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Effects of DMARD and Anti-TNF Therapies on Inflammatory Markers, Lipid Profile, and Insulin Resistance in Rheumatoid Arthritis: A Controlled Study

Romatoid Artritte DMARD ve Anti-TNF Tedavilerinin İnflamatuvar Belirteçler, Lipid Profili ve İnsülin Direnci Üzerine Etkileri: Kontrollü Bir Çalışma

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Abstract

Aim: This study aimed to compare the effects of disease-modifying antirheumatic drugs (DMARDs) and anti-tumor necrosis factor (anti-TNF) therapy on inflammatory markers, lipid profile, and insulin resistance in rheumatoid arthritis (RA) patients, and to evaluate the potential cardiovascular impact of biological treatments.

Material and Method: This single-center, prospective study included 122 participants between May 2012 and May 2013: 35 RA patients treated with DMARDs, 31 RA patients treated with anti-TNF agents, and 56 healthy controls. Inflammatory markers [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF)], lipid profile [total cholesterol, triglycerides, high-density lipoprotein (HDL), atherogenic index of plasma (AIP)], and glycemic parameters [fasting glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR)] were assessed.

Results: ESR and CRP levels were significantly higher in RA groups compared with controls (p<0.001), and CRP was higher in the anti-TNF group than in the DMARD group. RF positivity was markedly increased in RA patients (p<0.001). No significant differences were found among groups for lipid profile or AIP (p>0.05). Insulin and fasting glucose levels were similar, while HOMA-IR was higher in controls and marginally lower in RA groups (p=0.049).

Conclusion: RA patients exhibited significantly elevated inflammation, whereas lipid profile and AIP did not differ between treatment groups. Suppression of inflammation was associated with partial improvement in insulin resistance. Cardiometabolic risk in RA should be assessed by considering not only conventional lipid parameters but also inflammation and insulin resistance as multifactorial determinants.

Keywords: Rheumatoid arthritis, antirheumatic agents, tumor necrosis factor inhibitors, insulin resistance, lipid metabolism

Öz

Amaç: Bu çalışmanın amacı, romatoid artrit (RA) hastalarında hastalık modifiye edici anti-romatizmal ilaçlar (DMARD'lar) ile anti-tümör nekroz faktör (anti-TNF) tedavisinin inflamatuvar belirteçler, lipid profili ve insülin direnci üzerindeki etkilerini karşılaştırmak ve biyolojik tedavilerin olası kardiyovasküler etkilerini değerlendirmektir.

Gereç ve Yöntem: Bu tek merkezli, prospektif çalışmaya Mayıs 2012 ile Mayıs 2013 tarihleri arasında toplam 122 katılımcı dahil edilmiştir: DMARD tedavisi alan 35 RA hastası, anti-TNF ajanları ile tedavi edilen 31 RA hastası ve 56 sağlıklı kontrol. İnflamatuvar belirteçler [eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), romatoid faktör (RF)], lipid profili [toplam kolesterol, trigliserit, yüksek yoğunluklu lipoprotein (HDL), plazmanın aterojenik indeksi (AIP)] ve glisemik parametreler [açlık glukozu, insülin, insülin direncinin homeostaz modeli değerlendirmesi (HOMA-IR)] incelenmiştir.

Bulgular: ESR ve CRP düzeyleri, kontrol grubuna kıyasla RA gruplarında anlamlı derecede yüksek bulunmuştur (p<0,001) ve CRP düzeyi anti-TNF grubunda DMARD grubuna göre daha yüksek saptanmıştır. RF pozitifliği RA hastalarında belirgin şekilde artmıştır (p<0,001). Lipid profili veya AIP açısından gruplar arasında anlamlı bir fark bulunmamıştır (p>0,05). İnsülin ve açlık glukoz düzeyleri benzer iken, HOMA-IR kontrol grubunda daha yüksek ve RA gruplarında marjinal olarak daha düşük bulunmuştur (p=0,049).

Sonuç: RA hastalarında inflamasyon belirgin şekilde artmışken, lipid profili ve AIP tedavi grupları arasında farklılık göstermemiştir. İnflamasyonun baskılanması, insülin direncinde kısmi bir iyileşme ile ilişkilendirilmiştir. RA'daki kardiyometabolik risk değerlendirmesi yapılırken yalnızca klasik lipid parametreleri değil, inflamasyon ve insülin direnci gibi çok faktörlü belirleyiciler de dikkate alınmalıdır.

Anahtar Kelimeler: Romatoid artrit, anti-romatizmal ajanlar, tümör nekroz faktörü inhibitörleri, insülin direnci, lipid metabolizması

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune rheumatologic disease. It most commonly affects the small joints of the hands and feet symmetrically, and in the long-term leads to joint deformities and functional loss. The prevalence of RA ranges between 0.5–1% worldwide and is approximately three times more common in women than in men.[1,2] The disease typically develops between the ages of 30 and 50, causing high morbidity, loss of work capacity, and reduced quality of life.[3]

The pathogenesis of the disease involves T and B cells, macrophages, fibroblast-like synoviocytes, and especially proinflammatory cytokines such as TNF-α, IL-1, and IL-6, which play a central role.[4] Clinically, RA typically presents with morning stiffness, joint pain, swelling, and restricted movement. As the disease progresses, structural deformities such as swan-neck deformity, boutonnière deformity, and ulnar deviation emerge. In addition, various complications may develop in the lungs, heart, eyes, skin, and hematopoietic system.[5] RA is a systemic disease that can shorten life expectancy by approximately 5–10 years, with much of this effect mediated through cardiovascular diseases (CVD).[6] Dyslipidemia in RA is defined as the "lipid paradox," characterized by low total cholesterol and HDL cholesterol levels. In individuals with high disease activity, reduced HDL levels increase the risk of cardiovascular events.[7] Furthermore, insulin resistance is reported to be more common in RA, contributing to the development of both metabolic syndrome and CVD.[8]

As a treatment approach, early diagnosis of the disease and the rapid initiation of disease-modifying antirheumatic drugs (DMARDs) play a critical role in preventing permanent joint damage.[9] In patients with high disease activity or poor prognostic factors, biological DMARDs (particularly TNF-α inhibitors, IL-6 receptor antagonists, B-cell–targeting agents, and costimulation inhibitors) are added to the treatment regimen.[10] However, the effects of biological therapies on lipid profile and insulin resistance remain controversial; while some studies have shown that biological agents reduce inflammation and thereby improve cardiovascular risk markers, others have reported adverse changes in lipid levels.[11]

Cardiovascular morbidity and mortality remain significant clinical problems in RA. Controlling disease activity is critically important not only for joint health but also for improving metabolic and cardiovascular outcomes. Current literature provides conflicting findings regarding the effects of DMARDs and biological therapies on lipid profile, insulin resistance, and consequently cardiovascular risk, highlighting the need for further clinical research. The aim of this study was to investigate whether there are differences in lipid profile and insulin resistance between RA patients receiving DMARD therapy and those treated with TNF-α inhibitors, and to evaluate the potential effects of biological therapies on cardiovascular disease risk.

MATERIAL AND METHOD

Study Design

This study was designed as a prospective, single-center trial. After obtaining approval from the ethics committee, eligible participants were selected among patients who applied to and were followed up at the Internal Medicine and Physical Therapy outpatient clinics of Haydarpaşa Numune Training and Research Hospital between May 2012 and May 2013. Ethical approval was obtained from the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 02.04.2012, Decision no: 2012/07). Written informed consent was obtained from all participants, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Inclusion criteria for the study were: receiving anti-TNF or DMARD therapy for at least three months, being between 20–80 years of age, not receiving steroid treatment, having a body mass index (BMI) between 18–25 kg/m², no prior diagnosis or treatment for diabetes mellitus or hyperlipidemia, having a Disease Activity Score in 28 joints (DAS28) ≤2.6, indicating remission, being diagnosed with rheumatoid arthritis (RA) in remission, and not being pregnant. A total of 122 participants meeting these criteria were included in the study: 35 patients receiving DMARD therapy, 31 patients receiving anti-TNF therapy, and 56 healthy controls with similar age and sex distribution.

Data Collection

Hematological and biochemical parameters of all participants were evaluated. These included measurements of hemoglobin, hematocrit, platelet count, mean corpuscular volume, erythrocyte sedimentation rate, and C-reactive protein levels. Liver and kidney function tests comprised alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, and creatinine levels. In addition, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies were analyzed.

For the lipid profile, total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL) levels were assessed. Glycemic parameters included fasting blood glucose, hemoglobin A1c, and insulin levels. Insulin resistance was calculated using the HOMA-IR formula [fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5]. Cardiovascular risk was evaluated using the atherogenic index of plasma (AIP), calculated as the triglyceride/HDL-cholesterol ratio.

Statistical Analysis

Data obtained in the study were analyzed using SPSS 19.0. Descriptive statistics were presented as mean±standard deviation (Mean±SD) or percentage (%). For continuous variables (ESR, CRP, total cholesterol, triglycerides, HDL, AIP, insulin, fasting blood glucose, HOMA-IR), one-way ANOVA was used to compare groups. When ANOVA results indicated a significant difference, independent sample t-tests (post-hoc) were applied for pairwise group comparisons. For categorical variables, the chi-square test (χ^2 test) was used, and in cases of insufficient cell frequencies, Fisher's exact test was applied for confirmation. A p-value of <0.05 was considered statistically significant in all analyses.

RESULTS

A total of 122 individuals were included in the study. Of the participants, 78.7% were female (n=96) and 21.3% were male (n=26). The DMARD group consisted of 35 patients, the anti-TNF group included 31 patients, and the control group comprised 56 individuals (**Table 1**).

Table 1. Descriptive characteristics of participants

Group	n	Female	Male
DMARD	35	26	9
Anti-TNF	31	26	5
Control	56	44	12

DMARD: Disease-modifying antirheumatic drug; Anti-TNF: Tumor necrosis factor inhibitor.

Table 2 presents the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of the study groups (Control, DMARD, and Anti-TNF), along with their statistical comparisons. ESR and CRP values were significantly higher in the patient groups compared to the control group (both p<0.001). CRP levels were significantly higher in the Anti-TNF group than in the DMARD group (p<0.001).

Table 2. Comparison of inflammatory parameters

Parameter	Control (Mean±SD)	DMARD (Mean±SD)	Anti-TNF (Mean±SD)	p value
ESR (mm/hour)	12.5±4.0	25.9±8.0	29.2±9.0	<0.001*
CRP (mg/dL)	0.49±0.20	1.14±0.40	2.12±0.70	<0.001*

*ANOVA, ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein

Table 3 presents the total cholesterol, triglyceride, HDL levels, and AIP values of the study groups (Control, DMARD, and Anti-TNF), along with their statistical comparisons. No significant differences were observed among the groups in terms of total cholesterol, triglycerides, HDL, and AIP (p>0.05 for all parameters). These findings indicate that lipid profile and AIP values remained at similar levels across the treatment groups.

Table 3. Comparison of lipid profile and AIP values among groups

Parameter	Control (Mean±SD)	DMARD (Mean±SD)	Anti-TNF (Mean±SD)	p value
Total cholesterol (mg/dL)	184.4±32.0	197.6±34.0	196.0±36.0	0.218
Triglycerides (mg/dL)	118.3±28.0	111.8±27.0	117.7±30.0	0.542
HDL (mg/dL)	47.4±7.0	48.9±7.5	47.6±6.8	0.611
AIP	0.38±0.08	0.36±0.07	0.33±0.06	0.456

ANOVA, HDL: High-density lipoprotein; AIP: Atherogenic index of plasma.

Table 4 presents the insulin levels, fasting blood glucose levels, and HOMA-IR values of the participants, along with their statistical comparisons. No significant differences were found among the groups in terms of insulin levels and fasting blood glucose levels (p=0.412 and p=0.335, respectively). In contrast, HOMA-IR values were higher in the control group and lower in the patient groups, with this difference showing borderline statistical significance (p=0.049).

Table 4. Comparison of glycemic parameters and HOMA-IR among groups

Parameter	Control (Mean±SD)	DMARD (Mean±SD)	Anti-TNF (Mean±SD)	p value
Insulin (mU/L)	10.2±3.0	9.1±2.8	9.9±3.2	0.412
Fasting blood glycose (mg/dL)	94.2±9.5	92.6±10.0	90.9±9.0	0.335
HOMA-IR	2.43±0.85	2.13±0.80	2.04±0.75	0.049

ANOVA, HOMA-IR: Homeostasis model assessment–insulin resistance.

DISCUSSION

Rheumatoid arthritis, as a chronic inflammatory disease, affects not only the joints but also metabolic processes and the cardiovascular system. In this study, RA patients receiving DMARD and anti-TNF therapies were compared with controls, and inflammatory parameters, lipid profile, and glycemic indicators were evaluated. The results obtained are largely consistent with current literature, although some differences were observed in certain aspects.

In the present study, the inflammatory markers ESR and CRP were found to be significantly higher in the patient groups compared to the control group, which is consistent with the systemic inflammatory nature of RA. Moreover, the higher CRP levels observed in the Anti-TNF group compared to the DMARD group may reflect the clinical practice pattern in which biological therapies are typically initiated in patients with higher disease activity or those unresponsive to DMARDs. In the literature, Anti-TNF treatments have repeatedly been shown to reduce inflammatory markers such as ESR and CRP.[12] In one study, a 6-month treatment with Adalimumab in RA patients led to a marked decrease in ESR and CRP levels; suppression of inflammation and reduction in systemic markers were also accompanied by improvements in insulin resistance and body composition.[13] However, some cohorts have reported that, due to a heavier disease burden at baseline, the Anti-TNF group may show higher absolute values of inflammatory parameters.[9,14] A similar finding was observed in our study. The markedly higher rates of RF positivity in the patient groups compared to the control group are also consistent with the literature. RF is an important serological marker in the diagnosis and prognostic evaluation of RA, and high positivity rates have been associated with disease activity and the risk of joint damage.[2]

In terms of lipid profile, no significant differences were found among the groups in our study. Total cholesterol, triglyceride, and HDL levels were similar, and AIP also showed no significant variation. These results may be related to the concept of the "lipid paradox" described in RA. It has been demonstrated that during periods of high inflammation, total cholesterol and LDL levels decrease while cardiovascular risk increases, whereas with inflammation control, lipid levels may rise but the risk diminishes.[15] This phenomenon is thought to be due to impaired HDL function, atherogenic changes in LDL particle size, and the direct effects of inflammatory cytokines on lipoprotein metabolism.[16] In our study, the lack of significant differences in lipid values among the groups may be attributed to the fact that most patients were in remission or had low disease activity. Similarly, in a meta-analysis conducted by Daïen et al.[17] anti-TNF therapy was found to moderately increase total cholesterol and HDL levels; however, these changes were concluded to have no major clinical impact. Our findings are consistent with these results, as no marked differences were observed between the anti-TNF and DMARD groups in terms of lipid parameters.

Studies on the prognostic value of AIP have reported that in RA patients, AIP may be associated with subclinical atherosclerosis.[18] However, short-term clinical studies may not reveal significant differences between treatment groups. In our study as well, AIP values were found to be similar across the three groups. Gonzalez-Gonzalez et al.[19] reported that AIP is associated with subclinical atherosclerosis markers such as carotid intima-media thickness, but short-term treatment-related changes are limited. Therefore, our findings support the notion that AIP may not reflect short-term treatment differences, but could be useful in predicting long-term cardiovascular risk.

With regard to glycemic parameters, no significant differences were observed in insulin and fasting blood glucose levels, while HOMA-IR was higher in the control group and showed borderline lower values in the patient groups. The prevalence of insulin resistance is increased in RA, which has been associated both with the disruption of insulin signaling pathways by inflammatory cytokines and with factors such as physical inactivity and corticosteroid therapy.[8] There is also evidence suggesting that anti-TNF therapies may reduce insulin resistance. In the systematic review by Lim et al.[20] anti-TNF therapy was reported to improve insulin sensitivity, and similarly, Van den Oever et al.[13] also observed an improvement in insulin resistance following anti-TNF treatment. However, the literature suggests that this effect is more pronounced only in patients with high inflammatory activity, while it is less evident in those with low activity or in remission.[21] In our study, the borderline lower HOMA-IR values compared to the control group indicate that suppression of inflammation through treatment may lead to a partial improvement in insulin resistance.

In light of these findings, our study supports the notion that in RA management, not only joint health but also metabolic and cardiovascular risk factors should be taken into consideration. Although suppression of inflammation did not result in major changes in lipid profile and insulin resistance, this suggests that the metabolic effects of biological therapies may be limited or that their impact could become more evident over the long term.

Among the strengths of this study are the simultaneous evaluation of control, DMARD, and Anti-TNF groups, and the comprehensive assessment of not only joint health but also inflammatory parameters, lipid profile, and glycemic indicators; this allows cardiometabolic risk in rheumatoid arthritis to be addressed from a multidimensional perspective. Furthermore, the fact that participants were in remission or had low disease activity indicates that the findings reflect a relatively stable population under treatment. Nevertheless, the study also has certain limitations. First, the sample size was relatively small, which may have reduced statistical power, particularly for secondary endpoints. In addition, factors that could influence lipid profile and insulin resistance, such as dietary habits, physical activity level, and menopausal status, were not controlled in detail, which constitutes another limitation of this study.

CONCLUSION

Our study demonstrated significant differences in inflammatory parameters between patient and control groups, no differences among groups regarding lipid parameters and AIP, and a borderline significant improvement in insulin resistance. When considered alongside the conflicting findings in the current literature, these results suggest that cardiometabolic risk in RA should be assessed not only through conventional lipid measurements but also by incorporating multiple parameters such as inflammation control and insulin resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 02.04.2012, Decision no: 2012/07).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment in the study..

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