is defined by the presence of *at least three* of the following anomalies [2]:

- abdominal obesity: waist circumference> 80cm for women and> 94cm for men;
- hypertriglyceridemia (≥ 150mg/dl); or the use of lipid-lowering medication,
- low serum levels of high-density lipoproteins: low HDL-cholesterol (<40 mg/dl in men and <50 mg/dL in women);
- arterial hypertension: systolic TA (arterial tension) ≥ 130 mm Hg, diastolic TA ≥ 85 mm Hg or use of antihypertensive medication;

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– fasting glycemia (blood glucose) ≥ 100 mg/dl or antidiabetic treatment.

The importance of MS resides in several aspects: first of all, it allows the identification of subjects with high risk for cardiovascular disease and type 2 diabetes mellitus (T2DM). Depending on the definition used, subjects with MS have a 5 times higher risk of developing T2DM and 2-3 times higher risk of cardiovascular disease than those without MS. Secondly, by considering the relationship between the components of the MS we can understand better the pathophysiology of the link between them and the cardiovascular risk. Thirdly, it facilitates epidemiological and clinical studies that allow for a pharmacological approach, lifestyle change and a preventive approach.

Analyzing the relationship between UA and systemic arterial hypertension (HT), dyslipidemia, chronic kidney disease and cardiovascular disease, according to the literature, two conclusions emerge. One that supports the direct existence of causal links [3] and another that questions the previously mentioned links.

A new interesting period with regard to the history of uric acid has begun. In the past, UA was mainly referred to patients suffering from gout and renal lithiasis (stones), but today it is known to be associated with DM, cardiovascular disease, and obesity. In this situation above, it is recommended that intensive clinical studies should be done in order to identity possible connections between lowering UA and preventing/treating the diseases associated with UA to further provide better guidelines for lowering UA levels.

Changes in serum UA levels depend on various demographic factors, such as race, sex, the presence of cardiovascular comorbidities and medication. Generally, men have higher UA than women, older (over 65 years), those with high blood pressure, those with high levels of creatinine, cholesterol, a higher body mass index high [4-6]. Higher levels of UA are also associated with the use of diuretics, meat, seafood, excess and alcohol [4,7]. One study found that the AU is lower among Africans than Caucasian men [8], although others found higher is compared to blacks [4]. It also appears that the genetic influence of the AU level matters in different racial / ethnic groups [9]. Of the drugs, thiazide diuretics are most commonly incriminated, they can cause hyperuricemia, elevated serum glucose and dyslipidemia, mainly elevated cholesterol levels [10].

Uric acid as a component of the metabolic syndrome

What is Uric Acid?

UA is a weak acid (Molecular weight = 168.112 g/mole) activated especially in the liver, muscles and intestines [11]. Purines are the primary source of the UA. Xanthine-oxidoreductase (XO) is the special enzyme having the role in making the UA. UA is found in a high quantity in exogenous sources as: game meat, organs (liver), seafood and beans, etc [12]. Fructose is also an important source of UA, it is present in fruits. UA is directly responsible for the pathogenesis of gout and renal lithiasis. At any rate, more than 140 years ago, the coexistence of hyperuricemia with many diseases, including HTA [13], CKD and DM, was assumed [14]. Serum UA is highly attached to the insulin resistance (IR). Hyperuricemia found in cases of IR increase is a consequence of low clearance of the renal urea [15]. Analyzing the actual data, one may ask if the UA could have any role in the pathogenesis of MS or not [16]. It had been demonstrated that the associated diseases were solved if the treatment for reducing the UA is administrated. The classes of medicine could be XO inhibitors or

those that increase renal excretion of UA. One knows that the excess fat which is hold in the adipose tissue, it will lead, lately, at the formation of MS. Excessive intake of sugars in addition to purine-rich foods may increase the hyperuricemia, DM and obesity [17]. At the patients normally ponderal, MS is 10 times more frequent in the group with UA> 10 mg/dl as compared to those with serum UA <6 mg/dl [18].

There has been a major recent meta-analysis of 11 studies, regarding over fifty-four thousand participants which demonstrated that hyperuricemia increase the risk of MS and non-alcoholic fatty liver disease [19].

Because MS components or integral MS affect a very large percentage of the population both worldwide and in our country, it is important to analyze to what extent the treatment of hyperuricemia can influence and improve MS progression. The uric acid is not included in any definition of the metabolic syndrome, but the studies we may found nowadays demonstrate a high correlation between hyperuricemia and MS. This international concern and approach have led to numerous clinical trials and remarkable results with regard to the central role of UA and the benefits of lowering UA serum treatment.

The prevalence of MS increased from 5.9% for UA levels below 6 mg/dL to 59.0% for 10 mg/dL or higher levels [20]. Furthermore, on the basis of a recent revision, which included 13 studies with approximately 190,000 patients with hyperuricemia have a high risk of developing CKD [21]. Studies on animals have shown that hyperuricemia causes IR, possibly because of the proinflammatory effect of UA in adipocytes [22,23] and affects insulin dependency and glucose uptake. In rat kidneys, hyperuricemia increased juxtaglomerular renin and neuronal NO synthase in the descending region [24]. In vitro, UA inhibited NO production in endothelial cells [25] and inhibited, depending on the dose, the endothelial vasodilator response to acetylcholine [22], which determine the decrease of the renal flux of the kidneys. Obviously, lowering the UA level can have beneficial effects in MS.

The coexistence of hyperuricemia with HT has been known for a long time [26]. The studies have demonstrated that the patients who have an increased UA will develop in the future HT. [27,28]. Experimentally, the rats developed arterial hypertension after the administration of the uricase inhibitor [29]. It was analyzed the relationship between the artheryal hypertension and the seric level of UA. In mice, blood pressure increases by 10 mmHg for each 0.03 mmol/l (0.5 mg/dl) of increase in serum UA [24]. Allopurinol, a medicine that lowers UA, prevented prophylactic hyperinsulinemia, hypertriglyceridemia and HTA [23]. The hyperuricemia induces inflammatory changes in the kidney which will determine, in the future, a hypertensive to salt effects [30]. This suggests that hyperuricemia plays a role in triggering arterial hypertension, but in the course of time, microvascular changes at kidney level maintain the hypertensive state. By using a uricase inhibitor which leads to hyperuricemia, it was possible to see the direct relationship between blood pressure and UA.

Increased uric acid is also associated with poorly controlled blood pressure and significant arterial stiffness in hypertensive subjects. There is an article [31] on this topic which recently published the results of the trial performed in Italy, in Bologna, showing that increased serum UA was associated with an increased incidence of arterial hypertension inadequately controlled by hypertensive medication, as well as an increase in arterial stiffness which could in itself lead to a weaker response to the medicine therapy. That's why it is important the

determination of serum UA level and the correct treatment to the hypertensive patients especially if they don't respond to the therapy.

Can HU be a competitive additionally risk factor for the apparition of atrial fibrillation? The answer is not clear because several aspects and illnesses influencing the occurrence of atrial fibrillation. But an interesting study was published in Japan that clarified the role of hyperuricemia as determinant factors for atrial fibrillation through the general population. A retrospective analysis of the medical records of approximately 90,000 Japanese subjects who presented themselves each year for regular health checkups at the International Hospital in Tokyo for a period of six years. The main result was primarily that groups with atrial fibrillation had higher serum UA levels than the non- atrial fibrillation group. The conclusion was that: Hyperuricemia is an independent risk factor for atrial fibrillation [32]. Future studies are required in order to demonstrate whether the lowering of the UA level might be important for atrial fibrillation prevention or not.

Hyperuricemia and Diabetes Mellitus

From a historical point of view, there exist dates from the early 1800's [33] which suspected the association of hyperuricemia with T2DM. There is known that the high level of UA can predict the forming and development of T2DM [35]. It has been demonstrated that to the patients with SM, the IR may of IR be significantly regenerated when the level of UA is reduced. There are several studies on animals (mice) with SM, but on people the studies that follow the decreasing effect of UA on the IR are limited [36]. Though, there had been demonstrated that there exist an improvement of IR (HOMA index) after the treatment with benzpromarona [37] and allopurinol [38] in two studies. Also, another study has demonstrated an amelioration of A1C hemoglobin values to the patients with T2DM without HTA, treated with allopurinol [39].

Hyperuricemia and mortality

It seems that the UA also influences mortality. A significant meta-analysis comes to support this statement, which was published with regard to Uric Acid and mortality in CKD. (24 studies involving over 25,000 patients with CKD were included), the majority of the studies have demonstrated a strong relationship from the mortality of the patients with CKD and hyperuricemia [40-44]. Many studies show that hyperuricemia predicts mortality risk [40,41,43], while other studies suggest that low serum UA level increases the risk of mortality [42,44]. It was hypothesized that increased uric acid is an independent mortality predictor for participants with CKD, therefore a systematic and quantitative analysis was performed, a meta-analysis of all available studies that reported the effects of plasma concentrations of the uric acid on mortality in patients with CKD. This meta-analysis shows that hyperuricemia was associated with a higher risk of mortality. An increase of 1 mg/dl in the serum UA level was associated with an 8% increase of the mortality risk. In conclusion, the Meta-analysis (being the first) presented showed that hyperuricemia increase the risk of mortality to patients with CKD. The findings presented were consistent with the conclusions of two previous meta-analyses in the general population and in patients with type 2 diabetes mellitus [45]. Another meta-analysis of 11 prospective studies involving approximately 170.000 participants concluded that Hyperuricemia appears to significantly increase the risk of mortality from any cause – in men, but not in women [45].

Also, in the case of CKD, but in patients undergoing renal function substitution by

hemodialysis, recent data [46] have shown that serum UA may be a nutritional marker in patients undergoing hemodialysis. Unlike in the general population, it is a lower level of serum UA, not the higher one, which is associated with increased mortality in all cases in hemodialytic patients, especially in those with low protein intake.

Hyperuricemia and the economic and financial effort

And last but not least, chronic HU involved in joint diseases and cardio-nephro-metabolic disorders is a major problem with economic implications and very high costs in terms of health care and hospitalization of patients. An article was published in Italy [47] which analyzed retrospectively a clinical register of approximately 112000 subjects. Individuals were divided into four groups according to their serum UA levels. The population group with the highest serum UA levels was associated with an increased risk of hospitalization, of developing CKD, cardiovascular disease and overall mortality and, consequently, with much higher health care and hospitalization costs per patient.

Conclusion

Having analyzed all the data presented above, it may be concluded that UA, although often neglected and probably minimized in terms of its effect by clinicians, is, however, an important player in MS development and progression. Therefore, raising sensitivity and awareness with regard to the major influence exerted in multiple respects by MS and a more thorough treatment of Hyperuricemia will lead to positive results and the probable establishment of new conducts in the approach of MS in people with hyperuricemia.

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