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Efficiency Of Allopurinol On Cholesterol Value In Hyperuricemic Patients.

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ABSTRACT

The subject of the research in this study was the effect of allopurinol on the value of cholesterol in hyperuricemic patients. The study covered 40 hyperuricemic patients, both male and female, of different age groups. Patients were classified into groups according to co-morbid diagnoses. All patients were clinically treated for a period of four years. The study ranges from average cholesterol values before, and after three and six months treatment with allopurinol. It has been found that the average cholesterol values have slightly increased, but were within the limits of the reference values and did not statistically significantly differ from $p>0.05$. In subjects with established gout diagnosis, who were being treated with statins and allopurinol, cholesterol values decreased statistically significantly ($p<0.05$). Also, in the treatment with allopurinol, in patients with metabolic syndrome with severe heart disease the average value of uric acid was statistically significantly reduced, but cholesterol values increased significantly ($p<0.05$). In the analysis of cholesterol values in patients with type 2 diabetes mellitus, it was found that the uric acid significantly decreased after three months of treatment with allopurinol ($p=0.037$), but statistically significantly increased after six months compared to the values established after three month of use of this medicine ($p=0.042$) The analysis found that the use of allopurinol affects cholesterol values in hyperuricemic patients.

Keywords: allopurinol, cholesterol, hyperuricemia.

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INTRODUCTION

Gout is a hereditary or acquired metabolic disease characterized by increased levels of uric acid in plasma, hypersaturation of uric acid, precipitation of its salts (urate), so called tofi, inside the joints, in the tissues around the joint and the articular cartilage, tendons, which triggers an inflammatory reaction. In addition to the occurrence of acute crystalline arthritis and the aforementioned hotbeds of accumulated urate, it is clinically manifested both in renal calculus and in insufficiency [1, 2]. Hyperuricemia occurs at a concentration of uric acid of 416 µmol/L. At lower concentration the of the above-mentioned, uric acid is released (dissolved) from the monosodium urate, and above that concentration, the formation of precipitate of the crystal is observed. However, some authors state that normal values of uric acid would be values up to 458 µmol/L for men, and up to 392 µmol/L for women [3, 4]. Alopurinol is a structural analog of the natural purine base, hypoxanthine. The mechanism of action is reflected in the inhibition of xanthine oxidase enzymes, the enzyme responsible for the conversion of hypoxanthine into xanthine and xanthine into uric acid, as the final product of purine metabolism in humans. It should be noted that in some patients with hyperuricemia, beside inhibition of the purin catabolism, de novo biosynthesis of purine is reduced by the inhibition of hypoxanthin-guanine phosphoribosyltransferase inhibition [5-8]. The serum level of urate and lipid values was analyzed in several interesting studies that are somewhat contradictory. A number of studies indicate a direct relationship between lipids and hyperuricemia in patients with metabolic syndrome [9-11].

In this pharmacological-clinical study, the primary goal was to analyze the value of uric acid and cholesterol in patients on allopurinol therapy over three or six months of treatment. Within the secondary targets, the values of these analytes were monitored, depending on the co-morbid diagnosis of patients. The hypothesis from which we started was: Initial therapy of hyperuricemic patients with allopurinol in six months of monitoring shows additional effects on cholesterol.

METHODS

This retrospective-prospective cohort study was conducted on 40 clinically treated patients (a four-year period) both sexes and different age groups, classified into subgroups for co-morbid diagnoses, and all patients have already had diagnosed hyperuricemia. A special group consisted of patients who, in addition to diagnosed hyperuricemia, used, before treatment with allopurinol, statin therapy, where the statin dosing during 6 months of our observation was not changed. The first values of uric acid and cholesterol (prior to administration of therapy) were control values (each patient was self-controled). The therapeutic effects were observed with allopurinol (a dose of 100 mg daily) during the three-month and six months treatment. The inclusion of patients in this analysis was done according to the following criterion: by a doctor verified hyperuricemia based on laboratory diagnostics; the availability of treatment data, including eventual complications; availability of indicators by sex and age, and anamnestic data.

The following methods were used in the development of the work: explicative, content analysis, statistical and comparative methods. All clinical measurements were performed using standard IFCC methods on appropriate biochemical analyzers. For the continuous variables in the test, was analyzed first the symmetry of their distribution using the Kolmogorov-Smyrnov test. When the distribution was symmetrical, we used the arithmetic mean and the standard deviation to represent the mean values, and for the comparison of these variables the parametric tests (Student t-test, Paired t-test) was used. When the distribution of continuous variables was asymmetric, to represent the mean and scattering measures, the median and interquartile range, and nonparametric tests for their comparison was used. SPSS for Windows software (Version 20.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (Version 13. Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis of the obtained data.

RESULTS

All patients were analyzed for uric acid for the observed period. The average values of uric acid measured before treatment, compared to those measured after 3 and 6 months from the start of treatment, showed that allopurinol exhibited a pharmacotherapeutic effect. It was found that the average value of uric acid before treatment was 523.45 µmol/L, after 3 months of treatment with allopurinol 433.25 µmol/L, and after 6 months of treatment 435.77 µmol/L. Using the t-test, it was found that the average value of uric acid

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statistically significantly differed from the reference values before treatment (p=0.04), while after 3 and 6 months, the average values were within the limits of the upper (tolerant) reference values.

In Tables 1, 2 and Figures 1 and 2 the average cholesterol values in patients on allopurinol prior to treatment and 3 and 6 months after treatment were analyzed. The average cholesterol value in the test group before treatment was 4.40 mmol/L, after 3 months of treatment 4.89 mmol/L, and after 6 months of treatment, 5.16 mmol/L. Cholesterol values slightly increased, but were within the limits of the reference values and did not statistically significantly differ from p>0.05.

Table 1: Analysis of average cholesterol values

	X	N	SD	SEM	T	df	p
Before treatment	4,40	40	1,31	0,21	0,199	39	0,841
After 3 months of treatment	4,89	40	1,54	0,24	1,233	39	0,255
After 6 months of treatment	5,16	40	1,63	0,26	0,130	39	0,897

SEM - standard error of mean. **df** - degrees for freedom, **p** - p-values (t-test), t - t values (t-test)

Table 2: Differences in average cholesterol values in the study period

	X	t	Df	p
Before treatment- After 3 months of treatment	-0,38	-1,641	39	0,110
After 3 months of treatment – After 6 months of treatment	-0,21	-0,985	39	0,331

SEM - standard error of mean. **df -** degrees for freedom, **p** - p-values (t-test), **t** - t values (t-test)

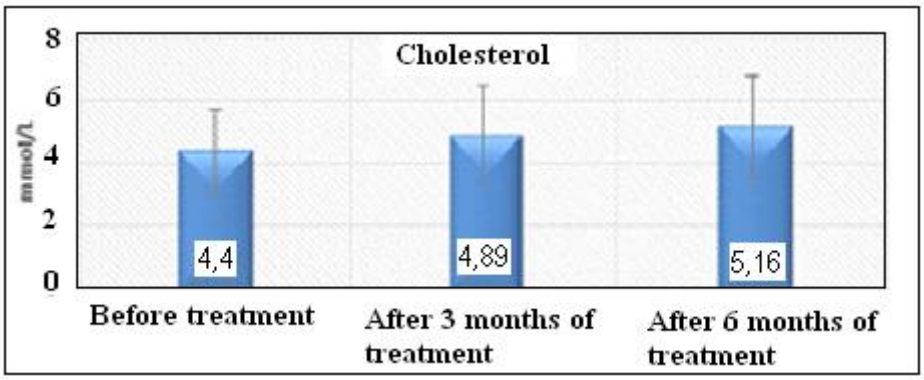

Fig. 1: Analysis of average cholesterol values

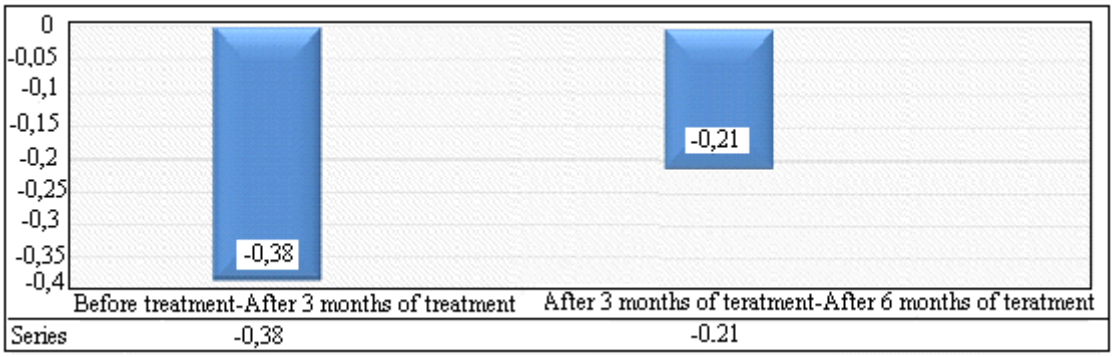

Fig 2: Differences in average cholesterol values in the study period

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Using a paired t-test, differences in cholesterol values were established before administration of allopurinol and after 3 and 6 months of therapy. There is no statistically significant difference in the average cholesterol value before administration of allopurinol and after 3 months of therapy (p=0.110). The cholesterol value increased by 0.38 mmol/L, but was within the limits of the reference values. There was no statistically significant difference in the average cholesterol values after 3 and 6 months of treatment (p=0.331). When we looked at patients according to their co-morbid diagnoses within defined subgroups, we came to the following results (Tables 3, 4, 5, 6).

A. Analyzes of subjects with a diagnosis of gout cholesterol were statistically significant (p<0.05),
B. In subjects with diagnosed gout, who were on statin and allopurinol therapy, cholesterol values were found to have a statistically significant decline after 3 and 6 months of therapy (p<0.05)
C. Analyzes of subjects with metabolic syndrome (severe heart disease-hypertension), cholesterol values have statistically significantly increased (p<0.05).
D. In subjects with type 2 diabetes mellitus, and cholesterol increased after 3 months of therapy (p=0.015), and after 6 months retained the same value.

Table 3: Average values of uric acid and cholesterol during treatment subjects with gout

	Before treatment			After 3 months			After 6 months		
	X	SD	SEM	X	SD	SEM	X	SD	SEM
Uric Acid	528,48	178,29	35,65	439,96	186,23	37,24	448,16	204,66	40,93
	p=0.039								
Cholesterol	4,30	1,24	0,25	4,99	1,72	0,34	5,26	1,93	0,39
	p<0.05								

SEM - standard error of mean. **df -** degrees for freedom, **p** - p-values (t-test), **t** - t values (t-test)

Table 4: Average values of uric acid and cholesterol during treatment subjects with gout and statin therapy

	Before treatment			After 3 months			After 6 months		
	X	SD	SEM	X	SD	SEM	X	SD	SEM
Uric Acid	510,6	82,48	36,88	464,00	183,02	81,84	395,60	95,25	42,59
	p<0.05								
Cholesterol	5,84	0,94	0,42	4,84	0,63	0,28	4,84	0,62	0,28
	p<0.05								

SEM - standard error of mean. **df -** degrees for freedom, **p** - p-values (t-test), **t** - t values (t-test)

Table 5: Average values of uric acid and cholesterol during treatment of subjects with heart disease

	Before treatment			After 3 months			After 6 months		
	X	SD	SEM	X	SD	SEM	X	SD	SEM
Uric Acid	499,40	54,87	24,54	447,60	123,51	55,23	396,00	66,07	29,54
	p<0.05								
Cholesterol	3,42	1,57	0,78	4,04	1,59	0,71	4,87	1,51	0,67
	p<0.05								

SEM - standard error of mean. **df -** degrees for freedom, **p** - p-values (t-test), **t** - t values (t-test)

Table 6: Average values of uric acid and cholesterol during treatment of subjects withtype 2 diabetes mellitus

	Before treatment			After 3 months			After 6 months		
	X	SD	SEM	X	SD	SEM	X	SD	SEM
Uric Acid	535,20	137,34	61,42	354,60	79,79	35,68	453,80	247,75	110,58
	p=0.037			p=0.042					
Cholesterol	4,24	0,84	0,37	5,39	0,99	0,49	5,32	1,01	0,45
	p=0.015			p=0.889					

SEM - standard error of mean. **df -** degrees for freedom, **p** - p-values (t-test), **t** - t values (t-test)

Correlation ratio

There is a statistically significant negative correlation in the values of uric acid and cholesterol after 3 months of therapy, r = -0.326; p = 0.043.

There is no statistically significant correlation in the values of uric acid and cholesterol after 6 months of therapy, p> 0.05.

DISSCUSION

In the analysis of the average cholesterol values in patients before treatment, when it was 4.40 µmol/L and after treatment with allopurinol for three months when it was 4.89 µmol/L and six months when it was 5.16 µmol/L, it was found that the average cholesterol values were mildly increased, but remained within the limits of the reference values, i.e. they did not differ significantly (p> 0.05).

Using a comparative t-test, it was found that there was a statistically significant difference in the average cholesterol value before and after the use of allopurinol for a period of three months (p = 0.110), an increase in cholesterol by 0.38 µmol/L, but this is within the limits of the reference values. A statistically significant difference was not found in the average cholesterol values after six months of treatment with allopurinol (p = 0.331).

In the analysis of patients with gout diagnosis, it was found that the values of uric acid statistically significantly declined after a three-month treatment with allopurinol (p=0.039), while in the next three months of the therapy it remained in approximately the same values. In addition, cholesterol values had statistically significantly increased (p<0.05),in subjects with established gout diagnosis, who were on the treatment with statins and allopurinol, it was found that the value of uric acid decreased after three and six months of use of allopurinol (p<0.05). Cholesterol has statistically significantly decreased (p<0.05) .In addition, in the treatment with allopurinol,subjects with metabolic syndrome with severe heart disease (Hypertension present), the mean values of uric acid statistically decreased significantly, but cholesterol values increased significantly (p<0.05). In the analysis of cholesterol values in patients with type 2 diabetes mellitus, it was found that the uric acid statistically significantly decreased after three months of treatment with allopurinol (p=0.037), but statistically significantly increased after six months compared to the values established after three month of use of this medicine (p=0.042).

Cholesterol values increased after three-month therapy (p=0.015), and after six months they maintained the same value. The results of similar studies have shown contradictory results. The uric acid values are positively correlated with triglycerides which significantly contributes to the level of total cholesterol and HDL (9-12). The study conducted by Heimbach et al., which included 66 patients (allopurinol therapy) with diagnosis of metabolic syndrome and gout, showed that the uric acid was not a good predictor of total cholesterol [12]. In their study, Kackov and coworkers monitored the correlation of metabolic disorders (hyperglycemia, dyslipidemia) with hyperuricemia in the general population, and led to conclusions, which are in correlation with the results of this study, that patients with hyperuricemia had a more frequent increase in total cholesterol concentration (69, 6% according to 51, 9%; P<0, 001), compared with patients whose serum uric acid concentrations were within the reference range [13].

CONCLUSION

Evaluation of the efficacy of allopurinol on the value of uric acid and the effect on cholesterol values was achieved by applying the t-test to the indicator that the average value of uric acid statistically differs significantly from the reference values before the beginning of treatment of patients with allopurinol (p = 0.04). In the analysis of the average cholesterol values before the start of treatment with allopurinol, and after a three-months and six-months long therapy, it was found that they were slightly increased but remained within the limits of the reference values.

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