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Frequency and clinical implications of metabolic syndrome in different rheumatic diseases: Relationship with disease activity and severity

Metabolik sendromun romatizmal hastalıklar üzerindeki klinik etkileri: Hastalık aktivitesi ve şiddetiyle ilişkisi

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Abstract

Objective: To assess the frequency of metabolic syndrome (MetS) in various rheumatic diseases and to depict its association with disease characteristics, activity, and/or severity.

Methods: Two hundred fifty-seven patients [47 rheumatoid arthritis (RA), 100 systemic lupus erythematosus (SLE), 49 systemic sclerosis (SSc), 33 axial spondyloarthritis (axSpA), and 28 vasculitis (21 with primary vasculitis and 7 with Behçet's disease (BD)] and 70 controls were recruited, with a suitable number of controls matched for each corresponding disease. Demographic data, body mass index, waist circumference, comorbidities, and clinical and laboratory data were collected. Disease activity and/or severity were determined. MetS was defined according to the Adult Treatment Panel criteria.

Results: In RA, MetS was comparable to the control group with no significant association to the disease activity score (p=0.33), but there was a significant difference according to the activity grading (p=0.007). In SLE, MetS was significantly more frequent (42%) versus the control (14.9%) (p=0.001) and was significantly related to disease activity (p=0.001). In SSc, axSpA, and vasculitis, the frequency of MetS was comparable to their corresponding controls (p=0.24, p=0.4, p=0.08) and was not related to their disease activity scores (p=0.7, p=0.4, p=0.97; respectively), as well as p=0.45 and p=0.14 for BD activity and damage. When comparing the different rheumatic diseases, MetS was significantly more frequent in SLE (p=0.04). Regarding MetS components, there was a significantly higher frequency of hypertension (p<0.0001) and significantly higher triglycerides (p=0.004) in SLE versus the other rheumatic diseases. No significant association was found between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with MetS in RA (p=0.4, p=0.4), SLE (p=0.35, p=0.73), SSc (p=0.46, p=0.14), axSpA (p=0.35, p=0.45) and vasculitis (p=0.72, p=0.29).

Conclusion: MetS is frequently associated with rheumatic diseases, being significantly more frequent in SLE, and could be related to disease activity.

Keywords: Rheumatic diseases, metabolic syndrome (MetS), disease activity, severity

Öz

Amaç: Bu çalışmanın amacı farklı romatizmal hastalıklarda metabolik sendromun (MetS) sıklığını değerlendirmek ve hastalık özellikleri, aktivitesi ve/veya şiddetiyle ilişkisini incelemektir.

Yöntem: İki yüz elli yedi hasta [47 romatoid artrit (RA), 100 sistemik lupus eritematozus (SLE), 49 sistemik skleroz (SSc), 33 aksiyel spondiloartrit (axSpA) ve 28 vaskülit (21'i primer vaskülit ve 7'si Behçet hastalığı (BH)] ve 70 kontrol, ilgili her hastalık için uygun sayıda kontrol eşleştirilerek alınmıştır. Demografik veriler, vücut kitle indeksi, bel çevresi, komorbiditeler ve klinik ve laboratuvar verileri toplanmıştır. Hastalık aktivitesi ve/veya şiddeti belirlenmiştir. MetS, Yetişkin Tedavi Paneli kriterlerine göre tanımlanmıştır.

Bulgular: RA'da MetS, hastalık aktivite skoru ile anlamlı bir ilişkisi olmayan kontrol grubu ile karşılaştırılabilir düzeydeydi (p=0,33), ancak aktivite derecelendirmesine göre anlamlı bir fark vardı (p=0,007). SLE'de MetS, kontrol grubuna (%14,9) kıyasla anlamlı derecede daha sık (%42) görülmüş (p=0,001) ve hastalık aktivitesiyle anlamlı derecede ilişkili bulunmuştur (p=0,001). SSc, axSpA ve vaskülitte, MetS sıklığı karşılık gelen kontrollerle karşılaştırılabilirdi (p=0,24, p=0,4, p=0,08) ve hastalık aktivite skorlarıyla ilişkili değildi (sırasıyla p=0,7, p=0,4, p=0,97); ayrıca BH aktivitesi ve hasarı için p=0,45 ve p=0,14 idi. Farklı romatizmal hastalıklar karşılaştırıldığında, MetS SLE'de anlamlı olarak daha sık görülmüştür (p=0,04). MetS bileşenleri açısından, SLE'de diğer romatizmal hastalıklara kıyasla anlamlı derecede daha yüksek hipertansiyon (p<0,0001) ve anlamlı derecede daha yüksek trigliserit (p=0,004) sıklığı vardı. Nötrofil-lenfosit oranı ve trombosit-lenfosit oranı ile MetS arasında RA (p=0,4, p=0,4), SLE (p=0,35, p=0,73), SSc (p=0,46, p=0,14), axSpA (p=0,35, p=0,45) ve vaskülitte (p=0,72, p=0,29) anlamlı bir ilişki bulunmamıştır.

Sonuç: MetS, romatizmal hastalıklarla sıklıkla ilişkilidir, SLE'de önemli ölçüde daha sık görülür ve hastalık aktivitesi ile ilişkili olabilir.

Anahtar Kelimeler: Romatizmal hastalıklar, metabolik sendrom (MetS), hastalık aktivitesi, şiddet

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Introduction

Metabolic syndrome (MetS) is marked by the presence of several components, including dyslipidemia, insulin insensitivity, hypertension, hyperglycemia, and central obesity, which together form a constellation of cardiovascular disease (CVD) risk factors.[1] There are several definitions of MetS, with the Adult Treatment Panel (ATP III) criteria being one of the most commonly used.[2] There is evidence that inflammation contributes to the pathogenesis of MetS, with pro-inflammatory cytokines playing a significant role in insulin resistance.[3] Moreover, heightened inflammation is associated with dysregulated lipid parameters, such as decreased high-density lipoprotein (HDL) and elevated triglycerides (TG).[4]

Rheumatic diseases (RDs) have been associated with an increased risk of CVDs.[5] MetS has been reported in several RDs, including rheumatoid arthritis (RA),[6] systemic sclerosis (SSc),[7] and primary vasculitis.[8] Inflammatory mediators, such as interleukin-6, can induce insulin resistance through various mechanisms,[9] suggesting a possible explanation for the link between chronic inflammatory conditions like RDs and MetS.

Inflammatory indices, such as the neutrophil-lymphocyte ratio (NLR), can predict the risk of CVDs.[10] Furthermore, NLR has been a common inflammatory marker in RDs,[11] indicating its potential as a predictor of systemic inflammation. MetS has been correlated with disease activity and severity in several RDs,[8,12,13] implying that chronic inflammation may contribute to the pathogenesis of MetS and subsequent metabolic and vascular complications.

This study aimed to investigate the frequency of MetS in various RDs and assess its relationship with disease characteristics, activity, and/or severity.

Materials and Methods

The study included 257 adult patients with different RDs. Exclusion criteria included subjects diagnosed with hypothyroidism, liver impairment, Cushing syndrome, malignancy, or infection, as well as those who had been on drugs altering the lipid profile in the past 3 months. Patients with a history of smoking and alcohol consumption were also excluded. Seventy age- and sex-matched healthy control subjects were enrolled, with a suitable number of controls for each corresponding RD: 50/70 for RA, 50/70 for systemic lupus erythematosus (SLE), 50/70 for SSc, 30/70 for axial spondyloarthritis (axSpA), and 30/70 for vasculitis patients.

Patients underwent full history taking and physical examination, including measurements of body mass index and waist circumference (cm). Complete blood count with differential was recorded. A lipid profile was performed for all patients after 12-14 hours of fasting, including total cholesterol (TC), HDL, TG, low-density lipoprotein (LDL), and very LDL. MetS was diagnosed in accordance with the ATP III criteria.[2] Disease activity was assessed using the disease activity score (DAS-28)[14] for RA, the SLE disease activity index (SLEDAI)[15] for SLE, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[16] for axSpA, the Birmingham Vasculitis Activity Score[17] for primary vasculitis, and the Arabic version of the Behçet's Disease Current Activity Form (Ar-BDCAF)[18] for BD. Disease severity/damage was evaluated using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index[19] for SLE, the modified Rodnan Skin Score (mRss)[20] for SSc, the vasculitis damage index (VDI)[21] for primary vasculitis, and the Behçet's Disease Damage Index (BDI)[22] for BD patients.

Statistical Analysis

Data were statistically described as mean ± standard deviation, median and range, or frequencies and percentages. Numerical data were tested for normality using the Kolmogorov-Smirnov test. Comparisons of numerical variables between two study groups were conducted using the Mann-Whitney U test, while the Kruskal-Wallis test was applied for comparisons among more than two groups. The chi-square (χ^2) test was performed to compare categorical data. The exact test was used when the expected frequency was less than 5. Results were adjusted for missing variable values. Two-sided p-values <0.05 were considered statistically significant.

For numerical data, effect size was represented by Cohen's d for differences between two groups and eta-squared (η^2) for differences among more than two groups. For qualitative data, effect size was expressed as odds ratio (OR) and 95% confidence interval (CI). Cohen's d standards were 0.2, 0.5, and 0.8 for small, medium, and large effect sizes, respectively. For eta-squared, the standards were 0.01, 0.059, and 0.138 for small, medium, and large effect sizes, respectively. If the generated two-tailed 95% CIs for qualitative data did not cross 1, the results were considered statistically significant.

Multivariate logistic regression analysis was conducted to estimate independent risk modifiers for the occurrence of MetS among different diseases. Risk factors included in the model were those with significant results in univariate analysis. IBM SPSS (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY, USA), version 22 for Microsoft Windows, was used for statistical analysis.

The patients provided informed consent, and the study was approved by the Scientific Research and Ethical Committee in accordance with the 1964 Helsinki Declaration.

The members of the Scientific Research and Ethics Committee of the Rheumatology and Rehabilitation Department, Cairo University (SReC-RCU) have reviewed and approved the aforementioned M.Sc. protocol (approval number: 40-SReC-RCU2021, date: 20.03.2021).

Results

The current study included 47 subjects with RA, 100 with SLE, 49 with SSc, 33 with axial spondyloarthritis (axSpA), and 28 with vasculitis [21 with primary vasculitis and 7 with Behçet's disease (BD)]. All participants were recruited from the Rheumatology Department and met the corresponding classification criteria for RA,[23] SLE,[24] SSc,[25] and axSpA.[26]

Twenty-one patients with primary vasculitic syndromes were included: 5 with Takayasu arteritis, 3 with granulomatosis with polyangiitis, 1 with microscopic polyangiitis, 1 with eosinophilic granulomatosis with polyangiitis (Churg-Strauss), 2 with polyarteritis nodosa, 2 with Cogan syndrome, 1 with urticarial vasculitis, 1 with cryoglobulinemic vasculitis, and 5 with undifferentiated vasculitis, classified according to the 2012 Chapel Hill Consensus.[27] Additionally, 7 patients with BD were included.[28]

The characteristics of the RD patients are illustrated in Table 1. The matched control group for RA and SSc patients included 6 males (12%) and 44 females (88%) (p>0.05), with ages ranging from 18-60 years and a mean age of 40.8±11.6 years (p>0.05). The matched control group for SLE patients comprised 8 males (16%) and 42 females (84%) (p>0.05) with ages ranging from 16-55 years and a

Table 1. Characteristics of the studied rheumatic diseases

Mean ± SD or n (%)	RA (n=47)	SLE (n=100)	SSc (n=49)	axSpA (n=33)	Vasculitis (n=28)		p
					PV (n=21)	BD (n=7)	
Age (years)	44.3±13.7 (21-75)	33.8±10.3 (18-63)	43.3±13.7 (18-79)	40.7±10 (17-62)	40.4±15.8 (19-77)	34.4±6.6 (29-44)	**<0.0001**
Gender							
Male	4 (8.5)	7 (7)	7 (14.3)	24 (72.7)	10 (47.6)	6 (85.7)	**<0.0001**
Female	43 (91.5)	93 (93)	42 (85.7)	9 (27.3)	11 (52.4)	1 (14.3)	
Disease duration	12.3±7.4 (1-27)	8.9±7.02 (1-27)	7.4±5.6 (1-24)	12.4±8.1 (1-35)	6.1±6.1 (1-22)	8±8.4 (1-25)	**<0.0001**
Age at onset	31.9±13.02	24.6±10.9	36.1±12.5	28.2±10.9	34.3±16.2	26.4±3	**<0.0001**
BMI	29.4±5.6 (19.7-45.2)	27.9±6 (15.1-48.9)	25.8±5.9 (14.6-46)	28±3.3 (23.4-35.9)	28.7±8.1 (15.6-51)	26.5±3.8 (22.7-32.7)	**0.04**
MetS components							
DM	7 (14.9)	11 (11)	3 (6.1)	2 (6.1)	3 (14.3)	1 (14.3)	0.68
Hypertension	9 (19.1)	47 (47)	8 (16.3)	1 (3)	12 (57.1)	1 (14.3)	**<0.0001**
WC (cm)	100.2±16.4 (46-130)	98.9±13.7 (70-137)	96.6±11.6 (70-123)	103.1±11.8 (80-127)	100±14.1 (68-133)	102.8±14 (90-125)	0.36
TG (mg/dL)	121.4±54.3	167.9±91.6	125.1±67.5	130.9±72.7	135.5±99.9	122.7±62.3	**0.004**
HDL (mg/dL)	53±17.6	48.7±19.4	46.3±11.9	47.4±17.7	52.8±13.9	51.4±15.6	0.3
MetS	11 (23.4)	45 (42)	14 (28.6)	5 (15.2)	7 (33)	1 (14.3)	**0.04**
NLR	3.7±3.9	4.4±3.3	3.2±2.7	1.8±0.97	4.3±3.6	4.4±1.99	**<0.0001**
PLR	217.4±165.3	257.3±186.9	178.8±101.9	138.7±50.2	286.7±484.9	209.5±115.2	**0.004**
TC (mg/dL)	188.5±37.1	204.5±59.3	183.6±34.9	191.7±36	200±48.2	199.6±56.4	0.4
LDL (mg/dL)	113.8±30.8	124.7±52.3	113.4±30.3	116±26.5	126.9±40.7	132±44.1	0.7
VLDL (mg/dL)	24.2±10.8	34±18.5	25±13.7	25.7±14.7	26.1±19.9	26.2±13.4	**0.002**
Disease activity and/or severity	**DAS-28** 5.2±2.27 (0-8.5)	**SLEDAI** 8.3±5.9 (0-29)		**BASDAI** 4.9±1.8 (2.1-8)	**BVAS** 5±3.9 (0-12)	**BDCAF** 5.14±2.7 (1-10)	–
		SLICC-DI 0.45±0.79 (0-4)	**mRss** 22.9±8.3 (2-43)		**VDI** 1.9±2.3 (0-6)	**BDI** 3.2±2.9 (0-7)	–

axSpA: Axial spondyloarthritis, BD: Behçet's disease, BASDAI: Bath ankylosing spondylitis disease activity index, BDCAF: BD current activity form, BDI: Behçet damage index, BMI: Body mass index, BVAS: Birmingham vasculitis activity score, DAS-28: Disease activity score-28, DM: Diabetes mellitus, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MetS: Metabolic syndrome, mRss: Modified Rodnan skin score, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, PV: Primary vasculitis, RA: Rheumatoid arthritis, SD: Standard deviation, SLE: Systemic lupus erythematosus, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinic-damage index, SSc: Systemic sclerosis, TC: Total cholesterol, TG: Triglycerides, WC: Waist circumference, VDI: Vasculitis damage index, VLDL: Very-low density lipoprotein. Statistically significant p-values are in bold. Significant effect sizes were found for comparison of the characteristics of RDs; age (0.19), age at disease onset (0.2), disease duration (0.1), BMI (0.5), WC (0.2), NLR (0.7), PLR (0.97), TC (0.5), HDL (0.4), LDL (0.5), TGs (0.6) and VLDL (0.3)

mean of 36.7±9.3 years (p>0.05). The matched control group for axSpA and vasculitis patients included 19 males (63.3%) and 11 females (36.7%) (p>0.05) with ages ranging from 16-83 years and a mean of 44.8±14.7 years (p>0.05).

When comparing the RD patients to their corresponding controls, the occurrence of MetS was comparable (p>0.05) except for SLE patients (42%) versus their controls (14.9%) (p=0.001) (Figure 1). In terms of effect size, MetS was significantly more frequent in SLE (OR 4.5, 95% CI: 1.8-10.9) and vasculitis patients (OR 5.6, 95% CI: 1.1-29.2) compared to their controls. The frequency of MetS in RA (OR 1.6, 95% CI: 0.9-4.4), SSc (OR 1.8, 95% CI: 0.7-4.72), and axSpA (OR 2.5, 95% CI: 0.5-13.9) was not significantly different from their controls.

Tables 2 and 3 summarize the comparison between RA, SLE, SSc, and vasculitis patients with and without MetS.

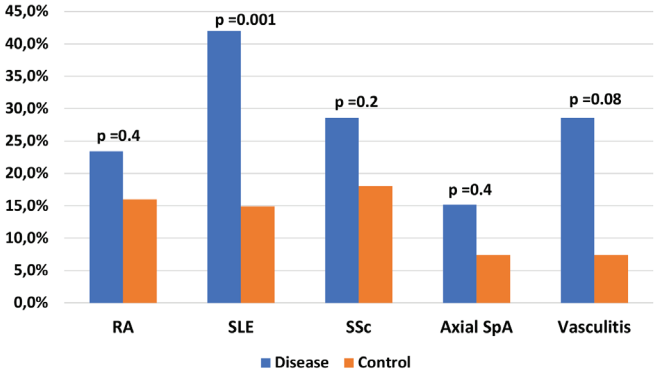

Figure 1. Frequency of metabolic syndrome among different rheumatic diseases and their corresponding control
RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, SSc: Systemic sclerosis, axSpA: Axial spondyloarthritis

Table 2. Comparison between RA and SSc patients with and without metabolic syndrome

Variable Mean ± SD or n (%)	Metabolic syndrome in RA patients (n=47)			Metabolic syndrome in SSc patients (n=49)		
	With (n=11)	Without (n=36)	p	With (n=14)	Without (n=35)	p
Age (years)*	55.6±11.7	40.8±12.4	**0.003**	45.2±9.5	42.5±15.1	0.49
Gender						
Male[t] Female	2 (18.2) 9 (81.8)	2 (5.6) 34 (94.4)	0.23	0 (0) 14 (100)	7 (20) 28 (80)	0.17
Disease duration (years)*	13.5±7.7	11.97±7.4	0.53	8.1±6.9	7.1±5.1	0.79
Neutrophils (%)	69.5±11.4	63.6±13.6	0.38	63.2±11.6	60±12.5	0.53
Lymphocytes (%)	22.7±9	25.8±10.7	0.67	28.8±10.5	27.4±11.4	0.39
NLR*	4.9±6.3	3.3±2.6	0.44	2.9±2.35	3.3±2.8	0.46
PLR*	199.8±143.2	223.2±173.5	0.44	146.1±91.9	193.1±104.1	0.14
ESR (mm/hour)*	51.5±39.8	44.4±28.3	0.72	56.7±38	40.4±27.2	0.19
Uric acid (mg/dL)	4.2±1.4	3.7±1.1	0.41	4.8±1.5	4.3±1.2	0.36
Creatinine (mg/dL)	0.76±0.4	0.66±0.19	0.71	1.2±1.5	0.7±0.3	0.66
Positive RF	5/6 (83.8)	13/18 (72.2)	1	-	-	-
Positive anti-CCP	2/2 (100)	9/11 (81.1)	1	-	-	-
Positive ANA	-	-	-	8/10 (80)	28/31 (90.3)	0.58
DAS-28* Active (≥2.6)[t] Remission (<2.6)[t]	4.6±1.8 7 (63.6) 4 (36.4)	5.4±2.4 28 (80) 7 (20)	0.33 0.42	-	-	-
High disease activity[t] Moderate disease activity[t] Low disease activity	2 (28.6) 5 (71.4) 0 (0)	19 (67.9) 4 (14.3) 5 (17.9)	**0.007**	-	-	-
mRss*	-	-	-	23.8±7.3	22.5±8.7	0.7
Current steroid dose*	9±6.3 (0-20)	6.5±3.7 (0-18)	0.24	8.9±11.9 (0-40)	6.6±7.5 (0-25)	0.67
Leflunomide[t]	4 (40)	17 (47.2)	0.74	0 (0)	3 (8.6)	-

Table 2. Continued

Variable Mean ± SD or n (%)	Metabolic syndrome in RA patients (n=47)			Metabolic syndrome in SSc patients (n=49)		
	With (n=11)	Without (n=36)	p	With (n=14)	Without (n=35)	p
Biologics[t]	3 (27.3)	13 (36.1)	0.73	0 (0)	1 (2.9)	-
Methotrexate[t]	4 (36.4)	10 (27.8)	0.71	1 (7.1)	6 (17.1)	0.66
Hydroxychloroquine[t]	1 (9.1)	8 (22.2)	0.66	1 (7.1)	4 (11.4)	1
Sulfasalazine	0 (0)	2 (5.6)	-			
Cyclophosphamide[t]	1 (9.1)	0 (0)	-	1 (7.1)	6 (17.1)	0.66
AZA[t]	-	-	-	1 (7.1)	2 (5.7)	1

*ANA: Antinuclear antibodies, Anti-CCP: Anti-cyclic citrullinated peptide, AZA: Azathioprine, CI: Confidence interval, DAS-28: Disease activity score-28, ESR: Erythrocyte sedimentation rate, mRss: Modified Rodnan skin score, NLR: Neutrophil-lymphocyte ratio, OR: Odds ratio, PLR: Platelet-lymphocyte ratio, RA: Rheumatoid arthritis, RF: Rheumatoid factor, SSc: Systemic sclerosis. Statistically significant p-values are in bold. *Effect sizes (Cohen's d) in RA: age (1.2), disease duration (0.2), NLR (0.4), PLR (0.1), ESR (0.2), DAS-28 (0.4) and current steroid dose (0.6). *: Effect sizes (Cohen's d) in SSc: Age (0.2), disease duration (0.2), NLR (0.2), PLR (0.5), ESR (0.5), mRss (0.2) and current steroid dose (0.3). t: Effect sizes (OR, 95% CI) in RA: Gender (OR 3.8, 95% CI: 0.5-30.6), DAS-28 (active) (OR 0.5, 95% CI: 0.1-2.2), DAS-28 (remission) (OR 2.4, 95% CI: 0.5-10.4), high disease activity (OR 0.2, 95% CI: 0.04-1.1), moderate disease activity (OR 6.7, 95% CI: 1.4-32.3), leflunomide (OR 0.6, 95% CI: 0.2-2.6), biologics (OR 0.7, 95% CI: 0.2-2.9), methotrexate (OR 1.5, 95% CI: 0.4-6.2) and hydroxychloroquine (OR 0.4, 95% CI: 0.04-3.2). t: Effect sizes (OR, 95% CI) in SSc: Methotrexate (OR 0.4, 95% CI: 0.04-3.4), hydroxychloroquine (OR 0.6, 95% CI: 0.06-5.9), cyclophosphamide (OR 0.4, 95% CI: 0.04-3.4) and AZA (OR 1.3, 95% CI: 0.1-15.2)*

Table 3. Comparison between SLE and vasculitis patients with and without metabolic syndrome

Variable Mean ± SD (range) or n (%)	Metabolic syndrome in SLE patients (n=100)			Metabolic syndrome in vasculitis patients (n=28)		
	With (n=42)	Without (n=58)	p	With (n=8)	Without (n=20)	p
Age (years)*	33.1±9.9	34.3±10.6	0.62	45.6±10.4	36.2±14.8	**0.04**
Gender						
Male[t] Female	3 (7.1) 39 (92.9)	4 (6.9) 54 (93.1)	1	5 (62.5) 3 (37.5)	11 (55) 9 (45)	1
Disease duration (years)*	10.14±7.2	7.98±6.8	0.08	7.1±9.2	6.3±5.6	0.66
Neutrophils (%)	72.4±10.3	66.9±14.6	0.09	69.88±11.1	68.85±12.5	1
Lymphocytes (%)	16.9±7.2	23.9±13.3	0.34	21.38±12.2	22.85±11.4	0.74
NLR*	4.77±3.57	4.03±2.99	0.35	4.8±4.159	4.146±2.8	0.72
PLR*	241.1±162	269.2±203.9	0.73	162.9±96.89	309.18±493.4	0.29
ESR (mm/1st hour)*	73.1±30.1	56±37.9	**0.02**	50.3±49.1	40.6±29.8	0.87
Uric acid (mg/dL)*	6.4±2.2	5.4±2.6	**0.03**	5.6±1.5	4.8±1.48	0.39
Urea (mg/dL)*	67.1±43.3	44.4±39	**<0.0001**	30.5±6.7	28.3±10.1	0.48
Creatinine (mg/dL)*	1.8±2.9	0.98±1.2	**0.001**	0.9±0.39	0.815±0.2	0.39
24 hours urinary proteins (gm/dL)*	2.5±2.2	1.25±1.6	**0.001**	-	-	-
Consumed C3[t]	16/24 (66.7)	13/24 (54.2)	0.38	-	-	-
Consumed C4[t]	5/22 (22.7)	10/24 (41.7)	0.2	-	-	-
Positive ANA	36/38 (94.7)	57/57 (100)	0.16	-	-	-
SLEDAI*	10.8±5.7	6.5±5.4	**0.001**	-	-	-
SLICC-DI*	0.6±0.98	0.33±0.6	0.15	-	-	-
Primary vasculitis BVAS* VDI* BD: BDCAF* BDI*	- -	- -	- -	5±3.7 0.6±1.1 6±0 (6-6) 7±0 (7-7)	5±4.2 2.5±2.4 5±2.96 2.4±2.5	0.97 0.07 0.45 0.14
Current steroid dose (mg/day)*	24.8±12.5 (5-50)	20.5±12.1 (5-50)	0.08	26.3±13 (0-40)	22.5±11.6 (0-40)	0.39
AZA[t]	15 (35.7)	23 (39.7)	0.7	1 (12.5)	5 (25)	0.64
Hydroxychloroquine[t]	28 (66.7)	41 (70.7)	0.67	1 (12.5)	0 (0)	-
Biologics[t]	2 (4.8)	1 (1.7)	0.57	0 (0)	2 (10)	-
MMF[t]	9 (21.2)	10 (17.2)	0.6	0 (0)	1 (5)	-
Cyclophosphamide[t]	9 (21.4)	5 (8.6)	0.07	4 (50)	6 (30)	0.4

Table 3. Continued

Variable Mean ± SD (range) or n (%)	Metabolic syndrome in SLE patients (n=100)			Metabolic syndrome in vasculitis patients (n=28)		
	With (n=42)	Without (n=58)	p	With (n=8)	Without (n=20)	p
Methotrexate[t]	1 (2.4)	2 (3.4)	1	1 (12.5)	0 (0)	-
Leflunomide	0 (0)	1 (1.7)	-	-	-	-
Cyclosporine	-	-	-	0 (0)	2 (10)	-

*ANA: Antinuclear antibodies, c-ANCA: Cytoplasmic ANCA, AZA: Azathioprine, BD: Behçet's disease, BDCAF: Behçet's disease current activity form, BDI: Behçet's disease damage index, BVAS: Birmingham vasculitis activity score, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, MMF: Mycophenolate mofetil, NLR: Neutrophil-lymphocyte ratio, OR: Odds ratio, PLR: Platelet-lymphocyte ratio, SD: Standard deviation, SLE: Systemic lupus erythematosus, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinics-damage index, VDI: Vasculitis damage index. Statistically significant p-values are in bold. *: Effect sizes (Cohen's d) in SLE: Age (0.1), disease duration (0.3), NLR (0.2), PLR (0.2), ESR (0.5), uric acid (0.4), urea (0.7), creatinine (0.4), 24-hours urinary proteins (0.7), SLEDAI (0.8), SLICC-DI (0.4) and current steroid dose (0.4). *: Effect sizes (Cohen's d) in vasculitis: Age (0.7), disease duration (0.1), NLR (0.2), PLR (0.3), ESR (0.3), BVAS (0), VDI (0.9), BDCAF (0.4), BDI (2.2) and current steroid dose (0.3). t: Effect sizes (OR, 95% CI) in SLE: Gender (OR 1, 95% CI: 0.2-4.9), consumed C3 (OR 1.7, 95% CI: 0.5-5.4), consumed C4 (OR 0.4, 95% CI: 0.1-1.5), AZA (OR 0.9, 95% CI: 0.4-1.9), hydroxychloroquine (OR 0.8, 95% CI: 0.4-2), biologics (OR 2.9, 95% CI: 0.3-32.5), MMF (OR 1.3, 95% CI: 0.5-3.6), cyclophosphamide (OR 2.8, 95% CI: 0.9-9.4) and methotrexate (OR 0.7, 95% CI: 0.1-7.8). t: Effect sizes (OR, 95% CI) in vasculitis: Gender (OR 1.4, 95% CI: 0.3-7.3), AZA (OR 0.4, 95% CI: 0.04-4.4) and cyclophosphamide (OR 2.3, 95% CI: 0.4-12.6)*

None of the recruited patients with different RDs had chronic kidney disease.[29] The clinical characteristics of SLE patients with and without MetS were not significantly different (p>0.05) except for nephritis, which was more frequent among patients with MetS (83.3%) compared to those without (48.3%) (OR 5.4, 95% CI: 2.1-14.1, p<0.0001). In SSc, no significant differences were observed (p>0.05) except for myositis, which was reported in 28.6% of patients with MetS compared to 2.9% of those without (OR 13.6, 95% CI: 1.4-135.9, p=0.02). Table 4 presents the comparison between axSpA patients with and without MetS.

In regression analysis, age was independently associated with MetS (B=0.2, p=0.02) in RA patients, while the association between DAS-28 disease activity grading and MetS was not significant (B=-0.2, p=0.8). In SLE, nephritis, SLEDAI, and creatinine were associated with MetS (B=2.6, p=0.01; B=0.2, p=0.01; and B=3.2, p=0.03, respectively). The associations of erythrocyte sedimentation rate (ESR), urea, 24-hour urinary proteins, and serum uric acid with MetS were not significant (B=0.02, p=0.1; B=-0.02, p=0.5; B=-0.2, p=0.5; and B=-0.3, p=0.2, respectively).

Discussion

Inflammation contributes significantly to the pathogenesis of MetS.[3] Moreover, hematological indices have been strongly associated with multiple metabolic conditions, such as CVDs[30] and diabetes,[31] and have been correlated with pro-inflammatory cytokines.[32] In this study, MetS was found in 23.4% of RA patients, with no significant difference compared to controls. MetS has been reported in 30-42% of RA patients,[6] however, lower frequencies, such as 19%, have also been reported.[33]

Regarding DAS-28, no significant association was found with MetS in this study, but a significant difference was observed based on DAS-28 activity grading, where a higher disease activity grade was noted in RA patients without MetS. A statistically significant difference was observed in DAS-28 grading (moderate disease activity) between RA patients with and without MetS (OR 6.7, 95% CI: 1.4-32.3). Similarly, a significant difference was found regarding the current steroid dose (effect size, 0.6). In line with these findings, some studies reported no association between DAS-28 and MetS,[34,35] whereas others found a significant increase in DAS-28 among RA patients with MetS compared to those without.[12]

MetS was present in 42% of SLE patients, significantly higher than in controls (p=0.001). This aligns with previous studies, which reported MetS in 32.4% of SLE patients.[36] In this study, SLEDAI and ESR were significantly higher in SLE patients with MetS, while the damage index did not differ significantly. Regression analysis revealed that SLEDAI was independently associated with MetS, supporting earlier findings,[13] though some studies reported no such association.[37]

Nephritis was significantly more frequent in SLE patients with MetS (83.3%) compared to those without (48.3%) (OR 5.4, 95% CI: 2.1-14.1, p<0.0001). Urea, creatinine, serum uric acid and 24 hour-urinary proteins were also significantly higher in SLE patients with MetS. Regression analysis showed that nephritis and creatinine were independently associated with MetS. Dyslipidemia has been linked to SLE nephritis, with elevated TC, TG, and LDL levels, along with reduced HDL.[38] Dyslipidemia can contribute to renal disease progression in SLE by damaging the endothelium, glomerular filtration barrier, and causing tubular-interstitial lipid deposition.[39] In line, dyslipidemia was significantly associated with proteinuria in SLE nephritis patients.[40] Consistent with previous findings, hyperuricemia was significantly associated with dyslipidemia,[41] though some

Table 4. Comparison between axSpA patients with and without metabolic syndrome

Variable Mean ± SD or n (%)	Metabolic syndrome in axSpA patients (n=33)		
	With (n=5)	Without (n=28)	p
Age (years)*	47.6±10.4	39.5±9.6	0.15
Gender			
Male[ŧ] Female	4 (80) 1 (20)	20 (71.4) 8 (28.6)	1
Disease duration (years)*	10±1.9	12.9±8.7	0.63
Neutrophils (%)	51.6±2.96	55.2±10.96	0.49
Lymphocytes (%)	35.2±5.2	33.6±10.2	0.48
NLR*	1.5±0.3	1.9±1.04	0.35
PLR*	119.2±34.1	142.4±50.4	0.45
ESR (mm/hour)*	31±15.6	26.6±19.6	0.35
Uric acid (mg/dL)	5.5±0.7	4.7±1.6	0.33
Creatinine (mg/dL)	0.8±0.3	0.8±0.3	0.88
BASDAI*	5.6±1.3	4.8±1.9	0.4
Psoriasis	2 (40)	5 (17.9)	0.28
Pyoderma gangrenosum	0 (0)	1 (3.6)	-
Peripheral arthritis	1 (20)	4 (14.3)	1
Uveitis	0 (0)	2 (7.1)	-
IBD	0 (0)	3 (10.7)	-
Enthesitis	0 (0)	1 (3.6)	-
Dactylitis	0 (0)	1 (3.6)	-
Current steroid dose	0.5±1.1 (0-3)	0.6±2.9 (0-15)	0.19
Biologics	2 (40)	17 (60.7)	0.63
Methotrexate	1 (20)	4 (14.3)	1
Sulfasalazine	0 (0)	2 (7.1)	-

*axSpA: Axial spondyloarthritis, BASDAI: Bath ankylosing spondylitis disease activity index, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, IBD: Inflammatory bowel disease, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, OR: Odds ratio, SD: Standard deviation. Statistically significant p-values are in bold. *: Effect sizes (Cohen's d): Age (0.8), disease duration (0.4), NLR (0.4), PLR (0.5), ESR (0.2) and BASDAI (0.4). ŧ: Effect sizes (OR, 95% CI): Gender (OR 1.6, 95% CI: 0.2-16.6)*

studies found no significant difference in uric acid levels between SLE patients with and without MetS.[13]

Interestingly, corticosteroid use was not significantly associated with MetS in this SLE cohort, potentially due to the predominance of young female patients. However, since cumulative steroid doses were not analyzed, the impact of corticosteroids on MetS development remains unclear.

In SSc, MetS was present in 28.6% of patients, comparable to controls. This is consistent with previous findings reporting MetS in 20% of SSc patients versus 14.3% in controls.[42] No significant differences were observed between SSc patients with and without MetS regarding age, disease duration, gender, ESR, mRss, or current steroid dose. However, myositis was significantly more frequent in SSc patients with MetS (28.6%) compared to those without (2.9%) (OR 13.6, 95% CI: 1.4-135.9, p=0.02).

In axSpA, MetS prevalence was 15.2%, similar to controls. While some studies reported higher MetS prevalence in ankylosing spondylitis patients compared to controls,[43] this study found no significant association between BASDAI scores and MetS, consistent with prior findings.[43] A small effect size (0.4) was, however, noted when comparing BASDAI scores in axSpA patients with and without MetS.

In vasculitis, MetS was found in 28.6% of patients, comparable to controls. This contrasts with studies showing significantly higher MetS prevalence in ANCA-associated vasculitis patients.[8,44] In BD patients, MetS prevalence was also similar to controls, with no significant difference in BDCAF scores between patients with and without MetS.[45] Notably, large effect sizes were observed for the VDI and BDI in primary vasculitis and BD patients, respectively.

This study is one of the first to assess the association of NLR and platelet-lymphocyte ratio (PLR) with MetS across different RDs. No significant associations were found, although a medium effect size was noted for PLR in axSpA patients. Some studies have reported increased platelet counts in MetS patients compared to controls, though PLR was not significantly different.[46] In contrast, other studies

have shown significant associations between NLR and MetS and correlations with its components.[47,48]

The current study had a few limitations. Being a cross-sectional design, we cannot delineate a causal relationship between disease characteristics and MetS. Moreover, we did not record data on treatment duration and compliance, limiting our ability to estimate the effect of these factors on MetS development. The relatively small number of cases may warrant future larger-scale, and even prospective, studies to better assess the impact of anti-rheumatic medications on MetS diagnosis. Additionally, given the small sample size, interpreting results solely based on p-values is not recommended;[49] however, estimating effect sizes and their respective uncertainty might provide better insight into the magnitude of the observed differences.

There were many variations between patient groups in the current study; therefore, a simple correlation analysis between variables provided limited strength to the results. Accordingly, logistic regression analysis was conducted, adjusting for one or two confounding variables, especially those related to lipid metabolism. Other confounders for MetS, including physical activity and dietary habits, were not available in the current study cohort. Nonetheless, by adjusting for several confounding variables, this analysis offers insights for future larger-scale longitudinal studies.

The clinical relevance of the current study is strengthened by the fact that it is among the few studies assessing the frequency of MetS and its components across different RDs, including rare diseases such as primary vasculitis. RDs are considered a diverse array of conditions that, despite their differences, share overlapping features, the use of common non-specific therapies, and the potential for progression from one disease to another, suggesting common pathogenic mechanisms.[50] In this study, MetS was frequently associated with various RDs, with a significantly higher prevalence in SLE patients compared to controls, potentially related to disease activity. When comparing different RDs, MetS was significantly more frequent in SLE (42%) than in other RDs. Regarding MetS components, there was a significantly higher frequency of hypertension and elevated TG in SLE patients compared to those with other RDs. In contrast, no significant difference in MetS diagnosis was reported among RA, SLE, and SSc patients.[51] However, lower HDL levels and increased abdominal circumference have been reported in SLE and RA patients, respectively.[51]

Conclusion

The current study delves into the complex relationship between metabolic alterations, inflammation, and disease activity in a group of RDs. Encompassing different RDs in the same setting was one of the objectives of this analysis, aiming to determine which disease warrants the most attention. Moreover, this study is among the first to assess the association of NLR and PLR with MetS across different RDs. Investigating NLR and PLR in this context may provide insights into the link between inflammation, MetS, and atherosclerotic CVDs in RD patients. Given the heightened frequency of MetS among SLE patients, larger-scale prospective studies are warranted to explore the impact of MetS on atherogenesis and CVDs in RDs.

Ethics

Ethics Committee Approval: The members of the Scientific Research and Ethics Committee of the Rheumatology and Rehabilitation Department, Cairo University (SReC-RCU) have reviewed and approved the aforementioned M.Sc. protocol (approval number: 40-SReC-RCU2021, date: 20.03.2021).

Informed Consent: An informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Concept: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Design: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Data Collection and Processing: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Analysis or Interpretation: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Literature Search: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Writing: S.S.A-A., P.N.E-H., N.N.E., T.A.G.

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