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ASSESSMENT OF HEMODYNAMICS IN RENAL ARTERIES IN PATIENTS WITH GOUT AND ESSENTIAL HYPERTENSION AND EFFECTIVENESS OF QUERCETIN TREATMENT

T.D. NYKULA, V.E. KONDRATIUK, Y.P. SYNYSIA

Bogomolets National Medical University, Kyiv, Ukraine

SUMMARY.

The purpose of this work was to study the structural and functional status of the renal arteries in patients with gout in combination with essential hypertension (EH) and to assess the dynamics of the addition of quercetin to the standard treatment regimen.

Materials and methods: 63 male patients with gout and EH were examined and divided into the main group – 43 (68.3%) patients, who received quercetin in addition to standard antihypertensive and urate-lowering therapy and 20 (31.7%) patients – in the comparative group, who took the same treatment regimen without quercetin. Duration of therapy is 6 months. The urine acid (UA) of blood and urine, blood creatinine were determined in the study groups, followed by the calculation of the rate of glomerular filtration (GFR) and an ultrasound examination of the renal arteries with the calculation of the index of resistance of the renal arteries (RI) was performed.

Results: The positive dynamics was observed in the main group among the indicators characterizing the renal function: the level of creatinine significantly decreased by 10.8% ($p = 0.03$) in 3 months and continued to decrease to 22.0% ($p < 0.01$) in 6 months of therapy. A similar picture was observed with an increase in GFR in 3 and 6 months by 6.9% ($p = 0.04$) and by 13.3% ($p < 0.01$) respectively. There was a significant decrease in RI among the patients in the main group on both sides by 16.3% ($p < 0.01$) after a 6-month course of therapy when in the comparative group the corresponding parameter decreased only by 8.7% ($p > 0.05$). Decreased level of UA by 33.7% ($p < 0.001$) and normalization of blood pressure.

Conclusion: the addition of quercetin to the standard treatment regimen is accompanied by a combination of nephroprotective, urate-lowering and antihypertensive effects.

Key words: gout, essential hypertension, renal arteries, quercetin.

INTRODUCTION

Gout is a metabolic system heterogeneous disease that develops due to inflammation in places of sedimentation of crystals of sodium monourate in people with elevated levels of uric acid (UA) due to external factors and/or genetic factors and leads to structural and functional changes in various organs and systems [1]. According to epidemiology, at least 1.0 – 4.0% of the adult population suffers from gout [2]. The concentration of UA is determined by the intensity of its formation in the body and the processes of excretion by the kidneys (70.0%) and through the gastrointestinal tract (30.0%) [3]. Kidneys are a vascular organ and their activity completely depends on the state of systemic hemodynamics. Therefore, it is important to study the functional state of the kidneys in patients with gout and essential hypertension (EH), since they are the target organ in hypertension, and can also be secondary in the presence of gout with the development of gouty nephropathy.

Actively searching for new drugs that would be effective and safe for patients with a combination of gout and hypertension. According to the latest research, one of these drugs is flavonoid – quercetin, which stimulates Na⁺ -K⁺ -2Cl⁻-cotransporter-1 (NKCC1), an important ion conveyor in controlling the concentration of Cl⁻ in the cytosol of the cell. Activating NKCC1 and increasing the concentration of Cl⁻ suppressed expression of epithelial-Na⁺ channels in the renal arteries, which reduces the reabsorption of Na⁺ and causes a decrease in blood pressure (BP) [4]. In addition, quercetin has antioxidant, anti-inflammatory, immunostimulating and antiradiation effects [5, 6].

The aim. To evaluate the efficacy of the addition of quercetin to standard antihypertensive and urate-lowering therapy in comparison with non-quercetin treatment based on studies of changes in uricemia level, structural and functional status of renal arteries in patients with gout in combination with EH.

MATERIALS AND METHODS

The study included 63 males. These patients by random sampling were divided into two groups: the

main one, which included 43 (68.3%) persons, and the comparative – 20 (31.7%) patients. Groups do not differ statistically from the main indicators (Table 1).

Table 1

Clinical characteristics and biochemical profile of the subjects (M ± m)

Indicator	Main group (n = 43)	Comparative group (n = 20)	p
Middle age, years	57.2 ± 0.9	56.2 ± 0.8	0.59
Duration of EH, years	6.7 ± 0.4	6.3 ± 0.3	0.40
Duration of gout, years	6.6 ± 0.6	6.0 ± 0.4	0.31
Creatinine of blood, μmol/l	108.3 ± 2.1	103.23 ± 2.3	0.30
GFR, ml/min/1.73 m ²	81.4 ± 4.0	82.7 ± 2.9	0.85
Blood UA, μmol/l	532 ± 24.1	496.3 ± 14.3	0.21
Systolic blood pressure, mm Hg	147.2 ± 2.3	149.0 ± 2.2	0.65
Diastolic blood pressure, mm Hg	94.4 ± 1.6	94.4 ± 1.5	0.21

Allopurinol was recommended to correct UA level (the initial dose was 100 mg per day for 2 weeks, after which the dose increase every 2-4 weeks for 100 mg to achieve the required UA blood concentration (<360 μmol/l). For the correction of BP, the preparation of the group of antagonists of angiotensin II receptors – losartan (in the average dose of 50-100 mg per day) was selected. The second drug was a blocker of calcium channels – amlodipine (in the average dose of 5-10 mg per day). Patients in the main group, in addition to antihypertensive and urate-lowering therapy, received additionally quercetin in granules, 2 g three times per day, 30 minutes before eating for 3 months, followed by a transition to maintenance doses of 2 g per day for another three months. The comparator group was on the same therapy, but without the addition of quercetin.

All patients were assessed for the concentration of BP and UA, blood creatinine and subsequent calculation of GFR using the formula CKD-epi (Chronic Kidney Disease Epidemiology Collaboration), 2009. Using an ultrasound apparatus TOSHIBA Aplio 500 (Japan), renal arteries were investigated with the calculation of the total peripheral resistance renal arteries, the marker of which was the index of resistance of the renal arteries to the right and to the left (RI) [7]. The reference values were 0.60 – 0.70. An increase in the RI parameter indicates a hypertensive renal artery disease. Patient treatment groups were screened before treatment and after 3 and 6 months with treatment.

Statistical processing of the results of the study was conducted using the STATISTICA 8.0 program. In the normal distribution, the quantitative data is represented as M ± m (M is the arithmetic mean

value; m is the mean error). To assess the reliability of the clinical and laboratory changes detected during the proposed regimen, a reverse measurement (ANOVA) for remeasurement (Repeated Measures Analysis of Variance with Effect Sizes and Powers) was used. Statistically significant differences were found for p < 0.05.

RESULTS AND DISCUSSION

In the main group, the level of creatinine significantly decreased by 10.8% (p = 0.03) in 3 months and continued to decrease to 22.0% (p < 0.01) against the background of 6 months of therapy. A similar picture was observed with an increase in GFR in 3 and 6 months by 6.9% (p = 0.04) and 13.3% (p < 0.01) respectively. In the comparator group, creatinine decreased by 6.4% (p = 0.27) and 10.8% (p = 0.03) at 6 months in the 3rd month of therapy, and the GFR increased by only 3.5% (p = 0.65) and 8.5% (p = 0.07) respectively.

Against the background of baseline therapy in the main and in comparative study groups, the urate-lowering effect was detected. In the main group, the level of blood glucose decreased by 24.6% (p < 0.01) for 3 months of treatment and by 33.7% (p < 0.01) for 6 months. In the comparative group, after 3 months of therapy, blood glucose levels decreased by 14.5% (p = 0.01) and by 20.3% (p < 0.01) in 6 months. In both groups, there was an increase in urine the level of UA. The value of UA urine increased by 12.0% after 3 months of treatment, and after 6 months – by 16.0% (p < 0.05). The level of UA urine in the comparative group was unreliable, but there was a positive trend – urinary urine increased by 6.0 and 8.0% after 3 and 6 months of treatment, respectively (Table2).

Table 2

Dynamics of the level of average indicators of creatinine blood, GFR and SC blood and urine (M ± m)

Time of observation	Main group			Comparative group		
	M	m	n	M	m	n
Creatinine of blood, µmol/l						
Before treatment	108.3	2.1	43	103.2	2.3	20
After 3 months	96.9*	1.8	43	96.6	2.1	20
After 6 months	84.8 **	1.9	43	92.1*	1.9	20
GFR, ml/m²						
Before treatment	81.4	1.9	43	82.7	2.1	20
After 3 months	87.0	2.0	43	85.6	2.3	20
After 6 months	92.2 **	1.9	43	89.7	2.1	20
Blood UA, µmol/l						
Before treatment	452.5	13.2	43	448.3	14.3	20
After 3 months	341.2*	5.6	43	383.3*	7.6	20
After 6 months	301.1**	5.6	43	341.3**	10.2	20
Urine UA, µmol/l						
Before treatment	513.9	35.9	43	517.4	37.7	20
After 3 months	582.2	31.4	43	548.4	32.2	20
After 6 months	614.4**	25.6	43	561.1	29.7	20

Notes: * Probability of difference in treatment and after 3 months, p <0.05.
 ** Probability of difference in treatment and after 6 months, p <0.05.

Against the background of improvement of the function of the endothelium and the filtration function of the kidneys, there was a significant decrease in the total peripheral resistance of the renal arteries: the RI score among the patients in the main group on both sides decreased by 16.3%

(p < 0.001) after a 6-month course of therapy (Table 3). In the comparative group, no significant changes were observed in the right side (p = 0.69) and left (p = 0.89), although the tendency to improve the renal artery functionality also took place.

Table 3

Dynamics of RI on the right and left in the patients of the main and comparative groups, (M ± m)

Time of observation	Main group			Comparative group		
	M	m	n	M	m	n
RI right						
Before treatment	0.71	0.01	43	0.71	0.01	20
After 3 months	0.70	0.01	43	0.69	0.01	20
After 6 months	0.60*	0.01	43	0.69	0.01	20
RI left						
Before treatment	0.71	0.01	43	0.69	0.01	20
After 3 months	0.70	0.01	43	0.68	0.01	20
After 6 months	0.60*	0.01	43	0.67	0.01	20

Note. * The probability of difference in treatment and after 6 months, p <0.05.

The analysis of BP indications showed that after 6 months of course treatment with quercetin, systolic BP decreased by 5.5% (from 137.1 ± 2.3 mm Hg to 129.5 ± 2.7 mm Hg, $p = 0.03$), and diastolic BP by 3.6% (from 84.4 ± 1.9 mmHg to 80.8 ± 1.1 mm Hg, $p = 0.07$) in 6 months of treatment. In the control group, significant changes were observed for systolic BP (from 138.0 ± 1.1 mm Hg to 133.3 ± 1.3 mm Hg, $p = 0.40$) and for diastolic BP (from 83.2 ± 1.9 mm Hg to 80.8 ± 1.1 mm Hg, $p = 0.08$) was not detected.

CONCLUSIONS

The addition of quercetin to urate-reducing and antihypertensive therapy in patients with gout and hypertension contributes to the improvement of renal function after 3 months of therapy, and after 6 months, the normalization of renal hemodynamics, accompanied by subjective urate-lowering and antihypertensive effects.

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РЕЗЮМЕ

ЗМІНИ ГЕМОДИНАМІКИ В НИРКОВИХ АРТЕРІЯХ У ХВОРИХ НА ПОДАГРУ В ПОЄДНАННІ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ НА ТЛІ ЛІКУВАННЯ КВЕРЦЕТИНОМ

Т.Д. Никула, В.Є. Кондратюк, Ю.П. Синиця

Національний медичний університет імені О.О. Богомольця, Київ

Метою даної роботи було вивчення структурно-функціонального стану ниркових артерій у хворих на подагру в поєднанні з артеріальною гіпертензією (АГ) та оцінити динаміку їх змін на тлі додаткового включення кверцетину до стандартної схеми терапії.

Матеріали та методи: було обстежено 63 осіб чоловічої статі хворих на подагру та АГ і розділено на основну групу – 43 (68.3 %) пацієнтів, котрі до стандартної антигіпертензивної та уратзнижувальної терапії додатково приймали кверцетин та порівняльну групу – 20 (31.7 %) пацієнтів, що приймали таку ж саму схему лікування, але без кверцетину. Тривалість терапії 6 місяців. У досліджуваних групах визначалися показники сечової кислоти (СК) крові та сечі, креатиніну крові з подальшим розрахунком швидкості клубочкової фільтрації (ШКФ) та проводили ультразвукове дослідження ниркових артерій із з розрахунком індексу резистентності ниркових артерій (PI).

Результати: позитивна динаміка спостерігалася в основній групі серед показників, що характеризують ниркову функцію: рівень креатиніну достовірно знизився на 10.8% ($p = 0.03$) вже через 3 місяці та продовжував знижуватися ще до 22.0% ($p < 0.01$) на тлі 6 місяців терапії. Аналогічна картина спостерігалася зі зростанням ШКФ через 3 та 6 місяців на 6.9% ($p = 0.04$) та на 13.3% ($p < 0.01$) відповідно. Спостерігалася достовірне зниження PI серед хворих основної групи з обох сторін на 16.3% ($p < 0.01$) після 6-місячного курсу терапії, коли в порівняльній групі відповідний параметр залишався торпідним. Поруч із поліпшенням функції нирок було виявлено зниження рівня СК крові на 33.7% ($p < 0.001$), збільшення урикозурії на 16% ($p < 0.05$) та нормалізацію артеріального тиску.

Висновок: додаткове включення кверцетину до стандартної схеми терапії хворих на подагру та АГ супроводжується суматійним нефропротекторним, уратзнижувальним та антигіпертензивним ефектами.

Ключові слова: подагра, артеріальна гіпертензія, ниркові артерії, кверцетин.

РЕЗЮМЕ

ИЗМЕНЕНИЯ ГЕМОДИНАМИКИ В ПОЧЕЧНОЙ АРТЕРИИ У БОЛЬНЫХ ПОДАГРОЙ В СОЧЕТАНИИ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ НА ФОНЕ ЛЕЧЕНИЯ КВЕРЦЕТИНОМ

Т.Д. Никула, В.Е. Кондратюк, Ю.П. Синиця

(Київ)

Целью данной работы было изучение структурно-функционального состояния почечных артерий у больных подагрой в сочетании с артериальной гипертензией (АГ) и оценить динамику их изменений на

фоне дополнительного включения кверцетина к стандартной схеме терапии.

Материалы и методы: было обследовано 63 больных мужского пола на подагру в сочетании с АГ и разделены на основную группу – 43 (68.3%) пациентов, которые к стандартной антигипертензивной и уратснижающей терапии дополнительно принимали кверцетин и сравнительную группу – 20 (31.7%) пациентов, принимавших такую же схему лечения, но без кверцетина. Длительность терапии 6 месяцев. В исследуемых группах определялись показатели мочевой кислоты (МК) крови и мочи, креатинина крови с подальним расчетом скорости клубочковой фильтрации (СКФ) и проводили ультразвуковое исследование почечных артерий с расчетом индекса резистентности почечных артерий справа и слева (PI).

Результаты: достоверная положительная динамика наблюдалась в основной группе: уровень креатинина достоверно снизился 22.0% ($p < 0, 01$), выросла СКФ на 13.3% ($p < 0.01$). Достоверно снизился PI среди больных основной группы с обеих сторон на 16.3% ($p < 0.01$) после 6-месячного курса терапии, когда в сравнительной группе соответствующий параметр снизился лишь на 8.7% ($p > 0.05$). Наряду с улучшением функции почек было выявлено снижение уровня МК крови на 33.7% ($p < 0.001$) и нормализацию артериального давления учитывая.

Вывод: дополнительное включение кверцетина к стандартной схеме терапии сопровождается сумационным нефропротекторным, уратснижающим и антигипертензивным эффектом.

Ключевые слова: подагра, артериальная гипертензия, почечные артерии, кверцетин.