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Impact of Anti-Tumor Necrosis Factor Alpha Treatment on Lipid Profile in Patients with Rheumatoid Arthritis

Romatid Artritli Hastalarda Anti-Tümör Nekroz Alfa Tedavisinin Lipid Profili Üzerine Etkisi

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ABSTRACT

Background: Rheumatoid arthritis (RA) primarily causes joint deformities. Epidemiologic and clinical studies have shown that chronic inflammation in RA increases the risk of cardiovascular disease. The physiopathology of the phenomenon has been attempted to be explained by the alteration of the lipid profile by inflammation triggered by cytokines such as tumor necrotizing factor (TNF). However, studies investigating the effect of anti-TNF agents used for treating RA on lipids are still needed.

Materials and Methods: Between January 2006 and March 2010, 93 RA patients admitted to the University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Rheumatology Outpatient were included in the study. Anti-TNF treatment was administered to 46 patients, and 47 patients who were not administered anti-TNF were kept under control. Cholesterol and triglyceride levels were evaluated separately by averaging. The mean lipid levels at the beginning of the study and 12 months later were statistically compared.

Results: Among 93 female patients diagnosed with RA, adalimumab was administered to 18, etanercept to 18, and infliximab to 10 of 46 patients who received anti-TNF. The 47 patients who were not administered anti-TNF were kept under control. There was no statistical difference between baseline and 1-year postoperative lipid levels between the groups (p>0.05).

Conclusion: In approximately half of patients with RA, mortality is due to cardiovascular causes. Anti-TNF agents reduce inflammation and alter the lipid profile. In the literature, studies have shown that anti-TNF therapy has a negative effect on the lipid profile. The reason for the absence of this result in our study may be the exclusion of patients with diabetes mellitus and the short duration of the study. In conclusion, we believe that monitoring lipid levels is important in patients with high cardiovascular mortality. We believe that this should be considered in the selection and continuation of treatment.

Keywords: Rheumatoid arthritis, anti-TNF, lipid profile

ÖZ

Amaç: Romatoid artrit (RA), öncelikle eklemlerde deformitelere neden olur. Epidemiyolojik ve klinik çalışmalar RA'de gözlenen kronik enflamasyonun kardiyovasküler hastalık riskini artırdığını göstermiştir. Olayın fizyopatolojisi, tümör nekrotizan faktörü (TNF) gibi sitokinlerle tetiklenmiş olan enflamasyonun lipid profilini değiştirmesi ile açıklanmaya çalışılmıştır. Ancak RA tedavisi için kullanılan anti-TNF ajanlarının lipitler üzerindeki etkisini araştıracak çalışmalara halihazırda ihtiyaç duyulmaktadır. Bu çalışmanın amacı; RA hastalarında anti TNF tedavinin serum lipid düzeylerine etkisini araştırmaktır.

Gereç ve Yöntemler: Ocak 2006-Mart 2010 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi Romatoloji Polikliniğine başvuran 93 RA hastası çalışmaya alındı. Kırk altı hastaya anti-TNF tedavi verildi, anti-TNF verilmeyen 47 hasta ise kontrol altında tutuldu. Diabetes mellitus tanılı ve antihiperlipidemik tedavi alan hastalar çalışmaya alınmadı. Kolesterol ve trigliserid seviyeleri ayrı ayrı ortalaması alınarak değerlendirildi. Çalışma başlangıcı ve 12 ay sonraki lipid düzeylerinin ortalamaları istatistiksel olarak karşılaştırıldı.

Bulgular: RA tanılı 93 kadın hastadan anti-TNF verilen 46 hastanın 18'e Adalimumab, 18'e Etanercept, 10'a İnfliksimab verildi. Anti-TNF verilmeyen 47 hasta ise kontrol altında tutuldu. Gruplara göre başlangıç ve 1 yıl sonrası lipid düzeyleri arasında istatistiksel farklılık bulunmadı (p>0,05).

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ÖZ

Sonuç: RA'lı hastaların yaklaşık yarısında mortalite kardiyovasküler nedenlere bağlıdır. Sistemik enflamasyon direkt endotel fonksiyonu üzerine, indirekt olarak da lipid profiline olan etkisiyle kardiyovasküler riske neden olur. TNF-alfa kronik enflamasyonda odak sitokindir. Lipid metabolizması, insülin rezistansı ve endotel fonksiyonunu etkiler. TNF-alfa blokerlerinin tedavi amaçlı kullanımı enflamasyonu azaltır ve hastaların lipid profilinde değişiklik yapar. Literatürde anti-TNF tedavinin lipid profilini olumsuz etkilediğini gösteren çalışmalar vardır. Bizim çalışmamızda bu sonucun olmamasının nedeni; diabetes mellituslu hastaların çalışmaya alınmaması ve kısa süreli olması olabilir. Sonuç olarak RA gibi kardiyovasküler mortalitesi oldukça yüksek olan bir hastalıkta, lipid düzeylerinin takibinin oldukça önemli olduğu inancındayız. O nedenle tedavi seçiminde ve devamında da bu durumun dikkate alınması gerektiği inancındayız.

Anahtar Kelimeler: Romatoid artrit, anti-TNF, lipid profili

Introduction

Rheumatoid arthritis (RA) primarily affects the joints, causing chronic inflammation and deformities. It is characterized by primary synovitis, which leads to the formation of pannus in the synovia and subsequent destruction of cartilage, bone tissue, and adjacent tissues, resulting in joint deformations (1). Inflammation can also affect other organs (2,3). RA can affect the cardiovascular system through various mechanisms, such as vasculitis, amyloidosis, serositis, valvulitis, fibrosis, and lesions resembling rheumatoid nodules (4). This involvement can lead to serious complications, such as pericarditis, myocardial dysfunction, coronary arthritis, conduction system involvement, heart valve involvement, aortitis, and pulmonary hypertension, which are associated with early mortality (5,6). Chronic inflammation is recognized as a risk factor for atherosclerosis and heart failure in patients with RA. Epidemiologic and clinical studies have shown that RA increases the risk of cardiovascular disease with chronic inflammation. Atherosclerosis is associated with disease duration and blood lipid levels (7,8). Cardiovascular causes account for approximately half of the mortality in patients with RA. Systemic inflammation increases the risk of cardiovascular disease by directly affecting endothelial function or indirectly affecting the lipid profile. The lipid profile is altered by the acute phase response activated by inflammation or infection. Cytokines, such as tumor necrosis factor (TNF), regulate an organism's immunological, inflammatory, and restorative responses to an agent. These hormone-like polypeptides are primarily secreted during immunological and inflammatory responses and act as signals in intercellular communication (9,10,11,12). TNF-α functions as a chemotactic agent for monocytes and neutrophils, stimulating phagocytosis and adhesion to the endothelium. In addition, it induces the release of superoxide derivatives and procoagulant activity in the endothelial tissue, leading to early vasodilation and leukocyte accumulation in the vessel (13,14). These effects include the suppression of cytokine/receptor functions, conversion of the immune response from Th1 to Th2, and inhibition of the three-molecule complex (TCR/peptide/MHC) (15). Anti-TNF agents reduce inflammation in the treatment of RA and are commonly used for this purpose.

The study investigated the impact of anti-TNF therapy on serum lipid levels in patients with RA.

Materials and Methods

This single-center study enrolled 93 patients with RA who applied to University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Rheumatology January 2006 and March 2010. The study group comprised 46 RA patients who were scheduled to start anti-TNF treatment, whereas the control group consisted of 47 RA patients who did not receive anti-TNF treatment. In this study, all patients provided informed consent to participate. The disease was diagnosed according to the revised RA diagnostic criteria of the American Rheumatism Association in 1987. This study excluded patients with liver or kidney failure, malignancy, systemic diseases other than hypertension, and additional inflammatory diseases. Patients using antihyperlipidemic drugs and those diagnosed with diabetes mellitus were also excluded because of their potential impact on the lipid profile. The study participants were interviewed regarding their symptoms, systemic diseases, medication use, and family medical history. A comprehensive physical examination, including an assessment of the musculoskeletal system, was conducted for all participants. Routine laboratory tests were performed to obtain a complete blood count and measure biochemical markers, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) levels. Blood samples were collected from the forearm vein between 08:30 and 09:00 after a 12 hours fast. Normal CRP measurement values range from 0 to 5 mg/L, while values higher than 5 mg/L are considered abnormal. A sedimentation value between 6 and 12 mm is considered normal. The normal value for RF is 0-15 IU/mL,

whereas values over 15 IU/mL are considered high. Lipid levels were evaluated separately by calculating the mean. Statistical comparison was conducted between the mean sedimentation, CRP, and lipid levels at the beginning and 12 months after the start of the study.

This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, with decision number 89513307/1009/389.

Statistical Analysis

Statistical analysis was performed using Number Cruncher Statistical System 2007 and PASS 2008 software (Utah, USA). Descriptive statistical methods, including mean and standard deviation, were used for data analysis. The Student's t-test was used to compare normally distributed parameters between the two groups. Furthermore, the Paired Samples t-test was used to compare changes after treatment with those before treatment. The data were compared using the chi-square test.

Results

Ninety-three female patients were included in the study, with 46 patients in the study group and 47 patients in the control group. The patients were screened between January 2006 and March 2010. The age range of the patients was 25-64 years, with a mean of 48.52±9.96 years.

Age at onset and disease duration were similar in both groups. The study analyzed CRP, ESR, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and total cholesterol levels, as well as smoking, presence of hipertension (HT), RF levels, and use of Methotrexate (MTX), Hydroxychloroquine (HQ), Deltacortil (Prednisolone) (DC), Arva (Leflunomide), and Salazopryn (Sulfasalazine) (SA) (p>0.05) (Table 1, Table 2).

The study group consisted of 18 patients who received Adalimumab, 18 patients who received Etanercept, and 10 patients who received Infliximab (Table 3).

Baseline CRP levels were comparable between the groups. Additionally, CRP levels did not show any statistically significant difference between the groups 1 year later (p>0.05). Baseline CRP levels were similar among the groups. No significant change in CRP levels was observed in the control group after 1 year compared with baseline levels (p>0.05) (Table 4).

Baseline sedimentation values were also not significantly different between the groups (p>0.05). After 1 year, there was no statistically significant difference in sedimentation levels between the groups (p>0.05). However, both groups showed a statistically significant decrease in sediment levels compared with baseline (p<0.01) (Table 5).

Additionally, there were no significant differences in total cholesterol, LDL cholesterol, and HDL cholesterol levels between baseline and 1-year follow-up measurements in

Table 1. Patient characteristics

	Study (n=50)	Control (n=47)	p-value
	Mean ± SD	Mean ± SD	
Age	47.60±10.15	49.42±9.78	**0.386**
Age at disease (month)	89.92±27.93	85.70±14.54	**0.414**
CRP	18.35±20.11	14.11±27.77	**0.402**
ESH	43.02±19.36	35.17±24.63	**0.092**
HDL	55.95±1.68	58.63±14.61	**0.195**
LDL	108.62±26.03	110.27±21.78	**0.798**
Triglyceride	116.71±41.21	124.21±55.05	**0.764**
Total cholesterol	86.32±42.42	191.31±25.43	**0.515**
Resume			
Smoking	2 (4.3%)	8 (17%)	**0.091**
HT	19 (41.3%)	22 (46.8%)	**0.593**
DM	0 (0%)	0 (0%)	-
RF			
Positive	25 (54.3%)	23 (48.9%)	**0.602**
Negative	21 (45.7%)	24 (51.1%)	

SD: Standard deviation, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HT: Hypertension, DM: Diabetes mellitus

Table 2. Therapeutic agents

	Study	Control	p-value
	n (%)	n (%)	
MTX	28 (56%)	20 (42.6%)	**0.186**
HQU	17 (37%)	23 (48.9%)	**0.243**
DC	21 (45.7%)	15 (31.9%)	**0.174**
ARAVA	12 (26.1%)	7 (14.9%)	**0.181**
SA	16 (32%)	9 (19.1%)	**0.148**

Chi-squared test, p<0.05, p<0.01, TX: Methotrexate, DC: Deltacortil, SA: Sulfasalazine, HQU: Hydroxychloroquine

Table 3. Anti-TNF usage and duration

	n	%
Currently using anti-TNF		
Adalimumab	18	39.1
Etanercept	18	39.1
Infliximab	10	21.7

TNF: Tumor necrotizing factor

either group (p>0.05). One year later, there was no significant difference in cholesterol levels between the study and control groups (p>0.05). Similarly, there was no statistically significant difference in triglyceride levels between the groups at baseline and after 1 year (>0.05). However, a significant difference in triglyceride levels was found in the control group 1 year after the first measurement (p<0.05) (Table 6).

Discussion

The treatment of RA, a condition characterized by chronic inflammation, joint deformity, and systemic complications, reduces inflammation and prevent joint deformity and systemic complications. Chronic inflammation is primarily caused by TNF-alpha, a cytokine that affects lipid metabolism, insulin resistance, and endothelial function. The therapeutic use of TNF-alpha blockers reduces inflammation and induces changes in the lipid profile of patients (16). Short-term anti-TNF therapy resulted in a significant increase in HDL cholesterol. However, this effect was temporary. Longer anti-TNF use leads to increased levels of cholesterol and LDL cholesterol (17,18).

The relationship between chronic inflammation and lipid metabolism is not yet fully understood (19,20). Biologic drugs targeting proinflammatory cytokines, such as TNF-alpha and IL-6, appear to increase lipid levels, but the mechanism underlying this effect is not yet fully understood (21,22,23).

The study compared the mean lipid levels of patients with RA who received anti-TNF at the beginning of the study and after 1 year. The mean lipid levels of patients with RA in the control group who did not receive anti-TNF were also compared after a 1-year follow-up. The study found no significant difference between the initial and one-year later total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels in patients with RA who received anti-TNF. Cholesterol levels did not significantly differ between the control and study groups. However, the study group experienced a significant decrease in triglyceride levels. The lipid averages at baseline and 1 year later were similar between the two groups.

In their study on patients with RA who received anti-TNF therapy, Cauza et al. (24) found no significant difference in

Table 4. CRP assessment

CRP	Study	Control	p-value
	Mean ± SD	Mean ± SD	
Beginning	18.35±20.11	14.11±27.77	**0.402**
1 year later	10.79±16.42	10.35±11.79	**0.883**
Beginning - 1 year later	**0.001**	**0.272**	

Student t-test, Paired Samples t-test, p<0.05, p<0.01
CRP: C-reactive protein, SD: Standard deviation

Table 5. Sedimentation assessment

ESR	Study	Control	p-value
	Mean ± SD	Mean ± SD	
Beginning	43.02±19.36	35.17±24.63	**0.092**
1 year later	28.50±16.13	24.27±14.99	**0.186**
Beginning - 1 year later	**0.001****	**0.001****	

Student t-test, Paired Samples t-test, **p<0.01
ESR: Erythrocyte sedimentation rate, SD: Standard deviation

Table 6. Cholesterol and triglyceride assessment

		Study	Control	p-value
		Mean ± SD	Mean ± SD	
Total cholesterol	**Beginning**	186.72±42.23	191.31±25.43	**0.515**
	1 year later	188.90±35.48	191.30±26.99	**0.718**
Beginning - 1 year later		**0.691**	**0.732**	
LDL	**Beginning**	109.02±25.79	110.27±21.78	**0.798**
	1 year later	103.30±29.11	107.72±24.82	**0.437**
Beginning - 1 year later		**0.229**	**0.634**	
HDL	**Beginning**	55.00±12.80	58.63±14.61	**0.195**
	1 year later	56.52±13.20	59.04±16.81	**0.419**
Beginning - 1 year later		**0.364**	**0.688**	
TG	**Beginning**	121.06±48.21	124.21±55.05	**0.764**
	1 year later	121.26±45.06	115.34±51.65	**0.557**
Beginning - 1 year later		**0.968**	**0.036***	

Student t-test, Paired Samples t-test, *p<0.05
SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride

the levels of total cholesterol and LDL cholesterol before and after 48 months. However, they found a significant increase in triglyceride levels after treatment and a significant decrease in HDL cholesterol levels (24). Our study did not find any negative effects, which may be due to the shorter follow-up period and the exclusion of patients with diabetes mellitus.

Two weeks after treatment, RA patients receiving anti-TNF therapy experienced a decrease cholesterol, LDL, and triglyceride levels. However, evaluations performed 6 months and 1 year later showed an increase in total cholesterol, LDL, and triglyceride levels, as well as a decrease in HDL cholesterol. These findings differ from those of our study (25). Our study suggests that the observed result may be attributed to the inclusion of patients with a higher average age and those diagnosed with diabetes mellitus who received antihyperlipidemic drugs. Seriolo et al. (26) reported an increase in total cholesterol, LDL cholesterol, and triglyceride levels 16 and 24 weeks after initiating anti-TNF treatment in patients with RA. Similarly, Tam et al. (27) found that total cholesterol, LDL cholesterol, and triglyceride levels increased at the 6-week evaluation and continued to increase at the 14th week evaluation. The result may have emerged due to the short control period compared with our study, the presence of additional chronic diseases in all patients, and high lipid levels before treatment initiation.

Study Limitations

One of the reasons why we found different results in similar studies may be that the height, weight, and body mass index of the patients were not considered. This is one of the important limitations of our study.

Conclusion

In conclusion, it is crucial to monitor lipid levels in patients with RA, a disease with high cardiovascular mortality. Therefore, it should be considered when selecting and continuing treatment.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, with decision number 89513307/1009/389.

Informed Consent: In this study, all patients provided informed consent to participate.

Authorship Contributions

Surgical and Medical Practices: R.Ç., G.G.O., Concept: R.Ç., G.G.O., Design: R.Ç., G.G.O., Data Collection or Processing: R.Ç., Analysis or Interpretation: R.Ç., G.G.O., Literature Search: R.Ç., Writing: R.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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