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GOUT AND RENAL DYSFUNCTION

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Abstract

Introduction. The frequency of nephrolithiasis positively correlates with the degree of hyperuricemia.
The objective of the study was the analysis of renal dysfunction in patients with gout from different age groups.
Material and methods. 237 patients with gout (mean age for males 60 ± 8.0 years and females 63 ± 9.0 years) were examined and analyzed retrospectively. The diagnosis of gout was carried out according to the classification criteria for gout of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2015. The patients were separated into two groups, depending on the age at gout onset: the age at onset up to and including 59 years (group I, 91 people) and the age at onset after 60 years, inclusive (group II, 146 people). The raw data was processed in SPSS version 26.0.
Results. The renal function was mostly preserved in patients from group I: 51% had a level of glomerular filtration rate (GFR) corresponding to stage 2 chronic

Résumé

Goutte et dysfonctionnement rénal

Introduction. La fréquence de la néphrolithiase est en corrélation positive avec le degré d'hyperuricémie.
L'objectif de l'étude a été l'analyse du dysfonctionnement rénal chez les patients atteints de goutte dans différentes groupes d'âge.
Matériel et méthodes. 237 patients goutteux ont été examinés rétrospectivement. Deux groupes: l'âge de début de la maladie jusqu'à 59 ans inclus (groupe I, 91 personnes) et après 60 ans inclus (groupe II, 146 personnes). Le diagnostic de goutte a été établi selon les critères de l'American College of Rheumatology et de la European League Against Rheumatism 2015. Les patients ont été séparés en deux groupes, selon l'âge d'apparition de la goutte: l'âge d'apparition £ 59 ans (groupe I, 91 patients) et l'âge d'apparition ³ 60 ans (groupe II, 146 patients). Les données brutes ont été traitées dans SPSS version 26.0.

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kidney disease (CKD) (in the presence of kidney damage), stage 4 CKD was determined in only 2 patients from group I. A pronounced decrease in kidney function was determined in group II, significantly more often there was stage 3 CKD (16 (22%) in group I and 59 (46%) in group II, p = 0.001). In 12 participants in group II, GFR was below 29 ml/min/1.73 m^2. Only in 6% of cases, a slight decrease in GFR was determined, which was 4 times lower than in group I.

Conclusions. With increasing age, the frequency of risk factors for gout increases, especially for people with kidney damage: taking small doses of acetylsalicylic acid increases the risk from 6 to 40%, diuretics from 18 to 44%, alcohol consumption from 14 to 28%, hypertension from 44 to 78%, consumption of foods saturated with purine from 51 to 68%, overweightness and obesity from 58 to 76%.

Keywords: gout, renal dysfunction, risk factors, uric acid, diuretics.

List of abbreviations:
ACR – American College of Rheumatology
CKD - chronic kidney disease
CHF - chronic heart failure
DM2 – diabetes mellitus type 2
GFR - glomerular filtration rate
IHD - ischemic heart disease
HU – hyperuricemia
EULAR – European League Against Rheumatism
HU – hyperuricaemia
UA – uric acid

Résultats. Dans le groupe I, 51% avaient un débit de filtration glomérulaire (DFG) correspondant au 2ème stade de la maladie rénale chronique (MRC), une MRC au 4ème stade n'a été déterminé que chez 2 représentants du groupe I. Dans le groupe II, il y avait une MRC stade 3 (16 (22%) dans le groupe I et 59 (46%) dans le groupe II, p=0,001). Douze participants du groupe II avaient un DFG inférieur à 29 ml/min/1,73 m^2. Dans 6% des cas, une diminution du DFG a été déterminée, soit 4 fois moins que dans le groupe I.

Conclusions. Avec l'âge, la fréquence des facteurs de risque de goutte augmente, notamment chez les personnes atteintes de lésions rénales: la prise de petites doses d'acide acétylsalicylique augmente le risque de 6 à 40%, les diurétiques de 18 à 44%, la consommation d'alcool de 14 à 28%, hypertension de 44 à 78%, consommation d'aliments saturés en purines de 51 à 68%, surpoids et obésité de 58 à 76%.

Mots-clés: goutte, dysfonctionnement rénal, facteurs de risque, acide urique, diurétiques.

Introduction

Kidney damage in gout is often associated with age, duration of the disease, concomitant pathology[1-4]. In the elderly, the function of the kidneys usually decreases[1,3], and chronic kidney disease (CKD), serum creatinine > 132.6 mmol/L in about 20% of cases precedes the development of gout[1,5]. In a multivariate analysis, the role of reduced renal function was demonstrated (adjusted OR 1.2 for every 10 ml/min decrease of glomerular filtration rate (GFR)) as an independent factor in gout development in patients with type 2 diabetes mellitus (DM 2)[2-4]. In addition to reducing GFR, other markers of kidney damage – proteinuria and hematuria – are also independently associated with the risk of gout[6-8].

The objective of the study was the analysis of renal dysfunction in patients with gout from different age groups.

Material and methods

A descriptive, selective study of 237 patients with gout (average age for males 60±8.0 years and for females 63±9.0 years) was conducted. The study was carried out in accordance with the requirements of the Ministry of Health for Clinical Research within the postdoctoral scientific program of the Rheumatology and Nephrology Discipline of "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova. The raw data was processed in SPSS version 26.0.

Clinical, paraclinical and treatment data of 658 patients with gout hospitalized during 2015 – 2022 were extracted from the database of the Departments of Arthrology, Rheumatology and Nephrology of the Republican Clinical Hospital "Timofei Mosneaga", Chisinau, Republic of Moldova. Of the 658 patients, 276 patients met the including criteria in the study and were selected for further analysis. The diagnosis of gout was carried out according to the American

College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2015 classification criteria for gout[2-3].

To study the clinical characteristics of gout in the elderly, all patients included in the study were divided according to age at the time of examination: group I (n = 91) was made up of patients with gout ≤ 59 years, the mean age 48.1±7.4 years (from 30 years to 60 years), group II (n = 146) >60 years inclusive, the mean age 69.2±6.0 years (60 - 86 years).

The mean age at gout onset in group II (55.3 ± 10.7 years) was 1.5 times higher than in patients in group I, 36.3 ± 7.3 years (p < 0.1). The ratio of males to females in both groups was not different, 79% men in group I and 81% in group II (p = 0.08).

The selection, elaboration and approval of the questionnaires were obtained within the Research Ethics Committee of the "Nicolae Testemitanu" State University of Medicine and Pharmacy (no.13/ 20.09.2019). All hospitalized patients, according to the Law of the Republic of Moldova No. 263-XVI of October 27, 2005, "The patient's rights and responsibilities", sign the informed consent. The criteria for including in the study were age over 18 years, established diagnosis of gout, presence of all data collected, presence of informed consent. The criteria for exclusion from the study were oncological pathology, lack of informed consent.

Results

The mean disease duration was comparable in both groups: 11±7.7 years (from 1 month to 23.7 years (p = 0.7) in group I and 11.4 ± 8.4 years (from 1.7 years to 21.9 years) in group II. The equivalent duration of arthritis allows to compare the evolution characteristics in groups. The chronic course of arthritis was slightly more common in group II than in group I, but had no significant differences, 17 (24%) and 44 (34%).

The number of tender joints at the time of examination was comparable in both groups (the mean number of joints affected during the disease in group I was 10.5 ± 6.0, in group II it was 10 ± 5.0 (p = 0.8). The mean number of swollen joints at the time of examination in group II was 0.5 ± 0.1, in group I it was 1.0 ± 0.1 (p = 0.6). The frequency of arthritis attacks in the recurrent course of gout also did not show significant differences between groups: 4.0 ± 2.0 in group I and 3.0 ± 2.0 in group II (p = 0.1). The frequency of the tophaceous form of gout was comparable in both groups, 45% in both group I and group II. The number of tophi on examination was no different: 2.0 [0; 9.0] in group I and 2.0 [1; 4.5] in group II. Hyperuricemia was detected in two thirds of patients in both groups (65% and 66%). The mean value of serum creatinine was significantly lower in group I – 107.2 ± 38.4 μmol/L, 128.8 ± 48.6 μmol/L, respectively, (p = 0.0016). The median amounts of protein in urine were comparable and exceeded the normal levels in both groups. The median of the GFR value was significantly lower in group II.

The renal function was more preserved in the representatives of group I: 51% had a level of GFR corresponding to stage 2 CKD (in the presence of kidney damage), stage 4 CKD was determined in only 2 patients from group I. A more severe decrease in kidney function was determined in group II representatives: significantly more often there was stage 3 CKD – 16 (22%) in group I and 59 (46%) in group II (p = 0.001). In 12 participants in group II, GFR was below 29 ml/min/1.73 m^2. Only in 6% of cases, a slight decrease in GFR was determined, which was 4 times lower than in group I.

Diuretics were administered in a third of patients from both groups (Table 1) at the moment of

Table 1. Treatment of patients included in the study (n %)

Indicators	*Group I (n = 91)*	*Group II (n = 146)*
Diuretics, n (%)	23 (32.4)	51 (39.5)
Loop diuretics, n (%)	2 (2.8)	18 (13.9)*
Thiazides, n (%)	18 (25.3)	45 (34.8)
Thiazide diuretics and loop diuretics, n (%)	0 (0)	12 (9)*
Allopurinol administration, n (%)	45 (63)	95 (74)
Permanent, n (%)	29 (41)	63 (49)
Sporadically, n (%)	16 (22)	32 (25)
Allopurinol dosage, (mg)	125.0 [100.0; 250.0]	100.0 [100.0; 200.0]*
Normalization of UA level against the background of allopurinol	10 (22%)	18 (20%)
Acetylsalicylic acid, n (%)	13 (18%)	65 (50%)*

*Note: * – statistical significance of the differences in comparison with patients in group I (p < 0.05)*

Table 2. Comorbidities of the patients included in the study (n %)

Disease	*Group I, (n = 91)*	*Group II, (n = 146)*
Arterial hypertension	56 (78.8)	126 (97.6)*
IHD	15 (21.2)	108 (83.7)*
CHF	6 (8.4)	73 (56.6)*
Nephrolithiasis	52 (73)	96 (74)
CKD	15 (21)	50 (39)*
Type 2 diabetes	24 (33.8)	54 (41.8)

*Note: * – statistical significance compared to patients in group I (p<0.05); IHD – ischemic heart disease, CHF – chronic heart failure, CKD – chronic kidney disease.*

data collection. In group II the frequency of loop diuretics were almost 5 times more often, the frequency of thiazide diuretics treatment did not have significant differences. Both thiazide and loop diuretics were administered in 12 (9%) patients of group II.

Allopurinol was used by 63% of patients in group I and 74% in group II, while 2/3 in both groups received the drug consistently. The dose of the drug in group I varied from 50 to 600 mg and was significantly higher than in group II (p = 0.02), where the dose ranged from 50 to 400 mg. Only in 20% of cases it was observed the normalization of serum uric acid after allopurinol administration.

Low-dose acetylsalicylic acid was much more often administered by patients in group II: 65 (50%) compared to 13 (18%) in group I (p = <0.1).

In patients from group II, arterial hypertension, ischemic heart disease (IHD), chronic heart failure (CHF), CKD (p < 0.05) were significantly more frequently. Type 2 diabetes was diagnosed in a comparable number of cases in groups. Also, in the same percentage of cases, nephrolithiasis was determined, in more than 70% of the representatives of each group (Table 2).

The frequency of diseases directly associated with gout – type 2 diabetes, nephrolithiasis and CKD – does not differ between the groups, which indicates the possible proximity of the pathogenetic mechanisms of these diseases with gout. The frequency of hypertension practically did not differ between the groups, which may also indicate a pathogenetic link with gout.

The average number of comorbidities was 2 times higher in group II, 2.17 [2.1; 3.1] and 4.11, respectively, [3.2; 5.1], (p < 0.1). Only 2 (1%) patients in group I did not have any comorbidity – both were men, aged 56.7 and 37.6 years at the time of the examination, with onset of gout at 47.1 and 28.3 years, respectively. The highest number of patients from group I had 2 comorbidities, 25 (35%) patients. In group II, 59% had 4 or 5 comorbidities. One patient in group I and 8 in group II had all 6 comorbid gout diseases.

Furthermore, different combinations and frequency of concomitant diseases in group I and II were analyzed. In group I, the combination of arterial hypertension and nephrolithiasis prevailed significantly: 17 patients (23.9%). In 10 patients (14.1%) gout was accompanied by arterial hypertension, nephrolithiasis and type 2 diabetes. Seven patients had only nephrolithiasis and 6 people only arterial hypertension. In 4 people (5.6%), a combination of gout with arterial hypertension, IHD, nephrolithiasis and type 2 diabetes was determined. The other combinations of diseases of group I occurred with a frequency of less than 5%.

Most commonly in group II there were patients with a combination of gout with arterial hypertension, IHD, CHF, nephrolithiasis and type 2 diabetes, 19 (15%) patients. In a significant number of patients, gout was associated with arterial hypertension, IHD, CHF, nephrolithiasis and CKD, 15 (12%) patients. In 11 (8.5%) patients, a combination of gout with arterial hypertension, IHD, CHF, nephrolithiasis was found. In 9 (7%) patients a combination of arterial hypertension, IHD, CHF was encountered and in 9 (7%) patients gout was associated with arterial hypertension, IHD, nephrolithiasis, and CKD. In 8 cases, arterial hypertension and IHD were determined as comorbid diseases, and in 7 cases arterial hypertension and nephrolithiasis. All other associations of comorbid diseases were determined with a frequency of less than 5%.

Most commonly, representatives of group I had a combination of arterial hypertension and nephrolithiasis (78.8%). Most often in group II there was a combination of gout with arterial hypertension and IHD (82.9%), with arterial hypertension and nephrolithiasis (72%), with arterial hypertension, IHD and nephrolithiasis (58.9%).

Discussion

To date, the question remains open about the causes of uric acid crystallization. All risk factors

solely affect the increase of uric acid, which indirectly contributes to the development of gout and worsens its course.

Most patients with gout regularly used thiazide diuretics and thiazide-like diuretics (93% at onset before 60 years of age and 86% at onset after 60 years of age). Treatment with these drugs is prescribed for a long time, which increases the risk of side effects. Since diuretics are first-line pharmacological treatment, and in certain cases it is impossible to exclude their administration, it is necessary to measure the risk of decompensation of heart function and the possibility of increased hyperuricemia when they are prescribed.

The results of the study are interesting, demonstrating that the early development of arterial hypertension (in group I, the average age of development of arterial hypertension before the onset of gout was 37.4 ± 9.6 years) leads to an earlier manifestation of gout. The pathogenesis of the influence of arterial hypertension on the development of gout is associated with damage to glomerular arterioles and glomerulosclerosis, which leads to the development of CKD and hyperuricemia[9-11]. High blood pressure is also a component of the metabolic syndrome associated with the risk of developing gout [3, 6, 12-14].

A decrease in GFR is significantly associated with gout in several studies (the average age of subjects with gout was 63 years)[2,6,7]. The analyzed data of 5085 patients with CKD showed an incidence of gout of 24.3%, increasing from 16.0% to 35.6% with GFR 60 - 30 ml/min/1.73 m^2.

The importance of CKD as an independent factor in the development of gout is demonstrated by many clinical-epidemiological studies: the relative risk of developing gout was determined in the participants through the Framingham study (2159 men and 2558 women) suffering from CKD. In total, during the observation period, there were 371 cases of gout (in 231 men and 140 women) in 140421 person-years. The incidence of gout per 1000 persons-years was 6.82 (95% CI 5.10 to 9.10 CI) and 2.43 (2.18 to 2.71) in the absence of CKD and the relative risk of gout in the multivariate status model was 1.88 (1.13 to 3.13) among men and 2.31 (1.25 to 4.24) among women[1-5].

Thus, the early development of arterial hypertension and obesity is associated with the early development of gout. The frequent occurrence of both pathological conditions preceding the development of gout suggests that they can act in synergy within the metabolic syndrome, which is a predictor of the development of gout[6,8,9,15].

Despite the isolated cases where CKD appeared before the onset of gout in the present study, the role of low kidney function as a risk factor for hyperuricemia and gout has been proven ny many studies[1-3,7,17,18].

A moderate decrease in kidney function in most cases does not lead to clinical manifestations and can develop for a long time. The analysis of medical records data of the participants in the study made it possible only to register a pronounced decrease in kidney function preceding the development of gout, previously defined by the term CKD.

The presented data support the hypothesis that the previous development of chronic non-communicable diseases associated with gout (arterial hypertension, CHF, nephrolithiasis, CKD, obesity) is accompanied by an earlier onset of gout. It can be assumed that the increase in the incidence of gout directly correlates with an increase in the frequency of these pathological conditions, which are currently the main risk factors for the development of gout.

In addition to pathogenetic associations, diuretic drug therapy, usually considered as a risk factor for gout, can also play a role. In this regard, it should be noted that in all 17 patients of group I who received diuretics before the onset of gout, they were indicated for the treatment of hypertension.

However, as mentioned earlier, kidney damage in gout can occur before the joint onset of the disease. The kidneys are the main organs that ensure the concentration of urates in the human body: 60-65% of the body urates are eliminated by the kidneys, while from the urates filtered by the kidneys, the main part is reabsorbed and only 3-10% are excreted from the body[4,11,19].

It is reasonable to assume that any pathological condition leading to a decrease in kidney function can lead to the development of hyperuricemia. In turn, a decrease in the efficiency of urea transport may be due both to genetic mutations of urea transporters[5,15,20] and to the presence of acquired pathological conditions, such as arterial hypertension.

However, CHF and nephrolithiasis may be directly related to gouty nephropathy, i.e. uric nephrolithiasis, in many cases preceding the joint manifestation of gout[3,6,7,19]. This relationship is confirmed by a significant number of patients diagnosed with nephrolithiasis at a young age, preceding the early development of gout in the study. Nephrolithiasis has been shown to be associated with the risk of developing gout[1-4]. The formation of urates can also be affected by insufficient function of ammonogenesis in the kidneys, manifested by aciduria and crystallization of uric acid[2-6], caused by the presence of any renal pathology, as well as associated with obesity, often preceding gout in patients from our study[11-17].

Conclusions

With age, the frequency of acquired risk factors for gout increases, especially for kidney damage. Taking small doses of acetylsalicylic acid increases the risk from 6 to 40%, diuretics from 18 to 44%, alcohol consumption from 14 to 28%, hypertension from 44 to 78%, consumption of foods saturated with purine from 51 to 68%, overweightness and obesity from 58 to 76% in groups of patients with gout ≤59 years and >60 years. The early age of the onset of hypertension is associated with the early development of gout and CKD.

Author Contributions:

Conceptualization, L.R.; methodology, E.R.; software, D.S.; validation, C.C.; formal analysis, L.R.; investigation, L.R.; resources, L.R.; data curation, L.R.; writing - original draft preparation, L.R.; writing - review and editing, E.R., D.S. visualization, R.P.; supervision, E.C.; project administration, L.G., L.R.. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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