Northwestern Med J.2021;1(2):83-9
doi: 10.5222/NWMJ.2021.98608

Original Article

The Comparison of Leptin, Proinflammatory Cytokines Levels and the Disease Activity Index Before and After Anti-TNF Treatment in Ankylosing Spondylitis

Ankilozan Spondilitte Anti TNF Tedavi Öncesi ve Sonrası Leptin ve Proinflamatuvar Sitokin Düzeyleri ile Hastalık Aktivite Göstergelerinin Karşılaştırılması

Tuba Yüksel Aydıner, Mehmet Kırnap

Cite as: Yüksel Aydıner T, Kırnap M. The comparison of leptin, proinflammatory cytokines levels and the disease activity index before and after anti- TNF treatment in ankylosing spondylitis. Northwestern Med J. 2021;1(3):83-9.

ABSTRACT

Objective: Ankylosing spondylitis (AS) is the major member of the spondyloarthropathies (SpAs), a group of diseases that mainly affect the spine in association with the inflammation of enthuses. Leptin is mainly synthesized by adipose tissue and shows several biological activities such as energy expenditure, nutrition, immunity, and metabolism. Tumor necrosis factor-alpha (TNF- α) is a potential modulator of adipocytokines. The aim of this study was to evaluate the effect of anti-TNF medicine such as infliximab and etanercept on leptin plasma levels in patients with AS.
Method: Seventy patients with ankylosing spondylitis were included in the study. Fourteen patients received infliximab IV at a dose of 3mg/kg at weeks 0, 2, 6 and thereafter every 8 weeks. Sixteen patients received 25 mg etanercept subcutaneously twice weekly. Forty AS patients were included in the control group. Their body mass index (BMI) and acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and serum cytokine profiles, including TNF-α, interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) were assessed. Serum levels of leptin and cytokines were measured using enzyme-linked immunosorbent assay (ELISA) methods, before and after 3-months treatment with infliximab or etanercept.
Results: When compared to inactive AS patients, the leptin levels were significantly higher in active AS patients ($p<0.001$). The IL-1β and TNF-α levels were increased after treatment with etanercept while serum IL-6 level was reduced. Etanercept treatment did not change serum levels of leptin ($p>0.05$). Serum TNF-α levels were increased after treatment with infliximab. Serum leptin levels were also increased after infliximab treatment ($p<0.05$).
Conclusion: Serum leptin levels did not change with etanercept treatment but increased after infliximab treatment and did not correlate with any disease activity parameters and proinflammatory cytokines.

Keywords: Ankylosing spondylitis, leptin, BASDAI, proinflammatory cytokine, anti TNF therapy

ÖZ

Amaç: Ankilozan spondilit (AS); sakroiliit ve spondilitten dolayı inflamatuar sırt ve bel ağrısı ile karakterize kronik, inflamatuar romatizmal bir hastalıktır. Adipoz dokudan derive leptin açlığı, enerji tüketimini, insülin duyarlılığını, endotel fonksiyonunu, üremeyi ve immüniteyi kontrol eder ve otoimmün hastalıklarda da rol aldığı düşünülmektedir. Fakat AS'deki rolleri net değildir. Tümör nekroz faktör alfa (TNF-α) adipositokinlerin potansiyel düzenleyicisidir. Anti TNF ilaçlar olan infliksimab ve etanerceptin plazma leptin seviyelerine etkisi AS'li hastalarda şimdiye kadar değerlendirilmemiştir.
Yöntem: Ankilozan spondilit tanılı 70 hasta çalışmaya alındı. 14 hastaya infliksimab, 16 hastaya etanercept tedavisi verildi. İnfliksimab 3 mg/kg 0, 2. ve 6. haftada ve devamında her 8 haftada bir IV olarak uygulandı. Etanercept grubundaki hastalara 25 mg etanercept haftada iki kez subkutan uygulandı. 40 AS'li hasta da kontrol grubuna dahil edildi. Hastaların vücut kitle indeksleri (VKİ), eritrosit sedimentasyon hızı (ESR) ve C-reaktif protein (CRP) gibi akut faz reaktanları, Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI), TNF-α, interlökin-1beta (IL-1β) ve interlökin (IL)-6'yı kapsayan serum sitokin profili değerlendirildi. Serum leptin düzeyleri ile serum sitokin profili ELISA (enzyme linked immunosorbent assay) metodu ile 3 aylık infliksimab ve etanercept tedavisi öncesi ve sonrası ölçüldü.
Bulgular: Leptin seviyeleri inaktif AS'li hastalarla kıyaslandığında aktif grupta anlamlı olarak daha yüksek bulundu ($p<0.001$). Etanercept tedavisi sonrası IL-1β ve TNF-α seviyeleri artarken, IL-6 seviyesi azaldı ($p<0.05$). Infliksimab tedavisi sonrası TNF-α seviyeleri arttı ($p<0.05$). Etanercept tedavisi serum leptin seviyelerini değiştirmedi ($p>0.05$). Serum leptin seviyelerinde infliksimab tedavisi sonrası artış gözlendi ($p<0.05$).
Sonuç: Serum leptin seviyeleri etanercept ile değişmezken; infliksimab tedavisi sonrası artış gözlendi, fakat hastalık aktivite parametreleri ve proinflamatuvar sitokinlerle korele değildi.

Anahtar kelimeler: Ankilozan spondilit, leptin, BASDAI, proinflamatuvar sitokin, anti TNF tedavi

Received: 25.02.2021
Accepted: 09.08.2021
Publication date: 17.09.2021

Corresponding Author:
Tuba Yüksel Aydıner
Atatürk Chest Diseases and Throcic Surgery Training and Research Hospital, Department of Physical Therapy and Rehabilitation, Turkey
drtuba_yuksel@hotmail.com
ORCID: 0000-0001-6339-9969

M. Kırnap 0000-0002-7472-2351
Erciyes University, Faculty of Medicine, Department of Physical Therapy and Rehabilitation, Kayseri, Turkey

*Bu çalışma 2011 tarihli 'ANKİLOZAN SPONDİLİTTE ANTİ TNF TEDAVİ ÖNCESİ VE SONRASI LEPTİN VE PROİNFLAMATUVAR SİTOKİN DÜZEYLERİ İLE HASTALIK AKTİVİTE GÖSTERGELERİNİN KARŞILAŞTIRILMASI' uzmanlık tezinden üretilmiştir.

INTRODUCTION

Ankylosing spondylitis (AS) is the major member of the spondyloarthropathies (SpAs), a group of diseases that mainly affect the spine in association with the inflammation of enthuses (1). Leptin is a 16kDa-cytokine-like peptide of 167 amino acids encoded by the obesity gene (ob-gen) and mainly synthesized by adipose tissue. Leptin shows several biological activities such as energy expenditure, nutrition, and metabolism (2). Leptin has been known to play important roles in the innate and acquired immunity. Anorexia is known to be a cytokine induced-acute phase response of the host during inflammation and infections. Therefore, cytokines, particularly tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6) are considered to be responsible for anorexia that occurs in inflammation and infections and this effect of cytokines is thought to be partly mediated by leptin (3). Using TNF-α blockers in AS is grounded in the increased TNF-α expression in serum and sacroiliac joints, demonstrated in the studies on ankylosing spondylitis and other SpAs (4). Etanercept consists of ligand binding portions of two human p75 part of TNF-α receptors linked to the crystallizable Fc part of human IgG1. Infliximab is a chimeric monoclonal antibody with a TNF binding domain from a mouse antibody and a constant domain from a human antibody. This study aimed at assessing the effect of anti-TNF treatment with etanercept and infliximab, on the inflammation in AS patients by comparing the pre-treatment and post-treatment IL-1β, IL-6, TNF-α, and leptin levels, which are parts of inflammatory process, and the use of these cytokines in monitoring AS patients.

MATERIALS AND METHODS

Patients: Seventy patients diagnosed with AS according to the 1984 Modified New York Criteria, who attended physical medicine and rehabilitation outpatient clinic between May 2010 and May 2011 were included in this study. Patients were divided into two groups as 30 patients in whom anti-TNF treatment was indicated and would receive anti-TNF medications and 40 controls who would not receive anti-TNF medications (in whom anti-TNF treatment was not indicated or who were not allowed to use anti-TNF treatment due to the presence of a contraindication). Infliximab therapy was started in 14 patients and etanercept therapy was started in 16 patients. Infliximab was administered as IV at a dose of 3mg/kg at weeks 0, 2, 6, and thereafter every 8 weeks in the physical medicine and rehabilitation clinic. Etanercept was administered subcutaneously 25 mg twice weekly and done by self-administered subcutaneous injection. All groups were reassessed 3 months later. All patients were informed about the study at the baseline, and they filled out and signed a consent form. The study protocol was approved by the Institutional Ethics Committee (2010-11).

Exclusion criteria were: (a) a history or presence of malignant disease; (b) an active infection or a concomitant inflammatory disease; (c) an endocrine disorder such as diabetes mellitus (DM), Cushing disease, or thyroid disease; (d) known an active liver disease or kidney disease; (e) a body mass index (BMI) higher than 30 kg/m^2; (f) steroid treatment in the last 3 months before the study. Patients were questioned about their age, height, body weight, age of the onset of disease-related complaints, disease duration, current and previous medications, the duration of morning stiffness, peripheral joint involvement and extraarticular symptoms. The BMI value was calculated using the body weight/height^2 formula (kilogram/meter^2).

Clinical assessment parameters used in the study were as follows: Visual Analogue Scala (VAS) for the measurement of pain, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for the measurement of morning stiffness and disease activity, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IL-1β, IL-6, TNF-α, and leptin levels.

Biochemical parameters: Laboratory studies were carried out in the biochemistry and serology laboratory. After dissolving previously collected and frozen serum samples at room temperature, Orgenium Laboratories' ELISA Kit® was used to

measure IL-1β and IL-6 levels and Diosurce' human ELISA Kit® was used to determine serum TNF-α and leptin levels.

Statistical analysis: A SPSS for Windows, version 15.0 software was used in statistical analyses. The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of quantitative data. Normally distributed data were described as mean ±SD. The Student t-test was used to determine intergroup differences and the Paired t-test was used to determine differences between two time points. Non-normally distributed data were described as median (minimum-maximum). The Mann-Whitney U test was used to determine intergroup differences and the Wilcoxon Signed test was used to determine differences between two time points. The Pearson's correlation test was used to determine the correlation between two normally distributed variables while Spearman's correlation coefficient was calculated for non-normally distributed variables. Qualitative data were described as percentages. A p value less than 0.05 was accepted as statistically significant.

RESULTS

A statistically significant positive correlation was found between the serum leptin level and BMI ($p<0.001$). The IL-1β and TNF-α levels were increased after the treatment with etanercept while the serum IL-6 level was reduced and the differences were statistically significant (p=0.007, p=0.007, p=0.02). No statistically significant difference was detected between the serum leptin levels before and after the treatment with etanercept (p=0.64). Serum TNF-α and leptin levels were increased after the treatment with infliximab and the difference was statistically significant (p=0.002, p=0.002). No statistically significant difference was detected between the serum IL-1β and IL-6 levels before and after the treatment with infliximab (Table 1).

No statistically significant correlation was found between IL-1β and IL-6 before the treatment with neither etanercept nor infliximab, while a significant correlation was found after the treatment. There was no statistically significant correlation between the leptin levels and BASDAI, ESR, and CRP at the baseline and after 3 months of treatment in the TNF groups. In the comparison of ESR, CRP, IL-1β, IL-6, TNF-α, and leptin values between the control and TNF groups at the baseline; ESR and CRP levels were statistically significantly higher in the TNF groups (p=0.004, p=0.001). No statistically significant difference was found between two groups in IL-1β, IL-6, TNF-α, and leptin values. Three months later, in

Table 1. Comparison of IL1β, IL6, TNF α and leptin in TNF groups at baseline and 3 months after Etanercept and Infliximab treatment.

		BASELINE Median(Min-Max)	3 MONTHS Median(Min-Max)	p
ETANERCEPT	IL1β (pg/mL)	20,1 (10,5-411,0)	36,1 (21,1-424,4)	0.007
	IL6 (pg/mL)	22,3 (1,8-803,2)	6,9 (2,9-262,3)	0.02
	TNF α (pg/mL)	11,8 (5,4-332,0)	47,2 (7,4-98,0)	0.007
	LEPTIN (ng/mL)	1,4 (0,16-76,0)	1,5 (0,01-13,7)	0.64
INFLIXIMAB	IL1β (pg/mL)	20,3 (13,2-144,1)	34,0 (21,0-136,6)	0.17
	IL6 (pg/mL)	13,2 (3,3-538,8)	6,2 (1,8-201,6)	0.22
	TNF α (pg/mL)	10,0 (4,1-25,6)	75,8 (6,3-158,7)	0.002
	LEPTIN (ng/mL)	0,5 (0,01-9,5)	1,6 (0,01-20,0)	0.02

IL, interleukin; TNF, tumor necrosis factor.

the TNF groups, IL-6 level was statistically significantly lower and TNF-α level was statistically significantly higher than those at the baseline. No statistically significant difference was found between the two groups in ESR, CRP, IL-1β, and leptin levels after 3 months of treatment (Table 2).

DISCUSSION

Ankylosing spondylitis is Human Leukocyte Antigen-B27 (HLA-B27) associated chronic inflammatory disease of unknown etiology. Recent studies on the pathogenesis of the disease have focused on defining the triggers, events that occur in the course of the disease, inflammation mediators and modulators in the course of the disease (5). The evidence of increased expression of TNF-α in serum and sacroiliac joints in patients with ankylosing spondylitis and other SpAs led to the use of TNF-α inhibitors in the treatment of AS (4).

In a study on nonspecific and antigen-specific T-cell responses during infliximab treatment in AS patients, Zou et al[6] found that there was a down regulation of nonspecific and antigen-specific T cell responses during the treatment with infliximab, however, any change was not induced in cytokines secreted by monocytes. In another study on the levels of TNF-α and interferon-gamma produced by T cells after etanercept treatment in AS patients, Zou et al[7] found that there was an up regulation after etanercept treatment. The investigators asserted that this difference depended on the different ways used by these two medications to affect T cell functions. In this study, no significant difference was found between two subgroups in terms of TNF-α levels before the treatment. After treatment with etanercept, a significant increase was observed in TNF-α levels, which provided further support to the results of previous studies. Unlike previous

Table 2. Comparison of ESR, CRP, IL1β, IL6, TNF α and leptin in control and TNF groups at baseline and 3 months later.

		CONTROL n:40 Median(Min-Max)	TNF n:30 Median(Min-Max)	p
BASELINE	ESR (mm/h)	29,0 (3-120)	47 (9-157)	0.004
	CRP (mg/L)	7,4 (3,2-166,0)	23,7 (3,4-125,0)	0.001
	IL1β (pg/mL)	18,0 (10,2-403,0)	20,1 (10,5-411,0)	0.15
	IL6 (pg/mL)	9,6 (2,2-141,6)	14,5 (1,8-803,2)	0.05
	TNF α (pg/mL)	9,9 (2,2-373,9)	11,7 (4,1-332,0)	0.69
	LEPTIN (ng/mL)	0,9 (0,001-31,3)	1,0 (0,01-76,0)	0.70
3 MONTHS	ESR (mm/h)	22,5 (6-75)	17 (2-120)	0.26
	CRP (mg/L)	5,3 (3,2-45,1)	3,8 (3,2-65,1)	0.68
	IL1β (pg/mL)	33,9 (14,4-418,6)	34,8 (21,0-424,4)	0.97
	IL6 (pg/mL)	12,0 (1,8-459,1)	6,5 (1,8-262,3)	0.04
	TNF α (pg/mL)	11,4 (2,8-118,0)	51,0 (6,3-158,7)	0.001
	LEPTIN (ng/mL)	2,0 (0,01-41,7)	1,5 (0,01-20,0)	0.52

ESR, erythrocyte sedimentation rate; CRP, C reactive protein; IL, Interleukin; TNF, tumor necrosis factor.

studies, an increase was observed in the TNF-α levels after treatment with infliximab. This difference might be resulted from the smaller study sample and shorter follow up duration. In a study conducted by Stone et al[8] the correlation between the clinical responses and cytokines was assessed in 22 patients after a 52-weeks infliximab therapy. Baseline TNF-α and CRP values were found to be important for response to treatment and particularly, the baseline CRP values were higher in patients who were responsive to treatment in comparison with patients not responding to treatment. However, a weak correlation was found between baseline CRP levels and other cytokines such as IL-1, IL-10, and INF-gamma in patients responding to treatment. In this study, no statistically significant difference was found between two subgroups of the TNF therapy in post-treatment values of IL-1β, while a statistically significant increase was found in values of IL-1β in the etanercept group compared with baseline and post-treatment. After anti-TNF treatment, a significant reduction was found in the IL-6 levels particularly in the subgroup treated with etanercept. When considering IL-6 as a disease activity parameter of AS patients, a reduction in the IL-6 levels is more likely after anti-TNF treatment.

Leptin is a 16kDa-cytokine-like peptide of 167 amino acids encoded by the obesity gene (ob-gen) and mainly synthesized by adipose tissue and shows a few biological activities such as energy expenditure, nutrition, and metabolism (2). A positive correlation was found between BMI and circulating leptin levels (9). In line with medical literature, this study revealed a positive correlation between the BMI and leptin levels. Leptin's role in immune responses and inflammation has become increasingly apparent recently. Leptin releases a variety of pro-inflammatory and anti-inflammatory factors, including cytokines and chemokines. The results of in vitro and experimental animal studies show that leptin acts mostly as a proinflammatory agent during adaptive immune responses, while anti-inflammatory effects of leptin are common in processes involving innate immunity. However, as different clinical studies have yielded inconsistent results so far, the role of leptin during inflammatory conditions in humans is difficult to clarify, suggesting that leptin plays an overly complex role in human immune response and inflammation (10). In the medical literature, there are several studies on the adipokines such as leptin and adiponectin and proinflammatory cytokines such as IL-1β, IL-6, TNF-α in AS and other inflammatory diseases including rheumatoid arthritis (RA), Behcet's disease, and systemic lupus erythematosus (SLE), however we did not find any study comparing the effects of various anti-TNF medications on the serum leptin levels.

Toussirot et al[11] demonstrated that the level of circulating leptin was lower in patients with active AS, in comparison with the control patients and no significant correlation was found between the circulating leptin levels and BASDAI, ESR, CRP and TNF-α.

In a study conducted by Sari et al[12], serum leptin levels were found significantly lower in patients with AS, compared to the control group. Body fat percentage, waist-to-hip ratio, CRP, and Bath AS Metrology Index (BASMI) were found to be significantly correlated with the serum leptin levels. They asserted that the chronic inflammatory state in AS might be responsible for the lower body fat content and lower circulating leptin concentrations. Unlike other investigators, Park et al[13] found higher levels of serum leptin, TNF-α, IL-1β, and IL-6 in AS patients when compared to the controls. However, they concluded that the role of leptin in AS might involve mononuclear cell activation rather than increasing anti-inflammatory activity. In the medical literature, similar controversial results have been reported in the studies on the relationship between inflammation or other rheumatic diseases and leptin levels. In this study, the active disease group and inactive disease group were determined by BASDAI which measure disease activity in AS, and leptin levels were significantly higher in the active group and a positive correlation was found between leptin levels and BASDAI. Based on these results, leptin levels may be used as a disease activity indicator in newly diagnosed patients who do not use anti-TNF

medication or patients who discontinued medical treatment a long time ago. However, one-to-one comparison of this study with the previous ones is not possible due to the lack of a healthy control group in this study and the primary objective of comparing serum leptin levels before and after treatment with anti-TNF medications. When considering the conflicting results in the medical literature, there is a requirement for further studies on leptin levels in AS patients.

In the study of Derdemezis et al[14], comparing leptin and adiponectin levels in 30 AS patients after a 6-months infliximab therapy, the adiponectin levels were statistically significantly higher in AS patients, however, the levels of leptin and adiponectin did not change after anti-TNF treatment. Therefore, they concluded that the anti-TNF treatment did not modulate leptin and adiponectin levels. In this study, although no significant difference was found between the serum leptin levels measured before and after treatment with etanercept, a significant increase was found between the serum leptin levels at the baseline and after the treatment with infliximab. No significant difference was found between the etanercept group and infliximab group in the post-treatment serum leptin levels. Furthermore, in none of these subgroups, any significant correlation was not found between the serum leptin levels and disease activity indicators such as IL-1β, IL-6, TNF-α, BASDAI, ESR, and CRP at the baseline and 3 months later.

Based on these results, serum leptin was not found to be an adequate indicator of disease activity after anti-TNF treatment. Therefore, long term studies with larger sample sizes are required to achieve a more accurate conclusion.

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee (2010-11)
Conflict of Interest: The authors declare no conflict interests.
Funding: This study was supported by the Scientific Research Projects Coordination Unit.
Informed Consent: Receipt

REFERENCES

1. Sieper J, Braun J, editor. Ankylosing spondylitis, Current medicine group, London 2009. https://doi.org/10.1007/978-1-907673-30-6_5
2. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue Nature. 1994; 372:425-32.64. https://doi.org/10.1038/372425a0
3. Fantuzzi G, Faggioni R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. J Leukoc Biol. 2000; 68:437-46.
4. De Keyser F, Van den Bosch F, Mielants H. Anti TNF-alpha therapy in ankylosing spondylitis. Cytokine. 2006;33(5):294-8. https://doi.org/10.1016/j.cyto.2006.01.004
5. Van der Linden S, Van der Heijde D, Maksymowych P W. Spondyloarthropathies. Firestein G, Budd R, Gabriel S, McInnes I, eds. Kelley's Textbook of Rheumatology. Vol.2. Saunders,2013 p.1181-1290.
6. Zou J, Rudwaleit M, Brandt J, Thiel A, Braun J, Sieper J. Down-regulation of the nonspecific and antigen-specific T cell cytokine response in ankylosing spondylitis during treatment with infliximab. Arthritis Rheum. 2003;48(3):780-90. https://doi.org/10.1002/art.10847
7. Zou J, Rudwaleit M, Brandt J, Thiel A, Braun J, Sieper J. Up regulation of the production of tumour necrosis factor alpha and interferon gamma by T cells in ankylosing spondylitis during treatment with etanercept. Ann Rheum Dis. 2003;62(6):561-4. https://doi.org/10.1136/ard.62.6.561
8. Stone MA, Payne U, Pacheco-Tena C, Inman RD. Cytokine correlates of clinical response patterns to infliximab treatment of ankylosing spondylitis. Ann Rheum Dis. 2004;63(1):84-7. https://doi.org/10.1136/ard.2003.006916
9. Maffei M, Halaas J, Ravussin E, Pratley R E, Lee G H, ZhangY, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nature Med. 1995; 1:1155-61. https://doi.org/10.1038/nm1195-1155
10. Bernotiene E, Palmer G, Gabay C. The role of leptin in innate and adaptive immune responses. Arthritis Res Ther. 2006;8(5):217. https://doi.org/10.1186/ar2004
11. Toussirot E, Streit G, Nguyen NU, Dumolin G, Huede L G, Saas P, et al. Adipose tissue, serum adipokines, and ghrelin in patients with ankylosing spondylitis. Metabolism. 2007;56(10):1383-9 https://doi.org/10.1016/j.metabol.2007.05.009

12. Sari I, Demir T, Kozaci LD, Akar S, Kavak T, Birlik M, et al. Body composition, insulin, and leptin levels in patients with ankylosing spondylitis. Clin Rheumatol. 2007;26(9):1427-32. https://doi.org/10.1007/s10067-006-0509-6
13. Park MC, Lee SW, Choi ST, Park YB, Lee SK. Serum leptin levels correlate with interleukin-6 levels and disease activity in patients with ankylosing spondylitis. Scand J Rheumatol. 2007;36(2):101-6. https://doi.org/10.1080/03009740600991760
14. Derdemezis CS, Filippatos TD, Voulgari PV, Tselepis AD, Drosos AA, Kiortsis DN. Leptin and adiponectin levels in patients with ankylosing spondylitis. The effect of infliximab treatment. Clin Exp Rheumatol. 2010;28(6):880-3.