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Effect of elevated levels of uric acid on thrombocyte hemostasis in patients with hypertonic disease of stage II

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Abstract

The effect of uric acid on the functional activity of platelets in patients with hypertension, hyperuricemia, and a combination of these two conditions was studied. In the study, 75 patients were examined: 15 physically healthy subjects (control group), 17 patients with hyperuricemia without hypertension (group I), 23 patients with hypertension and hyperuricemia (group II) and 20 patients with isolated hypertension 2 stages (group III). In order to study thrombocyte hemostasis, estimates of spontaneous platelet aggregation and induced aggregation with adenosine diphosphate (ADP), arachidonic acid (AA), collagen and epinephrine were performed. An assessment of endothelium dependent vasodilatation was also performed on Celermajer cuffs. Hyperuricemia was diagnosed with uric acid levels > 420 μmol / L. In the course of the investigation, we determined that patients with hypertension, hyperuricemia and their combination observed an increase in the functional activity of the platelets, which manifests itself in an increase in the degree of spontaneous aggregation, a significant activation of platelet aggregation induced by arachidonic acid and collagen. Hyperagracy was detected in all hypertension patients and was more pronounced in patients

with hypertension with concomitant hyperuricemia and was dependent on uric acid levels in plasma.

Key words: hypertonic disease, hyperuricemia, hemostasis, platelets, aggregation, cuff sampling.

Today, an increase in uric acid levels is increasingly being diagnosed, which may be more likely due to poor nutrition and the environment. Although the physiological solubility of uric acid occurs at a level of 380 μmol / l, the presence of uric acid binding proteins increases this solubility to 420 μmol / l until it reaches a supersaturated state. Therefore, hyperuricemia occurs when the level of uric acid exceeds 420 μmol / l and at this time it begins to crystallize in the human body. Asymptomatic increase in the level of uric acid according to various studies (in different age groups) is from 5 to 25% of the population. Hyperuricemia in patients with hypertension is one of the most pressing medical problems and is one of the main risk factors for the development of cardiovascular complications [1, 2]. Hypertension is a multifactorial disease and develops as a result of the interaction of neurohumoral, hemodynamic and metabolic factors. In a randomized, placebo-controlled study involving adolescents with arterial hypertension, there was a link between the high level of uric acid and the increase in blood pressure. Patients were randomized into two treatment groups - placebo and allopurinol. Allopurinol reduced hyperuricemia, which in turn led to a decrease in blood pressure [3].

Elevated uric acid levels are associated not only with cardiovascular diseases, but also cardiovascular mortality. In a cohort study involving 40,000 patients with hyperuricemia, a decrease in uric acid levels reduced the risk of cardiovascular death [4]. The dual role of uric acid was described as “The Uric Acid Paradox.” Under normal conditions, this biologically active molecule plays in the body The role of an antioxidant, however, is able to initiate oxidative stress, endothelial dysfunction, inflammation and vasospasm, which, in turn, play an important role in the development of CVD and their complications. Therefore, SC today is considered As an additional cardiovascular risk biomarker and a guideline for achieving treatment goals and CVDs. High levels of uric acid in the latest literature may be an independent risk factor for hypertension, coronary heart disease, and heart failure. In recent years, an independent relationship between hyperuricemia, cardiovascular diseases and mortality. Hyperuricemia was presented as an independent risk factor for acute myocardial infarction, and established The relationship between gout and overall cardiovascular death, with patient mortality increasing with increasing levels of uric acid. Thus, with each increase

in uric acid level by 1 mg / dL, the overall risk of mortality increases by 15%. These results have sparked a growing interest in research and on the possible benefits of a decrease in the uric acid content in cardiovascular diseases. Thus, according to the results of a meta-analysis of 10 studies using allopurinol at a dose of 200 mg twice a day for 7 weeks, patients with hyperuricemia and mild arterial hypertension showed a decrease in systolic blood pressure of 3.3 mm Hg. and diastolic blood pressure at 1.3 mHg. [4, 5].

Hyperuricemia initiates oxidative stress, endothelial dysfunction, inflammation and vasospasm, platelet stickiness, hemorheology and aggregation. Atherosclerotic plaque contains a significant amount of uric acid, which can increase platelet adhesion and increase blood clot formation [6].

In the pathogenesis of atherosclerosis, platelets occupy an important role. Activation, adhesion and aggregation of platelets are important in the development of platelet-rich thrombosis, which leads to such complications as myocardial infarction and acute cerebrovascular accident [7].

If the level of uric acid in the blood serum exceeds 420 mmol / l, uric acid, which remains dissolved in a blood vessel, is deposited as sodium monowrate crystals. The sodium monourate crystals precipitate on the wall and affect blood coagulation, which probably leads to arteriosclerosis. In blood vessels, sodium monourate crystals precipitate on the vessel wall due to mechanical stimuli caused by blood pressure. Sodium monourate crystals bind to plasma IgG, are recognized by Fc receptors on blood platelets and stimulate platelets to induce coagulation; cytokines and blood clots formed during this process, involved in the progression of atherosclerosis [8]. Thrombosis and platelet aggregation play an important role in the pathogenesis of atherosclerosis, since platelet aggregates and thrombotic masses have been found at the site of rupture of the coronary artery plaque. Platelets after their activation, further attract additional platelets, releasing thromboxane A2, adenosine diphosphate and cytokines that promote and produce surface thrombin formations and release of vasoconstrictor substances [9].

Given that there have been many studies of endothelial dysfunction in patients with hypertension and concomitant hyperuricemia, the issue of platelet hemostasis in this category of patients remains to be insufficiently studied.

Objective: Determine the state of functional activity of platelets in patients with hypertensive disease in combination with hyperuricemia.

Materials and methods of the study: In the course of the study, we conducted a survey of 75 patients who were treated at the therapeutic and cardiology department at the

base of the Kiev Clinical Hospital N 2 on the railway transport of Ukrzaliznytsya. The patients were divided into 3 groups. The first group included 17 patients with hyperuricemia without hypertension, 23 patients with hypertension and hyperuricemia (group II) and 20 patients with isolated hypertension 2 stages (group III). the second group - 35 patients with hypertension and uric acid levels> 420 μmol / l and the third group (control) - 15 patients. Of the patients examined, there were 35 men and 30 women. The average age of the patients was 53 ± 6.3 years. The groups were comparable in age and sex.

Hemostatic blood parameters were performed after hospitalization of the patient in the therapeutic or cardiology department. Blood sampling was carried out from the cubital vein, in compliance with all the rules of asepsis, 9 ml of blood was mixed with 1 ml of stabilizer (3.8% sodium citrate solution). After that, a cuff test was carried out with the determination of the latency and dilatation by the method of D. Celermajer [10] To study endothelium dependent vasodilatation, the upper third of the shoulder was superimposed on the sphygmomanometer cuff (above the localization of the shoulder artery), after which the arterial diameter was determined using a linear ultrasound scanner sensor, GeneralElectricVividP3 (USA). Then the air was sputtered in the cuff of the sphygmomanometer to 50mm.hr.st. higher than the disappearance of the pulsation of the brachial artery. Compression lasted 5 minutes. After that the cuff was removed and the diameter of the brachial artery was re-determined 1 min after the removal of the cuff. The calculation of endothelium-dependent vasodilatation was carried out in terms of the diameter of the lumen of the brachial artery of the baseline and after 3 minutes after compression. For normal reaction of the brachial artery it was accepted to extend it by more than 10% from the initial level. The study of platelet aggregation was performed in platelet-rich plasma, which was obtained by centrifuging citrated blood for 3 min at a speed of 1000 revolutions per minute, platelet-poor plasma was obtained during centrifugation of citrate blood for 20 minutes at a speed of 3000 revolutions per minute, which is generally accepted for this study. Platelet aggregation was studied using a laser aggregation analyzer To study the functional state of platelets, a laser analyzer 230-LA (NPF Biola) using the turbidimetric method.

Statistical analysis was performed using the Statistica 10 statistical package. The significance of differences in the mean indices was assessed using the U-test by Mann Whitney.

Results and discussion

For the purpose of statistically significant differences between the values of spontaneous and induced aggregation of thrombocytes of the samples studied, the Kruskela-

Wallis criterion was applied. There were significant differences in the groups of patients in terms of spontaneous aggregation (p = 0.0001), aggregation induced by ADP (p <0.05), collagen (p <0.05). Subsequently, the Mann-Whitney criterion was used for comparing two groups of patients for each of the aggregation indices.

Table 1. Indicators of functional activity of platelets in different groups of patients

Indicator	Control	I grup (hyperuricemia) (n=17)	II group (hypertension and hyperuricemia) (n=23)	III group (hypertension) (n=20)
spontaneous aggregation	0,84 (σ=0,32)	2,36* (σ=1,26)	6,24*** (σ=1,52)	3,17** (σ=1,90)
ADP-induced	34,69 (σ=7,42)	54,66** (σ=14,10)	68,92*** (σ=4,24)	44,96* (σ=16,26)
AA-induced	28,47 (σ=6,45)	32,94 (σ=14,65)	26,68* (σ=8,87)	31,64 (σ=9,15)
collagen-induced	20,99 (σ=6,22)	15,97** (σ=7,03)	8,63*** (σ=7,81)	16,10* (σ=9,36)
epinephrine - induced	18,67 (σ=13,77)	35,64 (σ=16,29)	36,54 (σ=16,58)	40,31** (σ=16,06)

Note: * - the validity of changes by Mann-Whitney (U Test) with respect to the control group, * - p <0,05; ** - p <0,01; *** - p <0,001.

ADP – adenosine diphosphate; AA - arachidonic acid

Spontaneous aggregation of platelets

During the study, there was a significant increase in the degree of spontaneous aggregation in patients in all groups compared with the control group: in patients with hyperuricemia, 2.8 times (p <0.001), in patients with GB II. in 3,8 times (p <0,05), in patients with GB II st. and concomitant hyperuricemia in 7.4 times (p <0.01) (Fig. 1). With intergroup comparison, we observe that the degree of spontaneous aggregation compared with hypertension was significantly higher in the group of patients with hyperuricemia associated with GB II st. at 97% (p <0.001) and 15% higher in patients with isolated pegururicemia (p <0.05).

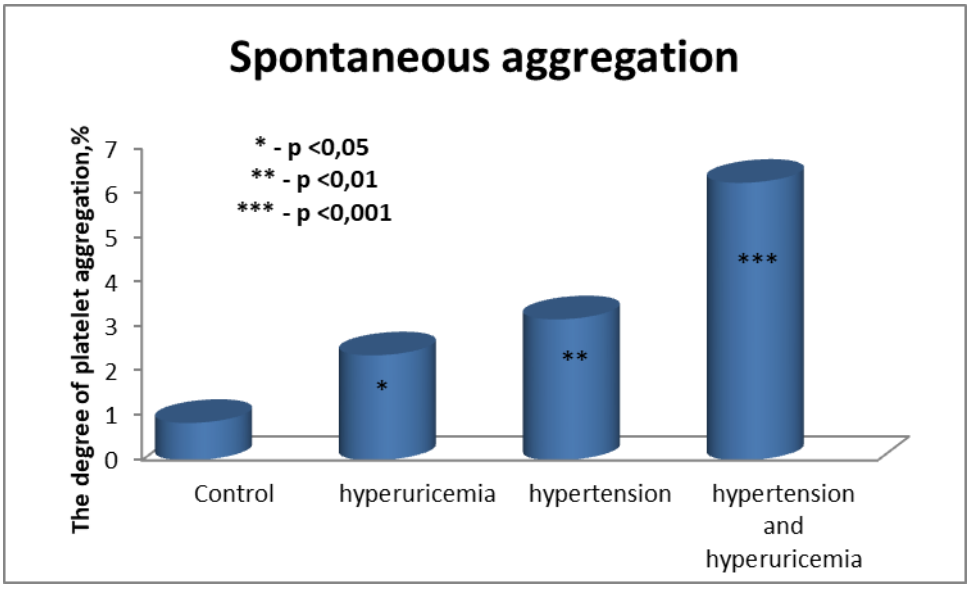

Fig. 1. Spontaneous platelet aggregation in different groups of patients in comparison with the control group

Induced platelet aggregation

The degree of ADP-induced platelet aggregation was significantly increased in all groups of patients compared with the control cohort. When analyzing intergroup differences, an increase in ADP-induced aggregation in the group of patients with comorbid pathology is observed by 62.3% ($p < 0.05$) compared with hyperuricemia and 69.2% ($p < 0.01$) compared with isolated hypertension.

The degree of AK-induced platelet aggregation was higher in the group of patients with hypertension and in the group with hyperuricemia, but significant changes were observed only in patients with hypertension and hyperuricemia, while the degree of aggregation decreased by 8.3% ($p < 0.05$).

Collagen-induced aggregation decreased in all groups of patients compared to control. A significant decrease was observed in all groups of a and with comorbid pathology by 85% ($p < 0.001$), compared with the group of hyperuricemia, and by 68% compared with hypertension.

Platelet aggregation, induced by adrenaline, is more pronounced in the groups with hypertension, but only patients with isolated GB II Art. Had significant differences from the control group. - an increase in the degree of aggregation 2.2 times ($p < 0.01$) (Fig. 2).

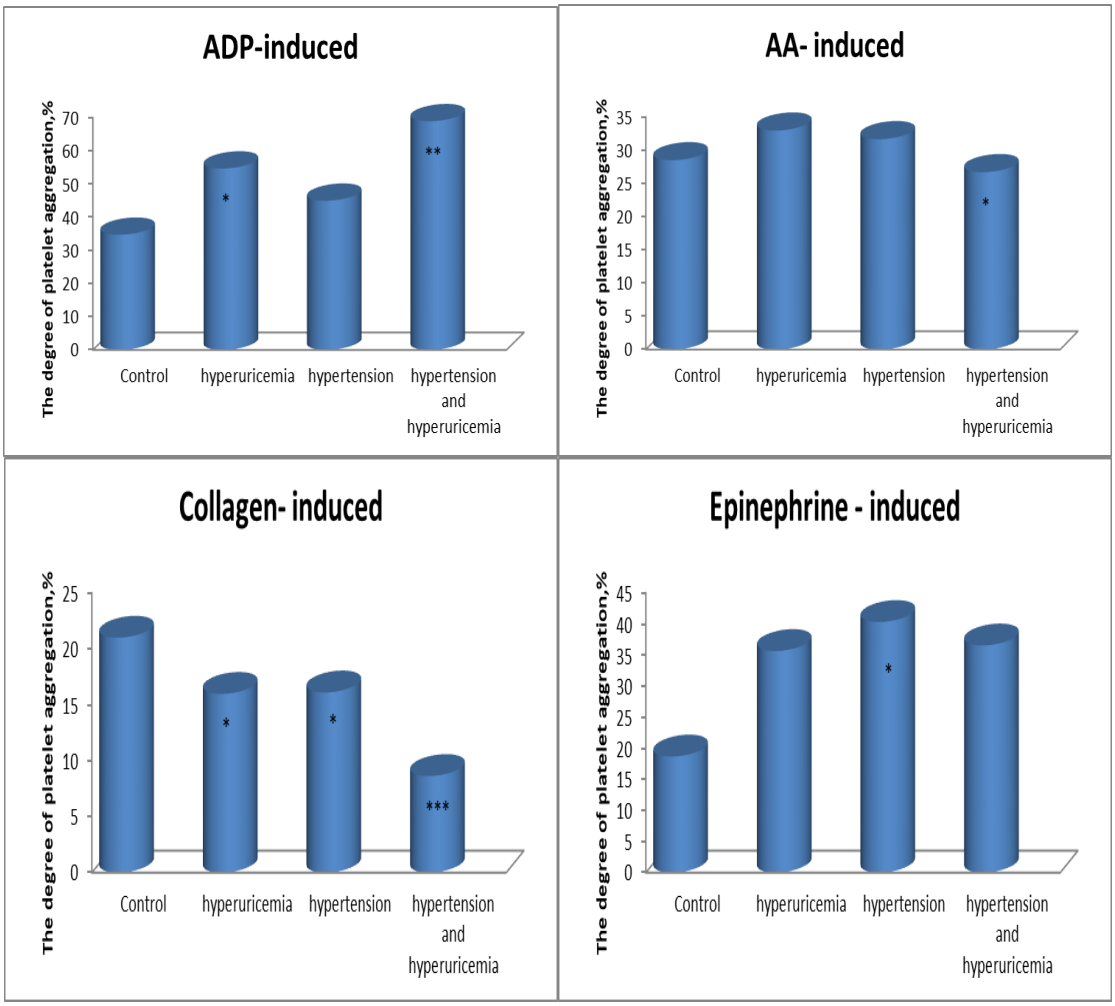

Fig. 2. Induced platelet aggregation in different patient groups compared to the control group

Note: * - the validity of changes in the Mann-Whitney (U Test) test with respect to the control group, * - p <0,05; ** - p <0.01; *** - p <0.001.

In the study of the endothelium of the dependent vase dilatation, we see that endothelium-dependent vasodilatation is insufficient (less than 10%) only in Group II (GH with hyperuricemia). In 8 patients with Group II, there was a paradoxical reaction, a decrease in the diameter of the brachial artery compared to baseline values, which may indicate increased vasoconstriction and in turn endothelial dysfunction and the risk of fatal cardiovascular events. (Table 2).

Table 2. Indicators of endothelium dependent vasodilation

Grroups	Control	I grup (hyperuricemia) (n=17)	II group (hypertension and hyperuricemia) (n=23)	III group (hypertension) (n=20)
Changes in the diameter of the brachial artery,%	+18,2	+16,5	+6,1	+14,6

Conclusions

1. Increasing the aggregation capacity of thrombocytes in patients with hypertension, which significantly progressed with elevated uric acid levels.

2. A statistically significant increase in thrombocyte aggregation by spontaneous and induced collagen was observed in patients with an isolated increase in uric acid levels, which may indicate an additional risk factor for uric acid in the development of thrombophilic changes in the primary linkage of hemostasis.

3. The presence of hyperuricemia was accompanied by a significant increase in the platelet response to ADP, which should be taken into account when selecting antiplatelet therapy, since ADP-induced aggregation reflects the sensitivity of clopidogrel treatment.

4. Taking into account the above parameters of hyperuricemia and endothelial dysfunction, it can be said that stimulation of platelet aggregates ADP, adrenaline and collagen may reflect changes in the activity of vascular thrombocyte hemostasis and may indicate a degree of vascular endothelial damage and a high risk of developing cardiovascular complications.

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