Correlation of Leptin with Severity of Plaque Psoriasis in Iraqi Male Patients

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Abstract

Background: psoriasis is a chronic inflammatory, immune mediated disease of the skin which is characterized by the presence of erythematous scaly plaques. The prevalence of psoriasis is 2-4% worldwide. It has a negative impact on the patient's health and may associate with serious medical comorbidities.

Objectives: to investigate the levels of leptin in male patients with plaque psoriasis and control group and their relationship with the clinical severity of psoriasis.

Methodology: the study was conducted on sixty male patients with plaque psoriasis and thirty healthy male individuals taken as a control group. The sera obtained from blood were used to determine the levels of leptin in both groups. Also, it was used to determine the correlation of leptin with severity of plaque psoriasis which measured by psoriasis area and severity index (PASI) score. Leptin concentration was estimated by enzyme-linked immuno-sorbent assay (ELISA) method.

Results: the results of this work showed a significant increase ($p<0.05$) of leptin concentrations in sera of plaque psoriasis compared to the control group. Also, the results of linear regression analysis showed significant positive correlations of leptin with psoriasis area and severity index, i.e, PASI score.

Conclusion: the pro-inflammatory biomarker leptin is involved in pathogenesis of plaque psoriasis and may be used as markers for severity of disease.

Recommendation: including a large sample size to confirm the association between leptin and severity of plaque psoriasis.

Keywords: plaque psoriasis**,** leptin, PASI score

الخلاصة

المقدمة: الصدفية داء التهابي مناعي مزمن يصيب الجلد ويتميز بلويحات متقشرة احمرارية. وينتشر الصدفية بنسبة 2-4% في العالم كما للصدفية تأثير سلبي على صحة المريض كذلك ممكن ان تصاحب الصدفية امراض اخرى.

الهدف: تهدف الدراسة الحالية الى فحص مستويات اللبتين في مجموعة مرضى الصدفية الذكور ومجموعة الاصحاء الذكور كذلك تهدف الدراسة الى علاقة اللبتين مع شدة الصدفية.

المنهجية: تم اجراء هذه الدراسة على ستين مريضا بداء الصدفية اللويحية وثلاثين شخص من الاصحاء كمجموعة سيطرة. أخذ عينة دم من المجموعتين كذلك تم قياس شدة المرض لمجموعة المرضى بواسطة حساب (PASI score). وتم قياس مستويات اللبتين في مصل الدم للمجموعتين بواسطة طريقة (ELISA).

النتائج: أظهرت النتائج زيادة ملحوظة ($P<0.05$) في تركيز اللبتين في مجموعة مرضى الصدفية مقارنة بمجموعة السيطرة. كما بينت الدراسة الحالية بأستخدام طريقة تحليل الانحراف الخطي ان الزيادة في اللبتين تتناسب مع شدة الصدفية المقاسة. حيث يتناسب اللبتين طرديا مع مع شدة الصدفية.

الاستنتاجات: اعتبار اللبتين عامل التهابي يزيد ويعنت الصدفية وكذلك ممكن استخدامة كعامل لشدة الصدفية.

التوصيات: استخدام عينات أكبر لتأكيد استخدام اللبتين كعامل لشدة الصدفية.

كلمات مفتاحية: الصدفية اللويحي, اللبتين, PASI

Introduction

The term of psoriasis is taken from the Greek language which means roughly "itching condition" (*psora* "itch" and *-sis* "action, condition") [Ritchlin, 2007]. The accumulation evidence proved that psoriasis is a chronic inflammatory, immune mediated disease of the skin which is characterized by the presence of erythematous scaly plaques [Reich, 2012]. The prevalence of psoriasis is 2-4% worldwide [Parisi, 2013]. It has a negative impact on the patient's health and may associate with serious medical comorbidities, and affects the quality of life of the affected patient and his family members [Dauden, 2012; Zhang, 2013].

The role of genetics in the psoriasis pathogenesis is well reported in family and twin studies. Therefore, some families repeatedly have psoriasis among their members. The individual has risk of psoriasis development is 41% when his mother and father are affected, but this ratio decreases to 14% if just his mother or father is affected. On the other hand, the risk ratio has been 6% only when one sibling is affected [Yang, 2013].

Genome regions of psoriasis disease most extremely associated with the disease development are associated with the immune system. The major histocompatibility complex such as Interleukin 23 receptor (*IL23R*), *IL12B*, and the human leukocyte antigen Cw6 (*HLA-Cw6*) have been tightly associated with psoriasis [Chandran, 2010; Lowes, 2013]. Also, several studies have described the important role of single nucleotide polymorphisms (SNPs) in the promoter region of the tumor necrosis factor gene (*TNF-α*) [Prieto-Perez, 2013].

Actually the precise cause of psoriasis up to now stills unclear, multifactorial etiology may contribute leading to psoriasis appearance. The combination of multiple susceptibility genes [Capon, 2007], a dysregulated immune system [Volpe, 2008] and environmental trigger factors [Krueger, 2002] may result in psoriasis development.

In psoriasis, the extremely high activity of a certain immune system cells that known as T-cells leads to attacking the skin. A number of events begin after this attack on skin that causes rapid multiplication of skin cells which in turn result in skin cells accumulating on the surface of skin [Yamamoto, 2013].

The predominant pathogenesis of psoriasis model suggests that hyper-proliferation of keratinocyte is triggered by cutaneous lymphocyte infiltration, increase inflammatory cells activation and differentiation, involving T-cells, dendritic cells and macrophages. On the other hand, these events lead to production of cytokines that in turn result in support and confirm the pathogenic cascade [Puig, 2014].

Psoriasis may be induced by environmental factors to occur. The persistence of these environmental factors may also cause maintenance and increase severity of psoriasis. These factors include chronic infections, stress, smoking, alcohol consumption, low humidity, obesity and several types of medications such as lipid-lowering drug, beta blockers, calcium channel blockers, antimalarial agents, lithium, and interferon [Gerdes, 2010; Kálmán, 2014].

Importantly, psoriasis cannot be captured from other people. Psoriasis can occur in children, teenagers, adults and older people. Therefore, it can occur at any time in the lifespan. Psoriasis affects both genders equally [Tsai, 2011]. There are several clinical types of psoriasis, but the most common type is plaque psoriasis. It affects 80% to 90% of people with psoriasis [Palfreeman, 2013]. Plaque psoriasis is characterized by elevated red patches of skin and also silvery scales with white color covered the skin. The aggregated cells of skin that are ready to shed form these silvery white scales. On the other hand, the redness of skin is consequent to the elevation of blood vessels that demanded to promote multiply skin cells [Di Lernia, 2014].

Psoriasis can grade in severity from mild to very severe. The plaques that characterize psoriasis disease have a well-defined edge distinct from surrounding skin. The diameter of plaques varied from a few millimeters to several centimeters also the size and shapes of these plaques are different in appearance [Schafer, 2012; Di Lernia, 2014].

Approximately, 10-30% of people who have psoriasis may develop to psoriasis arthritis. This type of psoriasis may affect several parts of body such as the neck, feet, wrists, hands, lower back and ankles. Furthermore, the joints in some psoriasis arthritis cases become disfigured leading to lack of ability [Schafer, 2012]. Psoriasis is characterized by variable progression of disease on the one hand and its response to treatment on the other hand. Therefore, some patients ameliorated after using some treatment while others not [Sua´rez-Farin˜as, 2010; Woolf & Smith, 2010].

Several scales exist for measuring the severity of psoriasis. Generally, Psoriasis Area Severity Index (PASI) score is the main scale that used to measure the severity of plaque psoriasis. The range of PASI score has been between zero (this meaning no disease) and 72 represent highest score in severity of disease. In general, PASI less than 10 defines as mild case, PASI score from 10-20 defines as moderate case while PASI more than 20 is considered severe plaque psoriasis [Duarte & Silva, 2014].

The appearance of psoriasis is not only restricted in the skin. Also a risk of comorbidities may complicate moderate to severe psoriasis. Particularly, the relative risks of diabetes, hypertension, ischaemic heart disease, stroke and dyslipidaemia are elevated in psoriasis patients [Lee, 2014; Baeta, 2014].

Leptin is a 16-kDa, 167-amino acid adipocytokine. Adipose tissues are responsible for produced leptin primarily, whereas other tissues such as skeletal muscle, placenta, ovaries, pituitary gland, liver and stomach, can also express leptin. The levels of leptin in females are higher two to three times than in males of same body weight [Gerkowicz, 2012].

Leptin has multi active functions including, energy expenditure, regulating food intake, satiety and appetite, and therefore is considered an important signal in the regulation of food intake and energy balance, moreover leptin level generally associated with body mass index. Depending on these facts, the circulating concentration of leptin indirectly is reflects body fat stores and fluctuate with acute changes in caloric intake. Also, leptin play a role in immunity, inflammation, hematopoiesis, cell differentiation and proliferation [Dalamaga, 2013]. Remarkably, the very obese person has low leptin level or leptin deficiency, whereas other obese patients have elevated leptin levels. The latter obese patients do not react to elevated levels of leptin by a reduction in their appetite. For this reason, it is assumed that obese patients have leptin resistance [Moon, 2013] and hyperleptinemia is considered a significant risk factor leading to the development of type 2 DM. Therefore, hyperleptinemia due to leptin resistance is associated to or lead to obesity and insulin resistance which in turn development to metabolic syndrome [Moran & Phillip, 2003; Moon, 2013]. Leptin links nutritional status with neuroendocrine and immune functions, and its role in the modulation of immune response and inflammation has recently become increasingly evident. The increase in leptin production that occurs during infection and inflammation strongly suggests that leptin is a part of the cytokine network that governs the inflammatory-immune response and the host defense mechanisms [Dalamaga, 2013; Moon, 2013]. Therefore, leptin plays an important role in inflammatory processes involving T cells and has been reported to modulate T-helper cell activity in the cellular immune response [Moon, 2013].

Leptin may be implicated in the pathogenesis of psoriasis by more than one role. In addition, to its role in inflammation and stimulating monocyte and macrophage cells and elevated production of the pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12, it also drives T cell differentiation to Th1 phenotype, therefore, it increases the expression of interferon (INF)-γ and IL-2. On the other hand, leptin suppresses the production of the T helper cells type2 (Th2) cytokine IL-4 by mononuclear cells or Tcells. Leptin also induces keratinocyte proliferation, angiogenesis and expression of adhesion molecules [Moon, 2013; Gerdes, 2011].

Aim of the study

1. To evaluate the leptin levels in plaque psoriatic patients in comparison with control group.
2. To determine the relationship between the levels of leptin with severity of plaque psoriasis according to Psoriasis Area and Severity Index (PASI) score.

Materials and methods

Sixty male adults with plaque psoriasis disease as patients group and thirty apparently healthy male adults (without chronic disease) as control group were enrolled in this study. The diagnosis of plaque psoriatic patients and calculation of severity of plaque psoriasis disease according to Psoriasis Area and Severity Index (PASI) score worksheet were done by specialist dermatologist. A questionnaire was designed to obtain the information from psoriasis patients and control groups. It contained the name, age, weight, height, gender, duration of disease, drug allergy and smoking. Venous blood samples were drawn from psoriasis and control subjects by using disposable syringe (5mL) in the sitting position. About five milliliter of blood were taken from each subject by vein puncture and pushed slowly into plain disposable tubes. Blood was allowed to clot at 37°C for 10-15 minutes. Leptin concentrations were estimated by enzyme-linked immuno-sorbent assay (ELISA) method for both plaque psoriasis group and control group. The kit used (R&D systems, USA); Catalog No. DLP00; Lot: 315640.

Results

General characteristics of psoriasis and control groups.

The mean ± SD of age and BMI for both plaque psoriasis group and control group were shown in Table (1).

Table (1): The mean and standard deviation of age and BMI for psoriasis patients and control groups.

Parameter	Patients (No. 60) Mean ± SD	Control (No. 30) Mean ± SD
Age (year)	33.65 ± 8.44	31.8 ± 7.58
BMI (kg/m^2)	27.43 ± 5.99	24.38 ± 3.51

Serum levels of leptin in psoriatic patients and control group.

The concentrations of leptin in psoriatic patients as well as in control group in this study were measured, the mean ± SD for leptin were shown in Table (2).

Table (2): Mean and standard deviation of leptin in psoriasis and control groups.

Parameter	Patients (No. 60) Mean ± SD	Control (No. 30) Mean ± SD	p value
Leptin ng/ml	18.21 ± 10.19	8.04 ± 3.32	<0.05

(p value of < 0.05 was considered to be statistically significant)

In this study we found that the mean ± SD of leptin concentration in psoriasis patients and control group was (18.21 ± 10.19 and 8.04 ± 3.32) ng/ml respectively. The results in table (2) showed a significant increase ($p<0.05$) in leptin concentration in sera of psoriasis group compared to leptin concentration in sera of control group.

Correlation of leptin with severity of plaque psoriasis (PASI) score.

To evaluate the relationship between leptin with severity of plaque psoriasis patients, the linear regression analysis was used to evaluate the data as in Table (3).

Table (3): Linear regression analysis of PASI score with leptin in patients with plaque psoriasis.

Parameter	r value	p value
Leptin	0.78	<0.05

A statistically significant positive correlation was found between serum leptin levels and PASI score in patients with plaque psoriasis ($r = 0.78$, $p<0.05$). See Figure (1).

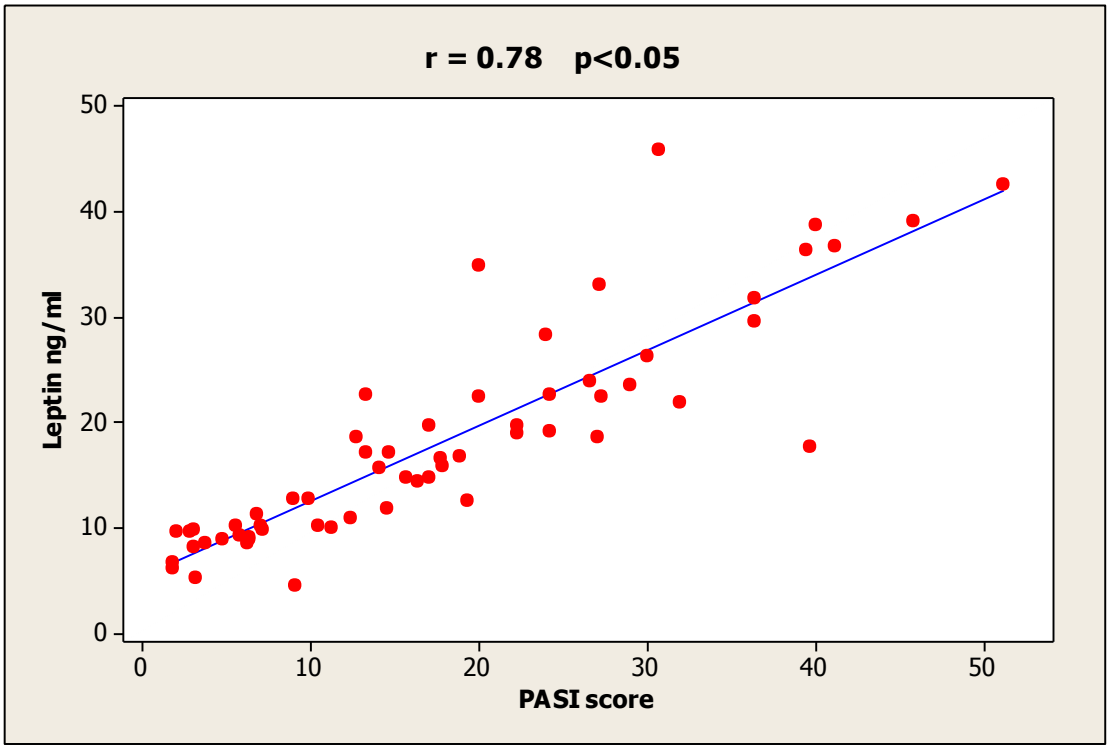

Figure (1): The correlation of leptin concentration with PASI score in plaque psoriasis patients.

Discussion

Leptin stimulates proliferation of keratinocyte, angiogenesis as well as expression of adhesion molecules [Gerdes, 2011]. In psoriasis, leptin stimulate macrophage to secretion several cytokines such as TNF-α, IL-1β and IL-6 result in exacerbate the psoriasis. The majority of studies that demonstration the relationship between leptin and psoriasis have reported that hyperleptinemia is associated with psoriasis [Gerdes, 2011; Zhu, 2013]. The severity of psoriasis disease in most of these studies is correlated with leptin level, and for this reasons our results in present study agree with the authors in considering leptin as a biomarker of chronicity and psoriasis severity. Furthermore, in severe psoriasis, elevated leptin receptor as well as leptin expression in skin biopsies are found [Cerman, 2008].

In our study the statistical analysis indicates that the leptin levels are significantly higher in plaque psoriatic patients compared with control group (healthy subjects) ($p<0.05$). In addition we observe a significant positive correlation between serum leptin level and Psoriasis Area and Severity Index (PASI) score. ($r = 0.78$, $p<0.05$).

Our results agree with [Zhu KJ, 2013] who has observed in a meta-analysis studies which compare leptin levels in controls and in psoriatic patients, in summation of eleven studies comprising 773 patients with psoriasis and 570 healthy controls, the levels of leptin are significantly higher in patients with psoriasis compared with controls on stratified analysis. The differences are significant in leptin levels between patients with psoriasis and controls [Zhu KJ, 2013]. In addition a study of 77 Taiwanese patients with psoriasis compared to 81 with age and sex matched healthy individuals as a control group, hyperleptinemia has proved to be an independent risk factor in psoriasis [Cerman, 2008]. Another cohort study from Japan involving 122 psoriasis patients compared to 78 controls also has showed an increase in mean leptin plasma level in psoriasis [Takahashi, 2008]. Furthermore, several studies have reported similar results [Xue, 2013; Oh, 2014]. In most of these studies, leptin concentrations are positively correlated with BMI. It is well known that the levels of leptin are correlated with mass of adipose tissue, and data on leptin levels should be controlled for the nutritional state when assessed in clinical studies [Xue, 2013]. Despite increase in leptin level is associated with obesity. Other study has showed an increasing leptin level in nonobese patients with psoriasis [Aly, 2013].

Conclusion

The pro-inflammatory biomarker leptin is higher in psoriasis patients compared to healthy subjects. On the other hand, leptin showed a significantly positively association with severity of plaque psoriasis which is measured by (PASI) score. Therefore, leptin may play important role in pathogenesis of plaque psoriasis and could serve as a biomarker for severity of plaque psoriasis.

Recommendation

Including of a large sample size to confirm the association between leptin and severity of plaque psoriasis.

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