Hyperuricemia and Cardiovascular Diseases
Clinical and paraclinical correlations

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Uric acid is the end product of endogenous and exogenous of purine nucleotides catabolism, the serum concentrate being determined by the production and elimination ratio. Elimination is achieved through renal excretion – two thirds- and the rest through digestive way. In most studies, hyperuricemia is defined as > 7 mg/dL uric acid in men and > 6 mg/dL in women, and the guides for gout treatment recommend target value of uric acid under 6 mg/dL [1]. According to the NHANES (National Health and Nutrition Examination Survey) register, the prevalence of hyperuricemia has increased by 3.2% and that of gout by 1.2% during the past twenty years[1].

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The excessive production of uric acid is responsible for hyperuricemia in 10% of the gout patients, through some specific enzimatic defects in the metabolism of purines, such as the fi deficitul de hypoxanthine-guanine phosphoribosyltransferase (Lesch-Nyhan syndrome), type i glycogenosis [2]. In these situations patients present early hyperuricemia and hyperuricozuria, with increased incidence of uric lithiasis (75% of the cases). Hyperuricemia can also associate with increased nuclei acids turn-over in lympho - and myeloproliferative disorders treated with cytostatics, chronic hemolysis, psoriasis, but also with increased consumption of purines and fructose in diet [3].

Deficient uric acid elimination explains hyperuricemia in 90% of gout patients through glomerular filtration decrease, increase of tubular reabsorption and the decrease of tubular secretion. Chronic kidney disease (CKD) is one of the most common causes of hyperuricemia because of the decrease in uric acid excretion. On the other hand, clinical studies showed that hyperuricemia in BCR is both a marker of the renal function reduction, and a factor contributing to the development of the chronic kidney disease [1].

It is well known that certain medicines, such as thiazide diuretics, acetazolamide, pyrazinamides, ethambutol block the uric acid tubular secreton causing hyperuricemia.

Experimental part

A large number of studies have showed a correlation between hyperuricemia and cardiovascular diseases and the metabolic syndrome, the uric acid being considered a risk marker [4].

5926 pacienti were studied for 16 years in the NHANES study and the conclusion was that uric acid was an independent risk factor for every 1.01 mg/dL increase in serum uric acid, the risk of cardiovascular mortality was 1.3 in women and 1.19 in men [5].

In MRFIT (Multiple Risk Factors Intervention Trial) number of 12,866 male patients were monitored for 6.5 years, and hyperuricemia was considered a risk factor for the onset of IMA[6]. On the other hand, the Framinghan study, which followed 117,276 patiets concluded that the level of serum uric acid did not significantly correlate with the cardiovascular risk [7].

Results and discussions

The mechanisms through which hyperuricemia contributes to the onset of cardiovascular diseases are incompletely explained; nevertheless, the following are incriminated: the activation of the renine-angiotensin-aldosteron system, the increase of oxidative stress, endothelial dysfunction, the decrease of nitric acid availability, with the proliferation of smooth muscle cells in the vascular walls [1]. Hyperuricemia causes the reduction of nitric oxide at endothelial level, the activation of renine-angiotensin-aldosteron system at kidney level, renal microvascular lesions. Endothelial dysfunction, commonly present in cardiovascular diseases, is attributted to oxidative stress, the endogenuous accumulation of NO

synthetase inhibitors, and more recent studies confirm the role of uric acid in its onset (e.g. Mercuro study) [8,9].

Numerous studies in literature attest the negative influence of oxidative stress. Extrapolating the importance of oxidative stress evaluation in patients , we mention the fact that some researchers proposed, even in the case of cerebral bleeding, the use of antioxidant enzymes for the evaluation on the intensity of the oxidative stress [10].

Aprroximately 30% of the hypertensive patients have associated hyperuricemia, especially when renal affectation, diabetes, diuretic medication (particularly thiazides) are involved [7].

We mention the fact that lately an important growth was observed in the number of patients with diabetes (especially amongst patients with low and medium income) and the association of diabetic nephropathy represents one of the complications with an important impact on extablishing the life expectacy of these patients [11,12].

On thee other hand, hyperuricemia can precede the onset of high blood pressure (HBP). In theFraminfham Heart Study, every increase of the serum uric acid by 1.3 mg/dL in the general population associated with a 1.17 relative risk for the onset of HBP [7], and in the MRFIT(Multiple Risk Factors Intervention Trial) study, the relative risk for the onset of HBP was 1.8 ori times higher in normotensive men with hyperuricemia and did not have diabetes mellitus or metabolic syndrome, compare with those with normal levels of serum uric acid [13].

The antihypertensive effect of allopurinol was demonstrated in a meta-analysis which included 10 studies including a group of hypertensive 738 patients, showing that blood pressure levels slightly decreased; the systolic BP decreased by 3.3 mmHg, and the dyastolic BP by 1.3 mm Hg [14]. Favourable effects were found following large doses of allopurinol (>300 mg/zi).

Uric acid involvement was associated with acute coronary syndromes, ischemic heart disease and heart faiThe incidence of cardiac failure and the relationship with the level of serum uric acid was studied in *Framingham Offspring Cohort*, a study which included 4912 young patients, medium age of 36, followed for 29 years. The conclusion was that hyperuricemia was an factor independent risk in the onset of cardiac failure, the rate of the incidence of cardiac insufficiency being 6 times higher in hyperuremic patients compared with those with normal levels of the serum uric acid [3].

Patients with cardiac insufficiency and hyperuricemie had a severe development, with more frequent cardiac decompensations, thus many studies consider uric acid a severity marker for cardiac insufficiency, following the increased oxidative stress [15]. In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) study 50% of the patients with decompensated cardiac insufficiency and low ejection fraction had hyperuricemia, with a mean value of serum uric acid of 9.1 mg/dL [1].

Xanthine oxidase, allopurinol or febuxostat inhibitors, which have fewer adverse effects and is better tolerated improve endothelial dysfunction and oxidative stress, lower the oxygen myocardial consumption, improves the systolic function, preventing cardial remodelling, the functional class of the cardiac insufficiency and increase the quality of life [16].

Although the treatment with probenecid, with uricosuric effect, lowered the level of serum uric acid, it did not favourably infuenced cardiac insufficiency [17].

Othe other hand, there are also studies which did not find any correlation between hyperuricemia and the prognosis of cardiac insufficiency, like the EXACT-HF(Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure

Patients) study, in which patients were administered large doses of allopurinol (600 mg/zi), with the significant decrease of the level of serum uric acid, yet without triggering an increase in effort tolerance, quality of life and cardiovascular-induced mortality. The authors of the study considered the lack of response to xanthine oxidase inhibitors because of advanced-stage cardiac insufficiency the patients in the study suffered from and the association of a large number of comorbidities [1].

Conclusions

In conclusion, many studies demonstrated that uric acid is both a marker for the cardiovascular risk, and an independent risk factor for the onset of high blood pressure and cardiac insufficiency, being proved that hyperuricemia produces endothelial dysfunction, inflammation and the activation of the renine-angiotensina-aldosteron system [18].

At present, the treatment with xanthine oxidase inhibitors is not a typical therapy in the prevention of cardiovascular disorders, but is always recommended in the treatment of hyperuricemia, especially in patients who associate high blood pressure, diabetes mellitus, metabolic syndrome, ischemic heart disease and cardiac insufficiency.

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