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ASYMPTOMATIC HYPERURICEMIA- THE NEW MARKER OF ENDOTHELIAL DISFUNCTION AND SUBCLINICAL ISCHEMIA

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Abstract:

The quality of marker of subclinical ischemia attributed to the uric acid is certified by the increased amount released following the adenosine catabolism.. We analyzed the observation papers of patients dispensed from the cardiology department of the County Emergency Clinical Hospital from Oradea, between 2015-2016, and we formed a study lot consisting of 25 patients. We made a selection of patients with normal levels of uric acid, representing the control group (CG), and patients with hyperuricemia, representing the reference group (RG). Hyperuricemia associated high blood pressure, grade II and III were found in 46.66% of cases and 33.33% of subjects from RG. Predominantly increasing uric acid values were associated with stable angina pectoris. Also unstable angina pectoris was associated with hyperuricemia , in 26.66% subjects of RG. The uric acid is easy to detect and provides essential data on the short term prognosis of patients with corornary heart disease.

Key words: hyperuricemia, endothelial dysunction, subclinical ischemia, myocardial infarction

INTRODUCTION

Cardiovascular diseases dominate the spectrum of human pathology through incidence, evolution and clinical consequences, and among them the ischemic coronary artery disease, in terms of the mode of appearance, the possibilities of evolution (myocardial infarction and sudden death), is occupying the first place. The main cause of these pathological manifestations is atherosclerosis. Atherosclerosis regardless of stage is maintained by inflammation.

During cardiac ischemia, adenosine synthesis increases in order to restore normal blood flow. The involvement of this feed-back mechanism implies an imbalance between supply and demand for oxygen in the coronary circulation. The nucleoside has a half-life of 10 seconds and will be rapidly degraded at the endothelial level via the xantionoxidase enzyme. [1] Uric acid resulting from this process increases blood flow due to low pH and negative membrane potentials. [3]

Studies show that xanthin oxidase activity and uric acid synthesis are elevated in vivo under ischemic conditions. The transient occlusion of a human coronary artery generates elevated uric acid levels in the local circulation.[1]

Xanthine oxidoreductase is a flavoprotein that retains iron, sulfur and molybdenum in its structure and possesses two forms acting under different conditions. [2] Xanthine dehydrogenase, the form that operates predominantly under physiological conditions, uses the oxidized form of nicotinamide adenine dinucleotide (NAD +) as an electron acceptor. [2] In case of ischemia, xanthine dehydrogenase is converted to xanthine oxidase, which uses molecular oxygen as the electron acceptor and produces, in addition to uric acid, free oxygen radicals. It is possible that this production of free radical represents the main factor responsible for vascular lesions attributed to high levels of uric acid.

Essentially, the superoxide anion can inactivate NO due to the ONOO-(peroxynitrit) synthesis, with a significant oxidizing role.[5] This process will inhibit vasodilatation of the endothelium and limit the favorable effect of NO on platelet aggregation and proliferation of vascular smooth myocytes.

Another negative effect is the oxidative process that occurs at the level of DNA and lipids. Promoting the oxidation of LDL cholesterol particles is a major step in the process of atherosclerosis.

Despite the fact that experimental studies shows the antioxidant effect of uric acid, which is superior to vitamin C, elevated uric acid levels are associated with proinflammatory effects such as decreased nitric oxide synthesis in endothelial cells, activation of the renin-angiotensin-aldosterone system, renal microvascular damage (arteriosclerosis). [6] These conditions are due to the fact that the uric acid promotes vascular smooth cell proliferation, modulation of cellular immune response, activation of proinflammatory immune response, stimulation of low density lipoprotein oxidation, and platelet activation.

Endothelial dysfunction represents a decrease in nitric oxide synthesis and an imbalance between relaxation-contraction promoting factors. The main mediator involved in the modulation of vasomotricity is nitiric oxide. When ischemia occurs, the action of the xantionoxidase enzyme resolves with the generation of reactive oxygen species. O_2-nitic oxide interaction generates ONOO-, compound with a lower capacity for activating guanylate-cyclase. [7] In this manner, the NO bioavailability will be considerably reduced.

Increased oxidative stress associated with cardiovascular risk factors causes vascular lesions and increased permeability of dysfunctional endothelial cells for LDL-cholesterol particles, followed by their oxidation

in the intima. Another mode of action is the production of transcription factors such as the nuclear factor IB and AP 1 that will participate in the increase of the adhesion molecule, VCAM 1 and ICAM 1, at the endothelial level. [4] It is well known that NF-IB exerts its effect on the smooth muscle cells, in the media of vessels affected by the atherosclerotic process, being inactivated by the antioxidant defense system and anti-inflammatory substance. [8]

Stimulation of the release of cellular and profibrotic growth factors along with pro-inflammatory cytokines by activated macrophages, T lymphocytes, smooth muscle cells and endothelial cells are the basis of the local inflammatory response. [9] Smooth muscle cells migrate from the media of the vessels to the intima layer, under the action of chemotactic cytokines and will become the source of future foam cells. [10] They are also involved in the synthesis of extracellular matrix components and collagen, elements that will form the outer fibrous layer of atherosclerotic lesions. [8] Apoptosis of the foam cells will form the lipid nucleus.

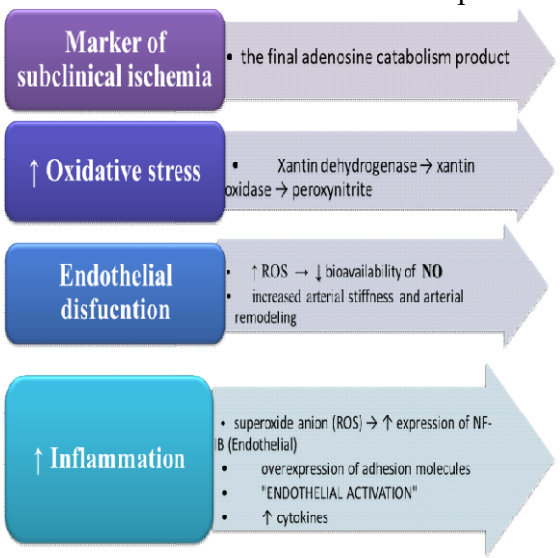

Fig 1. Semnification of high uric acid

MATHERIAL AND METHODS

We analyzed the observation papers of patients dispensed from the cardiology department of the County Emergency Clinical Hospital from Oradea, between 2015-2016, and we formed a study lot consisting of 25 patients. We made a selection of patients with normal serum levels of uric acid, representing the control group (CG), and patients with hyperuricemia, representing the reference group (RG). The exclusion criteria includes previously treatment with uricosuric agents, hepatic insufficiency, renal insufficiency, gout. We analyzed the risk factors, medical history, but

clinically evaluation, laboratory tests, electocardiogram and 2D echocardiography were performed too.

RESULTS AND DISCUSSION

The entire study group consisted of 25 subjects divided into two groups: the control group (CG) which brought together 10 persons (6 male and 4 female) and the reference group (RG) consisting of 15 patients (9 male subjects and 6 female subjects).

Parameter		**C.G.**	**R.G.**
►*Uric acid values (mg/dl)*		5	11,53
►*Average age*		54,2	62,27
►*BMI (kg/m)*		29,5	37,73
►*Abdominal circumference (cm)*		92,5	107,6
►*SBP (mmHg)*		150,30	172,13
►*DBP (mmHg)*		92,80	103,87
►*LDL (mg/dl)*		145	189,66
►*HDL (mg/dl)*		36,3	26
►*Creatinine (mg/dl)*		0,96	1,5
►*HBP*			
	►HBP gr I (%)	70	20
	►HBP gr II (%)	30	46.66
	►HBP gr III (%)	0	33.33
►*Coronary heart disease*			
	►Stable AP (%)	50	73,33
	►Unstable AP (%)	0	26,66
	►Myocardial infarction (%)	0	21,40

Fig 2. Clinical, cardiac and biochemical data of patients

Hyperuricemia is associated high blood pressure. The study of TAS and TAD values for patients in the control group led to the following conclusions: 70% of cases had HBP grade I (mild); 30% of cases had HBP grade II (mean); no cases of HBP grade III (severe) were detected. On the contrary analysis of SBP and DBP values for patients in the RG led to the following conclusions: 20% of cases had HBP grade I (mild) ; 46.66% of cases had HBP grade II (mean);33,33% of cases had HBP grade III (severe). The SBP and DBP variation study, in relation to uric acid values, found that

increased levels of uricemia were characterized by increased tensions, variables showing a positive correlation.

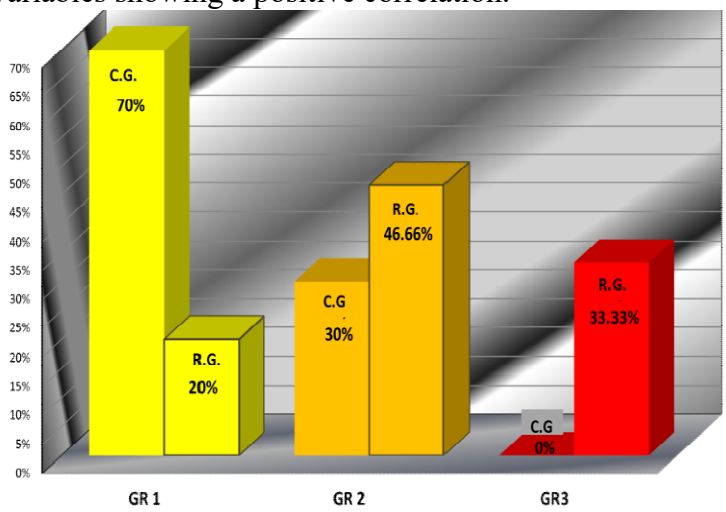

Fig 3. Comparrison between both groups regarding high blood pressure grades

The history of ischemic coronary artery disease and relationship with hyperuricemia revealed that for the entire study group, predominantly increasing uricemic values were associated with stable angina pectoris, the maximum incidence being characteristic of subjects with uric acid levels increased.The result of analyzing the presence of angina pectoris in the two batches reflects the following aspects: the control group accounted for a total of 50% of stable AP cases; the reference group showed a total of 73.33% of stable AP cases; the control group revealed a 1% AP cases; the reference group 26.66% of the subjects showed unstable AP.

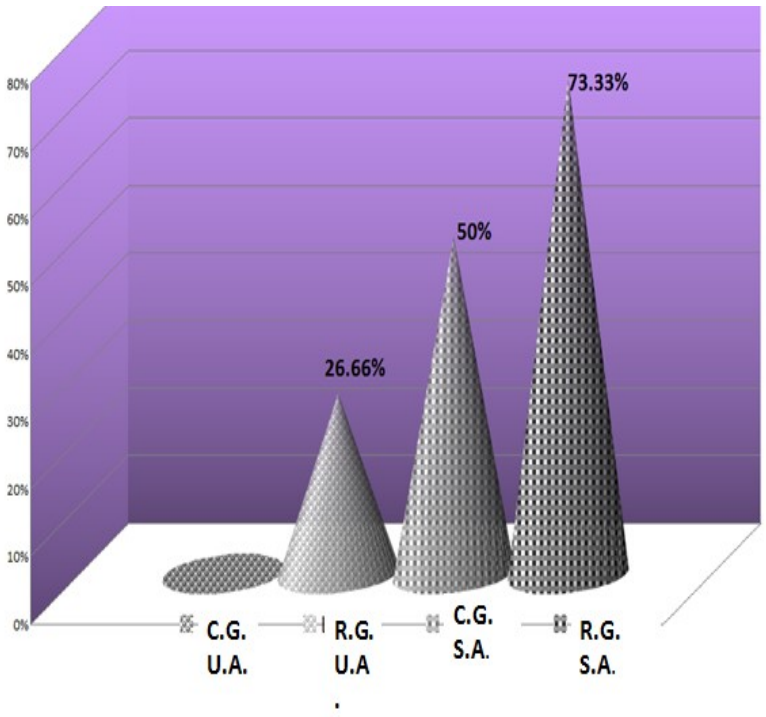

Fig 4. Comparrison between both gruops regarding stable angina pectoris (S.A.) and unstable angina pectoris (U.A)

The number of cases that reported major coronary events was reported in both study groups. We noticed the following aspect : major coronary events, especially acute myocardial infarction, were associated with 21.40% of patients in the reference group, but we didn't discover any case in the control group.

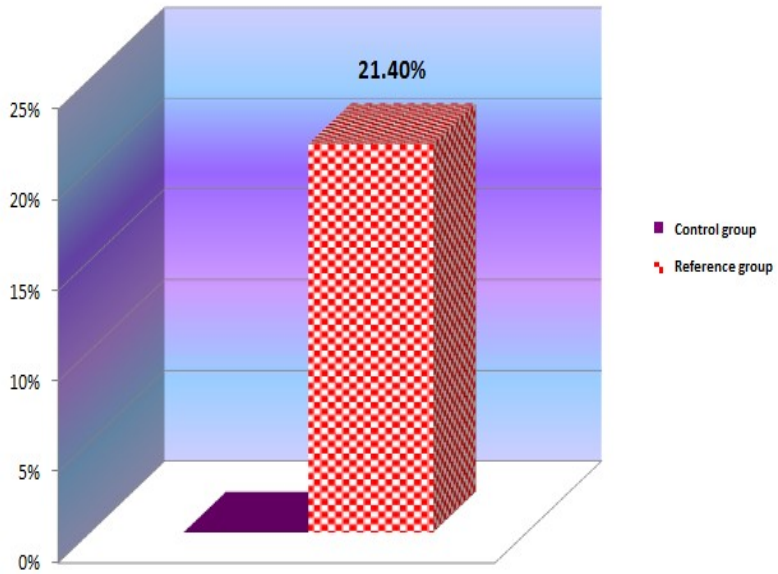

Fig 5. Incidence of major coronary events in both groups of subjects

CONCLUSIONS:

Uric acid is one of the components of the antioxidant system, providing almost half of the substrate capable of neutralizing the reactive species of oxygen and nitrogen. The dual value of this compound consists of changing the spectrum of activity under certain pathological conditions by exerting pro-oxidant effects, generating so- "paradox of uric acid".[1] Hyperuricemia shows close links with hypertension, especially grade II and III. It has been shown a positive correlation relationship between the increase of the values of the two parameters, thus increasing of hyperuricemia, reveals similar tendencies responsible for the occurrence of higher values of systolic and diastolic blood pressure. Another discovery is the connection between essential blood pressure, resistant forms on the one hand and hyperuricemia on the other hand. [7] Another pathology associated with hyperuricemia is ischemic coronary artery disease. The occurrence of this entity is related with the process of oxidative stress, initiated by elevated values of seric uric acid. The stable angina pectoris has experienced a higher incidence in the group of patients with hyperuricemia. As the process progresses, culminating with the unstable atheromatous plaque, the major coronary events such as unstable angina and acute myocardial infarction will occur. The determination of uric acid would be useful to asses the global cardiovascular risk and the outcome of cardiac patients. Hyperuricemia can also require future therapeutic intervention, and normal uric acid values brings many benefits.

Studies in the literature have shown that uric acid, along with C reactive protein, are proinflammatory and risk markers that are easy to detect in coronary artery disease and their contribution provides essential data on the short-term prognosis of these patients. The detection and management of hyperuricemia has become essential in patients with cardiovascular pathology and who have a high cardiovascular risk.

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