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Abstract

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HYPERURICEMIA AS A RISK FACTOR OF ARTERIAL HYPERTENSION

Introduction. Among the population of Central and Eastern Europe, hyperuricemia (HU) prevalence is 28 % in female and 23 % in male. In 2018, European Society of Hypertension has officially included HU to the independent risk factors for AH.

Objective: to integrate literature and own data that reflect contemporary views on the role of hyperuricemia in the progression of arterial hypertension and study the early effects of hyperuricemia on endothelial dysfunction.

Materials and methods. Total of 382 persons were analyzed to evaluate the prevalence of hyperuricemia in Sumy region. To study the early effects of hyperuricemia on endothelial dysfunction in normotensive patients two groups were formed: 31 patients with UA < 400 μmol/l (1st group) and 29 patients with UA > 400 μmol/l (2nd group). The groups were comparable in age and sex.

Test with reactive hyperemia for estimation of endothelium-dependent vasodilation (EDVD) was performed using the ultrasound system SonoScape S6. Increasing of brachial artery diameter less than 10 % during the test with reactive hyperemia was considered as a criterion of endothelial dysfunction.

Results: the prevalence of hyperuricemia in Sumy region is about 42 % for normotensive patients and 51 % – in hypertension patients from total cohort 382. Daily BP monitoring demonstrated daytime systolic blood pressure (DaySBP) 118 mmHg and daytime diastolic blood pressure (DayDBP) 72 mmHg in the 1st group; and in the 2nd group these were: DaySBP 130 mmHg, DayDBP 80 mmHg ($p < 0.05$).

Analysis of baseline levels of EDVD shows significant difference between groups: 12.9 % and 9.6 % in the 1st group and 2nd group, respectively ($p < 0.05$). The average UA level in the 1st group was 328 ± 24 μmol/l; in the 2nd group – 469 ± 34 μmol/l. The negative correlation was obtained between the level of UA and EDVD: -0.32 in the 1st group and -0.48 in the 2nd group ($p < 0.05$).

Conclusion. Study results demonstrated high prevalence of HU both in hypertensive and normotensive patients. Statistically significant relationship between endothelium-dependent vasodilation and uric acid levels in patients was established.

Keywords: hyperuricemia, arterial hypertension, endothelial dysfunction, uric acid.

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Резюме

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ГІПЕРУРИКЕМІЯ ЯК ФАКТОР РИЗИКУ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

Вступ. Серед населення Центральної і Східної Європи поширеність гіперурикеміі (ГУ) становить 28 % у жінок і 23 % у чоловіків. У 2018 року Європейська асоціація з вивчення АГ офіційно включила ГУ в число незалежних факторів ризику АГ.

Мета - зіставлення літературних і власних даних, що відображають сучасні уявлення про роль гіперурикемії в прогресуванні артеріальної гіпертензії, і вивчення впливу гіперурикемії на ендотеліальну дисфункцію.

Матеріали та методи. Було проаналізовано 382 особи для оцінки поширеності гіперурикемії в Сумській області. Для вивчення впливу гіперурикемії на ендотеліальну дисфункцію у нормотензивних пацієнтів були сформовані дві групи: 31 пацієнт з UA < 400 мкмоль/л (1-а група) і 29 пацієнтів з UA > 400 мкмоль/л (2-а група). Групи були співставні за віком і статтю. Тест з реактивною гіперемією для оцінки ендотелій-залежної вазодилатації (ЕЗВД) проводили з використанням ультразвукової системи SonoScape S6. Збільшення діаметра плечової артерії менш ніж на 10 % при проведенні тесту розглядалося як критерій ендотеліальної дисфункції.

Результати. Встановлено розповсюдженість гіперурикемії в Сумській області близько 42 % серед нормотензивних пацієнтів і 51 % - у пацієнтів з артеріальною гіпертензією із загальної когорти з 382 осіб. Добовий моніторинг АТ продемонстрував у 1-й групі рівень середньоденного систолічного артеріального тиску 118 мм рт.ст. і середньоденного діастолічного АТ – 72 мм рт.ст.; у 2-й групі - 130 мм рт.ст. і 80 мм рт.ст. відповідно ($p < 0,05$). Аналіз рівнів ЕЗВД показує достовірні відмінності між групами: 12,9 % і 9,6 % в 1-й групі і 2-й групі відповідно ($p < 0,05$). Середній рівень СК в 1-й групі склав 328 ± 24 мкмоль/л; у 2-й групі – 469 ± 34 мкмоль/л. Була отримана зворотна кореляція -0,32 між рівнем СК і ЕЗВД в 1-й групі і -0,48 у 2-й групі ($p < 0,05$).

Висновки. Результати дослідження показали високу поширеність ГУ як у пацієнтів з гіпертонічною хворобою, так і у нормотензивних пацієнтів. Встановлено статистично значущий зв'язок між ендотелійзалежної вазодилатацією і рівнем сечової кислоти у нормотензивних пацієнтів.

Ключові слова: гіперурикемія, артеріальна гіпертензія, ендотеліальна дисфункція, сечова кислота.

Резюме

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ГИПЕРУРИКЕМИЯ КАК ФАКТОР РИСКА АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

Вступление. Среди населения Центральной и Восточной Европы распространенность гиперурикемии (ГУ) составляет 28 % у женщин и 23 % у мужчин. В 2018 году Европейская ассоциация по изучению АГ официально включила ГУ в число независимых факторов риска АГ.

Цель – сопоставление литературных и собственных данных, отражающих современные представления о роли гиперурикемии в прогрессировании артериальной гипертонии, и изучение влияния гиперурикемии на эндотелиальную дисфункцию.

Материалы и методы. Было проанализировано 382 человека для оценки распространенности гиперурикемии в Сумской области. Для изучения эффектов гиперурикемии на эндотелиальную дисфункцию у нормотензивных пациентов были сформированы две группы: 31 пациент с уровнем мочевой кислоты МК < 400 мкмоль/л (1-я группа) и 29 пациентов с уровнем МК > 400 мкмоль/л (2-я группа). Группы были сопоставимы по возрасту и полу. Тест с реактивной гиперемией для оценки эндотелий-зависимой вазодилатации (ЭЗВД) проводили с использованием ультразвуковой системы SonoScape S6. Увеличение диаметра плечевой артерии менее, чем на 10 % при проведении теста рассматривалось как критерий эндотелиальной дисфункции.

Результаты. Установлена распространенность гиперурикемии в Сумской области 42 % среди нормотензивных пациентов и 51 % – у пациентов с артериальной гипертензией из общей когорты 382 человека. Суточный мониторинг АД продемонстрировал в 1-й группе уровень среднедневного систолического АД 118 мм рт.ст. и среднедневного диастолического АД – 72 мм рт.ст.; во 2-й группе – 130 мм рт.ст. и 80 мм рт.ст. соответственно ($p < 0,05$). Анализ исходных уровней ЭЗВД показывает достоверные различия между группами: 12,9 % и 9,6 % в 1-й группе и 2-й группе соответственно ($p < 0,05$). Средний уровень МК в 1-й группе составил 328 ± 24 мкмол/л; во 2-й группе – 469 ± 34 мкмоль/л. Была получена обратная корреляция -0,32 между уровнем UA и ЭЗВД в 1-й группе и -0,48 во 2-й группе ($p < 0,05$).

Выводы. Результаты исследования показали высокую распространенность ГУ как у пациентов с гипертонической болезнью, так и у нормотензивных пациентов. Установлена статистически значимая связь между эндотелий-зависимой вазодилатацией и уровнем мочевой кислоты у пациентов.

Ключевые слова: гиперурикемия, артериальная гипертензия, эндотелиальная дисфункция, мочевая кислота.

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Introduction

Among the population of Central and Eastern Europe, hyperuricemia (HU) prevalence is 28 % in female and 23 % in male. Patients with HU show propensity for cardiovascular diseases (CVD) (increase in blood pressure, overweight and obesity, hypercholesterolaemia, hypertriglyceridaemia). Patients with HU associated with arterial hypertension (AH) more often suffer from metabolic syndrome, diabetes mellitus, and chronic kidney disease [1]. Population-based studies in Asia region reveal that hyperuricemia prevalence is 9.3 % in female and 8.4 % in male [2]. An extensive study conducted by Chinese scientists that included 100226 participants shows that hyperuricemia prevalence is 6.87 % in female and 8.57 % in male [3]. A greater prevalence of hyperuricemia among Europeans compared to the Chinese can be attributed to traditional eating habits of people in western world where fast food prevails. Data on HU prevalence among the US population proves the significance of a dietary factor in HU progression: according to the national study conducted from 2007 to 2016, prevalence was 20.2 % in male and 20 % in female, compared to European countries [4].

The objective lies in integrating of literature and own data that reflects contemporary views on the role of hyperuricemia in the progression of arterial hypertension and study the early effects of hyperuricemia on endothelial dysfunction.

Discussions on the role of HU in the progression of CVD and AH in particular have been going on for long. Despite decades of researches on HU pathogenesis and discussions on its possible

negative influence on the progress of AH, as recently as 2018, European Society of Hypertension has officially included HU to the independent risk factors for AH [5]. Since Ukrainian doctors had the opportunity to use international protocols in practice, explaining the mechanisms of pathogenetic influence of HU and creating diagnostic algorithms in HU combining with CVD are considered to be relevant objectives.

Discussing clinical relevance of hyperuricemia, it is worth recalling that uric acid (UA) acts as a terminal metabolite of purine metabolism in humans; however, most mammals have uricase enzyme that decomposes urine to allantoin. But a human has lost this ability in the course of evolution. Adenine and guanine are purines that form UA. There are two routes of administration of purines in the organism: oral administration and biosynthesis that prevails in forming of common pool. UA is reached at a concentration 355 mcmol/L (6.4 mg/dL), but proteins increase solubility – UA begins to crystallize in the human body when 389 mcmol/L (7 mg/dL) level goes beyond. But some studies indicate that pathological effect of UA is possible at a concentration 389 mcmol/L. Fuzzy limits of reference values that vary depending on sex create number of concerns on UA threshold level that can be regarded as pathogenetically significant in CVD progression.

Mechanisms of AH initiation in HU are described as those that function through urate crystallization-dependent and non-crystallization-dependent ways. Arterial wall macrophages can absorb urate crystals that activate NLRP3 receptors with interleukin-1β release leading to inflammation and cause collagen hyperproduction. The above-mentioned processes cause the increase in arterial stiffness with the progression of AH and atherosclerosis. Non-crystallization-dependent mechanisms are related to activation of intracellular and mitochondrial routes of oxidative stress in HU that decreases bioavailability of endothelial nitric oxide and stimulates renin-angiotensin system [6]. UA production is known to be followed by xanthine oxidoreductase (XOR) that releases singlet oxygen throughout all time of its functioning. Some researchers note that UA can just indicate XOR activity and active oxygen that forms during its work negatively influence vessel wall. It is known that hypoxia has caused expression and intensification of XOR activity, while hyperoxia causes downregulation of the activity [7]. Inhibition of NO production by uric acid associated with the increased XOR activity can explain depression of vasodilatory effects caused by oxidation. Inhibition of XOR activity with the help of allopurinol has improved peripheral vasodilator capacity of regional and systemic blood flow in patients with chronic heart failure [8]. To prove that HU belongs to common mechanisms of AH progression, one has initiated the studies that revealed the ability of angiotensin II to increase XOR levels and activate the production of superoxide in endothelial cell culture [9]. Despite this, the issue of application of XOR inhibitors for the treatment of CVD needs to be discussed.

Nitric oxide NO is important in forming vascular tone and arterial stiffness. Decrease of NO bioavailability and reduction of its production lead to endothelial dysfunction and increase in BP [10, 11]. Contemporary views on pathogenesis of AH progression are in agreement with the statement about the ability of vascular endothelium to actively absorb UA with the help of GLUT 9/URATv1 receptors – it causes UA accumulation in endothelial cell, activates oxidative stress, and decreases eNOS activity [12].

Another important issue regards interrelation of HU with traditional risk factors for AH. Increase in UA level accompanies these risk factors so frequently that for a long time, scientists had a chicken-and-egg situation. In the course of time, advanced techniques of data processing clarified clinical relevance of HU.

According to PIUMA study, when serum UA level in patients with arterial hypertension is higher than 250 mcmol/L (4.5 mg/dL) in male and 178 mcmol/L (3.2 mg/dL) in female, probability of complications in cardiovascular system (CVS) and mortality rate increase significantly (J-curve phenomenon). Risk of AH development in patients with HU is 3.66 times higher. Moreover, mean level of uric acid was significantly higher in patients with firstly diagnosed essential AH compared to healthy people. Assuming comparable AH levels, patients with AH and HU had a statistically significant higher percentage of target lesions [13]. Higher concentrations of UA in serum and urine correlate with high systolic, diastolic, and pulse BP in 24-hour monitoring of BP [14, 15]. 1 mg/dL increase in UA level leads to increase in systolic BP up to 10 mm Hg [16]. The ability of HU to increase BP in patients with non-dipping 24-hour profile was proved [17].

The issue of HU comorbidity is so relevant that governments of some countries even fund national

studies – for example, Romanian SEPHAR III program was conducted to evaluate the influence of HU on prevalence of essential AH, to control BP, renal function, and progression of atherosclerosis [18]. An extensive study by Tokyo Health Service Association that included 85286 patients has shown that hyperuricemia is associated with the increase in BP in both sexes. Additionally, UA levels (315 mcmol/L in male and 256 mcmol/L in female) were associated with AH prevalence [19]. A lasting 9-year study aimed at evaluating the influence of UA levels on AH progression in healthy people has revealed direct correlational relationships. For this purpose, 5105 people without AH were divided into four quartiles based on UA level (median): 1 – 260 mcmol/L, 2 – 325 mcmol/L, 3 – 365 mcmol/L, 4 – 420 mcmol/L. Nine years later, AH was observed in 2259 people (43.3 %), wherein 9-year incidence in quartiles were the following: 1 – 36.6 %, 2 – 42.4 %, 3 – 44.1 %, 4 – 54.5 % [20]. UA levels higher than 389 mcmol/L (7 mg/dL) were observed in 90 % of teenagers with de novo AH [21]. Moreover, HU is an independent RF for high-normal BP both in men and women [22].

Meta-analysis of 97824 patients shows that a high UA level can be a reason for AH development [23]. Doctors' everyday practice shows that the issue of the BP control remains relevant despite the increase in the number of antihypertensive medications. Resistant hypertension is characterized by the increase in BP in the course of the treatment with not less than three antihypertensive medications at a maximum dose including diuretics [5]. Hyperuricemia increases the risk of resistant arterial hypertension in women, but not in men. Elderly women from overall population with UA levels higher than 377 mcmol/L (6.8 mg/dL) have a 3-fold increased risk of resistant AH [24]. Cicero AF et all. studies have found that HU is associated with inadequate BP control in people receiving antihypertensive therapy [25]. Moreover, the higher UA level within reference values, the higher the risk of AH [26].

HU negatively influences other risk factors of AH. A retrospective five-year study that included 6476 healthy people has found that HU was an independent predictor for increase of the level of low-density lipoproteins (LDL) in both sexes. Additionally, increase in UA level over the period of 5 years is a risk factor for hypertriglyceridaemia [27]. In overall healthy population, sub-optimal levels of LDL and UA are associated with a high risk of AH [28]. HU is a predictor for development of metabolic syndrome associated with arterial hypertension [29]. Meta-analysis that included 11 studies and 54 000 patients has shown that increase in UA level positively correlates with the development of metabolic syndrome [30].

Pulse wave velocity is used to measure arterial stiffness. It is proved that the higher the arterial stiffness is, the higher is pulse wave velocity. UA is one of the factors that influence arterial stiffness. While searching correlational relationships between UA level and pulse wave velocity (PWV), one has found a strong direct correlational relationship $r = 0.92$ ($p < 0.001$). Stepwise regression in backward direction shows that PWV can be predicted based on UA level [31]. Increase in BP is initiated through inflammation in arterial wall and increasing of its stiffness [32, 33].

Some authors note that UA levels can actually reflect early stage kidney disease – the same was found in previous studies [34]. The kidneys are responsible for removing of 70 % of a 24-hour uric acid pool [35]. Renal excretion of UA involves glomerular filtration, proximal tubular reabsorption, secretion, and post-secretion reabsorption. In experimental increasing of serum UA level, AH, glomerulosclerosis, and interstitial fibrosis developed. These changes were associated with the activation of NADPH oxidase that led to intracellular oxidative stress, mitochondrial damage, ATP depletion, and damage of endothelium followed by activation of renin-angiotensin-aldosterone system (RAAS) [36]. In the evaluation of renal function in patients with firstly diagnosed AH, one has found a direct correlation between serum creatinine level and UA and an inverse correlation between UA level and glomerular filtration rate [37].

Study results also indicate that there is a direct positive correlation between UA level and carotid intima-media thickness in patients with and without AH. This suggests a possible role of HU in the development of atherosclerotic vascular disease in normotensive patients and people with AH [38].

The role of UA in the development of left ventricular hypertrophy (LVH) was revealed. But discussions on the existence of an independent influence of HU on LVH are still taking place. It is associated with both a direct pathogenetic influence on the myocardium though the activation of oxidative stress and a secondary influence through the ability of HU to increase BP [39]. After monitoring of UA levels in 400000 patients that have been observed within 7-17 years in Stockholm healthcare centers, one has found direct correlation

between UA level and the risk of myocardial infarction, heart failure, and acute cerebrovascular event [40]. The influence of UA levels on progression and incidence rate of heart failure with preserved ejection fraction in patients with AH was studied particularly. One has found an independent role of HU as a predictor of incidence of HF with preserved ejection fraction (EF) in patients with AH associated with LVH and diastolic dysfunction [41]. Increase in XOR activity is considered to be one of the mechanisms responsible for HF that leads to abnormal energy metabolism in cardiomyocyte.

The issue of the application of XOR inhibitors for the treatment of patients with AH associated with HU remains unresolved. Six-month treatment with febuxostat significantly decreased the activity of renin in serum and aldosterone concentration; the treatment also strongly increased glomerular filtration rate in patients with AH in comorbidity with HU [42]. In another placebo controlled study, six-week application of febuxostat (80 mg a day) in patients with HU and AH have provided discouraging results. According to results of a 24-hour monitoring of BP, in the group of patients taking febuxostat, one has found no statistically significant decrease in BP compared to the placebo group [43]. These studies critically rethink the hypothesis stating that effects from HU are associated not with UA molecule itself, but with XOR induction and that positive pleiotropic results provided by the use of XOR inhibitors are associated with enzyme blocking itself, but not with the further decrease in UA [44].

Materials and methods

Total of 382 persons were analyzed to evaluate the prevalence of hyperuricemia in Sumy region.

To study the early effects of hyperuricemia on endothelial dysfunction in normotensive patients two groups were formed: 31 patients with UA < 400 μmol/l (1st group) and 29 patients with UA > 400 μmol/l (2nd group). The groups were comparable in age and sex.

Test with reactive hyperemia for estimation of endothelium-dependent vasodilation (EDVD) was performed using the ultrasound system SonoScape S6. BP cuff with the pressure 50 mm Hg higher than systolic BP was applied to the upper third of the arm – it blocked the blood flow in brachial artery. Compression was performed for 5 minutes, and then rapid decompression was performed. Artery size and blood flow criteria were defined one minute after decompression. Increasing of brachial artery diameter less than 10 % during the test with reactive hyperemia was considered as a criterion of endothelial dysfunction.

Results and discussion

Due to information obtained from literature, there are no exhaustive data about the prevalence of hyperuricemia in Ukraine. Our study had demonstrated the prevalence of hyperuricemia in Sumy region about 42 % for normotensive patients and 51 % – in hypertension patients from total cohort 382.

Daily BP monitoring demonstrated daytime systolic blood pressure (DaySBP) 118 mmHg and daytime diastolic blood pressure (DayDBP) 72 mmHg in the 1st group; in the 2nd group these were DaySBP 130 mmHg, DayDBP 80 mmHg ($p < 0.05$).

Analysis of baseline levels of EDVD shows significant differences between groups: 12.9 % and 9.6 % in 1st group and 2nd group respectively ($p < 0.05$). The average UA level in the 1st group was 328 ± 24 μmol/l; in the 2nd group - 469 ± 34 μmol/l. It was acquire the negative correlation values of -0.32 between the level of UA and EDVD in the 1st group and -0.48 in 2nd group ($p < 0.05$).

Considering a high prevalence of hyperuricemia and an established relationship between UA level and AH progression of AH and complications associated with it, the question arises of whether screening procedures aimed at identifying hyperuricemia in population with AH should be performed. State Statistics Service of Ukraine has no data on hyperuricemia statistics. Perhaps, implementation of eHealth online registration system will improve accounting and statistical processing of data on AH and HU comorbidity and initiate further studies that will help determine the role of HU in the progression of systemic disturbances and also deal with the issue of dietary, pharmacological, and physiotherapeutic correction of HU in patients with AH.

Conclusion

Study results demonstrated high prevalence of HU as in hypertensive so normotensive patients. Statistically significant relationship between endothelium dependent vasodilation and uric acid levels in patients was established. The observed negative correlation indicates the influence of hyperuricemia on the progression of endothelial dysfunction in the pre-hypertensive period.

Further research

Studying of comorbid hyperuricemia states will enable the use of prophylactic and therapeutic schemes for preventing the progression of complications associated with CVS and other organs. Considering the absence of a clear strategy on pharmacological correction of HU in patients with AH, there is an immediate need to develop new approaches to lowering UA level in patients not only with CVD but also on early preclinical study.

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