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Specifics of Treatment of Hyperuricemia with Febuxostat and Its Effects on Concentrations of Total, LDL and HDL Cholesterol, Compared to the Conventional Treatment with Allopurinol

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NZS, SS, NO, BP, DL and FB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KD, MD and AHT managed the analyses of the study. Author NZS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Hyperuricemia is a potential marker of cardiovascular diseases, and its relation to hypertension and arteriosclerosis, as well as the outcomes of certain cardiovascular events, is interesting. The research was carried out a sample of 50 subjects of both sexes, who were either on allopurinol or febuxostat treatment. Effects of allopurinol and febuxostat on concentrations of uric acid and some lipid fractions (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol) were observed in 25 subjects on allopurinol treatment, and in 25 subjects on febuxostat treatment, who were chosen by defined criteria, with each patient serving as his or her control. The total observation period was six months and the cut was made after the first three

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months and at the end of the research. Evaluating the effectiveness of allopurinol in subjects with hyperuricemia, it was established that concentrations of uric acid decreased by 126.28±20.36 μmol/L, at the end of the research, compared to the initial concentration. In subjects who used febuxostat, at the end of the research, concentrations of uric acid decreased by 252.80±94.17 μmol/L, compared to the initial concentration. Evaluating the effectiveness of febuxostat on concentrations of lipid fractions, a statistically significant increase of 0.17±0.02 mmol/L in concentrations of HDL and a statistically significant decrease of 0.37±0.14 mmol/L in concentrations of LDL were noted. Subjects with gout treated with allopurinol had significantly lower average concentrations of cholesterol compared to subjects with gout and metabolic syndrome (p=0.001). Subjects with gout and metabolic syndrome had significantly higher concentrations of LDL at the beginning and the end of the research, regardless of therapy (p=0.045;p=0.049, respectively). Both drugs showed effectiveness in the treatment of hyperuricemia, and a certain effect on concentrations of lipid fractions.

Keywords: Hyperuricemia; gout; metabolic syndrome; allopurinol; febuxostat.

1. INTRODUCTION

Gout is a hereditary or acquired metabolic disease characterized by an increased concentration of uric acid in plasma, super saturation of uric acid and precipitation of its salts (urates) so-called *tophi* inside joint spaces and in the tissue around the joint, joint cartilage and tendons, which starts an inflammatory reaction [1]. Aside from the occurrence of acute crystal arthritis and afore-mentioned hotspots of precipitated urates, kidney calculi and insufficiency are also clinically shown [2].

Prevalence of disease in older women increases with the increased use of diuretics. Usually, concentrations of urates are low in children, but increase in puberty, especially in boys. Most prone to developing gout are men ages from 40 to 50 [3-5].

Concentrations of uric acid, as a potential marker of cardiovascular and cerebrovascular diseases and mortality, have been in the focus of medical research for almost 50 years. The question about concentrations of uric acid during acute myocardial infarction (AMI) and its outcomes (uric acid is a potential predictor of AMI outcomes) poses as an interesting and an important one, and not just because of the lack of research on this topic, but also because of different results found by researchers [6-9].

Hyperuricemia is an independent risk factor of a stroke, and subjects with increased concentrations of urates have a worse outcome of a cerebrovascular event. Higher concentrations of urates pose as a risk factor of peripheral arterial diseases, such as atherosclerosis of the coronary artery. Hyperuricemia is a frequent finding in congestive heart failure, and increased concentrations of urates are connected with a worse and more serious outcome of heart insufficiency [10].

One of the reasons for the above is the fact that hyperuricemic patients are often diagnosed with hyperlipidemia. Correlation between serum urate and lipid values is interesting, but the results of some studies regarding this are contradictory. Certain studies have shown a significant link between serum lipid values and hyperuricemia in examinees with metabolic syndrome, with triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol being positively and low-density lipoprotein (LDL) cholesterol negatively correlated with hyperuricemia [11-14].

Since the serum concentration of uric acid is a risk factor of the genesis of certain diseases, including most difficult ones, with which we deal here, it is of utmost medical importance to put it under effective control.

In this pharmacological-clinical study, the primary objective pertained to the analysis of uric acid concentrations and lipid status (atherogenic index was also monitored) in patients on therapy with allopurinol or febuxostat, starting from its primary values, i.e. before the start of therapy, as control values (each patient is his/her control).

2. RESEARCH SAMPLE AND RESEARCH METHODS

This was a pharmaceutical-clinical retrospective-prospective study, done using the available literature and relevant databases. The research was conducted at the Clinical Center University of Sarajevo, General hospital “Prim. dr Abdulah

Nakaš" in Sarajevo, family medicine units and pharmacies, on a sample of 50 subjects of both sexes, who were either on allopurinol or febuxostat treatment. Effects of allopurinol and febuxostat on concentrations of uric acid and some lipid fractions (total, HDL and LDL cholesterol) were observed in 25 subjects on allopurinol treatment (group I), and in 25 subjects on febuxostat treatment (group II), who were chosen by defined criteria, with each patient serving as his or her control. The total observation period was six months and the cut was made after the first three months and at the end of the research.

Inclusion of subjects was done by the following criteria:

A) Hyperuricemia verified by a doctor, based on laboratory diagnostics
B) Availability of treatment data and its possible complications
C) Availability of indicators based on sex and age and an amnestic data.

All clinical measurements were conducted using standard methods of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) on appropriate biochemical analyzers.

For statistical analysis of the obtained results, Statistical Product and Service Solutions (SPSS) Software for Windows (version 20.0, SPSS Inc, Chicago, Illinois, The United States of America) and Microsoft Excel (version 13, Microsoft Corporation, Redmond, Washington, the United States of America) were used. Alpha (significance) level was 0.05.

3. RESULTS AND DISCUSSION

3.1 Results

In both groups, there were 14 (56%) male and 11 (44%) female subjects. Chi-square test did not find a statistically significant difference in sex-structure of subjects between the observed groups (χ^2=0.011; p=0.609).

The average age of subjects was 70.84±14.51 years (37–88) in group I, and 71.84±11.77 years (38–84) in group II. Analysis of variance (ANOVA) did not find a statistically significant difference in the average age of subjects between the observed groups (F=0.072; p=0.790).

In group I, 15 (60%) subjects had gout, where as in group II 18 (72%). Gout and metabolic syndrome were present in 10 (40%) subjects in group I and 7 (28%) in group II. Chi-square test did not find a statistically significant difference in established diagnoses of subjects between the observed groups (χ^2=0.786; p=0.276).

3.1.1 Analysis of biochemical parameters of subjects on allopurinol therapy

The initial concentration of uric acid in serum in subjects treated with allopurinol was 522.60±147.99 μmol/L, which was in the limits of high risk. At the end of the research, the concentration decreased by 126.28±20.36 μmol/L, compared to the initial concentration, and it was 396.32±138.97μmol/L, which was a statistically significant decrease (t=3.016; df=24; p=0.006) (Table 1).

The initial concentration of total cholesterol in subjects treated with allopurinol was 4.73±1.29 mmol/L, which was in the limits of desirable. After the second measuring, the concentration increased by 0.32±0.12mmol/L, and it was 5.05±1.60 mmol/L, which was not a statistically significant increase (t=-1.082; df=24; p=0.290). Between the second and the third measuring, the concentration increased by 0.03±0.02mmol/L, and it was 5.08±1.63 mmol/L, thus a statistically significant difference was not found (t=-0.166; df=24; p=0.870). At the end of the research, the concentration increased by 0.35±0.15 mmol/L, compared to the initial concentration, and it was 5.08±1.63 mmol/L, which was not a statistically significant increase (t=-1.151; df=24; p=0.261).

The initial concentration of HDL cholesterol in subjects treated with allopurinol was 1.08±0.21mmol/L. After the second measuring, the concentration decreased by 0.09±0.02 mmol/L, and it was 0.99±0.22 mmol/L, which was not a statistically significant decrease (t=1.900; df=24; p=0.070). Between the second and the third measuring, the concentration increased by 0.07±0.02 mmol/L, and it was 1.06±0.30 mmol/L, thus a statistically significant difference was not found (t=-1.109; df=24; p=0.287). At the end of the research, the concentration decreased by 0.02±0.01 mmol/L, compared to the initial concentration, and it was 1.06±0.30 mmol/L, which was not a statistically significant decrease (t=0.259; df=24; p=0.798).

Table 1. Average concentrations of uric acid during research in subjects treated with allopurinol

Uric acid μmol/L observation period	X	N	SD	SEM			
From the beginning of the research to the third month	522.60	25	147.99	29.59			
	430.48	25	201.25	40.24			
From the third month to the sixth month	430.48	25	201.23	40.24			
	396.32	25	138.97	27.79			
From the beginning of the research to the sixth month	522.60	25	147.99	29.59			
	396.32	25	138.97	27.79			
Uric acid μmol/L observation period	**Paired differences**					**t**	**df**	**p**
	X	**SD**	**SEM**	**95% CI**				
				Lower	**Upper**			
From the beginning of the research to the third month	92.12	17.29	5.05	19.76	164.47	**2.628**	**24**	**0.015**
From the third month to the sixth month	34.16	17.82	5.36	-38.82	107.14	0.966	24	0.344
From the beginning of the research to the sixth month	126.28	20.36	1.87	39.85	212.70	**3.016**	**24**	**0.006**

**standard error of the mean (SEM); *standard deviation (SD); *confidence interval (CI); *degrees of freedom (df)*
**p value-the level of statistical significance; *t-distribution (t)*

The initial concentration of LDL cholesterol in subjects treated with allopurinol was 3.14±1.38mmol/L. After the second measuring, the concentration decreased by 0.17±0.05 mmol/L, and it was 2.97±1.16 mmol/L, which was not a statistically significant decrease (t=0.584; df=24; p=0.565). Between the second and the third measuring, the concentration increased by 0.20±0.02 mmol/L, and it was 3.17±1.37 mmol/L, thus a statistically significant difference was not found (t=-1.020; df=24; p=0.318). At the end of the research, the concentration increased by 0.03±0.02 mmol/L, compared to the initial concentration, and it was 3.17±1.37 mmol/L, which was not a statistically significant increase (t=0.154; df=24; p=0.879).

The initial value of the atherogenic index in subjects treated with allopurinol was 3.50±1.36. After the second measuring, the value of the atherogenic index increased by 0.77±0.19, and it was 4.28±1.99, which was not a statistically significant increase (t=-1.950; df=24; p=0.063). Between the second and the third measuring, the value of the atherogenic index increased by 0.10±0.02, and it was 4.38±2.35, thus a statistically significant difference was not found (t=-0.207; df=24; p=0.838). At the end of the research, the value of the atherogenic index increased by 0.88±0.34, compared to the initial value, and it was 4.38±2.35, which was not a statistically significant increase (t=1.880; df=24; p=0.072).

3.1.2 Analysis of biochemical parameters of subjects on febuxostat therapy

The initial concentration of uric acid in serum in subjects treated with febuxostat was 577.04 ±120.25 μmol/L, which was in the limits of high risk. At the end of the research, the concentration decreased by 252.80±94.17 μmol/L, compared to the initial concentration, and it was 324.24± 45.77 μmol/L, which was a statistically significant decrease (t=13.4; df=24; p=0.001) (Table 2).

The initial concentration of total cholesterol in subjects treated with febuxostat was 5.12±0.82 mmol/L, which was in the limits of desirable. After the second measuring, the concentration increased by 0.03±0.01 mmol/L, and it was 5.15±0.65 mmol/L, which was not a statistically significant increase (t=-0.196; df=24; p=0.846). Between the second and the third measuring, the concentration decreased by 0.08±0.05 mmol/L, and it was 5.07±0.59 mmol/L, thus a statistically significant difference was not found (t=0.627; df=24; p=0.537). At the end of the research, the concentration decreased by 0.05±0.03 mmol/L, compared to the initial concentration, and it was 5.07±0.59 mmol/L, which was not a statistically significant decrease (t=0.439; df=24; p=0.664).

The initial concentration of HDL cholesterol in subjects treated with febuxostat was 1.13±0.27 mmol/L. After the second measuring, the

concentration decreased by 0.10±0.02mmol/L, and it was 1.06±0.21 mmol/L, which was not a statistically significant decrease (t=1.986; df=24; p=0.059). Between the second and the third measuring, the concentration increased by 0.17±0.02 mmol/L, and it was 1.20±0.21 mmol/L, thus a statistically significant difference was found (t=3.342; df=24; p=0.003). At the end of the research, the concentration increased by 0.07±0.03 mmol/L, compared to the initial concentration, and it was 1.20±0.27mmol/L, which was not a statistically significant increase (t=1.173; df=24; p=0.252).

The initial concentration of LDL cholesterol in subjects treated with febuxostat was 3.24±0.87mmol/L. After the second measuring, the concentration increased by 0.22±0.07 mmol/L, and it was 3.47±0.82 mmol/L, which was not a statistically significant increase (t=-1.703; df=24; p=0.101). Between the second and the third measuring, the concentration decreased by 0.37±0.14mmol/L, and it was 3.09±0.58 mmol/L, thus a statistically significant difference was found (t=2.524; df=24; p=0.019). At the end of the research, the concentration decreased by 0.14±0.09 mmol/L, compared to the initial concentration, and it was 3.09±0.58 mmol/L, which was not a statistically significant decrease (t=1.045; df=24; p=0.307).

The initial value of the atherogenic index in subjects treated with febuxostat was 3.83±1.50. After the second measuring, the value of the atherogenic index increased by 0.40±0.28, and it was 4.23±1.63, which was not a statistically significant increase (t=1.578; df=24; p=0.128). Between the second and the third measuring, the value of the atherogenic index increased by 0.35±0.29, and it was 4.58±1.07, thus a statistically significant difference was not found (t=0.752; df=24; p=0.459). At the end of the research, the value of the atherogenic index increased by 0.75±0.05, compared to the initial value, and it was 4.58±1.07, which was not a statistically significant increase (t=1.827; df=24; p=0.080).

3.1.3 Comparison of the analyzed biochemical parameters during research with regard to the observed groups

The following figures show a comparison of the analyzed biochemical parameters during the study with respect to the observed groups (Fig. 1, Fig. 2, Fig. 3, Fig. 4).

Table 2. Average concentrations of uric acid during research in subjects treated with febuxostat

Uric acid µmol/L Observation period	X	N	SD	SEM				
From the beginning of the research to the third month	577.04 338.12	25 25	120.25 50.40	24.05 10.08				
From the third month to the sixth month	338.12 324.24	25 25	50.40 45.77	10.08 9.15				
From the beginning of the research to the sixth month	577.04 324.24	25 25	120.25 45.77	24.05 9.15				
Uric acid µmol/L **Observation period**	**Paired Differences**					**t**	**Df**	**p**
	X	**SD**	**SEM**	**95% CI**				
				Lower	**Upper**			
From the beginning of the research to the third month	238.92	89.00	17.80	202.17	275.66	**13.4**	24	**0.001**
From the third month to the sixth month	13.88	1.80	6.36	0.75	27.00	1.18	24	0.089
From the beginning of the research to the sixth month	252.80	94.17	18.83	213.92	291.67	**13.4**	24	**0.001**

**standard error of the mean (SEM)*
**standard deviation (SD)*
**confidence interval (CI)*
**degrees of freedom (df)*
**p value-the level of statistical significance*
**t-distribution (t)*

3.1.4 Comparison of the analyzed biochemical parameters during research with regard to the sex of subjects

Average concentrations of total cholesterol at the beginning of the research in subjects on allopurinol treatment were not significantly different with regard to the sex of subjects (p=0.442). At the end of the research, concentrations of total cholesterol increased in both sexes, but a statistically significant difference between sexes was not established (p=0.405).

Average concentrations of total cholesterol at the beginning of the research in subjects on febuxostat treatment were not significantly different with regard to the sex of subjects (p=0.698). At the end of the research, concentrations of total cholesterol decreased in females and increased in males, but a statistically significant difference between sexes was not established (p=0.185).

Average concentrations of HDL cholesterol at the beginning of the research in subjects on allopurinol treatment were not significantly different with regard to the sex of subjects (p=0.442). At the end of the research, concentrations of HDL cholesterol increased in females and decreased in males, but a statistically significant difference between sexes was not established (p=0.405).

Average concentrations of HDL cholesterol at the beginning of the research in subjects on febuxostat treatment were not significantly different with regard to the sex of subjects (p=0.698). At the end of the research, concentrations of HDL cholesterol increased in both sexes, but a statistically significant difference between sexes was not established (p=0.185).

Average concentrations of LDL cholesterol at the beginning of the research in subjects on allopurinol treatment were not significantly different with regard to the sex of subjects (p=0.276). At the end of the research, concentrations of LDL cholesterol increased in males and decreased in females, but a statistically significant difference between sexes was not established (p=0.405).

Average concentrations of LDL cholesterol at the beginning of the research in subjects on febuxostat treatment were not significantly different with regard to the sex of subjects (p=0.380). At the end of the research, concentrations of LDL cholesterol decreased in both sexes, but a statistically significant difference between sexes was not established (p=0.594).

Fig. 1. Average concentrations of total cholesterol during research with regard to the observed groups

The ANOVA test did not establish a statistically significant difference in the initial concentrations of total cholesterol after the first, second and third measuring in group I compared to group II (p=0.200; p=0.784; p=0.959, respectively)

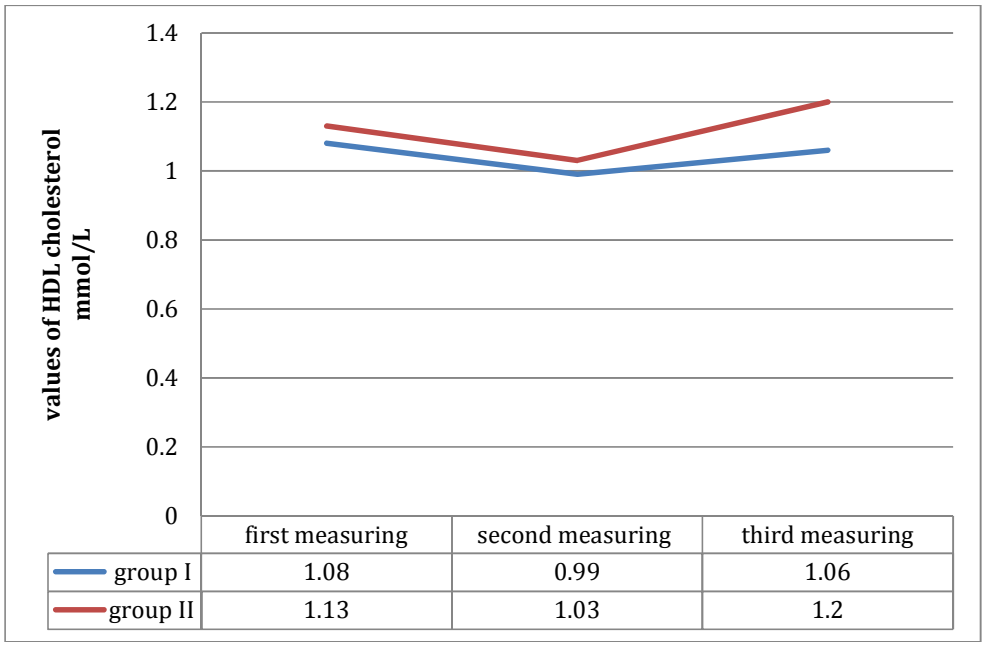

Fig. 2. Average concentrations of HDL cholesterol during research with regard to the observed groups

The ANOVA test did not establish a statistically significant difference in the initial concentrations of HDL cholesterol after the first, second and third measuring in group I compared to group II (p=0.467;p=0.535;p=0.102, respectively)

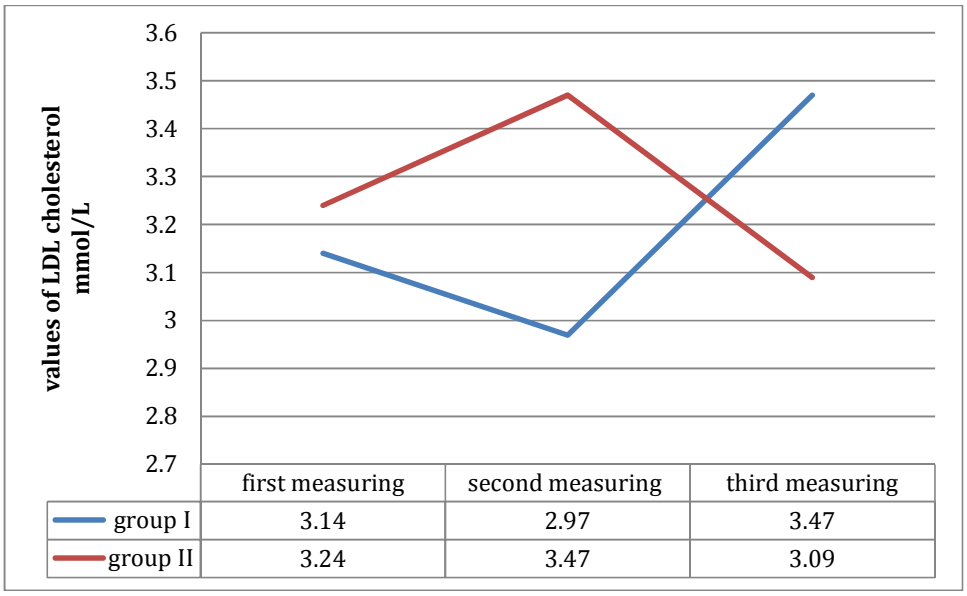

Fig. 3. Average concentrations of LDL cholesterol during research with regard to the observed groups

The ANOVA test did not establish a statistically significant difference in the initial concentrations of LDL cholesterol after the first, second and third measuring in group I compared to group II (p=0.759;p=0.086;p=0.782, respectively)

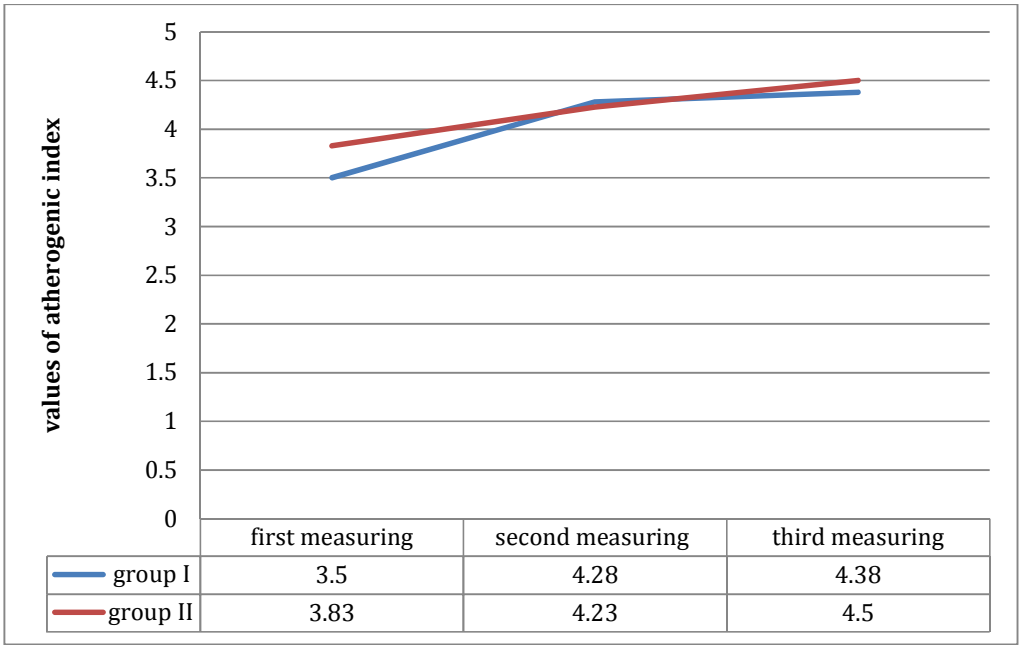

Fig. 4. Average values of the atherogenic index during research with regard to the observed groups

The ANOVA test did not establish a statistically significant difference in the initial values of the atherogenic index after the first, second and third measuring in the group I compared to group II (p=0.426, p=0.933, p=0.706, respectively)

The average value of the atherogenic index at the beginning of the research in subjects on allopurinol treatment was not significantly different with regard to the sex of subjects (p=0.800). At the end of the research, the value of the atherogenic index increased in both sexes, but a statistically significant difference between sexes was not established (p=0.753).

The average value of the atherogenic index at the beginning of the research in subjects on febuxostat treatment was not significantly different with regard to the sex of subjects (p=0.529). At the end of the research, the value of the atherogenic index increased in both sexes, but a statistically significant difference between sexes was not established (p=0.363).

3.1.5 Comparison of the analyzed biochemical parameters during research with regard to the established diagnoses

The average value of the observed laboratory parameters with regard to the established diagnoses and the research period is shown in Table 3.

3.2 Discussion

This research showed that both drugs were effective enough in treating hyperuricemia, although certain studies have proved that febuxostat was more effective [15-18]. At the end of the research, subjects with gout treated with allopurinol had significantly lower concentrations of total cholesterol compared to the subjects with gout and metabolic syndrome. A statistically significant difference in concentrations of HDL cholesterol in subjects with gout and both gout and metabolic syndrome was not established at the beginning and the end of the research regardless of the treatment. However, it was noticed that concentrations of HDL cholesterol in group II significantly increased after the treatment with febuxostat, which points to its positive effects. Subjects with gout and metabolic syndrome had significantly higher concentrations of LDL cholesterol at the beginning and the end of the research regardless of the treatment. However, a statistically significant decrease in concentrations of LDL cholesterol during the entire treatment with febuxostat was noticed in group II, which points to its positive effects. Some studies in which comparisons between the use of these two drugs and the risk of the

development of cardiovascular events and mortality were made have not shown cardioprotective effects of these drugs [19-20]. This research showed that the average values of the atherogenic index were higher in subjects with gout and metabolic syndrome at the beginning and the end of the research compared to subjects with gout in the group of subjects treated with allopurinol. In the group of subjects treated with febuxostat, a statistically significant difference in the average values of the atherogenic index was not established with regard to the established diagnoses in different stages of the research.

Table 3. The average value of the observed laboratory parameters with regard to the established diagnoses and the research period

Groups	Medical report	Period	Gout	Gout + MS	p
Allopurinol	Uric acid *unit μmol/L	Beginning of the research	537.26±153.58	500.60±144.28	0.555
		End of the research	385.00±165.32	413.30±91.93	0.628
Febuxostat		Beginning of the research	601.00±127.89	515.42±73.12	0.112
		End of the research	332.33±44.79	303.42±44.63	0.161
Allopurinol	Cholesterol *unit mmol/L	Beginning of the research	4.42±1.16	5.19±1.40	0.151
		End of the research	4.25±1.08	6.34±1.55	**0.001**
Febuxostat		Beginning of the research	4.84±0.64	5.85±0.81	**0.003**
		End of the research	4.89±0.49	5.50±0.61	**0.017**
Allopurinol	HDL cholesterol *unit mmol/L	Beginning of the research	1.10±0.19	1.03±0.24	0.406
		End of the research	1.04±0.27	1.09±0.35	0.646
Febuxostat		Beginning of the research	1.06±0.25	1.29±0.26	0.055
		End of the research	1.20±0.27	1.20±0.31	0.964
Allopurinol	LDL cholesterol *unit mmol/L	Beginning of the research	2.69±0.94	3.81±1.69	**0.045**
		End of the research	2.40±0.87	4.33±1.15	**0.001**
Febuxostat		Beginning of the research	3.02±0.71	3.78±1.06	**0.049**
		End of the research	2.96±0.44	3.43±0.77	**0.047**
Allopurinol	Atherogenic index	Beginning of the research	3.03±0.99	4.21±1.57	**0.030**
		End of the research	3.34±1.29	5.95±2.75	**0.004**
Febuxostat		Beginning of the research	3.87±1.57	3.73±1.42	0.844
		End of the research	4.34±0.83	5.19±1.42	0.073

**MS-metabolic syndrome*

**p value-the level of statistical significance*

The relation between concentrations of urates and lipids in serum is particularly interesting and somewhat contrary in studies. Some studies have shown a direct correlation between concentrations of lipids in serum and hyperuricemia in subjects with metabolic syndrome [11-13]. Studies have further shown that high concentrations of LDL cholesterol negatively correlated with hyperuricemia, while the positive correlation was noted regarding total and HDL cholesterol. A study conducted by Heimbach and associates in subjects with gout and metabolic syndrome showed that concentrations of uric acid were not a good predictor of concentrations of total cholesterol. Results have shown that the drug-modified concentrations of uric acid were in a weak correlation with concentrations of triglycerides and LDL cholesterol [21]. Zhang and associates noticed a statistically significant increase in concentrations of HDL cholesterol after the treatment with febuxostat. A statistically significant decrease in concentrations of total and LDL cholesterol was also noted [22]. As a part of this research, positive effects of febuxostat on concentrations of HDL and LDL cholesterol were noted, which surely lowered the potential risk of cardiovascular events?

4. CONCLUSION

The concentration of uric acid in serum occurs as a potential marker, not only of cardiovascular and cerebrovascular diseases, but it is also related to the insulin resistance, and it is the main risk factor for developing gout, which has been confirmed by numerous clinical studies. This research showed that subjects who received allopurinol, as well as those who received febuxostat, had pharmacologically acceptable concentrations of uric acid in serum, thus both drugs showed the effectiveness in treating hyperuricemia and certain effects on concentrations of some lipid fractions. Positive effects of febuxostat on concentrations of HDL and LDL cholesterol were noted, which surely lowered the potential risk of cardiovascular events.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The authors certify that the research protocol was in accordance with the ethical standards of the relevant ethics review committees and the Helsinki Declaration. This study was carried out after the approval was gained from the hospital ethics committee of General hospital „Prim. dr. Abdulah Nakaš" in Sarajevo and Clinical center University of Sarajevo -Clinic for Endocrinology, Diabetes and Metabolic Diseases.

DISCLAIMER

Products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between authors and producers of products because we do not intend to use these products as the avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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