Serum leptin levels in psoriatic patients with non-alcoholic fatty liver disease

Zahra Hallaji, MD [1,2]
Vahideh Lajevardi, MD [1,2]
Robabeh Abedini, MD [1,2]
Amir Soleymani, MD [1]
Azadeh Goodarzi, MD [3]
Mehrnaz Salehi-Taleghani, MD [4]
Sara Beygi, MD [1,5]

1. Autoimmune Bullous Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Dermatology, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Dermatology, Iran University of Medical Sciences, Tehran, Iran
4. Department of Dermatology, Zanjan University of Medical Sciences, Zanjan, Iran
5. National Elite Foundation of Iran, Tehran, Iran

Corresponding author:
Robabeh Abedini, MD
Razi Hospital, Vahdat Eslami Square, Tehran, Iran
Email: Rabedini@sina.tums.ac.ir

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Background: The prevalence of non-alcoholic fatty liver disease is higher in patients with psoriasis than in the normal population. Serum leptin levels are higher in patients with psoriasis and in patients with non-alcoholic fatty liver. The purpose of this study was to determine the serum levels of leptin in psoriatic patients with and without non-alcoholic fatty liver.

Methods: This cross-sectional study was conducted at Razi Dermatology Hospital, Tehran, Iran in 2013. A total of 50 patients with psoriasis were enrolled in the study. Fatty liver grade was assessed via ultrasonography and serum leptin levels were measured using the ELISA method.

Results: Ten patients had normal livers and 40 had fatty livers with different grades. The median serum leptin level was significantly higher in psoriatic patients with fatty liver (11.75 ng/mL) in comparison to those without fatty liver (2.80 ng/ml). Moreover, there was a direct correlation between the leptin level and the grade of fatty liver.

Conclusion: serum leptin can be elevated in the course of psoriasis and may have a role in the pathogenesis of non-alcoholic fatty liver disease and other metabolic co morbidities in psoriatic patients.

Keywords: psoriasis, non-alcoholic fatty liver, leptin

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with potential systemic involvement [1]. Patients with psoriasis are at increased risk for a variety of immune mediated inflammatory conditions including psoriatic arthritis, inflammatory bowel disease, and malignancy as well as metabolic conditions like obesity, insulin resistant type 2 diabetes mellitus, atherogenic dyslipidemia, myocardial infarction, and nonalcoholic fatty liver disease (NAFLD) [2-4].

NAFLD is an increasingly recognized condition affecting 10-24 % of the general population, and may progress to end-stage liver disease [5]. There is evidence of a considerably higher prevalence of NAFLD among patients with psoriasis [6-9]. The exact pathophysiological mechanisms behind this observation are unclear. However, adipokines including adiponectin, interleukin-6 (IL-6), resistin, tumour necrosis factor-α (TNF-α), and leptin are thought to play a role in the pathogenesis of both

psoriasis and NAFLD [10].

Leptin, the product of the *ob* gene, is a16-kDa peptide hormone synthesized and secreted by adipocytes. Leptin is a lipostatic signal which controls food intake, and is a key metabolic regulator linking the pro-inflammatory Th_1 immune response to the nutritional status and the energy balance [11]. Several recent studies have shown that the serum leptin level is remarkably elevated in patients with psoriasis [12-15]. Moreover, skin tissue leptin and leptin receptor expression have been found to be higher in patients with severe psoriasis than patients with mild to moderate psoriasis and healthy controls [16]. On the other hand, there is evidence of the higher levels of serum leptin in patients with NAFLD compared with normal subjects [17]. However, the association between leptin levels and the development and severity of NAFLD in psoriatic patients has rarely been studied. Therefore, we sought to compare serum levels of leptin in psoriatic patients with NAFLD vs. psoriatic patients with a normal liver. We also tried to figure out the relationship between leptin levels and severity of liver involvement in this population of patients.

PARTICIPANTS AND METHODS

This cross-sectional study was carried out in Razi Dermatology Hospital, Tehran, Iran in 2013. The study protocol was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences. A total of 50 consecutive patients with psoriasis attending the dermatology department were recruited. Psoriasis was diagnosed on the basis of clinical examination by one of our attending dermatologists. None of the patients were on systemic drug therapy in the past one month prior to evaluation. HBS antigen and HCV antibody were negative in all patients, and no one had autoimmune hepatitis. None of the subjects had a history of malignancy and chemotherapy during the past 5 years. Written informed consent was obtained from all participants before joining the study.

Basic clinical characteristics of each patient including gender, age, weight, height, body mass index (BMI), waist circumference, hip circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), history of cigarette smoking, alcohol consumption, diabetes mellitus, age at onset of psoriasis, and duration of the disease were collected using a checklist. The Psoriasis Area and Severity Index (PASI), the most commonly used clinical measure of the psoriasis severity [18], was determined through a thorough head-to-toe skin examination. All PASI scores were determined by the same dermatologist throughout the study. NAFLD was diagnosed and graded via ultrasonography by a radiologist who was blinded to the clinical and laboratory findings of the study subjects. Ultrasonography is a reliable and accurate tool for detection of moderate to severe fatty liver disease [19,20]. Then, 5 ml of venous blood was drawn from all patients, and serum levels of glucose, triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and leptin were measured using standard laboratory protocols.

Data were analyzed with IBM SPSS version 20. Normal distribution of data was assessed using the Shapiro-Wilk *W* test. Since most of the data were not normally distributed, nonparametric tests were used for all statistical analyses. Mann-Whitney *U* and chi-square tests were employed to find out differences in interval and categorical variables between psoriatic patients with and without NAFLD. The Kruskal-Wallis test was utilized to explore differences in the serum level of leptin in patients with different grades of fatty liver. Then, pair-wise comparison using multiple Mann-Whitney tests was performed to locate the differences more precisely. Potential associations between the leptin level and different interval variables were tested using the Spearman rho. Backward linear regression was used to find factors that independently predict the grade of the liver disease. Data are presented as median and interquartile range (IQR). Two-tailed $P<0.05$ were considered significant.

RESULTS

Of a total of 50 patients, 34 (68%) were men and 16 (32%) were women. The mean ± standard deviation (SD) age of the study population was 42.5 ± 13.2 years. Baseline characteristics of the patients with and without NAFLD are summarized

in Table 1. Ten patients had a normal appearing liver on ultrasonography and 40 had different grades (G1–G4) of fatty liver. Patients with NAFLD had significantly higher BMI, waist circumference, hip circumference, serum TG, LDL, and AST levels compared to those with normal liver (P<0.05). Moreover, NAFLD patients had a marginally significant increased serum total cholesterol (P=0.07), ALT (P=0.05), and duration of psoriasis (P=0.05) versus psoriatic patients with normal liver.

The median (IQR) serum level of leptin was 9.75 (3.47–23.30) ng/ml. Leptin levels were significantly higher in female patients with psoriasis compared to males (P=0.004). Furthermore, patients with concomitant NAFLD had higher concentrations of serum leptin as compared to their counterparts with a normal appearing liver (P<0.001, Figure 1). The Kruskal-Wallis test revealed an overall significant difference in the leptin level in patients with different fatty liver grades (P<0.001). Then, multiple pairwise comparison with the Mann-Whitney test showed that the patients with fatty liver grades 2, 3, and 4 had significantly higher leptin levels than those with normal liver (Figure 2).

The Spearman's test revealed a significant

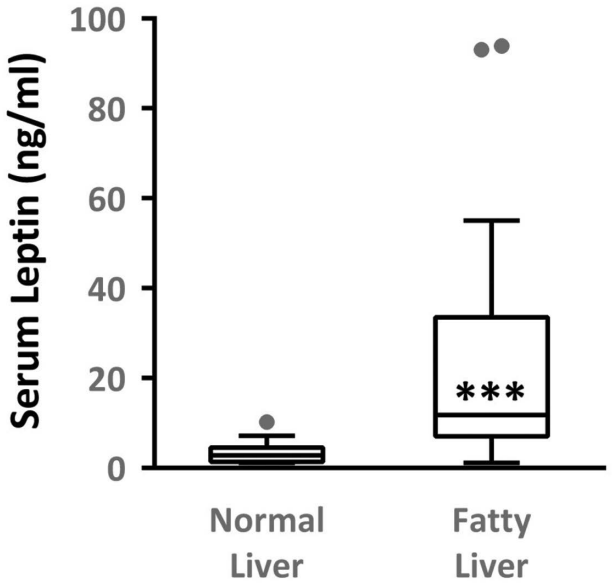

Figure 1. Serum leptin in psoriatic patients with or without NAFLD. Serum concentration of leptin was significantly higher in patients with psoriasis and NAFLD compared to psoriatic patients with normal liver. The boxes show IQR. The transverse line inside the box shows the respective median. The dots beyond the Tukey whiskers (1.5 × IQR) represent outlying data. Asterisks signify P<0.001.

Table 1. Basic clinical characteristics of the study patients with or without NAFLD.

	Patients without NAFLD	Patients with NAFLD	*P*
	10	40	–
Gender (Male/Female)	9/1	25/15	0.13
Diabetes mellitus (n)	0	8	0.18
Cigarette smoker (n)	2	9	1.00
Alcohol (n)	0	3	1.00
Age (years)	41 (30–48)	45 (31.25–54.5)	0.35
Weight (kg)	80 (73–83)	87 (71.25–99.25)	0.12
Height (cm)	170 (160–177)	168.5 (160–177.75)	0.52
BMI (kg/m^2)	28 (25–29)	30 (27.77–32)	0.02
Waist circumference (cm)	90 (80–98)	110 (100–116.75)	0.004
Hip circumference (cm)	104 (100–110)	115 (105.5–124.5)	0.01
SBP (mmHg)	110 (100–120)	120 (110–130)	0.12
DBP (mmHg)	80 (65–80)	80 (71.25–90)	0.16
FBS (mg/dL)	90 (83–103)	100 (90.75–124)	0.15
TG (mg/dL)	124 (80–150)	151.5 (119.25–197.5)	0.007
LDL (mg/dL)	94 (70–105)	120 (100–136.5)	0.01
HDL (mg/dL)	45 (35–56)	39.5 (30.25–49.75)	0.73
TC (mg/dL)	145 (121–166)	169.5 (150–197.75)	0.07
AST (U/dL)	19 (12–23)	22.50 (18–34)	0.03
ALT (U/dL)	18 (15–29)	29 (19.25–49.5)	0.05
ALP (U/dL)	180 (178–205)	218 (185.25–327.75)	0.29
Duration of the psoriasis (years)	3 (0.87–4.25)	5.5 (3–12.75)	0.05
PASI	5 (2–18)	10 (5–19)	0.12

ALP: alkaline phosphatase; ALT: alanine aminotransferase, AST: aspartate aminotransferase; BMI: body mass index; DBP: diastolic blood pressure; FBS: fasting blood sugar; HDL: high density lipoprotein; LDL: low density lipoprotein; PASI: psoriasis area and severity index; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride.

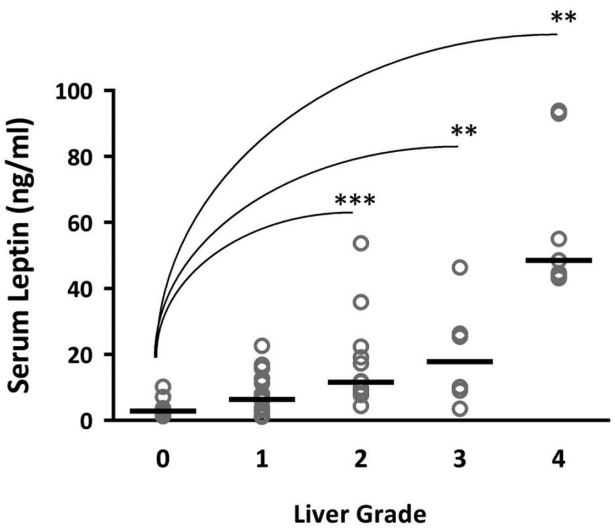

Figure 2. Serum leptin in psoriatic patients with different grades of fatty liver. Apparently, serum leptin level increases as the fatty liver grade rises. Psoriatic patients with fatty liver grades 2, 3, and 4 had significantly higher leptin levels than those with normal liver. Number of patients with fatty liver grades 0–4 were 10, 14, 13, 6, and 7 respectively. The transverse lines show the respective medians. Each circle represents one patient. **: P<0.01, ***: P<0.001.

correlation between the leptin level and the grade of fatty liver (Spearman *rho*: 0.75, P<0.001). A significant correlation was also found between serum leptin and weight, BMI, waist and hip circumference, TG, TC, LDL, AST, ALT, and ALP (Table 2). Additionally, serum leptin had a marginally significant correlation with SBP (P=0.06), DBP (P=0.06), and PASI score (P=0.05).

Table 2. Correlation between serum leptin levels and other measured variables.

	Correlation coefficient (Spearman's rho)	*P*
Age (years)	0.13	0.37
Weight (kg)	0.31	0.02
Height (cm)	-0.19	0.17
BMI (kg/m^2)	0.47	0.001
Waist circumference (cm)	0.60	<0.001
Hip circumference (cm)	0.57	<0.001
SBP (mmHg)	0.27	0.06
DBP (mmHg)	0.27	0.06
FBS (mg/dL)	0.22	0.13
TG (mg/dL)	0.49	<0.001
LDL (mg/dL)	0.33	0.01
HDL (mg/dL)	0.03	0.83
TC (mg/dL)	0.40	0.004
AST (U/dL)	0.35	0.01
ALT (U/dL)	0.41	0.003
ALP (U/dL)	0.33	0.02
Duration of the psoriasis (years)	0.07	0.61
PASI	0.28	0.05
Fatty liver grade	0.75	<0.001

Backward linear regression revealed that weight (β=−0.29, P=0.001), waist circumference (β=0.31, P=0.001), SBP (β=0.22, P=0.004), TG (β=0.14, P=0.04), LDL (β= 0.28, P< 0.001), AST (β=0.28, P=0.001), and leptin (β=0.34, P<0.001) were independent predictors of fatty liver grades in psoriatic patients.

DISCUSSION

This study was primarily designed to compare the leptin level between psoriatic patients with and without NAFLD. We not only detected higher levels of leptin in patients with NAFLD, but also found that serum leptin was an independent predictor for the degree of fatty change.

Leptin, which is synthesized mainly in the white adipose tissue and circulates in the blood, appears to have a wide range of roles as a growth factor for various types of cells, a mediator of energy expenditure, a permissive factor for puberty, and a signal of metabolic status between fetus and mother [21].

Recent studies have shown that serum leptin concentration is also increased in patients with psoriasis [12,13,15,16] and is possibly associated with higher prevalnece of metabolic syndrome, hypertension, diabetes mellitus, and insulin resistance in psoriatic patients [11]. There is also evidence of increased levels of leptin in NAFLD patients [17]. In fact, our findings regarding the increased leptin level in psoriatic patients with fatty change of the liver supports previous observations and provides more robust evidence for the possible role of leptin as an etiologic factor. We also found a marginal correlation between the psoriasis severity and leptin level. The marginal correlation (P=0.05) could be related to the inadequate power of the study to reach a statistical significance. Thus, if our sample size was slightly larger, we would probably be able to detect a significant correlation between the PASI score and leptin levels. This finding is consistent with previous reports of a connection between psoriasis severity, obesity, and metabolic syndrome, and development of fatty changes in the liver of psoriatic patients [6-9]. In fact, it could be hypothesized that increased severity of the psoriasis may lead to increased synthesis of leptin, and high

leptin levels subsequently induce fatty changes in the liver. It is suggested that leptin may precipitate NAFLD through reduction of insulin sensitivity and induction of hepatic fibrogenesis [10]. Increased leptin in the setting of more severe psoriasis could be attributed to a higher inflammatory burden of the disease. Since inflammatory mediators including IL-1 and TNF-α are implicated in the increased production of leptin [21], and also the more extensive skin involvement in psoriasis is thought to be associated with a higher burden of inflammation [22], the increased levels of leptin in psoriatic patients with higher PASI scores could be a result of higher active inflammation. On the contrary, it is possible that leptin itself may trigger or exacerbate psoriasis through increased keratinocyte proliferation, angiogenesis, and production of pro-inflammatory cytokines by monocytes and macrophages [10]. As a matter of fact, G-2548A polymorphism of the leptin gene, which leads to a higher plasma leptin concentration, is shown to be associated with increased risk of developing symptomatic psoriasis [11]. Moreover, the close association of leptin and BMI [23] added to the strong relationship between psoriasis and obesity [24-26], and even improvement of psoriasis symptoms after gastric bypass surgery [27] could further highlight the role of leptin in the pathogenesis and probably severity of psoriasis. Although it could be argued that psoriasis in the setting of obesity may be attributed to a different mechanism besides leptin, the increased levels of leptin in psoriatic patients with a normal BMI could be a testament to the important role of this marker [28].

In conclusion, psoriatic patients with non-alcoholic fatty liver disease have higher serum leptin levels as compared to patients with normal liver, and the level of this marker may even predict the degree of liver involvement. Finally, large scale prospective studies are warranted to further substantiate the contribution of leptin to the pathogenesis of psoriasis and its complications including non-alcoholic fatty liver disease.

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