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Original article

Association of the Disease Duration and Administered Therapy with Metabolic Syndrome in Patients with Systemic Lupus Erythematosus

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SUMMARY

Aim. The aim of the paper was to examine the impact of disease duration and administered therapy on the development of metabolic syndrome (MetS) in patients with systemic lupus erythematosus (SLE).
Material and methods. This study involved 55 patients (50 females and 5 males) with the diagnosis and 49 healthy controls of similar age. MetS was defined according to modified NCEP-ATP III diagnostic criteria, and obesity was defined by body mass index BMI > 30.
Results. In the group of SLE patients with MetS, there were 23 individuals (41.82%). In the control group, there were 10 (20.4%) patients with MetS. There were significantly more SLE patients with MetS in comparison to the controls (p = 0.04). Duration of the disease in the group with MetS was longer in comparison to those without MetS, but it was not statistically significant (15.35 ± 10.26 vs 10.44 ± 7.88, p = 0.073). The study confirmed that there is a moderate association (CC = 0.355) between disease duration and number of MetS parameters, however, this dependency was not statistically significant (p = 0.439). In the group without MetS, there were statistically more patients treated with antimalarial drugs monotherapy (p = 0.023). It has been found that the patients with MetS were treated with corticosteroid therapy longer than those without MetS, but it was not statistically significant (153.57 ± 103.34 vs 114.75 ± 83.32, p = 0.129).
Conclusion. Patients with longer SLE duration have more often MetS. It has been shown that, statistically, more patients without MetS were treated with antimalarial drugs monotherapy, and that long-term CS use, in our study, was not associated with higher incidence of MetS.

Keywords: **systemic lupus erythematosus, metabolic syndrome, corticosteroids, antimalarial drugs**

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a rheumatoid autoimmune disorder affecting almost any organ system and is characterized by the production of numerous autoantibodies. It is most common in females, especially during the generative period (1). It has been known for a long time that an increased risk of cardiovascular (CV) events is linked with autoimmune diseases. Accelerated atherosclerosis, being a consequence of chronic autoimmune inflammation, traditional risk factors and immunosuppressive treatment (primarily corticosteroids), is associated with a five-fold increased risk of CV events (2).

Metabolic syndrome (MetS) is a combination of metabolic abnormalities, increasing the risk of cardiovascular diseases and diabetes mellitus. According to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), MetS is defined as the presence of three or more of the following criteria: waist circumference over 102 cm in men and over 88cm in women – which is equivalent to body mass index (BMI) ≥ 30 kg/m^2 (3), blood pressure values over 130/85 mmHg (or use of antihypertensive drugs), plasma triglycerides ≥ 1.7 mmol/L, HDL values < 1mmol/L in men and < 1.3 mmol/L in women, and fasting blood glucose ≥ 6.1 mmol/L (or use of medication for diabetes mellitus) (4). Although the prevalence of MetS in SLE patients varies in different parts of the world, it is higher than in the general population, as confirmed by numerous studies (5).

The use of corticosteroids plays an essential part in the management of SLE patients, and although they reduce the CV risk by reducing inflammation and disease activity in SLE patients on the one hand, their chronic and long-term use, on the other hand, increases the presence of traditional risk factors, primarily hypertension and hyperglycemia (6).

The aim of our study was to examine whether the disease duration and the type of administered therapy may impact MetS manifestation in SLE patients.

MATERIAL AND METHODS

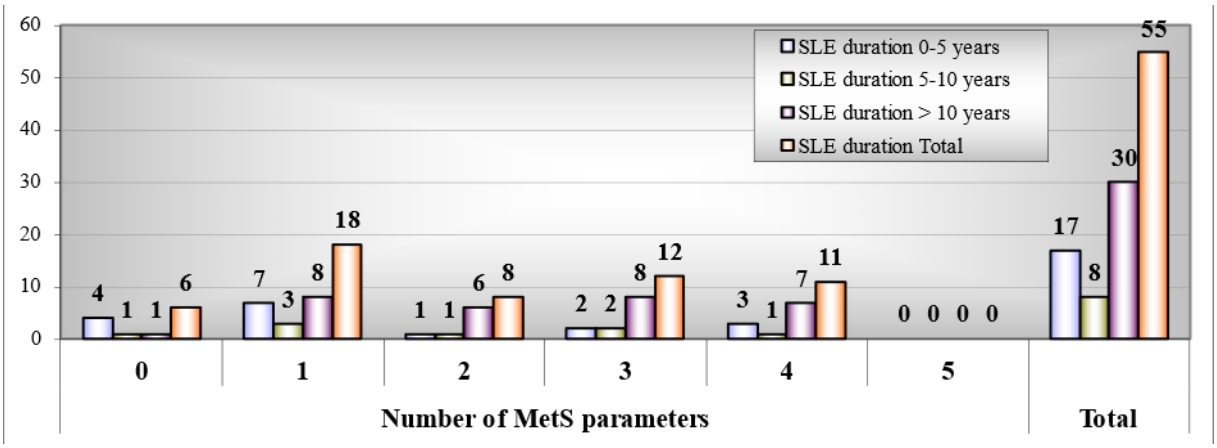
The study enrolled 55 patients with SLE diagnosis established according to the 2012 SLICC criteria (7). All the patients were treated at the Rheumatology Clinic of the Institute "Niška Banja" in the period from 2014 to 2018. The control group included 49 patients with similar age, treated for osteoarthrosis. MetS was defined according to modified NCEP-ATP III diagnostic criteria. Laboratory analyses included measurements of fasting blood glucose, plasma triglycerides, high density lipoprotein (HDL) by using standard methods. Furthermore, blood pressure, patients' height and weight were measured, followed by body mass index (BMI) calculation (using the formula – patient's weight in kilograms divided by height in meters squared). Data on administered treatment were obtained retrospectively from the available medical records. Prednisone dose referred to the dose over the previous six months before the cross-section. Differences in the incidence of observed parameters were tested by using a z-test. Differences in mean values of continuous characteristics were tested by using t-test and Mann-Whitney U test depending on normality of data. Chi square test along with the contingency coefficient was used to examine if there was an association between disease duration and the number of parameters defining MetS.

RESULTS

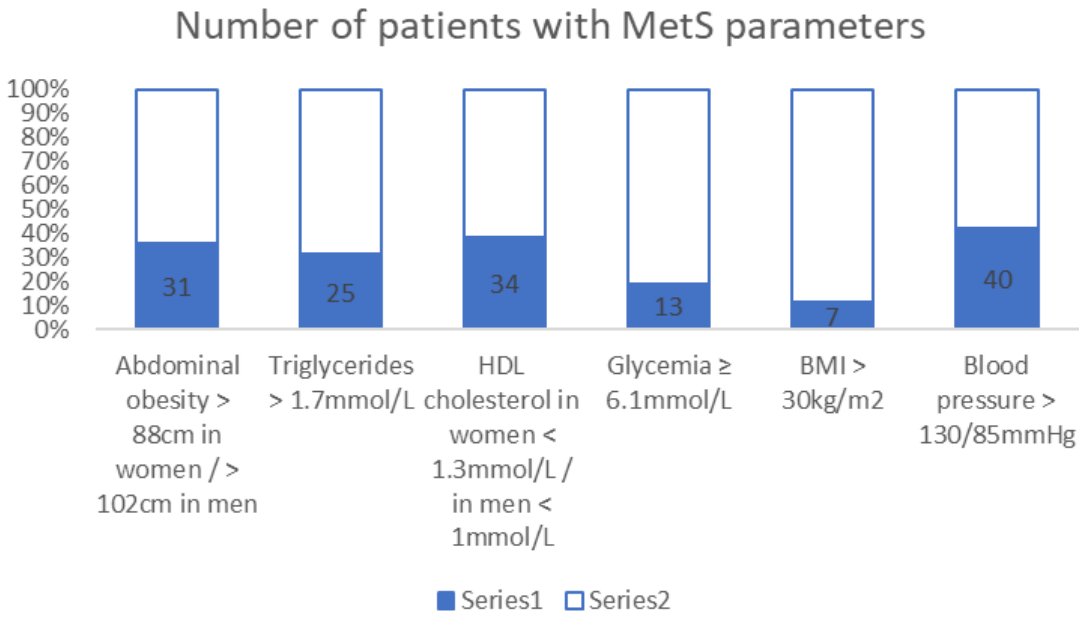
A total of 55 SLE patients underwent examination (50 females and 5 males). The control group comprised 49 patients (42 females and 7 males). In the group of SLE patients with MetS there were 23 patients (41.82%). There were 10 patients with MetS in the control group (20.4%). The number of patients with MetS was significantly higher in the SLE patients group in comparison to the controls ($p = 0.04$). The mean age of patients in SLE group was 51.06 ± 10.39 and 51.07 ± 8.13 years in the control group. There was no statistical difference in age between these two groups of patients ($p = 0.62$). SLE patients with MetS were older in comparison to SLE patients without MetS, but there was no statistically significant difference between these two groups (51.44 ± 11.42 vs 50.68 ± 9.34, $p = 0.506$). Depending on SLE duration, the patients were divided into three groups: I group 0 - 5 years (17 patients), II group 5 - 10 years (8 patients), III group over 10 years (30 patients). Most patients without MetS parameters were in the group I - 4 patients, while the largest number of patients with 3 or more MetS parameters were in the group with longest SLE duration – 15 patients. The study confirmed, according to the

value of the contingency coefficient, that there is a moderate association between disease duration and number of MetS parameters. However, according to the results of Chi square test, this dependency was not statistically significant ($\chi^2 = 7.942$, CC = 0.355, df = 8, p = 0.439) (Graph 1).

The number of patients with individual MetS parameters within the entire group of SLE patients was shown in Graph 2.



Graph 1. *Number of MetS parameters in relation to SLE duration*
* SLE- Systemic lupus erythematosus; MetS -Metabolic syndrome



Graph 2. *Number and percentage of patients with individual MetS parameters in the whole group*

Also, it has been found that SLE duration in the group with MetS was not significantly longer in comparison to the patients without MetS (15.35 ± 10.26 vs 10.44 ± 7.88, p = 0.073).

A total of 19 patients (34.55%) were treated with antimalarial drug - chloroquine phosphate, 15 of them (46.88%) were in the group without MetS, and 4 (17.39%) in the group with MetS. Combined therapy – antimalarial drug and azathioprine were received by 17 (30.91%) patients. There were 19 (34.55%) patients on azathioprine monotherapy. In the group without MetS, there were statistically significantly more patients treated with antimalarial drugs administered as monotherap y (p = 0.023) (Table 1).

There were 54 (98.18%) patients on corticosteroid treatment receiving prednisone at a dose of 5 – 30 mg daily. According to prednisone dose they received over the period of 6 months before a cross-section, the patients were divided into three groups. Group I comprised the patients receiving prednisone at a dose of 5 – 10 mg daily (n = 38), patients in the group II received 11 – 20 mg daily (n = 16), and there was one patient receiving prednisone at a dose higher than 20 mg daily in the group III.

There was no statistically significant difference in the number of patients with prednisone therapy up to 20 mg daily between those with MetS and without MetS, however, in the group taking a dose of 20 mg or higher daily there was one patient and he had MetS (Table 2). It was found that the patients with MetS were treated with corticosteroids for a longer period of time in comparison to those without MetS, but the result was not statistically significant (153.57 ± 103.34 vs 114.75 ± 83.32, p = 0.129) (Table 1).

Table 1. *The number of SLE patients according to administered therapy in relation to the presence of MetS*

	Without MetS (n = 32)	With MetS (n = 23)	Total (n = 55)	Significance
Chloroquine phosphate	15 (46.88%)	4 (17.39%)	19 (34.55%)	**p = 0.023**
Chloroquine phosphate and azatioprin	7 (21.88%)	10 (43.48%)	17 (30.91%)	p = 0.070
Azatioprin	10 (31.25%)	9 (39.13%)	19 (34.55%)	p = 0.544
Prednison	31 (96.88%)	23 (100%)	54 (98.18%)	0.388
Dose of prednison 5 – 10 mg	21 (65.63%)	17 (73.91%)	38 (69.09%)	0.430
Dose of prednison 11 – 20 mg	11 (34.38%)	5 (21.74%)	16 (29.09%)	0.059
Dose of prednison > 20 mg	0 (0%)	1 (4.35%)	1 (1.82%)	**< 0.001**
Prednison/number of months	114.75 ± 83.32	153.57 ± 103.34	130.98 ± 93.32	0.129

Table 2. *Number of SLE patients with MetS compared to those without it, according to the presence of single MetS parameters and SLE duration*

SLE duration	Without MetS (n = 32)	With MetS (n = 23)	Total (n = 55)	Significance
SLE duration 0 - 5 years	12 (37.5%)	5 (21.74%)	17 (30.91%)	**0.025**
SLE duration 5 - 10 years	5 (15.63%)	3 (13.04%)	8 (14.55%)	**< 0.001**
SLE duration > 10 years	15 (46.88%)	15 (65.22%)	30 (54.55%)	0.068

* SLE- Systemic lupus erythematosus, MetS – Metabolic syndrome

DISCUSSION

In our group of SLE patients, 42% of them had MetS. Previous studies showed that the prevalence of MetS in patients with SLE ranged from 3.3% to 45.2% (8). There are different prevalence rates of MetS in SLE patients in different countries, with increasing tendency in developed countries and in patients with poor lifestyle habits – sedentary lifestyle and unhealthy diets (with higher consumption of fat, salt and sugar).

Patients with autoimmune diseases are at a higher risk of developing cardiovascular complications due to the presence of traditional risk factors (individual components of metabolic syndrome), as well as the presence of chronic inflammation and use of certain drugs that may result in the development and increase in the incidence of traditional risk factors (2). SLE patients are at a 5 - 6-fold risk of developing cardiovascular diseases (CVD) and at almost 50-fold higher risk of developing myocardial infarction (9).

Hypertension as one of the leading factors of CVD in SLE (10) and its development may be explained by renal damage in SLE, as well as by renal vascular endothelial dysfunction. However, hypertension occurs in SLE patients without renal damage as well. Its development may be explained by other causes, such as elevated levels of endothelin-1 that may result in renal vasoconstriction, as well as increased activity of renin-angiotensin-aldosterone system (RAAS) in these patients, leading to an increase in oxidative stress (11). Also, on the other hand, hypertension in these patients is associated with serological markers of the disease activity, pro-inflammatory cytokines levels (TNFalpha, IL6, BAFF), as well as oxidative stress parameters and insulin resistance, suggesting that chronic inflammation may have a role in the development of hypertension in these patients (12, 13). In our experimental group of SLE patients, there were 40 (72.73%) patients with elevated blood pressure, or they were using antihypertensive drugs, statistically significantly more in the group with MetS in comparison to those without it, but in our patients we did not examine the kidney function, which is one of the limitation of the study.

Older age at the time of diagnosis, longer duration of the disease, prolonged use of corticosteroids, as well as hypercholesterolemia, are more common in patients suffering from SLE and having some cardiovascular event in comparison to those without cardiovascular (CV) event (14). In our group of patients there was no significant difference in age between those with and without MetS, but it was found that patients with longer duration of SLE had more often MetS parameters, but it is not known if there is a direct relationship between the duration of SLE and the occurrence of MetS.

Dyslipidemia in SLE refers to increased total cholesterol, triglycerides and LDL particles and decreased HDL particles in the blood (15). One retrospective study reported higher prevalence of elevated total cholesterol, triglycerides, LDL, and low HDL in SLE patients in comparison to healthy population (16). A possible cause of dyslipidemia in SLE is chronic systemic inflammation that may lead to specific changes in lipoprotein metabolism. Autoantibodies in SLE may induce endothelial damage, activate pro-inflammatory cytokines and alter expression of cell adhesion molecules that intensely take up LDL particles and metabolize them into the intima of blood vessels, leading to atherosclerotic plaque formation. Antibodies to oxidized LDL particles are formed, correlating with anti-ds-DNA antibodies and SLE activity. Increased level of TNF alpha correlates with triglyceride levels and disease activity (17). Also, dyslipidemia in these patients may be induced by the administration of certain drugs. First of all, chronic long-term use of corticosteroids (primarily prednisone at doses over 10 mg daily) is linked with an increase of total cholesterol, LDL and plasma triglyceride levels (18).

Corticosteroids are definitely most strongly associated with an increase in developing cardiovascular risk and mortality in these patients, since they increase the risk factors for CVD (hypertension, hyperglycemia, obesity). It is known that higher cumulative dose of corticosteroids (CS) is associated with greater cardiovascular (CV) risk (19). Long-term CS use, in our study, was not associated with higher incidence of MetS.

On the other hand, hydroxychloroquine, i.e. its long-term chronic usage in these patients, has a protective effect on dyslipidemia. These results are in accordance with our results that show statistically significantly more SLE patients in the group without MetS who were on antimalarial monotherapy in comparison to SLE patients with MetS.

The prevalence of obesity in SLE patients is high, even up to 30 - 40%, as described in previous studies (12). In our experimental group there were 7

(12.73%) patients with BMI > 30 kg/m^2. Some earlier studies reported that disease activity assessed by using SLEDAI score, as well as the duration of SLE, correlates with the presence of MetS and cardiovascular risk among these patients (13). In our study, we have not assessed SLE activity, which is one of the limitation of the study. It is also known that antimalarial drugs may have a cardioprotective role in SLE patients (they have antithrombotic effect, reduce levels of LDL, triglycerides and glucose, and also reduce development of carotid plaque (20, 21). Although their exact mechanism of action is not known, it has also been found in our experimental group that the majority of patients without MetS were treated with antimalarial-based monotherapy.

CONCLUSION

Our study showed that patients with longer SLE duration have more often MetS, regardless of patients' age. Also, it was registered that statistically more patients without MetS were treated with antimalarial drugs in monotherapy in comparison to those with MetS, and that long-term use of CS, in our group of patients, was not associated with higher incidence of MetS in SLE patients.

Ethical standards

The study was conducted according to the guidelines of the Declaration of Helsinki.

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Povezanost dužine trajanja bolesti i primenjene terapije sa metaboličkim sindromom kod pacijenata obolelih od sistemskog eritemskog lupusa

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SAŽETAK

Cilj rada. Cilj rada bio je ispitati uticaj dužine trajanja bolesti i primenjene terapije na ispoljavanje metaboličkog sindroma (MetS) kod bolesnika sa sistemskim eritemskim lupusom (*systemic lupus erythematosus*, SLE).
Materijal i metode. Ispitano je 55 bolesnika (50 žena i 5 muškaraca) i 49 zdravih ljudi sličnih godina starosti (kontrolna grupa). MetS je definisan prema modifikovanim NCEP-ATP III dijagnostičkim kriterijumima, tako da je gojaznost predstavljena indeksom mase tela BMI > 30.
Rezultati. U grupi SLE bolesnika sa MetS bilo je 23 bolesnika (41,82%). U kontrolnoj grupi bilo je 10 (20,4%) bolesnika koji su imali MetS. Bilo je značajno više ispitanika sa SLE koji su imali MetS u odnosu na kontrolnu grupu (p = 0,04). Dužina trajanja bolesti u grupi sa MetS bila je veća u odnosu na one bez MetS, ali nije bilo statističke značajnosti (15,35 ± 10,26 prema 10,44 ± 7,88; p = 0,073). Ispitivanjem je potvrđeno da postoji povezanost srednje jačine između trajanja bolesti i broja parametara MetS (CC = 0,355), ali nije bilo statističke značajnosti (p = 0,439). U grupi bez MetS bilo je značajno više bolesnika koji su lečeni primenom antimalarika u monoterapiji (p = 0,023). Nađeno je da su bolesnici sa MetS bili duže lečeni kortikosteroidnom terapijom u odnosu na one koji nisu imali MetS, ali bez statističke značajnosti (153,57 ± 103,34 prema 114,75 ± 83,32; p = 0,129).
Zaključak. Bolesnici sa dužim trajanjem SLE češće imaju MetS. Pokazano je da je statistički veći broj bolesnika bez MetS lečen antimalarikom u monoterapiji u odnosu na one sa MetS i da duža upotreba KS nije bila povezana sa većom učestalošću MetS.

Ključne reči: **sistemski eritemski lupus, metabolički sindrom, kortikosteroidi, antimalarici**