ORIGINAL ARTICLE

Impact of physical activity on the progression of atherosclerosis in patients with antiphospholipid syndrome

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Summary

Introduction: Antiphospholipid syndrome (APS) is linked to an increased risk of cardiovascular diseases due to the interplay between traditional risk factors and antibody-induced endothelial damage. Limited data exist on the level of physical activity (PA) in APS patients. This study aimed to analyze PA domains in Serbian APS patients and their association with atherosclerosis progression.

Materials and Methods: Fifty-one APS patients (29 with primary APS (PAPS), mean age 44.0 ± 11.5, and 22 with APS/SLE (sAPS), mean age 48.4 ± 11.7) completed the long form of the International Physical Activity Questionnaire (IPAQ), translated into Serbian. PA was categorized into leisure time, domestic activities, work-related, and transport-related domains, and classified as low, moderate, or high. Carotid Doppler ultrasound scans were performed to detect atherosclerotic plaques.

Results: The total PA in a PAPS group ranged from 0 to 26.880 MET-minutes/week and in sAPS from 0 to 19.200. Work-related and domestic activities had the highest scores, while leisure time PA was lowest. Most patients had low (37.3%) or moderate (43.1%) PA levels, with only 19.6% in the high PA category. No significant PA differences were found between PAPS and sAPS patients. However, PAPS patients were more likely to have high PA (27.6% vs. 9.1%), though not significantly. Patients with lower PA scores had a higher prevalence of carotid plaques, particularly for vigorous (p=0.001) and total PA (p=0.002).

Conclusion: Younger Serbian APS patients predominantly exhibit low or moderate PA, especially during leisure time. Low PA strongly correlates with atherosclerosis progression, underscoring the need to promote physical activity in this population.

Keywords: antiphospholipid syndrome; atherosclerosis; physical activity.

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INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized clinically by recurrent thrombosis (venous and/or arterial) and/or recurrent spontaneous abortions, in conjunction with persistently elevated antiphospholipid antibodies (defined as a significant increase in these antibodies at least once every 12 weeks) (1). This syndrome can manifest either as a primary condition (PAPS) or be associated with other diseases (sAPS), including autoimmune, hematological, infectious, malignant, or neurological disorders. Antiphospholipid antibodies (aPL) constitute a family of autoantibodies with an affinity for negatively charged phospholipids complexed with phospholipid-binding proteins, and they are closely linked to the development of arterial and/or venous thrombosis, as well as obstetric complications.

The prevalence of APS is higher among women than men, with a ratio of 5:1, and it exhibits no predisposition concerning ethnicity. The annual incidence stands at 5 cases per 100,000 individuals, while the overall prevalence ranges between 40 and 50 cases per 100,000 people (2).

Circulating aPL often exhibit limited responsiveness to immunomodulatory treatments (3). Their persistent presence, often in varying titers, triggers numerous pathophysiological mechanisms (4). The chronic vasculopathy associated with APS is primarily characterized by endothelial dysfunction as a central hallmark of vascular abnormalities (5). Subsequent stages of vascular involvement lead to the progressive thickening of the intima, possibly due to endothelial cell proliferation (6-8). These vascular changes related to APS have initially been observed in the renal microvasculature (9,10). Similar occlusive lesions are likely under-recognized in organs and tissues that are not routinely subjected to biopsy, such as the brain, heart, and mesentery. Cerebrovascular and cardiovascular disorders, specifically stroke and myocardial infarction, are the leading causes of morbidity and mortality in APS patients, especially among young individuals. Primary APS patients have demonstrated that the risk of (sub)clinical atherosclerosis is associated with APS itself, independent of other underlying conditions (11).

Engaging in physical activity is associated with a lower risk of atherosclerotic cardiovascular disease, with greater volume and intensity of exercise leading to further reductions in risk. Research indicates that the most significant decline in risk occurs when transitioning from a sedentary lifestyle to approximately 5000 MET-minutes per week, equivalent to around 13–14 hours of walking weekly. This activity level is linked to an estimated 30% reduction in risk. Beyond this threshold, the benefits tend to plateau, with the maximum expected risk reduction reaching approximately 40–50% (12).

To support cardiovascular health, the World Health Organization (WHO) currently advises engaging in 150–300 minutes of moderate-intensity aerobic exercise or 75–150 minutes of vigorous-intensity exercise per week (13). In clinical settings, recommending an increase in daily step count may be a practical approach. Evidence suggests that adding 1000 steps per day—starting from a baseline of 2000 to 5000 steps—is associated with a 5–10% reduction in risk, with benefits continuing up to a total of 10,000 daily steps (14). Given the clear evidence of accelerated atherosclerosis in patients with APS, promoting physical activity in this population is of significant importance.

The primary objective of this study is to assess the levels of physical activity within a cohort of Serbian APS patients and investigate its potential correlation with the progression of the atherosclerotic process, as indicated by the presence of atherosclerotic plaques in the carotid arteries, as determined by Doppler ultrasound examination.

MATERIALS AND METHODS

This cross-sectional cohort study enrolled 51 APS patients between October 1, 2022, and January 31, 2023. The diagnosis of APS was established following the revised Sydney criteria (both laboratory and clinical) from 2006 (15). Diagnosis of Systemic Lupus Erythematosus (SLE) was made by a rheumatologist following the revised ARA (American College of Rheumatology) criteria (16). Disease activity was assessed at the time of enrollment using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (17). This study included 29 PAPS patients (25 females and 4 males, mean age 44.0±11.5) and 22 sAPS patients (18 females and 4 males, mean age 48.4±11.7). Exclusion criteria comprised conditions that could influence endothelial perturbation (acute or chronic infection, malignancy, or marked renal, cardiac, and hepatic impairment), as well as a diagnosis made less than 6 months prior. SLE patients lacked active central nervous system lupus manifestations, lupus nephritis, cytopenias, or any skin manifestations. The mean SLEDAI for SAPS patients was 4.7 ± 1.9. All patients received appropriate therapy in accordance with the activity of the disease (18).

The study obtained approval from the University Hospital Clinical Centre Bezanijska kosa Ethical committee (7673/1/2021; date: 19.10.2021.), and written informed consent was obtained from all individual participants. All procedures performed on patients adhered to the Helsinki Declaration and its subsequent amendments or equivalent ethical standards.

Patients

During routine outpatient visits, all patients underwent the following procedures: physical examination and electrocardiography (ECG) recording, Doppler carotid ultrasound, blood sampling, and assessment of physical activity via questionnaire.

In the clinical examination, the presence of standard risk factors for atherosclerosis was determined. Hypertension was defined as systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg recorded on two or more consecutive examinations before initiating antihypertensive therapy. Body weight and height were utilized to calculate the body mass index (BMI) using Adolphe Quetelet's formula (height/weight^2). A normal BMI value was considered below 26 kg/m^2, while a BMI of 26-30 kg/m^2 indicated overweight, and a BMI above 30 kg/m^2 categorized patients as obese. Diabetes mellitus was diagnosed by an endocrinologist (19). Hypercholesterolemia was defined as a total cholesterol value exceeding 5.2 mmol/L on two or more consecutive measurements or if the patient was already receiving lipid-lowering drug therapy. Smoking habits were also recorded.

Carotid artery ultrasound examinations, encompassing both common and internal carotid arteries, were performed using a high-resolution 7.0 MHz linear probe equipped with a 4 MHz pulsed color Doppler for flow measurement (Acuson, Sequoya 216). Carotid arteries were visualized from two lateral and one transverse section. Patients were positioned supine with head extension and rotated at a 45-degree angle to the opposite side of the examined artery. The left and right common carotid arteries (1 cm proximal to the bifurcation), the left and right carotid bifurcations, and the left and right internal carotid arteries (1–2 cm distal to the bifurcation) were examined for the presence of atherosclerotic plaques (20). The examinations were conducted by the same experienced operator who was unaware of the subjects' diagnoses.

All patients underwent laboratory blood tests to detect aPL, as well as routine biochemical blood tests and a complete blood count. Lupus anticoagulant (LA) was tested following the International Society on Thrombosis and Haemostasis guidelines, while anticardiolipin antibodies (aCL) and/or anti-beta2glycoprotein I (anti-β2GPI) antibodies of IgG and/or IgM isotype at medium or high titers were measured using standardized ELISA (21). LA testing was not performed on patients receiving anticoagulant therapy. Anticardiolipin (aCL: IgG/IgM) and anti-ß2glycoprotein I (ß2GPI: IgG/IgM) antibodies were determined by enzyme-linked immunosorbent assay (ELISA) and expressed in GPL or phospholipid (MPL) units (GPL-U and MPL-U). Following the revised laboratory criteria for APS diagnosis, the analysis of aPL was repeated at an interval of at least 12 weeks (12). All APS patients were categorized into the following categories: category I when more than one laboratory criterion was present in any combination, category IIa when only LA was present, category IIb when only anticardiolipin antibodies (aCL) were present, and category IIc when only anti-β2 glycoprotein-I antibodies (anti-β2GPI) were present (22).

The level of physical activity was assessed using The International Physical Activity Questionnaire (IPAQ) for evaluating physical activity levels over the past week, translated into Serbian (Appendix I). The physical activity level was scored as low, medium, or high, and MET-min/week was calculated according to the current protocol (https://sites.google.com/view/ipaq/score#h.sqdsh530qc5o).

Statistical Analysis

Descriptive and analytical statistical methods were employed in this study. Descriptive methods included absolute and relative numbers (n, %), measures of central tendency (arithmetic mean, median), and measures of dispersion (standard deviation). Analytical methods involved difference tests, both parametric (t-test) and non-parametric (Pearson's chi-square test, Fisher's exact probability test, Mann-Whitney U test). The choice of test depended on the data type and distribution. Parametric methods were used when the distribution was normal, while non-parametric methods were used for non-normal distributions. Distribution normality was assessed based on descriptive parameters, normality tests (Kolmogorov-Smirnov and Shapiro-Wilks test), and graphical methods (histogram, box plot, QQ plot). Univariate and multivariate logistic regression analysis was employed for association analysis. The level of statistical significance was set at $p<0.05$. All data were processed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Table 1 presents the clinical and laboratory characteristics of both patient groups. Patients with PAPS were significantly more likely to exhibit obstetric APS (69.0% vs. 36.4% in the sAPS group, p=0.022). Conversely, patients in the sAPS group were substantially more likely to possess positive aCL IgG (54.5% vs. 27.6% in the PAPS group, p=0.053), anti β2 GPI IgG antibodies (50.0% vs. 24.1% in the PAPS group, p=0.058) and triple aPL positivity (40.9% vs 13.8%, p=0.029). However, there were no differences in age, gender, and the prevalence of standard atherosclerotic risk factors between these two groups of subjects. Notably, the prevalence of standard atherosclerotic risk factors was less than 40% for both groups of respondents.

Regarding the different types of PA including a total time spent, there was no statistically significant difference between PAPS and sAPS patients. These results are summarized in **Table 2**.

While a notably higher percentage of PAPS patients exhibited a high level of physical activity (27.6% vs. 9.1%), statistically significant differences in the various levels of physical activity (low, medium, and high) were not observed between the examined groups (p=0.129). **Figure 1** provides a graphical representation of these findings.

Table 1. Demographic and clinical features of PAPS and sAPS patients

Variable	PAPS (n=29)	sAPS (n=22)	p-value
Age	44.0± 11.5	48.4 ± 11.7	0.185
Gender (m/f)	(4/25)	(4/18)	0.713
BMI (kg/m2)	25.0 (18.3-27.8)	25.1 (22.5-28.1)	0.549
Standard atherosclerotic risk factors			
Arterial Hypertension	5 (17.2%)	9 (40.9%)	0.063
Diabetes mellitus	1 (3.4%)	0 (0.0%)	0.384
Smoking	9 (31.0%)	6 (27.3%)	0.772
Hyperlipidemia	6 (20.7%)	8 (36.4%)	0.219
Specific clinical features			
Obstetric APS	20 (69.0%)	8 (36.4%)	**0.022**
Thrombosis	11 (37.9%)	12 (54.5%)	0.242
Arterial thrombosis	6 (20.7%)	10 (45.5%)	0.062
Venous thrombosis	5 (17.2%)	5 (22.7%)	0.628
apL characteristics			
LA	17 (58.6%)	13 (59.1%)	0.973
aCL IgG	8 (27.6%)	12 (54.5%)	0.053
aCL IgM	11 (37.9%)	11 (50.0%)	0.393
anti β2 GPI IgG	7 (24.1%)	11 (50.0%)	0.058
anti β2 GPI IgM	13 (44.8%)	12 (54.5%)	0.496
Category I	20 (69.0%)	17 (77.3%)	
Category IIa	5 (17.2%)	3 (13.6%)	0.489
Category IIb	3 (10.3%)	2 (9.1%)	
Category IIc	1 (3.4%)	0 (0.0%)	
Triple apL positivity	4 (13.8%)	9 (40.9%)	**0.029**

PAPS: primary antiphospholipid syndrome, sAPS: antiphospholipid syndrome associated with systemic lupus erythematosus, LA – lupus anticoagulant, apL – antiphospholipid antibody, aCL – anticardiolipin antibody GPI – glycoprotein1

Table 2. Level and type of physical activity in antiphospolipid syndrome patients

Variable	PAPS (n=29)	sAPS (n=22)	p-value
Total physical activity (MET-min/weekly)	0 (0-29.454)	0 (0-20.109)	0.177
Working place(MET-min/ weekly)	0 (0-26.880)	0 (0-19.447)	0.138
In-home activities (MET-min/ weekly)	1.080 (0-21.000)	900 (0-7920)	0.379
Leisure (MET-min/ weekly)	231 (0-2910)	297.5 (0-2772)	0.497
Transport (MET-min/ weekly)	693 (0.0-6930)	214.5 (0-2.772)	0.390
Walking (MET-min/ weekly)	1386 (0-6930)	528 (0-5544)	0.226
Moderate physical activity (MET-min/ weekly)	0 (0-14.400)	0 (0-5040)	0.210
Vigorous physical activity (MET-min/ weekly)	0 (0-26.880)	0 (0-19.200)	0.382

PAPS: primary antiphospholipid syndrome, sAPS: antiphospholipid syndrome associated with systemic lupus erythematosus

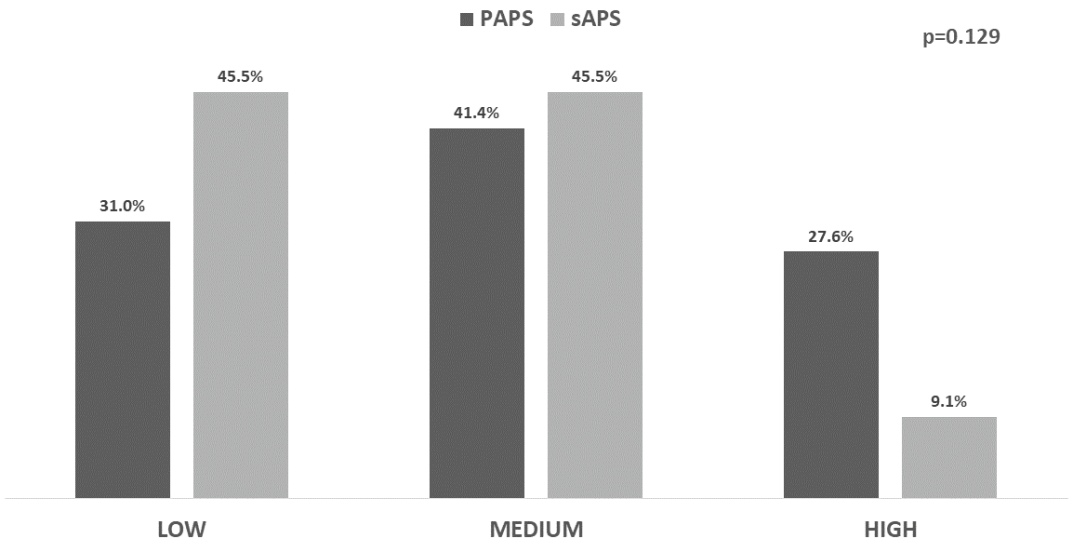

Figure 1. Level of physical activity among groups

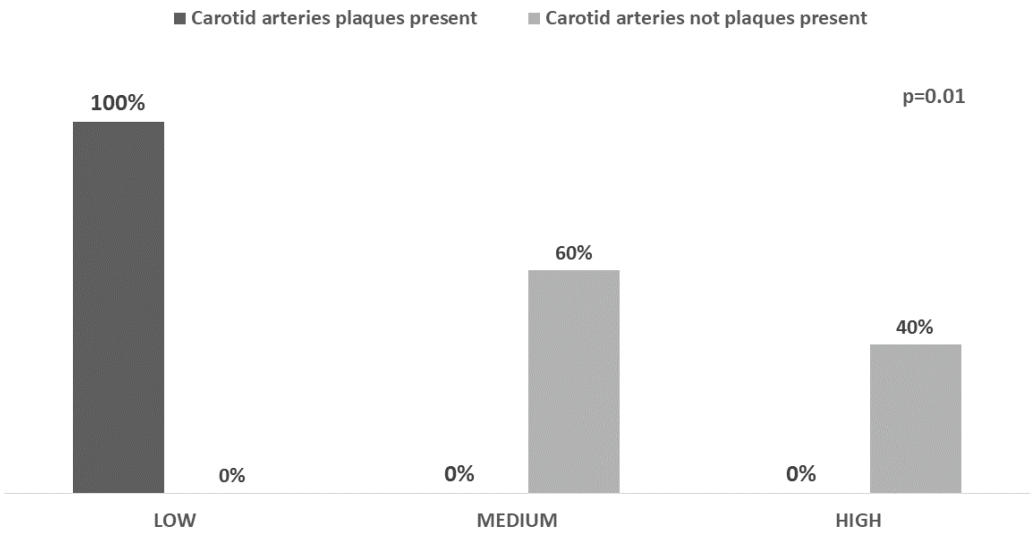

Figure 2. Level of physical activity considering carotid atherosclerotic plaque presence

The presence of carotid artery plaques was highly statistically significantly correlated with the level of PA in APS patients (p=0.01). All APS patients with plaques fell into the category of low physical activity. **Figure 2** visually represents these results.

APS patients with carotid artery plaques spent significantly fewer minutes engaged in physical activity at the workplace, during transportation, walking and in vigorous activities, as well as in total physical activity (p=0.042, p=0.011, p=0.021, p=0.001, p=0.002, respectively). **Table 3** provides a detailed presentation of these findings.

DISCUSSION

To date, there has been limited exploration of the impact of PA on APS patients in the literature. Our study sheds light on the fact that APS patients tend to have low levels of PA, and we have established a significant association between greater PA and a reduced prevalence of atherosclerotic plaques in the carotid arteries. This is particularly crucial given the predisposition of APS patients to cardiovascular diseases.

Karakis et al. demonstrated that APS patients had significantly elevated values of common carotid artery intima-media thickness (IMT), internal carotid artery IMT, and carotid bifurcation IMT, and they were more frequently diagnosed with atherosclerotic plaques compared to controls (11). Due to the heightened risk of atherosclerosis, the authors concluded that these patients require early and disease-specific atherosclerosis prevention. APS patients have been reported to have a 2.5–4-fold higher risk of subclinical atherosclerosis compared to the general population (11,23), a risk comparable to that seen in patients with diabetes mellitus (24, 25). Traditional risk factors such as hypertension and dyslipidemia, in combination with non-traditional factors including antiphospholipid antibodies (aPL), inflammation, and low anti-phosphorylcholine levels, contribute to the elevated risk of cardiovascular disease in Systemic Lupus Erythematosus (SLE) (26, 27).

Common risk factors for atherosclerosis typically encompass elevated cholesterol and triglyceride levels, high blood pressure, smoking, diabetes mellitus, obesity, and a sedentary lifestyle. Despite continuous advancements in therapeutic methods to manage these risk factors, the global prevalence of cardiovascular diseases remains high. Alarmingly, awareness of the risk of developing or exacerbating cardiac disorders in individuals with APS or other autoimmune diseases is often suboptimal. Bolla et al. conducted a study on 61 APS patients and found a similar or even higher prevalence of traditional cardiovascu-

Table 3. Time of the physical activity considering carotid atherosclerotic plaque presence

	Carotid artery plaque presence		
	Yes	No	p-value
Total physical activity (MET-min/weekly)	2580 (0-24.390)	8379 (0-29.454)	**0.002**
Working place (MET-min/ weekly)	0 (0-19.200)	693 (0-26.880)	**0.042**
In-home activities (MET-min/ weekly)	855 (0-11.040)	1890 (0/21.00)	0.328
Leisure (MET-min/ weekly)	99 (0-2097)	693 (0-2910)	0.072
Transport (MET-min/ weekly)	214.5 (0-6930)	792 (693-2772)	**0.011**
Walking (MET-min/ weekly)	561 (0-6930)	2079 (2079-6276)	**0.021**
Moderate physical activity (MET-min/ weekly)	0 (0-14.400)	0 (0-10.500)	0.851
Vigorous physical activity (MET-min/ weekly)	0 (0-19.200)	0 (0-26.880)	**0.001**

lar risk factors in APS compared to patients with rheumatoid disease and diabetes mellitus (28). Their study also hinted at an improvement in the control of certain risk factors over the past decade, possibly indicating a growing awareness of their significance.

This same group of researchers conducted a larger study involving 414 APS patients to investigate whether increasing physical activity reduces the risk of developing metabolic syndrome. They confirmed that physically active patients had a lower likelihood of developing metabolic syndrome (29).

Studies examining the effect of physical activity on cardiovascular risks in APS are limited. The beneficial impact of physical activity on preventing cardiovascular diseases and slowing the atherosclerotic process has been most extensively investigated in SLE patients. Legge et al. studied 100 SLE patients and found that just 10 minutes of light exercise reduced systolic and diastolic blood pressure as well as the 10-year risk of cardiovascular diseases. Increased physical activity led to more significant effects (30). Similarly, Tanaka et al. analyzed the influence of physical activity on arterial stiffness, measured through carotid-femoral pulse wave velocity (cfPWV), and found that arterial elasticity was higher in individuals engaged in moderate and substantial physical activity (31). A similar study conducted on Swedish subjects by Fernberg et al. yielded comparable results (32).

The low level of physical activity observed in PAPS patients can often be attributed to chronic fatigue and kinesiophobia. Bearne et al. emphasized that chronic fatigue is a significant limiting factor for achieving an adequate level of physical activity in this patient population, which can worsen their mental and physical condition and accelerate the progression of the primary disease (33). Bağlan Yentür and colleagues conducted a study on kinesiphobia and its impact on patients with SLE, highlighting that the fear of pain can deter movement and exacerbate atherosclerosis (34). Adequate treatment of kinesiphobia is thus crucial for the rehabilitation of these patients. A recent meta-analysis by Belgian authors included available studies on physical activity in SLE and demonstrated that appropriate physical activity significantly reduces chronic fatigue, emphasizing the need for more randomized studies to enhance rehabilitation strategies (35). Another meta-analysis by Blaess et al. underscored the issue of low physical activity levels in SLE patients and the favorable effects of aerobic training in this population, calling for clear recommendations (36).

LIMITATIONS

Our study has several limitations. Being a single-center study, its generalizability is restricted. The small sample size and the use of the IPAQ, which assesses physical activity only over the past week, pose challenges for drawing broader conclusions. Additionally, the cross-sectional design prevents the determination of causality or the assessment of longitudinal changes. Nevertheless, these limitations highlight the need for future research to validate and build upon our findings.

CONCLUSION

To the best of our knowledge, our study stands as the sole investigation to analyze the relationship between physical activity levels and the progression of the atherosclerotic process, as manifested by the prevalence of atherosclerotic plaques in the carotid arteries among APS patients. Beyond establishing a significant correlation between the level of physical activity measured in MET-min/week and the advanced stage of the atherosclerotic process, our study revealed that a significant proportion of APS patients, both primary and associated with SLE, exhibit low or moderate levels of physical activity. These findings underscore the need for clear guidelines and the promotion of physical activity within this patient population.

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Ethical approval: The study obtained approval from the University Hospital Clinical Centre Bezanijska kosa ethical committee (7673/1/2021; date: 19.10.2021.).

Informed consent: Informed consent was obtained from all subjects involved in the study.

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UTICAJ FIZIČKE AKTIVNOSTI NA PROGRESIJU ATEROSKLEROZE KOD BOLESNIKA SA ANTIFOSFOLIPIDNIM SINDROMOM

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Sažetak

Uvod: Antifosfolipidni sindrom (AFS) je povezan s povećanim rizikom od kardiovaskularnih bolesti usled interakcije tradicionalnih faktora rizika i antifosfolipidnih antitela na endotel. Cilj ove studije bio je analiza fizičke aktivnosti (FA) kod srpskih AFS bolesnika i njena povezanost s progresijom ateroskleroze.

Materijal i metode: Ispitan je 51 bolesnik sa AFS-om (29 sa primarnim AFS-om, PAFS, prosečne starosti 44.0 ± 11.5 godina, i 22 sa AFS-om udruženim sa SLE-om, sAFS prosečne starosti 48.4 ± 11.7 godina) korišćenjem IPAQ upitnika, prevedenog na srpski jezik. FA je analizirana kroz domene: slobodno vreme, kućne aktivnosti, posao i transport, i klasifikovana u nizak, umeren i visok nivo. Svim ispitanicima urađen je Doppler ultrazvučni pregled karotidnih arterija radi utvrđivanja prisustva plakova.

Rezultati: Ukupna FA u PAFS kretala se od 0 do 26.880 MET-min/nedeljno a u sAFS od 0 do 19.200, sa najvišim vrednostima za posao i kućne aktivnosti, a najnižim za slobodno vreme. Većina bolesnika imala je nizak ili umeren nivo FA (37,3% i 43,1%). Pacijenti s nižim skorom FA imali su značajno veću prevalencu karotidnih plakova, razlika je bila značajna za FA velikog intenziteta (p=0.001) i ukupnu FA (p=0.002).

Zaključak: Mladi AFS bolesnici u Srbiji imaju uglavnom nizak ili umeren nivo FA, s najnižim vrednostima u slobodnom vremenu. Nizak nivo FA povezan je s progresijom ateroskleroze, naglašavajući važnost promocije fizičke aktivnosti u ovoj populaciji.

Ključne reči: antifosfolipidni sindrom; ateroskleroza; fizička aktivnost;

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