Changes in Body Mass Index and Lipid Profile in Psoriatic Patients After Treatment With Standard Protocol of Infliximab

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Abstract- Psoriasis is a chronic and inflammatory dermatologic disease. Psoriasis may predispose to cardiovascular disease and diabetes. However, the role of tumor necrosis factor (TNF) inhibitor in mediating this risk is controversial. Regarding frequent use of infliximab in psoriasis, and the hypothesis that anti TNF-α treatment may increase Body Mass Index (BMI) and alter lipid profile in these patients, the aim of this study was to assess changes in BMI and Lipid Profile and level of leptin in Psoriatic Patients under Treatment of Standard Protocol of Infliximab in a 24 week period**.** This study was accomplished as a before-after study. Twenty-seven psoriatic patients were included, and standard infliximab therapy was applied. All patients underwent 3 times of blood collection and in each session; LDL, HDL, Total Cholesterol, Triglycerides, Leptin, and PASI score were measured at the start of the study and at the 12th and 24th week of follow-up. Twenty-five patients consisted of 18 (72%) male and 7 (28%) female subjects were evaluated. The mean age of the patients was 36.91±13.31 years. PASI score demonstrated significant decrease after 24 weeks; however, BMI and HDL and leptin showed a significant increase during treatment. Significant negative correlation was seen between Leptin and PASI score changes (r=0.331, *P*=0.042). HDL and BMI had the most correlations with leptin (positive correlation) and PASI score (negative correlation). Results demonstrated a dramatic decrease in PASI, increase in BMI and HDL and increased in leptin; somewhat correlated to each other. These results suggest that patients taking infliximab should take more care of their weight and lipid profile, while on treatment.

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Keywords: Body mass index; Lipid profile; Psoriasis; Infliximab

Introduction

Psoriasis is a chronic and recurrent dermatologic disease, which despite several treatment protocols, has no definite cure (1). The etiology of this disease consists of epidermal growth and differentiation disturbance, and biochemical, immunological and vascular disorders. It affects both sexes equally, and its prevalence ranges 0.1% to 11.8% in different populations (2-4). Several types of psoriasis have been demonstrated, and therefore, different types of treatment have been proposed (5).

Anti-Tumor necrotizing factor type alpha (TNF-α) drugs are widely used in immunologic and rheumatic diseases such as rheumatoid arthritis and psoriasis. TNF-α is a type of cytokine produced by the immune system in rheumatic diseases. This biochemical marker reduces when the immunologic response and inflammation decreases resulting by treatment of anti-TNF-α drugs such as infliximab (6-8). This biomarker can decrease appetite and body weight and Body Mass Index (BMI). TNF-α induces synthesis of catabolic hormones such as Insulin-like Growth Hormone-1 and increases lipolysis in adipose tissue, resulting in lower leptin production (9-10). Counter-wise, it is hypothesized that anti TNF-α treatment may increase BMI. This weight gain can be problematic in some cases, which can influence compliance with the treatment. Furthermore, increased inflammation in psoriatic patients potentially increases cardiovascular (CVD) risk factors and along with

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increased BMI and systematic inflammation, the odds of CVD exponentially increase.

Therefore, regarding frequent use of infliximab in psoriasis, the aim of this study was to assess the change in Body Mass Index and Lipid Profile and level of leptin in Psoriatic Patients under Treatment of Standard Protocol of Infliximab

Materials and Methods

Design

Patients with the confirmed diagnosis of Psoriasis were selected from January 2013 till January 2014. Patients were selected from those referred to the dermatologic referral center of Tehran University of Medical Sciences affiliated hospital; Razi. We used convenient sampling and patients were entered regarding eligibility criteria. The clinical assessment of the disease was based on Psoriasis Area and Severity Index (PASI) score that made it possible to select patients who needed advanced treatment. Infliximab was prescribed to patients suffering from moderate to severe forms of the disease according to clinical scores. Based on previous studies patients with PASI score more than 10 were classified as the moderate to severe form of psoriasis (3,24). Prior to the study, the patients were asked if they previously experienced any hypersensitivity reactions after using any drugs especially anti-TNF agents.

Infliximab 5 mg/kg was prescribed intravenously at the initial time and then at the second and the sixth week and then every 8 weeks up to 48 weeks. The patients were advised to refer for clinical assessment after 12 and 24 weeks of the first session. Before the initiation of the study and after anti-TNF therapy BMI, blood pressure, serum triglyceride and cholesterol, LDL and HDL and PASI score were all assessed in our patients. Thyroid stimulating hormone (TSH) and creatinine were also checked before and after the therapeutic period. BMI was achieved by weight (kg) to the square of height (m^2). Furthermore, all patients underwent Leptin measurement in all 3 sessions.

Eligibility criteria

According to our inclusion criteria, all included patients were checked if they intended to get pregnant or used any cytotoxic drugs simultaneously. Also, lactation, poor cooperation and difficult accessibility for follow-up, the presence of positive beta-HCG or intolerable side effects during the study were considered as other exclusion criteria. During the study, patients were checked for probable complications such as activation of latent infections (exp.; Tuberculosis and new positive PPD), hematologic changes, and deterioration of the initial dermatologic findings and any new onset of the disease. Therapeutic approach was changed or modified regarding the patient's problem. Patients' diet and physical activities were asked in every session, and if there were any significant changes during the study, the patients were excluded.

Assays

10 ml of venous blood was taken from subjects in the morning after overnight fast. Glucose (mg/dl), TG (mg/dl), HDL-C (mg/dl), levels were measured using photometric assay with intra- and inter-assay CV less than 2% (Pars Azmoon Company; Iran) with Hitachi (Japan) photo-analyzer. Leptin (ng/ml) levels were measured using a radioimmunoassay kit from Linco Research (St Louis, USA) with intra- and inter-assay CV less than 5%.

Ethical approval

This study was approved by the research committee of Tehran University of Medical Sciences, and ethical approval was achieved by the related review board. Every person was oriented with the aim of the study via a written letter and signed the attached written consent. All personal information were preserved regarding Helsinki's' declaration.

Statistical analysis

All clinical and laboratory data and basic characteristics were entered into SPSS software version 18 (PASW 18). Frequencies and percentages were used to show qualitative analysis and mean±SD was used to show quantitative analysis. Prior to any deductive analysis, we used one sample Kolmogorov-Smirnov test to check distribution pattern. Repeated measure ANOVA was used to check the progression of the disease or repeated laboratory findings within the time. Furthermore, Pearson correlation was used to find possible relations between variables. The significance level was considered less than 0.05.

Results

At the initial stage, 27 patients were included in the study; however, 2 patients were excluded due to Atherogenic diet and neotigazone (Acitretin) usage in the middle of the study. At the end, 25 patients were evaluated, consisted of 18(72%) male and 7(28%)

female subjects. The mean age of the patients was 36.91±13.31 years, with no significant difference between genders.

All patients underwent 3 measurements for PASI, BMI, and Leptin and lipid profile. As seen in table 1, PASI, BMI, and HDL had significant changes during the course of treatment after measurements in week 12 and 24; PASI score was significantly reduced and a significant increase in BMI and HDL level was shown. However, no significant difference of these measurements was noticed among gender.

Table 1. The mean of three times of Lipid Profile, BMI and leptin measurements and changes with treatment course and gender. HDL, Leptin, and BMI had significant changes in the treatment course. A significant difference was seen between males and females in HDL and Leptin. (*: Mann-Whitney-U test, Ɨ: repeated measurement test)

		Total	Male	Female	*P**
	First	173.0±99.3	172.2±100.1	175.91±91.3	0.532
TG	**Second**	186.1±109.3	185.1±111.2	190.0±99.5	0.726
	Third	218.7±174.3	221.7±150.2	212.1±199.9	0.921
p Ɨ		0.141	0.116	0.203	
	First	101.9±38.1	101.3±37.9	103.0±34.1	0.867
LDL	**Second**	97.2±40.1	97.0±40.0	97.6±39.3	0.902
	Third	90.5±41.8	90.2±41.5	91.1±41.1	0.822
p Ɨ		0.074	0.061	0.08	
	First	175.6±42.4	175.1±43.1	177.1±39.4	0.863
Cholesterol	**Second**	174.36±36.0	173.2±34.4	174.9±35.1	0.827
	Third	179.9±50.8	179.4±50.0	180.1±50.1	0.892
p Ɨ		0.496	0.502	0.463	
	First	39.0±8.2	37.5±7.2	42.1±9.3	<0.001
HDL	**Second**	40.92±10.8	38.6±7.6	42.9±10.2	<0.001
	Third	45.6±14.7	44.1±8.0	48.9±13.7	<0.001
p Ɨ		0.004	0.003	0.005	
	First	20.2±22.2	17.5±6.4	27.1±6.4	<0.001
Leptin	**Second**	31.31±22.9	29.2±19.0	29.2±19.76	<0.001
	Third	37.7±26.0	39.5±33.6	39.5±33.6	<0.001
p Ɨ		<0.001	<0.001	<0.001	
	First	26.2±5.1	26.3.±4.7	26.1.±4.9	0.529
BMI	**Second**	27.2±4.5	27.3±3.9	27.1±4.0	0.556
	Third	28.8±5.1	29.0±4.6	28.5±5.0	0.591
p Ɨ		0.014	0.011	0.021	

*: Mann-Whitney-U test, Ɨ: repeated measurement test

As demonstrated in table 2, the correlation of Leptin and PASI with changes in BMI and lipid profile changes were assessed; a significant correlation was seen between Leptin and PASI score changes with changes in HDL and BMI. Furthermore, table 3 demonstrates details of each measurement corresponding to sampling times; HDL and BMI had the most correlations with leptin and PASI score.

Table 2. Correlation assessment between changes (Δ) of Leptin and PASI Score with lipid profile and BMI changes (second column) through the study period, changes in HDL and BMI were statistically correlated with changes in leptin and PASI.

		Correlation with	
		Δ leptin	**Δ PASI**
ΔTG	45.72±150.5	r=0.1118, *P*=0.942	r=0.056, *P*=0.790
ΔChol	4.3±35.38	r=0.218, *P*=0.331	r=0.255, *P*=0.219
ΔHDL	6.6±10.23	r=0.389, *P*=0.041	r=0.310, *P*=0.023
ΔLDL	-11.4±28.9	r=-0.019, *P*=0.407	r=-0.219, *P*=0.293
ΔBMI	0.58±1.29	r=0.489, *P*<0.001	r=0.558, *P*<0.001

Table 3. Correlation test between PASI score and Leptin levels with lipid profile and BMI; a significant correlation was detected among HDL and BMI measurements with PASI score and leptin level.

		Correlation	
	# of sampling	**Leptin**	**PASI**
TG	1	r=0.07, *P*=0.736	r=0.169, *P*=0.408
	2	r=0.359, *P*=0.079	r=0.173, *P*=0.379
	3	r=0.297, *P*=0.141	r=0.463, *P*=0.017
Total cholesterol	1	r=0.178, *P*=0.384	r=0.155, *P*=0.449
	2	r=0.178, *P*=0.384	r=0.349, *P*=0.800
	3	r=0.251, *P*=0.216	r=0.280, *P*=0.165
HDL	1	r=0.305, *P*<0.001	r=-0.587, *P*<0.001
	2	r=0.384, *P*<0.001	r=-0.496, *P*<0.001
	3	r=0.321, *P*<0.001	r=-0.504, *P*<0.001
BMI	1	r=0.355, *P*=0.087	r=-0.072, *P*=0.369
	2	r=0.368, *P*=0.105	r=-0.296, *P*=0.021
	3	r=0.488, *P*=0.032	r=-0.547, *P*<0.001

Discussion

Our results demonstrated that patients treated with infliximab exhibit reduced PASI score, increased weight, leptin, and HDL; which all these three parameters more or less, had a correlation with each other; however, no significant change was observed in LDL and TG. The cause of leptin increase is maybe due to enhance biphasic excretion of leptin from adipocytes in minimum or maximum levels of TNFs (12).

Nearly all studies regarding anti-TNF agents in rheumatic disease demonstrated significant changes in leptin serum levels; however, there are researchers who have stated otherwise. Magera *et al.*, (13) and Nishio *et al.*, (14) both demonstrated increase in leptin in infliximab treated RA patients. Unlike our study, Gay *et al.*, (15) did not find any changes and Tokarczyk-Knapik *et al.*, (16) found inverse changes.

TNF and lipid profile

There are several debates regarding TNF and lipid profile in rheumatic disease: Poloono *et al.*, (17) demonstrated HDL rise by Adalimumab after 2 weeks and Castro *et al.*, (18) demonstrated HDL rise after 2 weeks of infliximab. However, there are some controversies regarding other lipids; e.g. in Castro *et al.*, (18) study, VLDL and TG increases in arthritic psoriasis patients by infliximab. Cauza *et al.*, (19) also demonstrated the same results.

TNF is an inflammatory biomarker indicating infective, immunologic or rheumatologic reactions. TNF can induce TG and HDL increase, theoretically, by means of three pathways: 1-activating Insulin, TNF and Gi receptors and inducing free fatty acids (FFAs) release in the blood 2-activation of hepatocytes, which facilitate the change of FFA to TG by increasing intercellular citrates; 2-blocking activated lipoprotein lipase (LPL) in all cells. However, fast increase of TGs can activate negative feedbacks and stabilize this process (14-18). By reviewing this information, it seems that administering anti-TNF agents will deactivate these pathways and TG decreases in the result but most studies demonstrated that these changes are not significant or showed slight increase (like our study) and concluded that this slight changes (sometimes less than 10 mg/dl) are not that much important clinically (14-18). The debate regarding cholesterols does not fall far from TG. Animal models demonstrated a rise in LDL and TG by TNF injection in mice; however, nearly all published literature indicate that TNF induces a reduction in cholesterols (especially HDL) by interfering with LDL receptors, Apo-lipoprotein A and B, and 7A1 and 7B1 cytochromes with no changes in HMG-co reductase action (12,17-21). Therefore it is logical to conclude that Anti-TNF drugs will result in increased HDL. Furthermore, drugs such as infliximab can inhibit lecithin cholesterol acyltransferase and cholesteryl ester transfer protein, which blocks LDL catabolism and secretion in

hepatocytes (23). This will result in reduced plasma LDL. As mentioned above, all these changes are temporary, and the negative feedback will balance these changes over time. However, the changes in LDL are greater than HDL; which results in lower LDL/HDL ratio as one of the most important risk factors for CVDs (11), but infliximab will stop this chain. Although, our study demonstrated an insignificant 5% increase in LDL and TG, HDL increases by nearly 20%, approving the above theories.

TNF and weight

Our study demonstrated that infliximab therapy would result in significant 1-3 kg weight gain in psoriatic patients within a 24 weeks period; furthermore, a significant correlation was found between BMI and leptin. Although there are not so many studies regarding this issue, Gisondi *et al*., (20) and Briot *et al*., (21) demonstrated the same results. Basic studies have suggested that these weight gains are not "fat" gain and anti-TNF agents increase lean body mass. We should know that not all patients exhibit this weight gain, which can be due to immunologic reaction differences or genomic pool. The reason is still unknown. Molecular studies have demonstrated that TNF along with cachectin can result in the catabolism of myocytes and therefore, the anti-TNF agent can block this pathway. Furthermore, studies showed that infliximab increased appetite (20-21). The most important difference between our result and other published literature was the negative significant correlation between PASI score and BMI; not found in other studies. Furthermore, these BMI increase is frequently seen in "fatter" patients. Thus, it is recommended that patients with higher BMI exert more diet control while receiving Infliximab because psoriasis itself (rather than other etiologies such as depression, immobility, and corticosteroid treatment) can increase their weight by 10-15%; also demonstrated in other diseases such as Crohn's disease. Nakahigashi *et al*., (22) have suggested that infliximab treatment can induce food craving (due to better health quality), leptin increase (seen in our study) and infliximab itself.

However, we cannot leave the role of Insulin resistance unnoticed. A review study has demonstrated that infliximab reduced insulin resistance. But there are not too many evidence to enroll it as an important factor of weight in psoriasis; while most of the patients in our study were young.

While our study did demonstrate interesting results, we should be aware of our study's limitations: 1-low sample size due to strict exclusion criteria; and 2-lack of the control group. We suggest studies with higher sample sizes and more molecular concerns.

We studied leptin, lipid profile and BMI changes in psoriatic patients treated with infliximab. Results demonstrated a dramatic decrease in PASI, changes in BMI and HDL and increased in leptin; somewhat correlated to each other. These results suggest that patients taking infliximab should take more care of their weight and lipid profile, while on treatment.

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