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Effect of Lupus Nephritis on Cardiac Remodeling and Left Ventricular Relative Wall Thickness

Lupus Nefritinin Kardiyak Yeniden Yapılanma ve Sol Ventriküler Göreli Duvar Kalınlığı Üzerine Etkisi

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ÖZET

Amaç: Sistemik Lupus Eritematozus (SLE), yüksek kardiyovasküler komplikasyonlara yol açabilen otoimmün bir hastalıktır. Amacımız SLE'de böbrek tutulumunun sol ventrikül rölatif duvar kalınlığına (RWT) etkisini araştırmaktır.

Yöntem: Lupus nefriti olan ve olmayan SLE hastalarının ekokardiyografik özelliklerini karşılaştırmak için tek merkezli gözlemsel bir çalışma yapıldı. Çalışmaya toplam 125 hasta dahil edildi.

Bulgular: Lupus nefriti olan hastaların ortalama yaşı 31, lupus nefriti olmayanlarda ise 40 idi. Lupus nefriti olan hastalarda interventriküler septum kalınlığının daha ince olduğu görüldü. Lupus nefritli hastalarda Mitral A dalgası daha düşüktü (62,5±17 vs. 74,9±20,5, p<0,05). Lupus nefritli hastalarda sol ventrikül RWT daha düşük olduğu hesaplandı (0,38±0,06 vs. 0,43±0,07, p<0,05).

Sonuç: SLE yüksek kardiyovasküler komplikasyonlara yol açan ilerleyici bir hastalıktır. Lupus nefritinin gelişimi önemli miyokardiyal etkiye neden olur. Sol ventrikül RWT olumsuz kardiyovasküler sonuçları gösteren önemli bir parametredir.

Anahtar Kelimeler: Sistemik Lupus Eritematozus, lupus nefriti, sol ventrikül, rölatif duvar kalınlığı, diyastolik fonksiyon bozukluğu

ABSTRACT

Aim: Systemic Lupus Erythematosus (SLE) is an autoimmune disease associated with an increased risk of cardiovascular problems. Our objective is to investigate the effect of renal involvement in SLE on left ventricular relative wall thickness (RWT).

Methods: A single-center observational study was conducted to compare the echocardiographic characteristics of patients with SLE who had lupus nephritis and those without. A total of 125 patients were included in the study.

Results: The mean age was 31 years in patients with lupus nephritis and 40 years in those without. In patients with lupus nephritis, the interventricular septum thickness was found to be thinner. The Mitral A wave was lower in patients with lupus nephritis (62.5±17 vs. 74.9±20.5, p<0.05). Left ventricular relative wall thickness (RWT) was calculated to be lower in patients with lupus nephritis (0.38±0.06 vs. 0.43±0.07, p<0.05).

Conclusion: The development of lupus nephritis has a significant impact on myocardial function, and left ventricular RWT is an important parameter associated with adverse cardiovascular outcomes.

Keywords: Systemic Lupus Erythematosus, lupus nephritis, left ventricle, relative wall thickness, diastolic dysfunction

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic progressive autoimmune disease associated with high cardiovascular risk, where the underlying pathophysiological mechanisms are not fully understood. In SLE patients, myocardial and pericardial diseases increase the risk of heart failure (1-4). Although SLE alone carries a high cardiovascular risk, the development of nephritis, medications, lupus anticoagulant, and antiphospholipid antibodies can further exacerbate cardiac damage (5). Over time, myocardial fibrosis occurs in SLE patients, providing a basis for the development of heart failure. Approximately 50% of SLE patients experience kidney involvement (6). The development of lupus nephritis typically presents as the initial organ manifestation and can lead to end-stage renal failure. The rate of cardiovascular

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disease development in patients with lupus nephritis is twice as high as in those without (7).

Abnormalities in left ventricular relative wall thickness (RWT) have been identified as independent predictors in diseases affecting cardiovascular mortality and morbidity, such as heart failure, coronary artery disease, atrial fibrillation, and stroke (8). RWT is a parameter that reflects left ventricular geometry. Abnormal RWT is associated with cardiac remodeling. In hypertensive individuals with normal left ventricular mass, abnormal RWT is related to concentric remodeling, indicating early adaptation of the heart to hypertension (9). Pathological changes in left ventricular RWT may serve as an early indicator of systolic and diastolic dysfunction. Detecting these changes early is crucial for predicting cardiovascular complications and ensuring close monitoring of patients. In our study, we aimed to demonstrate the pathological alterations in left ventricular RWT in patients with lupus nephritis compared to those without nephritis.

METHODS

Participants

This is a single-center, retrospective, observational study performed at the Rheumatology Clinic. A total of 125 patients diagnosed with systemic lupus erythematosus who underwent routine echocardiography between 2020 and 2023 were included in the study. Patients with pathologically confirmed lupus nephritis were included in the study. Patients with other comorbidities or conditions that can confound SLE-associated echocardiography findings were excluded: History of coronary artery disease (n=6), heart failure (n=8), atrial fibrillation (n=4), ischemic stroke (n=1), hematological diseases (n=2), chronic kidney failure (n=2), malignancy (n=2), severe valvular disease (n=3), and pacemaker implantation (n=2). Patients with a direct impact on left ventricular function and dimensions and those with a history of active infection within the last month were also excluded. After excluding 30 patients, from the remaining 95 patients 22 had pathologically reported lupus nephritis and 73 without renal involvement. The flow chart in Figure 1 illustrates the inclusion and exclusion of patients. The present study followed the tenets of the Declaration of Helsinki. Ethics committee approval for the study was received with the ethics committee approval number 4901 of 2024.

Transthoracic echocardiography:

Comprehensive transthoracic echocardiography were performed by two experienced cardiologists. Philips Epiq 7c device was used. Echocardiographic measurements were performed according to the American Society of Echocardiography guidelines (10). The end-diastolic diameter of the left ventricle was measured. The posterior wall thickness of the left ventricle during diastole was also measured. RWT was calculated using the following formula RWT = 2 × PWT (posterior wall thickness)/LVDd (left ventricular diastolic diameter).

Data collection and data analysis

Patients' medical charts were reviewed to collect their demographic characteristics and clinical data, including laboratory tests. Data analysis was conducted using SPSS software (version 20.0; SPSS Inc, Chicago, IL) and presented as mean ± standard deviation or median (interquartile range [IQR]). Independent Student t-tests were used to compare differences between the two groups, while the Mann–Whitney U test was employed for non-normally distributed variables. Categorical variable differences were assessed using the Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Participants

The mean age of patients with lupus nephritis was 31.4 (SD=12.9), while the mean age of patients without lupus nephritis was 40.3 (SD=4.4) (p=0.009). The female sex was predominantly in both groups. There was no statistical difference in the duration of the disease, as well other comorbidities such as hypertension, diabetes mellitus, and obesity which showed homogenization in between groups. Most of laboratory findings did not show significant difference with the exception of complement and proteinuria which were higher in the lupus nephritis group (Table 1).

Transthoracic echocardiography

Echocardiographic features of the patients are shown in Table 2. No significant difference was found in left ventricular ejection fraction between the two groups (59±8.8 vs. 60.1±4.6, p>0.05), indicating the absence of systolic dysfunction. Patients with lupus nephritis had a thinner interventricular septum, and this difference was statistically significant (0.89±0.17 vs. 0.98±0.16, p=0.02). The Mitral A wave velocity, representing left ventricular diastolic pressure, was significantly different

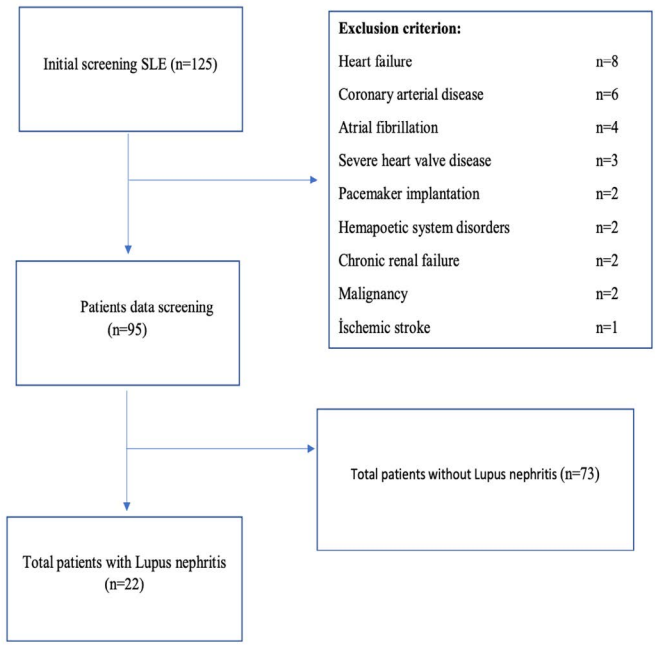

Figure 1. Study flow chart.

Table 1. Demographic and clinical characteristics of the patients

Variables	With Lupus nephritis (n=22)	Without Lupus nephritis (n=73)	P value
Age, years*	31.4±12.9	40.3±14.4	0.009
Sex, n, %			NS
Male	2(9.1)	6(8.2)	
Female	20(90.9)	67(91.8)	
ANA, n, %	20(23.8)	64(76.2)	NS
Anti-Ds DNA, n, %	21(25)	63(75)	NS
Disease duration, years*	5.6±4.3	7.4±4.9	NS
HT, n, %	9(20.5)	35(79.5)	NS
DM, n, %	1(14.3)	6(85.7)	NS
Obesity, n, %	2(25)	6(75)	NS
WBC, (µl/ml)*	7.5±2.4	6.5±2.8	NS
PLT, (103/L)*	233.7±86.3	251.7±89.4	NS
ESR, mg/h*	30±27.1	21.2±18.9	NS
CRP, mg/L*	4.0±5.3	5.5±6.9	NS
Proteinuria, mg/day*	3152.8±4056.7	841.9±1744.2	0.022
C3, mg/dl*	0.65±0.31	0.97±0.34	0.001
C4, mg/dl*	0.08±0.05	0.16±0.08	0.001

ANA: Antinuclear antibody, HT: Hypertension, DM: Diabetes mellitus, WBC: White blood cell, PLT: Platelet, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, C3: Complement 3, C4: Complement 4, NS: No significant
*Student t-test was used

Table 2. Echocardiographic parameters of the patients

Variables	With Lupus nephritis (n=22)	Without Lupus nephritis (n=73)	P value
EF, %	59±8.8	60.1±4.6	NS
IVS thickness, cm	0.89±0.17	0.98±0.16	0.02
Posterior wall thickness, cm	0.88±0.16	0.95±0.14	NS
End-diastolic diameter, cm	4.6±0.53	4.4±0.48	NS
End-systolic diameter, cm	2.8±0.51	2.65±0.44	NS
Mitral E, cm/sec	78.5±20.1	79.3±19.6	NS
Mitral A, cm/sec	62.5±17	74.9±20.5	0.014
E/A ratio	1.3±0.49	1.1±0.35	NS
Relative posterior wall thickness, cm	0.38±0.06	0.43±0.07	0.011

EF: Ejection Fraction, IVS: Interventricular septum, NS: No significant

in patients with lupus nephritis (p=0.014). Although the components of relative posterior wall thickness (RWT), including left ventricular posterior wall thickness and end-diastolic diameter, were similar between the groups and did not show statistically significant differences, the left ventricular RWT, was lower in patients with lupus nephritis, and the results were statistically significant (0.38±0.06 vs. 0.43±0.07, p=0.011). These findings suggest that despite normal systolic function, patients with lupus nephritis develop different cardiac remodeling than patients without nephritis, and changes could represent diastolic disfunction.

DISCUSSION

This study is one of the investigations focused on the ability of left ventricular relative wall thickness (RWT) to predict cardiac outcomes in patients with lupus nephritis.

SLE is a progressive disease that can lead to diastolic dysfunction and heart failure. Over time, SLE patients may develop dilation in the left ventricle and left atrium (11). Several echocardiographic parameters are used to assess diastolic dysfunction in SLE patients. Among these, the E/e' ratio, E/A ratio, left ventricular end-diastolic diameter, and left ventricular mass are commonly employed (12). However, there is no definitive data on which parameter is superior. RWT is a frequently used parameter in clinical practice and offers higher specificity compared to other diastolic parameters. While studies on diastolic dysfunction in SLE patients exist in the literature, limited data are available regarding the condition in patients with lupus nephritis. Our study demonstrated that RWT values were lower in patients with lupus nephritis compared to those without renal involvement. When examining the pathogenesis of lupus nephritis, inflammation and fibrosis are prominent factors that contribute to cardiovascular complications. These factors disrupt the structure and function of the left ventricle (LV), leading to adverse cardiovascular outcomes. Inflammatory markers such as HE4, along with changes in other biomarkers, have been linked to both renal and cardiovascular damage in patients with lupus nephritis (13). Systemic inflammation and the development of fibrosis further contribute to LV remodeling and dysfunction, potentially exacerbating cardiovascular risks. This suggests that if renal involvement develops in SLE patients, more severe

diastolic dysfunction may accompany the clinical picture. In a study by He et al., lupus nephritis patients were found to have more significant myocardial involvement based on global longitudinal strain (GLS) values (14). These findings are consistent with our study results. Although GLS is a parameter indicative of diastolic dysfunction and myocardial damage, it is not easily applicable or accessible in clinical practice. Especially in economically challenged countries, implementing such parameters can be challenging. Instead, as in our study, evaluating RWT is practical, cost-effective, and easy to use with high accuracy.

Gardin et al. demonstrated an association between RWT and ventricular arrhythmias. Specifically, each 0.01 decrease in RWT was associated with an approximately 10% increase in the risk of ventricular arrhythmia and death (15). Several mechanisms can explain this relationship. Decreased RWT is often associated with fibrosis. Fibrosis can lead to reentry circuits and early depolarizations, increasing the risk of malignant arrhythmias. In patients with fibrosis, oxidative stress and diastolic dysfunction in the left ventricle contribute to the likelihood of ventricular arrhythmias. While left ventricular end-diastolic diameter and left ventricular mass are important for predicting malignant arrhythmias, RWT can be considered a more sensitive echocardiographic indicator. Patients with lupus nephritis have higher rates of myocardial fibrosis. Based on these results, patients with lupus nephritis require closer monitoring for ventricular arrhythmias and heart failure.

Many studies on left ventricular function focus on the left ventricular mass index. However, an essential point to remember is that while these parameters are used for assessing cardiac remodeling, the left ventricular mass index may be normal while the RWT value is abnormal. Eguchi et al. conducted a study in hypertensive individuals with type 2 diabetes mellitus and found that RWT, unlike left ventricular mass index and other echocardiographic parameters, independently predicted cardiovascular events [8]. Similarly, Hashem et al. investigated patients with non-cardioembolic stroke and identified abnormal RWT values despite a normal left ventricular mass index, emphasizing the importance of RWT for accurately assessing left ventricular geometry (16). These findings align with the results of our study. In our research, although initial classic echocardiographic measurements indicated normal left ventricular systolic function in patients, pathological differences were detected at the diastolic level. Additionally, the Mitral A wave velocity, representing left ventricular diastolic pressure, was lower in patients with lupus nephritis, further supporting the presence of diastolic dysfunction in this group. The development of lupus nephritis may lead to earlier and more severe cardiac dysfunction compared to SLE patients without renal involvement.

Limitations

One of the limitations of our study is the absence of ProBNP measurements, which are typically used to evaluate heart failure status in patients. In our study, inflammatory markers such as ESR, CRP, and WBC were evaluated; however, more specific chronic inflammatory markers were not assessed. This can be considered one of the limitations of the study. MRI (magnetic resonance imaging) is used to show cardiac involvement in patients with lupus. The fact that we did not use MRI in our study can be considered among our limitations. As is known, kidney diseases cause an increased risk of diastolic heart disease. Adding non-lupus-related kidney disease to the groups and comparing this group with lupus nephritis could have made the study more meaningful. Comparison of patients without lupus nephritis with a healthy control group could also have increased the quality of the study.This situation can be counted among our limitations. Our study's single-center design and lack of assessment of strain echocardiography parameters, which are indicative of diastolic dysfunction, are among our limitations. Additionally, the follow-up duration for patients was not sufficiently long, and their outcomes related to cardiovascular complications during this period were not evaluated. In future studies, we hope to better understand the significance of RWT in predicting cardiovascular complications during long-term follow-up of patients with lupus nephritis.

CONCLUSION

Systemic Lupus Erythematosus (SLE) is a progressive disease that leads to high cardiovascular complications. The development of lupus nephritis results in significant myocardial impact. Relative wall thickness (RWT) is an important parameter indicating that patients with lupus nephritis should be closely monitored for ventricular arrhythmias, heart failure, and diastolic dysfunction.

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