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Frequency of Metabolic Syndrome in Individuals Diagnosed with Rheumatoid Arthritis and Its Relationship with Inflammatory Parameters

Romatoid Artrit Tanılı Bireylerde Metabolik Sendrom Sıklığı ve İnflamatuvar Parametrelerle İlişkisi

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ABSTRACT

OBJECTIVE: The aim of this study is to investigate the relationship between rheumatoid arthritis (RA) and metabolic syndrome (MetS), to evaluate the prevalence of MetS in patients with RA and its association with biomarkers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile, vitamin D], and to explore the effects of antirheumatic therapies on metabolic parameters. It is known that MetS increases cardiovascular risk in RA patients; thus, clarifying this relationship is critically important for patient management.

MATERIALS AND METHODS: This study was designed as a cross-sectional cohort analysis, including 270 RA patients followed in a single center. Demographic, clinical, and laboratory data of patients were collected retrospectively. MetS diagnosis was established according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. Disease activity markers for RA (CRP, ESR), lipid profiles, vitamin D levels, and treatment details were recorded. Student's t-test, Mann-Whitney U test, and chi-square test were used for statistical comparisons between groups.

RESULTS: The prevalence of MetS among RA patients was found to be 31.7%. Patients with MetS had significantly higher metabolic risk factors, such as body mass index (32.7 kg/m^2), hypertension (95%), and hypertriglyceridemia (86%). No significant differences were observed in CRP and ESR levels between patients with and without MetS. Although vitamin D deficiency was common, it was not significantly associated with MetS. Furthermore, no significant relationship was identified between RA treatments (methotrexate, biological agents) and MetS.

CONCLUSION: The prevalence of MetS in patients with RA is higher compared to the general population, leading to increased cardiovascular risk. In RA patients whose disease activity is well-controlled, the inflammation-metabolic risk relationship may diminish. A "treat-to-target" approach in RA management should encompass both joint-related and cardiometabolic outcomes. Early diagnosis and management of MetS can improve quality of life and prognosis in RA patients.

Keywords: Rheumatoid arthritis, metabolic syndrome, cardiovascular risk, inflammation, antirheumatic treatment, vitamin D

ÖZ

AMAÇ: Bu çalışmanın amacı, romatoid artrit (RA) ve metabolik sendrom (MetS) arasındaki ilişkiyi incelemek, RA hastalarında MetS prevalansını ve biyobelirteçlerle [C-reaktif protein (CRP, eritrosit sedimantasyon hızı (ESH), lipid profili, D vitamini] ilişkisini değerlendirmek, ayrıca anti-romatizmal tedavilerin metabolik parametreler üzerindeki etkilerini araştırmaktır. RA'lı hastalarda MetS'nin kardiyovasküler riski artırdığı bilinmekte olup, bu ilişkinin aydınlatılması hasta yönetimi açısından kritik öneme sahiptir.

GEREÇ ve YÖNTEM: Kesitsel bir kohort analizi olarak tasarlanan bu çalışmada, tek merkezde takipli 270 RA hastası incelendi. Hastaların demografik, klinik ve laboratuvar verileri retrospektif olarak toplandı. MetS tanısı Ulusal Kolesterol Eğitim Programı (NCEP ATP III) kriterlerine göre konuldu. RA hastalık aktivitesi (CRP, ESH), lipid profili, D vitamini düzeyleri ve tedavi detayları kaydedildi. İstatistiksel analizlerde gruplar arası karşılaştırmalar için Student t-testi, Mann-Whitney U testi ve ki-kare testi kullanıldı.

BULGULAR: RA hastalarında MetS prevalansı %31,7 olarak bulundu. MetS'li hastalarda vücut kitle indeksi (32,7 kg/m^2) ve hipertansiyon (%95), hipertrigliseridemi (%86) gibi metabolik risk faktörleri belirgin şekilde daha yüksekti. CRP ve ESH düzeyleri MetS'li ve MetS'siz gruplar arasında farklılık göstermedi. D vitamini eksikliği yaygın olmakla birlikte, MetS ile anlamlı bir ilişki saptanmadı. RA tedavileri (metotreksat, biyolojik ajanlar) ile MetS arasında belirgin bir ilişki gözlenmedi.

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SONUÇ: RA hastalarında MetS prevalansı genel popülasyona göre daha yüksektir ve kardiyovasküler riski artırmaktadır. İyi kontrol altındaki RA hastalarında enflamasyon-metabolik risk ilişkisi hafifleyebilir. RA tedavisinde "tüm hedefler için tedavi" yaklaşımı hem eklem hem de kardiyometabolik sonuçlar için benimsenmelidir. MetS'nin erken tanı ve yönetimi, RA hastalarının yaşam kalitesini ve prognozunu iyileştirebilir.

Anahtar Kelimeler: Romatoid artrit, metabolik sendrom, kardiyovasküler risk, enflamasyon, antiromatizmal tedavi, D vitamini

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune joint disease characterized by systemic inflammation. Patients with RA have a significantly increased long-term risk of cardiovascular disease; systemic inflammation in these patients can reduce life expectancy by approximately 5 years (1,2). Metabolic syndrome (MetS), a cluster of metabolic disorders including obesity, insulin resistance, dyslipidemia, and hypertension, substantially elevates cardiovascular risk (1,3). While the prevalence of MetS in the general population is around 20-25%, higher rates have been reported among RA patients due to systemic inflammation and insulin resistance (1,3). Additionally, a recent meta-analysis indicated a MetS prevalence of approximately 30% in RA patients, highlighting a significantly greater risk compared to healthy individuals (3). Correspondingly, RA patients commonly exhibit atherogenic lipid profile changes [such as low high-density lipoprotein (HDL) and high triglycerides] and adipokine imbalances (1).

The relationship between RA and MetS appears bidirectional. Chronic inflammation associated with RA can promote the development of MetS components, while the presence of MetS may increase the risk of developing RA. For instance, obesity and abdominal adiposity are known risk factors for RA; individuals with MetS have a higher likelihood of developing RA in the future (a 12-year cohort study reported a ~22% increased RA incidence among individuals with MetS) (4). Inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), can disrupt insulin receptor signaling, leading to insulin resistance and adversely affecting lipid metabolism in RA (5). Consequently, RA patients are more likely to exhibit MetS components such as visceral obesity, hyperglycemia, and dyslipidemia. Conversely, the presence of MetS has been associated with increased RA disease activity; studies indicate higher Disease Activity Scores (DAS28) and acute-phase reactant levels among RA patients with MetS (6). Therefore, a vicious cycle may exist between chronic inflammation and metabolic disturbances. Clarifying the link between RA and MetS is critical both for understanding disease pathogenesis and improving long-term cardiometabolic outcomes in RA patients.

In light of existing literature, the present study aims to investigate the relationship between RA and MetS, examine associations between MetS and biomarkers [e.g., C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profiles, 25(OH) vitamin D levels] in RA patients, and explore the impact of antirheumatic treatments on metabolic parameters.

MATERIALS & METHODS

Study Design and Patient Selection

This study was designed as a cross-sectional cohort analysis involving RA patients followed in a single center. Data from patients were meticulously collected and evaluated according to national ethical guidelines for research involving human subjects. Ethical approval for this study was obtained from the Ethics Committee of Balıkesir University Faculty of Medicine (decision no: 2025/70). Patients included in the study were adults aged over 18 years, diagnosed with RA according to the American College of Rheumatology classification criteria. Patient data were collected retrospectively from medical records and electronic health information systems.

For each patient, demographic data (age, sex), anthropometric measurements [height, weight; body mass index (BMI) calculated], duration of RA and treatment details, comorbidities, and laboratory results were recorded. Disease activity indicators such as CRP (mg/L) and ESR (mm/h), as well as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, were collected. Metabolic profile assessments included fasting blood glucose or presence of diabetes, lipid parameters [triglycerides, total cholesterol, low-density lipoprotein (LDL), HDL], arterial blood pressure values, and serum 25(OH) vitamin D levels.

Definition of Metabolic Syndrome

The diagnosis of MetS in patients was established according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. According to this definition, the presence of at least three of the following five criteria was considered diagnostic of MetS (3):

- Abdominal obesity: Waist circumference ≥102 cm in men, ≥88 cm in women (since waist circumference measurements were unavailable, patients with BMI ≥30 kg/m² were considered as having abdominal obesity).
- Hyperglycemia: Fasting plasma glucose ≥100 mg/dL or previously diagnosed diabetes mellitus.
- Hypertension: Blood pressure ≥130/85 mmHg or current antihypertensive therapy.
- Hypertriglyceridemia: Triglyceride levels ≥150 mg/dL or current treatment for elevated triglycerides.
- Low HDL cholesterol: HDL <40 mg/dL in men or <50 mg/dL in women, or current treatment aimed at increasing HDL cholesterol.
- Patients meeting at least three of these criteria were classified as having MetS.

Therapeutic Management

RA treatments were categorized into conventional synthetic disease-modifying antirheumatic drugs (csDMARDs, e.g., methotrexate, sulfasalazine, hydroxychloroquine), biological agents (bDMARDs, e.g., TNF inhibitors, IL-6 receptor inhibitors), and targeted synthetic DMARDs (tsDMARDs). Additionally, glucocorticoid use was recorded. Comorbidities such as hypertension, diabetes, coronary artery disease, and demographic data including age, sex, BMI, smoking history, and disease duration were documented.

Statistical Analysis

The prevalence of MetS within the RA cohort was calculated using descriptive statistics. Clinical and laboratory characteristics of RA patients with and without MetS were compared. Comparisons of continuous variables between groups were performed using Student's t-test or Mann-Whitney U test, depending on normality. Chi-square tests were used for categorical variables. A p-value of less than 0.05 was considered statistically significant. Results were interpreted in conjunction with relevant literature findings for comprehensive evaluation.

RESULTS

Patient Characteristics

A total of 270 patients with RA were evaluated (mean age ~59.3 years). The majority were female (approximately 75%). Hypertension was observed in 50.2%, type 2 diabetes in 26%, and dyslipidemia in 19% of the cohort. RF and/or anti-CCP antibody positivity (RA seropositivity) was present in 80% of patients. The RA seropositivity rate (RF and/or anti-CCP positivity) was determined to be 80%. A significant proportion of patients were treated with DMARDs: 57% were on at least one csDMARD (most commonly methotrexate, 45%), 19% were on a bDMARD, and 5% were on a tsDMARD. The proportion of patients currently receiving glucocorticoid treatment was 26%, usually at the low-dose prednisone level (≤5 mg/day).

Prevalence of Metabolic Syndrome

The prevalence of MetS among RA patients was similar to expected rates, with sufficient data available for diagnostic criteria in 104 patients. MetS prevalence was identified in 31.7% of patients. When comparing RA patients with and without MetS, demographic characteristics such as age (~60 years in both groups) and sex distribution (86% female in MetS[+], 81% female in MetS[-]) were comparable (p>0.05). Patients with MetS exhibited a significantly higher BMI (32.7 kg/m² vs. MetS[-]), with abdominal obesity noted in approximately 64% (14/22) of these patients based on BMI values.

Prevalence of MetS Components

In the cohort of 22 patients diagnosed with RA and MetS, the most prevalent metabolic risk components were high blood pressure and hypertriglyceridemia. A significant proportion of these patients met criteria for arterial hypertension (95%, 21/22) and high triglycerides (86%, 19/22). Additionally, LDL cholesterol levels were observed in 59% (13/22) of the MetS patients. Hyperglycemia or diabetes criteria were present in 73% (16/22) of patients, and 55% of the group with MetS were known diabetics. In comparison, the prevalence of hypertension was 35%, diabetes 18%, and hypertriglyceridemia 8% in RA patients without MetS (all p<0.001). The group without MetS exhibited significantly higher mean HDL cholesterol levels (62 mg/dL vs. 49 mg/dL, p<0.01). Interestingly, mean LDL cholesterol levels were slightly lower in patients with MetS (119 mg/dL vs. 134 mg/dL, p=0.08), which may be related to

the use of statins among some of these patients. The lipid profile of the RA cohort exhibited a negative correlation between CRP and HDL, with a r value of approximately -0.16, suggesting a "lipid paradox" in the context of active inflammation (6).

Inflammatory Markers and Disease Activity

No significant differences in RA-specific inflammatory markers (CRP, ESR) were identified between patients with and without MetS. Although MetS-positive patients tended to have slightly lower mean CRP (5.6 vs. 9.4 mg/L) and ESR values (27 vs. 30 mm/h), these differences were not statistically significant (CRP: p=0.94, ESR: p=0.67). Disease activity measured by inflammatory markers did not appear significantly different between groups, suggesting inflammation may have been effectively controlled in both cohorts.

Vitamin D Levels

Vitamin D deficiency was widespread among RA patients. In the 261 patients assessed, mean 25(OH) vitamin D levels were 25.6±14.1 ng/mL. Vitamin D deficiency was highly prevalent, observed in 67% of patients overall. However, no significant difference was noted in vitamin D levels between RA patients with and without MetS (23.4 ng/mL vs. 24.9 ng/mL, respectively, p=0.58), indicating that vitamin D status was not closely associated with MetS in this RA cohort.

RA Treatments and Metabolic Syndrome

The distribution of primary treatment groups (csDMARD, bDMARD, tsDMARD) utilized in patients with RA did not exhibit a discrepancy according to the presence of MetS. The distribution of patients with MetS who utilized csDMARD, bDMARD, or tsDMARD was 55%, 32%, and 14%, respectively, while the corresponding figures for the non-MetS group were 55%, 31%, and 8%, respectively (p>0.05 for all). The two groups exhibited significant similarity, particularly with regard to methotrexate use: The use of methotrexate was 8% (36%) in the MetS group and 23% (p=0.22) in the non-MetS group. TNF inhibitor biologic drug use was 32% in patients with MetS and 31% in those without MetS (p=0.89). The prevalence of glucocorticoid use was comparable between the two groups (30% vs. 25%, p=0.60). However, it has been observed that long-term, high-dose steroid use may contribute to the development of obesity and diabetes in some patients. These analyses, which were performed on the basis of treatment subgroups, did not demonstrate a clear effect of any particular RA treatment agent on the MetS in the current data.

DISCUSSION

In this study, we investigated the relationship between RA and MetS from multiple perspectives, including prevalence, risk factors, biomarkers, and therapeutic influences. The prevalence of MetS observed in our RA cohort (~31.7%) aligns closely with the rates (~30%) reported by recent meta-analyses and other international cohort studies (1,3). For example, previous meta-analyses have consistently reported MetS prevalence rates of approximately 30% in RA populations across diverse geographical settings (1,3). Although the observed prevalence in our cohort aligns with these findings, methodological differences, particularly the lack of direct waist circumference measurements, might have led to underestimation. Since we used BMI as an indirect measure for abdominal obesity, some patients meeting waist circumference criteria might have been overlooked. Indeed, abdominal obesity, a key MetS component, was indirectly inferred from BMI in approximately 34% of our MetS-positive patients. Given that waist circumference measurement directly reflects abdominal adiposity -a critical determinant of MetS- its absence likely affected accurate prevalence estimation.

The most common components of MetS observed in our RA cohort were hypertension (95%) and hypertriglyceridemia (86%). These findings are consistent with the literature, confirming hypertension and dyslipidemia as dominant cardiovascular risk factors in RA patients with MetS (1,4). The prevalence of hyperglycemia (73%) and low HDL cholesterol (59%) in our MetS-positive patients further highlights the metabolic complexity associated with RA. Notably, HDL cholesterol was significantly lower in patients with MetS compared to those without, aligning with previous reports indicating an inverse relationship between systemic inflammation and HDL cholesterol levels in RA patients (6). Interestingly, LDL cholesterol levels were slightly lower in MetS-positive individuals, potentially reflecting statin use among these patients.

The relationship between MetS and inflammatory markers (CRP, ESR) in RA patients remains controversial in the literature. While some studies report significantly higher inflammatory activity (DAS28, CRP, ESR) in RA patients with

MetS (1,3,4,6,7), others fail to identify such associations (8,9). In our cohort, no significant differences in CRP and ESR levels were identified between RA patients with and without MetS, suggesting well-controlled inflammatory activity overall. Indeed, our cohort showed relatively low inflammatory markers, reflecting effective disease control through treatment. This might partially explain why we did not observe a significant association between disease activity and MetS, aligning with studies suggesting inflammation-metabolic risk relationships become less prominent when RA is effectively managed (8-10).

Vitamin D deficiency was highly prevalent in our cohort (67% had 25(OH)D <30 ng/mL), but we found no significant difference between patients with and without MetS. Although some studies have reported a clear association between low vitamin D levels and increased MetS risk (11), our results did not confirm such a relationship. This discrepancy may be related to the widespread vitamin D deficiency across the entire study population, potentially reducing statistical power. Nonetheless, evidence from other studies indicates that vitamin D deficiency is associated with elevated cardiometabolic risk in RA patients, underscoring the importance of addressing vitamin D status as part of comprehensive RA care (11,12).

Regarding RA therapies, our study found no significant relationship between the use of conventional synthetic DMARDs (csDMARDs), biologics, targeted synthetic DMARDs, or glucocorticoids and the presence of MetS. The proportions of patients receiving these treatments were comparable across groups. Although methotrexate is known to reduce metabolic risk through its anti-inflammatory and insulin-sensitizing effects, we did not observe significant differences in MetS prevalence between methotrexate users and non-users. This might be attributed to the relatively small patient number, no follow-up or effective control of inflammation obscuring subtle metabolic effects (6,10,13). Similarly, TNF inhibitors did not significantly alter metabolic parameters, aligning with previous smaller studies that found minimal metabolic changes during short-term follow-up periods (10). While glucocorticoids are well-known to negatively influence metabolic parameters (weight gain, hyperglycemia, hypertension), the moderate usage (≤5 mg/day prednisone) in our cohort likely limited these adverse effects.

A study was conducted to assess the disease knowledge levels of RA patients, revealing a general dearth of knowledge. While no significant correlation was identified between knowledge level and disease activity (DAS-28) or functional status (SDA), it was observed that education level and disease duration positively influenced knowledge level (14). This finding underscores the necessity for enhanced educational resources and information for RA patients, particularly regarding disease management and comorbidities such as metabolic syndrome. In light of these findings, MetS screening and management should be a critical component in the follow-up of RA patients. International guidelines, such as the EULAR recommendations, advocate for regular screening and aggressive management of cardiovascular risk factors in RA patients (1,15). In patients diagnosed with RA, it is necessary to not only control joint inflammation but also closely monitor metabolic parameters such as blood pressure, blood sugar, and lipid profile. While the prevalence of MetS in our study population was approximately 12%, this low rate does not imply an absence of underlying risk, but rather underscores the need for further investigation to ascertain its true magnitude. Notably, the presence of insulin resistance in RA patients, even at the time of diagnosis, has been documented at rates as high as 50-70% (1).

Strengths of our study include a comprehensive, multidimensional evaluation of RA and MetS, emphasizing prevalence, biomarkers, and treatment outcomes. However, several limitations should be acknowledged. First, the cross-sectional design prevents establishing causality; prospective studies are needed to clearly demonstrate how RA treatments and disease activity affect metabolic outcomes over time. Second, the absence of direct waist circumference measurement, a key diagnostic criterion for MetS, likely resulted in underestimated MetS prevalence. Third, our patients predominantly had low disease activity, reducing the observable inflammatory burden and potentially masking the inflammation-metabolic relationship that might be more evident in active or untreated RA populations. Lastly, regional variability may affect findings, as the prevalence and relationship between RA and MetS may differ across populations due to genetic, environmental, and lifestyle factors (13).

Considering the existing literature, our findings reinforce the importance of evaluating and managing metabolic risk factors early in RA patients. Studies have shown that components of MetS significantly increase the risk of developing RA, and addressing these risk factors through lifestyle interventions (e.g., weight loss, dietary changes, and exercise) and pharmacological approaches (e.g., statins, antihypertensives) may mitigate RA incidence and cardiometabolic complications (4). Education and lifestyle modification strategies could thus be crucial preventive tools.

In conclusion, a multidisciplinary approach that encompasses both inflammation control and management of metabolic risk factors is essential for optimal RA patient care. Regular monitoring of metabolic syndrome, effective treatment of RA activity, lifestyle modifications, and targeted interventions such as vitamin D supplementation could significantly improve long-term cardiometabolic outcomes and reduce cardiovascular morbidity and mortality among patients with RA.

CONCLUSION

The relationship between RA and MetS is strongly supported by evidence at both epidemiological and pathophysiological levels. MetS is notably prevalent among RA patients, significantly increasing cardiovascular risk. Chronic inflammation in RA facilitates the development of MetS components such as obesity, insulin resistance, and dyslipidemia, while MetS itself can negatively affect disease activity and prognosis. DMARDs and biologic agents, commonly used in RA treatment, generally have beneficial metabolic effects by suppressing inflammation. Our findings suggest that, in patients with well-controlled RA, the inflammation-driven metabolic risk may be less pronounced. These observations underscore the necessity of adopting a comprehensive "treat-to-target" approach in RA management, not only focusing on joint-related outcomes but also considering cardiometabolic health. Early identification and active management of MetS in RA patients, including lifestyle modifications and targeted interventions, are crucial for improving long-term prognosis, disease activity, and overall quality of life.

Ethic: Data from patients were meticulously collected and evaluated according to national ethical guidelines for research involving human subjects. Ethical approval for this study was obtained from the Ethics Committee of Balıkesir University Faculty of Medicine (decision no: 2025/70).

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