ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/dermato.2020-74503

Impact of Treatment with Methotrexate and TNF Alpha Inhibitors on Insulin Resistance in Patients with Psoriasis

Psoriasis Hastalarında Metotreksat ve TNF Alfa İnhibitörleri Tedavisinin İnsülin Direncine Etkisi

Damla DEMİR[a], Ezgi AKTAŞ KARABAY[b], İlknur KIVANÇ ALTUNAY[a], Feyza YENER ÖZTÜRK[c]

[a]Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital, Department of Dermatology and Venereology, İstanbul, TURKEY
[b]Bahçeşehir University Faculty of Medicine, Department of Dermatology and Venereology, İstanbul, TURKEY
[c]Health Sciences University Sisli Hamidiye Etfal Training and Research Hospital, Department of Endocrinology, İstanbul, TURKEY

ABSTRACT Objective: A strong link between psoriasis and obesity, type 2 diabetes, insulin resistance dyslipidaemia and metabolic syndrome has been documented. The aim of this study was to investigate the effects of methotrexate (MTX), a conventional antipsoriatic agent, and tumour necrosis factor (TNF)-alpha inhibitors (TNFi) on insulin resistance in patients with psoriasis. **Material and Methods:** Thirty-one patients with psoriasis treated with MTX and TNFi were prospectively evaluated. Seventeen patients received MTX, while 14 received the TNFi treatment. At the baseline and at week 12 values of serum C-reactive protein (CRP), the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and lipid parameters were evaluated. **Results:** The decrease in CRP levels after the treatment was significantly higher in the TNFi group than in the MTX group (-1.76 vs. -0.1, p = 0.005; respectively). The levels of serum glucose showed increases in both therapy groups, which was statistically significant in only TNFi group (p = 0.012). Although it was not statistically significant, increases in the HOMA-IR values were noted in MTX and TNFi therapy groups (0.26 ± 1.77 vs. 0.59±1.81, p = 0.558, p = 249; respectively). **Conclusion:** In the present study, a significant increase in the levels of fasting serum glucose was observed in TNFi group, and an increase in HOMA-IR values was noted in both therapy groups, which is not consistent with the literature. Despite the short follow-up period and small sample size, we believe that the effects of the TNFi and MTX demand caution for the follow-up of psoriasis, which is already an insulin-resistant condition.

Keywords: İnsulin resistance; methotrexate; psoriasis; treatment; tumour necrosis factor-alpha inhibitors

ÖZET Amaç: Psoriasis ve obezite, tip 2 Diyabet, insulin direnci, dislipidemi ve metabolik sendrom arasında güçlü bir ilişki olduğu bilinmektedir. Bu çalışmanın amacı geleneksel bir antipsoriatik ajan olan metotreksat (MTX) ile tümör nekroz faktörü alfa inhibitörlerinin (TNFi) psoriasis hastalarında insulin direnci üzerine etkilerini araştırmaktır. **Gereç ve Yöntemler:** MTX ve TNFi tedavisi alan 31 psoriasis hastası prospektif olarak incelendi. 17 hasta MTX tedavisi, 14 hasta ise TNFi tedavisi aldı. Tedavi başlangıcında ve tedavinin 12. haftasında serum C-reactif protein (CRP), HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) ve lipid parametreleri değerlendirildi. **Bulgular:** Tedavi sonrası CRP değerlerindeki düşüş TNFi grubunda MTX grubuna göre anlamlı olarak daha fazlaydı (-1,76 vs. -0,1, p=0,005; sırasıyla). Serum glukoz değerleri her iki tedavi grubunda da artış gösterse de bu artış sadece TNFi grubunda istatistiksel olarak anlamlıydı (p=0,012). İstatistiksel olarak anlamlı olmasa da MTX ve TNFi tedavi gruplarında HOMA-IR değerlerinde artış izlendi (0,26±1,77 vs. 0,59±1,81, p=0,558, p= 249; sırasıyla). **Sonuç:** Bu çalışmada serum açlık glukoz düzeylerinde TNFi grubunda istatistiksel olarak anlamlı bir artış ve iki tedavi grubunda da HOMA-IR düzeylerinde artış izlenmiştir. Bu bulgular varolan literatür bilgisi ile uyumlu değildir. Kısa takip süresi ve küçük hasta grubuna rağmen insulin direncinin eşlik ettiği bir durum olan psoriasiste MTX ve TNFi tedavilerinde dikkatli olunmalıdır.

Anahtar Kelimeler: İnsulin direnci; metotreksat; psoriasis; tedavi; tümör nekroz faktörü-alfa inhibitörleri

Psoriasis, a chronic inflammatory skin disease, is also known to be associated with various comorbidities.[1] Recently, the increased prevalence of obesity, hyperglycaemia, dyslipidaemia and arterial hypertension, all of which are also components of metabolic syndrome, have also been reported in psoriasis patients. Psoriasis is also considered to be associated with increased risk of cardiovascular diseases.[2-5] The

Correspondence: Ezgi AKTAŞ KARABAY
Bahçeşehir University Faculty of Medicine, Department of Dermatology and Venereology, İstanbul, TURKEY/TÜRKİYE
E-mail: ezgiaktasmd@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Dermatology.

Received: 26 Feb 2020 ***Received in revised form:*** 02 Aug 2020 ***Accepted:*** 02 Sep 2020 ***Available online:*** 21 Sep 2020

ongoing inflammatory processes in psoriasis causes several insulin resistance and eventually atherosclerosis which has been defined as "psoriatic march".[6]

Systemic therapies for psoriasis may be efficient in decreasing the cardiovascular risk in psoriasis patients.[7] Still, the effect of systemic treatments for psoriasis on the comorbidities remains unclear. The objective of this study was to research the impact of tumour necrosis factor-alpha inhibitors (TNFi) and methotrexate (MTX) on the markers of comorbidities, including the C-reactive protein (as a general marker of inflammation), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), fasting glucose and insulin. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), a mathematical formula to count up insulin resistance, was used.

MATERIAL AND METHODS

STUDY POPULATION AND PROTOCOLS

The study was reviewed and confirmed by the local ethics committee (date of approval: 21.02.2017, no: 755), and whole the subscriber provided written informed assent. The study was actualized according to the rules expressed in the Declaration of Helsinki.

A single-centre prospective observational study was performed. Thirty-one patients diagnosed with chronic plaque type psoriasis vulgaris using clinical or histopathological examinations were enrolled from the department of dermatology. Patients who were approved to start MTX or TNFi therapy were included.

The information on baseline demographics, clinical characteristics (including the duration of psoriasis, medical history, tobacco smoking and alcohol habits), concomitant arthritis and/or nail involvement were listed.

Patients with chronic plaque type psoriasis, above the age 18 years, who had not received any topical and/or systemic psoriasis treatment prior to 6 months and who had a clinical indication to start MTX or TNFi therapy for psoriasis, by the European Psoriasis Treatment Guideline were included.[8]

Patients with a history of systemic and/or topical treatment within the last 6 months, any contraindication for therapy, any infection, immunodeficiency, malignancy and patients with a history of any systemic disease, those with any endocrinologic or metabolic disease that could affect insulin resistance or those under any treatment that could influence glucose metabolism were excluded. Pregnant and lactating females were also excluded.

TREATMENT REGIMES

The appropriate treatment option was decided together with the patient, according to the psoriasis treatment guidelines and the patients' characteristics.[8] Each patient was initiated on one of the following psoriasis treatments: MTX, adalimumab (ADA) or etanercept (ETA). Patients receiving ADA and ETA therapy were assigned to the TNFi group.

Before and during the treatment, each patient underwent laboratory and physical controls, as committed in the treatment guidelines.[9] The therapy was applied as follows: subcutaneous (SC) MTX doses (15-25 mg) once a week, an initial dose of ADA (80 mg) and SC injections (40 mg) every other week afterwards, followed by ETA (50 mg) SC injections once a week. The patients did not receive any topical agents other than moisturizers.

EVALUATION OF BIOCHEMICAL PARAMETERS AND PASI

The clinical examination and the blood tests were performed on the same day for all the subjects between the hours of 09:00 and 11:00 a.m. following overnight fasting. The levels of serum fasting glucose, fasting insulin, LDL-C, HDL-C, TG and CRP were plumbed at the baseline and at 12 weeks of treatment for all the subjects using fasting venous blood samples. The HOMA-IR was measured according to following formula: fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5.[9]

The severity of psoriasis was assessed using the Psoriasis Area Severity Index (PASI) calculated at the baseline and at 12 weeks of treatment by a single-blinded dermatologist who did not know the therapy the patient was receiving.

The patients were divided into two groups: one receiving MTX and the other TNFi. The changes in

the biochemical parameters between the baseline/before therapy and at 12 weeks of therapy were evaluated and compared between the two therapy groups.

STATISTICAL ANALYSIS

A statistical analysis was performed using the Number Cruncher Statistical System 2007 (NCSS; Kaysville, Utah, USA) program. The descriptive data were expressed in terms of mean ± standard deviation, number and percentages. Student's t-test was used to check the differences between the two groups for normally distributed variables. The Mann-Whitney U test was used to compare two groups of quantitative variables showing abnormal distribution. The intragroup comparisons of normally distributed data were performed with a paired samples test, whereas the non-normally distributed data of intragroup comparisons were evaluated with a Wilcoxon signed-rank test. Pearson x2 test and Fisher's exact were applied to compare the qualitative variables. The correlation analysis was performed by calculating the Pearson rank correlation. A p value of < 0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF THE SUBJECTS

The baseline patient demographics and disease characteristics are shown in Table 1. A total of 31 patients (19 female and 12 male) with chronic plaque type psoriasis were included in the study. The mean age of the patients was 33.90 ± 10.62 years. The mean disease duration was 127.10 ± 68.09 months. None of the patients had any accompanying disease; 45.2% of the patients were smokers and 25.8% of the patients had alcohol use.

Nail involvement was recorded in 61.3% (n = 19) of the patients, while 19.4% (n = 6) of the patients had attendant psoriatic arthritis. The mean PASI score of the patients at the baseline was 13,65 ± 6,75.

Seventeen patients received MTX, while 14 received the TNFi treatment. In MTX group, the mean age of 17 patients (10 female and 7 male) was 33.82 ± 10.51 years, mean disease duration was 115.76 ± 65.72 months, the mean BMI was 23.41 ± 2.92 and mean PASI score was 12.22 ± 5.99. The mean age of 14 patients (2 female and 12 male) who received TNFi was 34.00 ± 11.14 years, mean disease duration was 140.86 ± 70.80 months, mean BMI was 25.38 ± 3.61 and mean PASI score was 15.38 ± 7.42. No critical adverse events requiring therapy disruption appeared throughout the study.

ASSOCIATION OF CHANGES IN BIOCHEMICAL PARAMETERS, PATIENT CHARACTERISTICS AND CLINICAL IMPROVEMENTS

The serum levels of CRP, glucose, insulin, HOMA-IR values, lipid profile, and PASI scores were investigated before and after the treatment as shown in Table 2. The median decrease in PASI scores from the baseline to week 12 was 11.36 ± 6.54, which was statistically significant ($p < 0.001$). The reduction in

TABLE 1: Patient demographics and the characteristics of the disease.

	Total (n=31)	Methotrexate (n=17)	TNF-alpha inhibitors (n=14)	p
Age	33.90±10.62	33.82±10.51	34.00±11.14	[a]0.964
Gender (female/male)	12/19 (38.7/61.3)	10/7 (58.8/41.2)	2/12 (14.3/85.7)	[b]0.011*
BMI	24.30±3.34	23.41±2.92	25.38±3.61	[a]0.103
Smoking	14 (45.2)	8 (47.1)	6 (42.9)	[b]0.815
Alcohol	8 (25.8)	4 (23.5)	4 (28.6)	[c]0.999
Disease duration (Months)	127.10±68.09	115.76±65.72	140.86±70.80	[a]0.315
Systemic disease	0	0	0	-
Nail involvement	19 (61.3)	9 (52.9)	10 (71.4)	[b]0.293
Psoriatic arthritis	6 (19.4)	2 (11.8)	4 (28.6)	[c]0.370

[a]Independent groups t test [b]Pearson χ^2 test [c]Fisher's exact test
*p<0.05 **p<0.01.

TABLE 2: Comparisons between therapy groups in terms of PASI and biochemical parameters.

		Total (n=31)	Methotrexate (n=17)	TNF-alpha inhibitors (n=14)	p
PASI	Baseline	13.65±6.75	12.22±5.99	15.38±7.42	[a]0.200
	12-week	2.31±2.28	2.56±2.4	2.01±2.16	[a]0.506
	Change	-11.34±6.54	-9.66±5.11	-13.37±7.64	[a]0.117
	[e]p	<0.001**	<0.001**	<0.001**	
Fasting glucose (mg/dL)	Baseline	85.13±9.94	84.24±8.07	86.21±12.06	[a]0.590
	12-week	90.65±10.2	88.24±10.42	93.57±9.47	[a]0.150
	Change	5.52±9.27	4±9.07	7.36±9.5	[a]0.324
	[e]p	0.002**	0.088	0.012*	
‡Insulin (uIU/mL)	Baseline	8.34 (5.42, 11.8)	7.81 (5.18, 10.86)	10.14 (7.19, 18.22)	[d]0.064
	12-week	7.85 (5.79, 10.77)	6.61 (5.5, 9.36)	10.33 (6.92, 11.52)	[d]0.109
	Change	-0.43 (-2.09, 1.18)	-0.43 (-1.73, 1.15)	-0.45 (-3.7, 1.18)	[d]0.597
	[f]p	0.652	0.906	0.683	
HDL-C (mg/dL)	Baseline	50.62±10.83	52.23±11.11	48.65±10.54	[a]0.368
	12-week	49.37±9.71	48.27±9.66	50.72±9.96	[a]0.493
	Change	-1.24±9.49	-3.97±8.42	2.07±9.95	[a]0.077
	[e]p	0.472	0.070	0.450	
LDL-C (mg/dL)	Baseline	115.04±33.41	118.68±40.63	110.62±22.5	[a]0.513
	12-week	119.02±30.85	118.33±34.32	119.86±27.31	[a]0.893
	Change	3.99±28.31	-0.35±26.26	9.25±30.75	[a]0.356
	[e]p	0.439	0.957	0.281	
TG (mg/dL)	Başlangıç	121.64±57.69	117.73±49.68	126.4±67.81	[a]0.685
	12-week	124.76±60.82	115.22±54.53	136.35±67.91	[a]0.344
	Change	3.12±55.64	-2.51±55.52	9.95±57.07	[a]0.544
	[e]p	0.757	0.854	0.526	
‡CRP	Baseline	3.3 (3, 5)	3.3 (3, 3.3)	3.85 (3.3, 7.2)	[d]0.023*
	12-week	3 (1.52, 3.2)	3 (1.52, 3.2)	3.2 (1.94, 3.2)	[d]0.444
	Fark	-0.66 (-2.19, -0.1)	-0.1 (-0.69, 0)	-1.76 (-3.5, -0.66)	[d]0.005**
	[f]p	<0.001**	0.075	0.001**	
HOMA-IR	Baseline	2.01±1.4	1.67±0.82	2.43±1.84	[a]0.170
	12-week	2.41±2.21	1.92±1.78	3.01±2.58	[a]0.176
	Change	0.41±1.77	0.26±1.77	0.59±1.81	[a]0.615
	[e]p	0.212	0.558	0.249	

[a]Independent groups t test [b]Mann-Whitney U test [e]Dependent groups t test
[f]Wilcoxon signed-ranks test *p<0.05 **p<0.01.

the levels of CRP from the baseline to week 12 was 0.66, which was also statistically significant (p<0.001).

The mean increase in fasting glucose levels from the baseline to week 12 was 5.52 ± 9.27, which was statistically significant (p=0.002). Decreases in the values of insulin and HDL-C and increases in the values of LDL-C, TGs and HOMA-IR were also recorded; however, none showed statistical significance.

COMPARISONS BETWEEN THE TWO THERAPY GROUPS

No significant differences in terms of age, BMI values, smoking, alcohol use, disease duration, nail involvement and the concomitant arthritis were observed between the two therapy groups. Male dominancy was present in the TNFi group (Table 1). The decreases in the PASI scores from the baseline to the 12th-week visit were statistically significant in both MTX and the TNFi group ($p < 0.001$, $p < 0.001$, respectively). The change in each group did not show

statistical difference between the two groups (p=0.117).

The baseline CRP levels were higher in the TNFi group than in the MTX group (p = 0.023). The decrease in CRP levels after the treatment was statistically expressive in the TNFi group (p = 0.001) and also significantly higher in the TNFi group than in the MTX group (−1.76 vs. −0.1, p = 0.005, respectively).

The levels of serum glucose showed increases in both therapy groups; only the increase in TNF group (p = 0.012) was statistically significant. The increase in the serum fasting glucose levels between the baseline and at week 12 was higher in patients receiving TNFi treatment than in those under MTX treatment, but still showed no significant difference (7.36 ± 9.5 vs. 4 ± 9.07, p = 0.324, respectively). Although it was not statistically significant, increase in the values of HOMA-IR were noted in both the MTX and TNFi therapy groups (0.26 ± 1.77 vs. 0.59 ± 1.81, p = 0.558, p = 249, respectively).

No statistical difference was observed between the subgroups of treatment in terms of the changes in HDL-C, LDL-C, TG, insulin and HOMA-IR values (p > 0.05, for each) (Table 2). In TNFi group increase in the values of HDL-C (2.07 ± 9.95, p= 0.45) and LDL-C (9.25 ± 30.75) was observed, while reduction was observed in both HDL-C (-3.97 ± 8.42, p= 0.07) and LDL-C (-0.35 ± 26.26) values in MTX group.

CORRELATIONS BETWEEN THE PARAMETERS

The decrease in PASI scores was not correlated with any of the biochemical parameters examined (Table 3). In the whole study group, the reduction in PASI scores was observed to be correlated with nail involvement (p= 0.007). The patients in the TNFi group with a longer disease duration were shown to have a significant change in the values of LDL-C (r= 0.734, p= 0.003) (Table 4).

The presence of nail involvement and concomitant arthritis did not affect the changes in the parameters.

DISCUSSION

A growing body of evidence has demonstrated an association between psoriasis and cardiovascular diseases.[2] The ongoing systemic inflammation in psoriasis is considered the trigger of comorbidities.[4] Insulin resistance is described as reduced sensitivity to the metabolic action of insulin. Among with other ef-

TABLE 3: Correlation between change in PASI scores and other parameters after treatment.

		Change in PASI scores		
		Total (n=31)	Methotrexate (n=17)	TNF alpha inhibitors (n=14)
Change in glucose levels	r	-0.016	0.212	-0.096
	p	0.932	0.414	0.744
Change in insulin levels	r	-0.069	-0.001	-0.141
	p	0.712	0.998	0.631
Change in HDL-C levels	r	0.065	0.387	0.026
	p	0.730	0.125	0.929
Change in LDL-C levels	r	0.010	0.001	0.108
	p	0.956	0.997	0.714
Change in TG levels	r	-0.076	-0.098	-0.004
	p	0.686	0.709	0.988
Change in CRP levels	r	0.124	-0.010	0.021
	p	0.506	0.968	0.943
Change in HOMA-IR levels	r	-0.135	-0.042	-0.174
	p	0.468	0.872	0.551

r= Pearson rank correlation.

TABLE 4: Correlations between disease duration and changes in PASI scores, biochemical parameters after treatment.

		Disease duration		
		Total (n=31)	Metotreksat (n=17)	TNF inhibitörleri (n=14)
Change in PASI scores	r	-0.083	0.090	-0.125
	p	0.656	0.730	0.669
Change in glucose levels	r	-0.061	-0.062	-0.139
	p	0.744	0.814	0.635
Change in insulin levels	r	-0.261	-0.113	-0.394
	p	0.156	0.665	0.164
Change in HDL-C levels	r	0.063	-0.252	0.251
	p	0.735	0.330	0.387
Change in LDL-C levels	r	0.304	-0.183	0.734
	p	0.096	0.483	0.003**
Change in TG levels	r	-0.023	0.091	-0.198
	p	0.901	0.727	0.498
Change in CRP levels	r	0.067	-0.005	0.246
	p	0.720	0.983	0.397
Change in HOMA-IR levels	r	-0.223	-0.222	-0.274
	p	0.227	0.393	0.343

r= Pearson rank correlation **p<0,01

fects it also decreases the production of endothelial nitric-oxide which leads to endothelial dysfunction. As a result, insulin resistance contributes to the pathogenesis of cardiovascular disorders. The TNF-alpha, which is known as a key pro-inflammatory cytokine in the pathogenesis of psoriasis, also contributes to insulin resistance.[10] This cytokine also contributes to unfavourable long-term prognoses of psoriasis patients.[4] It has been reported that the severity of psoriasis is associated with the presence of insulin resistance and also metabolic syndrome.[10] Some researchers have suggested that the systemic inflammation defined as "psoriatic march" is revealed as an increase in the inflammatory mediators which lead to insulin resistance, a known factor of atherosclerosis.[6,10,11]

The role of different therapies, including topical agents, conventional systemic therapies and biological agents blocking this psoriatic march, have been evaluated in several studies, the results of which are conflicting.[12-17] Controversial data are available on the impact of treatment modalities on the lipid profile, insulin resistance and inflammatory parameters.[18-22]

Boehncke et al. evaluated the impacts of systemic anti-psoriatic therapy on the biomarkers of systemic inflammation.[17] They reported that a decrease in PASI scores was associated with a decrease of serum high sensitive-CRP levels, the vascular endothelial growth factor and resistin and an increase in adiponectin. They observed a better metabolic state with longer treatment duration.[17]

In a study evaluating the effects of 12 weeks of MTX therapy in patients with psoriasis, it was also shown to decrease inflammatory adipokines and insulin resistance and elevate adiponectin. However, in the same study, higher levels of inflammatory adipokines, insulin and insulin resistance were noted even after the treatment, compared with the controls, suggesting persistent inflammation.[18] In another study, it was observed that systemic therapy with MTX had a protective effect for cardiovascular comorbidities, probably due to its anti-inflammatory properties.[19,20]

Some researchers have investigated the effects of TNFi therapy on biomarkers and have observed that patients with psoriatic arthritis treated with ETA and ADA showed reductions in TG serum levels, glucose and increase in HDL-C serum levels

when compared to MTX groups. A 24-month ETA and ADA therapy session was reported to show a better metabolic profile compared to an MTX group in psoriatic arthritis patients.[21] Botelho et al.[22] reported increases in HDL-C levels and decreases in LDL-C and TG levels in patients with psoriasis treated with TNFi.

It was demonstrated that after 3 months of ETA therapy in psoriasis patients, fibrinogen and IL6 levels were significantly decreased. However, at 6 months, no significant difference was observed in the fibrinogen or IL6 levels after dose reduction checked against the baseline. No significant differences were devised in the levels of CRP, LDL-C, glucose, insulin or adiponectin. Interestingly, an increase in TNF-alpha levels was noted; the suggested explanation was that ETA prolongs the TNF-alpha half-life. In this study, it was concluded that ETA therapy lowers the cardiovascular risk profiles in psoriasis patients with metabolic syndrome; however, a lower dose treatment of 6 months did not provide a continuous effect.[23]

The role of inflammation in insulin resistance in atherosclerosis is now well established.[24] In this prospective analysis, we wanted to compare the impacts of systemic MTX and TNFi therapy on insulin resistance. In this study, we prospectively investigated the impacts of MTX and TNFi treatments on serum lipids and insulin resistance among patients with psoriasis, over a period of 12 weeks. A statistically significant decrease was observed for CRP in the overall population, and this decrease was more significant in the TNFi-receiving group than in the MTX group. CRP is a sensitive indicator of systemic inflammation. Several studies have demonstrated decreases in CRP levels after anti-TNF-alpha treatment in psoriasis patients.[16,17,25,26] TNF-alpha is a major factor in the inflammatory processes in psoriasis, inducing adipocytes apoptosis, promoting insulin resistance, increasing plasma triglycerides and promoting the synthesis of other pro-inflammatory adipokines and the reducing of anti-inflammatory adipokines.[27,28] We believe that may be the explanation for the significant reduction in CRP levels in the TNFi group.

In anti-TNF-alpha group, increases in both HDL-C and LDL-C were observed, while decreases in HDL and LDL were noted in the MTX group. The increase in fasting glucose levels after treatment seems relevant. The increase in glucose levels was statistically significant in only the TNFi group. An increase in HOMA-IR values was also noted, which was not statistically significant. There are few case reports demonstrating a link between TNFi therapy with hyperglycemia. A patient with type 2 diabetes and psoriasis was reported to develop recurrent hyperglycemia during adalimumab treatment that resolved after discontinuation of the medication.[29] Another patient with rheumatoid arthritis was reported to develop type 1 diabetes mellitus associated with new anti-glutamic asid decarboxylase antibodies after TNFi treatment. It has been hypothesized that TNF alpha may have inhibitory effects on the development of autoreactive islet-spesific T cells. Thus TNFi therapy may promote pancreatic beta cell destruction and may mediate the development of hyperglycemia.[30]

Insulin resistance, associated with psoriasis, is thought to be correlated with the severity of the psoriatic inflammation.[10] Insulin resistance is the pathophysiological basis of endothelial dysfunction, which leads to cardiovascular disease.[31,32] We believe that increase in glucose levels and HOMA-IR during the treatment should be closely monitored in this already insulin-resistant condition. Additionally, attention should be paid to the changes in HDL-C and LDL-C levels during the therapy. Although the changes on these parameters were not found to be statistically significant in our study, we believe that the small sizes of the groups may be the reason. No significant change was observed between the TNFi and MTX therapy groups in terms of changes in HOMA-IR and lipid parameters. The decrease in CRP levels was significantly higher in the TNFi group than in the MTX group. It still needs to be clarified whether TNF alpha inhibitors and MTX have similar efficacy on insulin resistance and on lipid parameters.

The limitations of our study include the small sample size and the short follow-up period. The missing data of the patients resulted in small sample size and it also limited including patients receiving different TNFi therapies. Another restriction was the self-reporting of history regarding smoking and al-

cohol consumption. Also, the therapy groups were not gender matched, as the therapy groups were created according to the therapy indications of the patients, not to provide a homogenous population. It has been reported that serum lipid parameters of rats have been influenced by gender differences.[33] Sex differences in glucose homeostasis was also established.[34] The differences in gender ratios in two groups limit us making conclusions.

Treatment efficacy in psoriasis is generally evaluated with scores of disease severity and quality of life. The impact of treatment modalities on the parameters of comorbidities in patients with psoriasis patients appears to be an important issue that may influence the therapeutic approaches suggested to treat not only the disease itself but also the comorbid conditions as an objective of the treatment. Additionally, the effect of treatment on the comorbid disorders must be carefully studied. Further studies with a longer follow-up and on a larger number of patients could answer these questions.

CONCLUSION

In the present study, the impacts of TNFi and MTX on the serum levels of CRP, fasting glucose, insulin, HOMA-IR, LDL-C and HDL-C, TG were investigated. A significant increase in the levels of fasting serum glucose was observed in the TNFi group, which is not consistent with the literature. Moreover, an increase in HOMA-IR values was noted in both therapy groups. While the short follow-up period and small sample size limit us in making conclusions, we still believe that this effect of TNFi and MTX demands caution in the follow-up of psoriasis, which is already an insulin-resistant condition.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Damla Demir;* ***Design:*** *Damla Demir, Ezgi Aktaş Karabay;* ***Control/Supervision:*** *İlknur Kıvanç Altunay, Feyza Yener Öztürk;* ***Data Collection and/or Processing:*** *Damla Demir;* ***Analysis and/or Interpretation:*** *Ezgi Aktaş Karabay, Feyza Yener Öztürk;* ***Literature Review:*** *Ezgi Aktaş Karabay; Writing the Article: Damla Demir, Ezgi Aktaş Karabay;* ***Critical Review:*** *İlknur Kıvanç Altunay, Feyza Yener Öztürk;* ***References and Fundings:*** *Damla Demir, Ezgi Aktaş Karabay.*

REFERENCES

1. Christophers E. Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26(4):314-20. [Crossref] [PubMed]
2. Raaby L, Ahlehoff O, de Thurah A. Psoriasis and cardiovascular events: updating the evidence. Arch Dermatol Res. 2017;309(3):225-8. [Crossref] [PubMed]
3. Robati RM, Partovi-Kia M, Haghighatkhah HR, Younespour S, Abdollahimajd F. Increased serum leptin and resistin levels and increased carotid intima-media wall thickness in patients with psoriasis: is psoriasis associated with atherosclerosis? J Am Acad Dermatol. 2014;71(4):642-8. [Crossref] [PubMed]
4. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, van Voorhees AS, et al. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol. 2017;76(3):377-90. [Crossref] [PubMed] [PMC]
5. Takahashi H, Lizuka H. Psoriasis and metabolic syndrome. J Dermatol. 2012;39(3):212-8. [Crossref] [PubMed]
6. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol. 2011;20(4):303-7. [Crossref] [PubMed]
7. Hugh J, Van Voorhees AS, Nijhawan RI, Bagel J, Lebwohl M, Blauvelt A, et al. From the medical board of the national psoriasis foundation: the risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol. 2014;70(1):168-77. [Crossref] [PubMed]
8. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277-94. [Crossref] [PubMed]
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9. [Crossref] [PubMed]
10. Boehncke S, Thaci D, Beschmann H, Ludwig RJ, Ackermann H, Badenhoop K, et al. Psoriasis patients show signs of insulin resistance. Br J Dermatol. 2007;157(6):1249-51. [Crossref] [PubMed]

11. Kyriakou A, Patsatsi A, Sotiriadis D, Goulis DG. Serum leptin, resistin, and adiponectin concentrations in psoriasis: a meta-analysis of observational studies. Dermatology. 2017;233(5):378-89. [Crossref] [PubMed]
12. Ucak S, Ekmekci TR, Basat O, Koslu A, Altuntas Y. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. J Eur Acad Dermatol Venereol. 2006;20(5):517-22. [Crossref] [PubMed]
13. Karadag AS, Yavuz B, Ertugrul DT, Akin KO, Yalcin AA, Deveci OS, et al. Is psoriasis a preatherosclerotic disease? Increased insulin resistance and impaired endothelial function in patients with psoriasis. Int J Dermatol. 2010;49(6):642-6. [Crossref] [PubMed]
14. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. Circulating adipokine levels in Portuguese patients with psoriasis vulgaris according to body mass index, severity and therapy. J Eur Acad Dermatol Venereol. 2010;24(12):1386-94. [Crossref] [PubMed]
15. Kawashima K, Torii K, Furuhashi T, Saito C, Nishio E, Nishida E, et al. Phototherapy reduces serum resistin levels in psoriasis patients. Photodermatol Photoimmunol Photomed. 2011;27(3):152-5. [Crossref] [PubMed]
16. Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H. Serum level of adiponectin increases and those of leptin and resistin decrease following the treatment of psoriasis. J Dermatol. 2013;40(6):475-6. [Crossref] [PubMed]
17. Boehncke S, Salgo R, Garbaraviciene J, Beschmann H, Hardt K, Diehl S, et al. Effective continuous systemic therapy of severe plaque-type psoriasis is accompanied by amelioration of biomarkers of cardiovascular risk: results of a prospective longitudinal observational study. J Eur Acad Dermatol Venereol. 2011;25(10):1187-93. [Crossref] [PubMed]
18. Rajappa M, Rathika S, Munisamy M, Chandrashekar L, Thappa DM. Effect of treatment with methotrexate and coal tar on adipokine levels and indices of insulin resistance and sensitivity in patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2015;29(1):69-76. [Crossref] [PubMed]
19. Ahlehoff O, Skov L, Gislason G, Lindhardsen J, Kristensen SL, Iversen L, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. J Intern Med. 2013;273(2):197-204. [Crossref] [PubMed]
20. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS, et al. Methotrexate reduces incidence of vascular diseases in veterans withpsoriasis or rheumatoid arthritis. J Am Acad Dermatol. 2005;52(2):262-7. [Crossref] [PubMed]
21. Costa L, Caso F, Atteno M, Del Puente A, Darda MA, Caso P, et al. Impact of 24-month treatment with etanercept, adalimumab, or methotrexate on metabolic syndrome components in a cohort of 210 psoriatic arthritis patients. Clin Rheumatol. 2014;33(6):833-9. [Crossref] [PubMed]
22. Hassan S, Milman U, Feld J, Eder L, Lavi I, Cohen S, et al. Effects of anti-TNF- α treatment on lipid profile in rheumatic diseases: an analytical cohort study. Arthritis Res Ther. 2016;10;18(1):261. [Crossref] [PubMed] [PMC]
23. Danesh MJ, Koo EB, Kimball AB. Effects of TNF-alpha antagonism in patients with metabolic syndrome and psoriasis. J Eur Acad Dermatol Venereol. 2016;30(11):e152-e4. [PubMed]
24. Qasim A, Mehta NN, Tadesse MG, Wolfe ML, Rhodes T, Girman C, et al. Adipokines, insulin resistance and coronary artery calcification. J Am Coll Cardiol. 2008;15;52(3):231-6. [Crossref] [PubMed] [PMC]
25. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008;159(2):322-30. [Crossref] [PubMed]
26. Kanelleas A, Liapi C, Katoulis A, Stavropoulos P, Avgerinou G, Georgala S, et al. The role of inflammatory markers in assessing disease severity and response to treatment in patients with psoriasis treated with etanercept. Clin Exp Dermatol. 2011;36(8):845-50. [Crossref] [PubMed]
27. Bacchetti T, Campanati A, Ferretti G, Simonetti O, Liberati G, Offidani AM, et al. Oxidative stress and psoriasis: the effect of antitumour necrosis factor-α inhibitor treatment. Br J Dermatol. 2013;168(5):984-9. [Crossref] [PubMed]
28. Scrivo R, Vasile M, Bartosiewicz I, Valesini G. Inflammation as "common soil" of the multifactorial diseases. Autoimmun Rev. 2011;10(7):369-74. [Crossref] [PubMed]
29. Wu JJ, Tsai TF. Recurrent hyperglycemia during adalimumab treatment an a patient with psoriasis. Arch Dermatol. 2008;144(10):1403-4. [Crossref] [PubMed]
30. Richez C, Blanco P, Gin H, Schaeverbeke T. Development of type 1 diabetes mellitus in a patient with rheumatoid arthritis receiving antitumor necrosis factor alpha. Clin Exp Rheumatol. 2006;24(5):607. [PubMed]
31. Jansson PA. Endothelial dysfunction in insulin resistance and type 2 diabetes. J Int Med. 2007;262(2):173-83. [Crossref] [PubMed]
32. Kearney MT, Duncan ER, Kahn M, Wheatcroft SB. Insulin resistance and endothelial cell dysfunction: studies in mammalian models. Exp Physiol. 2008;93(1):158-63. [Crossref] [PubMed]
33. Kayali R, Aydin S, Cakatay U. Effect of gender on main clinical chemistry parameters in aged rats. Curr Aging Sci. 2009;2(1):67-71. [Crossref] [PubMed]
34. Mauvais-Jarvis F. Gender differences in glucose homeostasis and diabetes. Physiol Behav. 2018;1;187:20-3. [Crossref] [PubMed] [PMC]