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Efficiency Of Allopurinol On The Value Of HDL And LDL And The Value Of The Aterogenic Index In Hyperuricemic Patients

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ABSTRACT: The subject of the study in this pharmacological-clinical paper was the effect of allopurinol on the values of HDL and LDL in hyperuricemic patients. The research sample included 40 clinically treated patients of both sexes (UKC Sarajevo and JU General Hospital "Abdulah Nakaš" Sarajevo) and various age groups, which according to the diagnosis of the disease were classified into several subgroups (gout, diabetics, patients with metabolic syndrome). 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 ($p < 0.05$). It was found that the values of LDL fraction were statistically significantly decreased after 3 and 6 months of therapy ($p < 0.05$), while the HDL fraction decreased after 3 months of therapy, but maintained the same to the sixth month of therapy. Also, in the treatment with allopurinol, subjects with metabolic syndrome with severe heart disease (hypertension present), the mean values of uric acid statistically decreased significantly, the values of LDL fractions were statistically significantly increased ($p < 0.05$), while the values of HDL fraction increased after 3 months of therapy, so that later this value remained constant.

KEYWORDS - allopurinol, HDL, LDL, atherogenic index, hyperuricemia.

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I INTRODUCTION

The serum potassium concentration (SUK) appears as a potential marker, not only for cardiovascular and cerebrovascular disorders, but there is also its relationship to insulin resistance, and as a major risk factor for gout development, as confirmed in a series of clinical studies [1].

Conditions of elevated or decreased levels of uric acid in accordance to physiological values are referred to as hyperuricemia and hypuricemia, while the increase in uric acid concentration in urine is known as hyperuricosuria [2]. Hyperuricemia occurs at a concentration of uric acid of 416 μmol / L [3-5]. Increased uric acid production may be due to increased degradation of nucleoproteides, excessive intake of purine via food or excessive uric acid synthesis as a result of a rare mutant enzyme defect [6].

Allopurinol 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 [7-8].

The serum level of urate and lipid values was the subject of several studies that were somewhat contradictory. A number of studies indicate a direct relationship between lipids and hyperuricemia in patients with metabolic syndrome [9-13].

In this pharmacologic-clinical study, the primary goal was to analyze the value of uric acid and HDL and LDL in patients on allopurinol therapy over three or six months of therapy. 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 is: Initial therapy of hyperuricemic patients with allopurinol in six month follow-up shows additional effects on HDL and LDL.

II METHODS

This retrospective-prospective cohort study was conducted on 40 clinically treated patients (a four-year period in UKC Sarajevo and JU General Hospital "Abdulah Nakaš"), both sexes and different age groups, with a diagnosis of hyperuricemia and classified into subgroups according to co-morbid diagnoses. A special group consisted of patients who, in addition to diagnosed hyperuricemia, used, before treatment with allopurinol, a statin therapy, whilst the dose of statins during 6 months of our observation was not modified. The first values of uric acid and HDL and LDL (prior to initiation 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.

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.

III 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 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. By analyzing the mean values of the HDL lipid fraction (Table 1., Fig. 1.), prior to treatment and after 3 and 6 months of treatment, it was found that the mean HDL value in the test group before the treatment was 1.00 mmol / L, after 3 months treatment with allopurinol 1.03 mmol / L, and after 6 months of treatment, 1.18 mmol / L. Using the t-test, it was found that the mean HDL value did not statistically differ significantly from the reference values prior to the treatment ($p = 0.153$), and after 3 months of treatment ($p = 0.257$), as well as after 6 months of treatment, the average HDL values were not statistically significantly higher than the reference values ($p = 0.501$).

Table 1: Analysis of average values of HDL

	X	N	SD	SEM	t	df	p
Before treatment	1,00	40	0,25	0,04	2,224	39	0,153
After 3 months of treatment	1,03	40	0,66	0,12	1,115	39	0,257
After 6 months of treatment	1,18	40	0,71	0,12	2,374	39	0,501

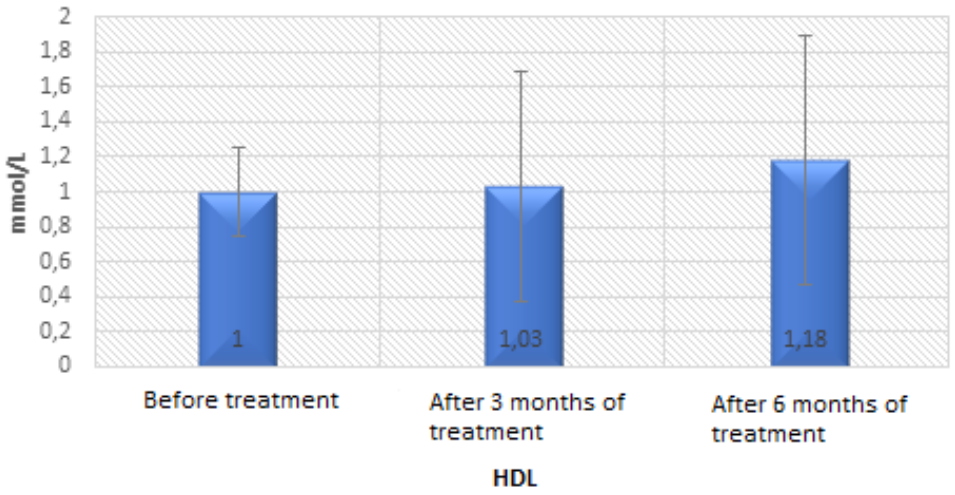

Fig. 1: Analysis of the average values of HDL

Using a paired t-test, statistically significant differences in HDL values were not noticed before administration of allopurinol and after 3 and 6 months of therapy. There is no statistically significant difference in the average HDL value before administration of allopurinol and after 3 months of therapy (p = 0.475). The HDL value increased by 0.03 mmol / L, but was within the limits of the reference values. There was no statistically significant difference (Table 2.) in the average HDL values after 3 and 6 months of treatment (p = 0.233)

Table 2: Differences in average HDL values in the investigated period

	X	t	df	p
Before treatment- After 3 months of treatment	-0,03	-0,726	39	0,475
After 3 months of treatment – After 6 months of treatment	-0,15	-1,233	39	0,233

Table 3. presents analyzed average values of LDL lipid fractions in patients on allopurinol prior to treatment and 3 and 6 months after treatment. The mean LDL value in the test group before treatment was 2.83 mmol / l, after 3 months of treatment, 2.96 mmol / L, and after 6 months of treatment, 3.30 mmol / L. LDL values slightly increased, but were within the limits of the reference values and did not statistically significantly differ from p> 0.05 (Fig. 2.).

Table 3: Analysis of average values of LDL

		X	N	SD	SEM	T	df	P
Before treatment		2,83	40	1,08	0,20	2,964	39	0,889
After 3 months of treatment		2,96	40	1,22	0,22	1,964	39	0,759
After 6 months of treatment		3,30	40	1,34	0,22	0,409	39	0,685

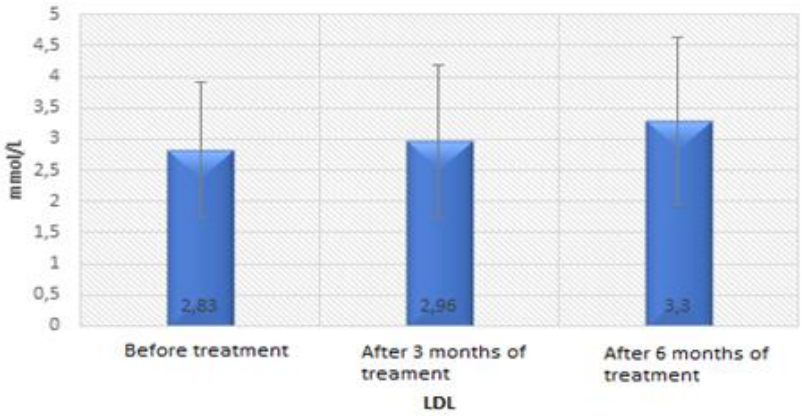

Fig. 2: Analysis of average values of LDL

Using a paired t-test, statistically significant differences in LDL values were not noticed before administration of allopurinol and after 3 and 6 months of therapy. There was no statistically significant difference in the mean LDL value before administration of allopurinol and after 3 months of therapy (p = 0.489). The value of LDL (Table 4.) increased by 0.13 mmol / L, but was within the limits of the reference values. There was no statistically significant difference in the mean LDL values after 3 and 6 months of treatment (p = 0.184).

Table 4: Differences in average LDL values in the investigated period

	X	T	df	p
Before treatment- After 3 months of treatment	-0,13	-0,704	39	0,489
After 3 months of treatment – After 6 months of treatment	-0,34	-1,366	39	0,184

When we looked at patients according to their co-morbid diagnoses within defined subgroups, we came up with the following results (Tables 5., 6., 7., 8.):

A. The analyzes of subjects with gout diagnosis revealed that LDL fractions had statistically significantly rose ($p < 0.05$). The HDL value did not statistically change before and during therapy ($p = 0.08$).

B. In subjects with established gout diagnosis who were on statin and allopurinol therapy, LDL fractions were found to have declined statistically significantly after 3 and 6 months of therapy ($p < 0.05$), while the HDL fraction decreased after 3 months of therapy, and maintained that value after 6 months of therapy.

C. Analyzes of subjects with metabolic syndrome (severe cardiac disease-hypertension), LDL fraction values increased statistically ($p < 0.05$), while the values of HDL fraction increased after 3 months of therapy, but later this value remained constant.

D. In subjects with type 2 diabetes mellitus, LDL fraction values increased after 3 months of therapy ($p = 0.015$) and after 6 months retained the same value. HDL was statistically significantly reduced after 3 months of therapy ($p = 0.009$) in order to return to the reference values after 6 months.

Table 5: Average values of uric acid and lipid fractions during treatment of 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								
HDL	1,04	0,21	0,05	0,93	0,29	0,06	1,06	0,30	0,06
	p=0,08								
LDL	2,80	1,09	0,25	2,95	1,28	0,28	3,38	1,59	0,33
	p<0,05								

Table 6: Average values of uric acid and lipid fractions during treatment of gout and on 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								
HDL	1,10	0,16	0,07	1,00	0,29	0,14	0,97	0,20	0,10
	p<0,05								
LDL	3,67	0,85	0,38	2,89	0,57	0,28	2,73	0,43	0,21
	p<0,05								

Table 7: Average values of uric acid and lipid fractions during treatment of subjects with metabolic syndrome (severe 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								
HDL	0,60	0,07	0,01	2,16	1,86	1,07	2,07	1,83	0,91
	P<0,05								
LDL	1,38	0,19	0,13	2,16	1,15	0,66	3,39	0,68	0,34
	P<0,05								

Table 8: Average values of uric acid and lipid fractions during treatment of subjects with diabetes mellitus type 2

	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**					
HDL	1,00	0,36	0,18	0,69	0,10	0,05	1,17	0,62	0,28
	p=0,009			**p=0,001**					
LDL	2,44	0,60	0,30	3,95	1,26	0,73	3,37	1,06	0,47
	p=0,027			**p=0,605**					

The average values of the atherogenic index in subject with gout and gout patients who were on statin therapy, during administration of allopurinol, after the 3 and 6 months of treatment did not differ significantly and were within the limits of the reference values. However, in the subjects with metabolic syndrome (heart disease) and subjects with type 2 diabetes mellitus, the atherogenic index was increased after 3 and 6 months of therapy, statistically significantly, and was at the upper limit of the reference values (Table 9., Fig. 3.)

Table 9: Analysis of the average values of the atherogenic index in relation to the diagnosis of the subjects on the treatment with allopurinol in the investigated period

		X	SD	SEM	P
Gout	Before treatment	3,60	1,17	0,23	p=0,369
	After 3 months of treatment	3,94	1,46	0,29	
	After 6 months of treatment	3,76	1,71	0,34	
Gout+Statin th.	Before treatment	3,70	1,71	0,76	p=0,081
	After 3 months of treatment	2,76	1,38	0,61	
	After 6 months of treatment	3,94	1,79	0,80	
Heart patients	Before treatment	3,06	1,35	0,60	**p=0,031**
	After 3 months of treatment	5,00	1,97	0,88	
	After 6 months of treatment	4,95	0,88	0,39	
Type 2 Diabetes mellitus	Before treatment	2,86	0,72	0,32	**p=0,019**
	After 3 months of treatment	3,02	1,46	0,65	
	After 6 months of treatment	4,23	2,37	1,06	

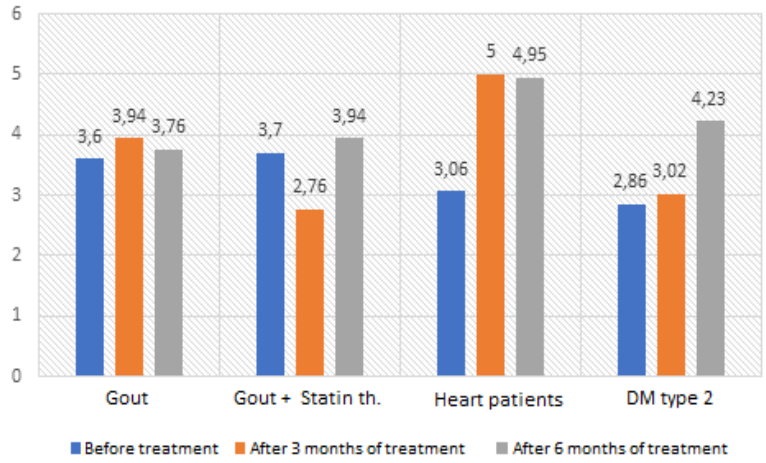

Fig. 3: Analysis of the average values of the atherogenic index in relation to the diagnosis of the subjects treated with allopurinol during the investigated period

Correlation ratio

There is a statistically significant negative correlation in the values of uric acid and LDL after 3 months of therapy, r = -0.352; p = 0.050.

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

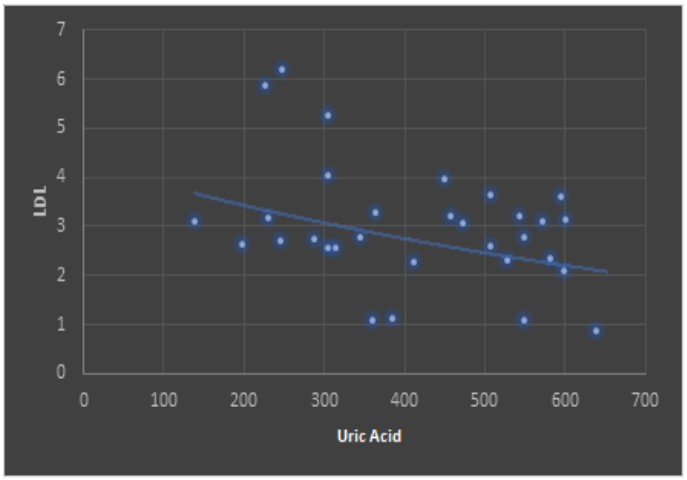

Fig. 4: Correlation between uric acid and LDL after 3 months of treatment

IV DISCUSSION

In the analysis of the mean value of the HDL lipid fraction, which was prior to the treatment 1.00 mmol/L, after three months of treatment with allopurinol 1.03 mmol/L, and after six months when it was 1.18 mmol/L, using t- the assay it was found that the mean HDL value was not statistically significantly different from the reference values prior to treatment with allopurinol. ($p = 0.153$), after three months of drug use ($p = 0.257$), and after six months of treatment ($p = 0.501$).

That there was no statistically significant differences in the mean HDL value before administration of allopurinol and after a three-month long treatment ($p = 0.475$), and between the three-month and six-month long treatment of patients with this drug ($p = 0.233$) was also concluded using a comparative t-test.

In the analysis of the mean LDL lipid fraction in patients before use of allopurinol, when it was 2.83 mmol / L, and after three months of therapy with this drug, when it was 2.96 mmol / L, and after six months, when it was 3 , 30 mmol / L, it was found that the values of LDL slightly increased but remained within the limits of the reference values, ie they did not differ statistically significantly ($p> 0.05$).

In the analysis of the mean value of the LDL lipid fraction, which was prior to the treatment with allopurinol 2.83 mmol / L, after three months of treatment with the medicine 2.96 mmol / L, and after six months when it was 3.30 mmol / L, it was found that the values of LDL slightly increased but remained within the limits of the reference values, i.e. they did not differ statistically significantly ($p> 0.05$). Also, by using a comparative t-test, statistically significant differences in LDL values prior to treatment of patients with allopurinol and after the use of this drug for three and six months were not noticed. Increases remained within the limits of the reference values: before and after the use of the drug in the three month period, when there was an increase of 0.13 mmol / L, but it was within the limits of the reference values; as well as after three and six months of treatment ($p = 0.184$).

In the analysis of the examinees with gout diagnosis, it was found that the values of uric acid statistically significantly decreased after a three-month treatment with allopurinol ($p = 0.039$), while in the next three months of therapy it remained in approximately the same values. The values of LDL fraction statistically significantly increased ($p <0.05$), and HDL values did not statistically significantly change before and during therapy ($p = 0.08$). In subjects with established gout diagnosis, who were on statin and allopurinol therapy, it was found that the value of uric acid decreased after three and six months of use of allopurinol ($p <0.05$). In this case, the LDL fraction decreased statistically significantly ($p <0.05$), and the HDL fraction decreased after three months of therapy and maintained the same value after six months of treatment with allopurinol. In the treatment with allopurinol in subjects with metabolic syndrome with severe heart disease (hypertension present), the mean values of uric acid statistically significantly decreased, but the value of the LDL fraction increased statistically significantly ($p <0.05$) and the HDL fraction value increased after three months of treatment and after that, in the next three months, remained constant. In the analysis of lipid fraction values in patients with type 2 diabetes mellitus, it was found that the uric acid was statistically significantly reduced after three months of treatment with allopurinol ($p = 0.037$), but statistically significantly increased after six months of treatment compared to the values established after three months of use of this medicine ($p = 0.042$). The value of the LDL fraction increased after a three-month therapy ($p = 0.039$), and after six months retained the same value. HDL was statistically significantly reduced after three months of treatment ($p = 0.009$), but its values returned within the limits of the reference values after six months of treatment with allopurinol.

The average values of the atherogenic index in patients with gout and patients with gout who were on statin therapy, during the administration of allopurinol, after three and six months of treatment did not differ

significantly and found themselves within the limits of the reference values. In subjects with heart conditions that were mentioned earlier and subjects with type 2 diabetes mellitus, the atherogenic index increased statistically significantly for three and six months of treatment, but was at the upper limit of reference values.

If we talk about studies that have dealt with the same problem, the results are rather contradictory. In studies by Chen et al., Lin et al., Rathmann et al., the results showed a positive correlation with triglycerides, total cholesterol relationship with HDL [9-11]. Esther J. Heimbacha et al., in their study, came to the result the uric acid is not a good predictor of total cholesterol in patients who had gout and metabolic syndrome diagnosis [14]. Kackov et al., in their study, came to the conclusion, which is in correlation with the results of this study, that subjects with hyperuricemia had a higher concentration of total LDL-cholesterol (64.5% to. 46.4%; P <0, 001), and HDL-cholesterol (24, 3% to 13%; P <0, 001) compared to subjects whose serum uric acid levels were within the reference range [15].

V CONCLUSION

Evaluation of the efficacy of allopurinol on the value of uric acid and the effects on the values of HDL and LDL which has been carried out with the application of the t-test, led to the indication that the average value of uric acid statistically differs significantly from the reference values before the beginning of treatment with allopurinol ($p = 0.04$). Also, it was found that the mean HDL value did not statistically significantly differ from the reference values before treatment with allopurinol, and after a three-month and six-month long treatment of patients, likewise in the analysis of the average value of the LDL lipid fraction, it was found that it slightly increased, but that remained within the limits reference values.

In subgroup patients with metabolic syndrome with severe heart disease (hypertension present), the mean uric acid value decreased statistically significantly, but LDL fractions statistically significantly increased ($p <0.05$) and the HDL fraction increased after three months of treatment, and after that, in the next three months, remained constant. In the subgroup of patients with type 2 diabetes mellitus, the LDL fraction values increased after three months of therapy, while the HDL fraction statistically significantly decreased ($p = 0.009$). In the analysis of the atherogenic index, it was found that in patients with metabolic syndrome (severe heart disease) and type 2 diabetes mellitus, the atherogenic index increased statistically significantly after three and six months of treatment, but was at the upper limit of the reference values.

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