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ORIGINAL ARTICLE

Association between insulin resistance and serum and salivary irisin levels in patients with psoriasis vulgaris☆

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ABSTRACT

Background/Objectives: Psoriasis is an inflammatory skin disease, which is associated with metabolic syndrome and insulin resistance. Irisin is an adipokine and myokine that regulates the metabolic status during times of increased insulin sensitivity. In this study, we aimed to investigate changes in the serum level of irisin in psoriasis patients in comparison with participants who did not have any disease (control group). We hope the results of our study would also aid in establishing a protocol aimed at understanding the etiopathogenesis and treatment of psoriasis.

Materials and methods: The study included 30 patients with psoriasis vulgaris, who presented to the dermatology outpatient clinic and were not receiving systemic treatment. The control group included voluntary participants who did not have any disease ($n = 30$). In addition to venous and salivary irisin levels, glucose, triglyceride, cholesterol, high-density lipoprotein, and low-density lipoprotein levels, and Homeostasis Model Assessment of Insulin Resistance scores were measured in both control and patient groups.

Results: Serum irisin and salivary irisin levels were significantly lower in the patient group compared with the control group ($p < 0.05$). In the patient group, serum irisin levels had a positive correlation with salivary irisin levels ($r = 418$; $p = 0.022$) and a negative correlation with Psoriasis Area and Severity Index ($r = -437$, $p = 0.016$) and Dermatological Life Quality Index ($r = -424$; $p = 0.02$) scores.

Conclusion: This is the first study evaluating irisin levels in patients with psoriasis vulgaris in the literature. The results of our study show that serum and salivary irisin levels were significantly lower in the patient group when compared with the control group. Irisin levels in patients with severe psoriasis were low, suggesting that irisin may have a role in the pathogenesis of psoriasis and may be a marker showing the severity of psoriasis, which could warn us against the development of insulin resistance and diabetes mellitus.

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Introduction

Psoriasis is a chronic, hyperproliferative inflammatory disease of the skin, which is clinically characterized by erythematous and squamous plaques. The disease is associated with a genetic background.[1] Because of the silvery, scaly appearance of the squamous plaques, in Turkish it is called “nacre disease” in layman's terms.[2,3] Psoriasis is observed in 1–3% of the general population.[4]

Irisin, first discovered by Bostrom et al, is made up of 112 amino acids.[5] It is an adipokine and myokine, and exhibits autocrine and paracrine effects. Irisin is mainly synthesized in skeletal muscle and adipose tissue.[5] Furthermore, irisin predominantly presents in peripheral nerve cells, sebaceous glands of the skin, as well as in many organs and tissues.[6] It induces the conversion of white adipose tissue into brown adipose tissue. In addition, it regulates thermogenesis, energy expenditure, weight loss, and ultimately glucose homeostasis by increasing uncoupling protein 1 in brown adipose

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Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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tissue.[6] Irisin, also called "exercise hormone," is produced by the cleavage of fibronectin type III domain-containing protein 5 (FNDC5), the extracellular portion of type I membrane protein, following activation by peroxisome proliferator-activated receptor-γ coactivator α.[6] Proteins associated with insulin resistance, such as adiponectin and ghrelin, are known to play a role in the pathogenesis of psoriasis.[7] Irisin is also a hormone associated with obesity and glucose homeostasis. Patients with type 2 diabetes mellitus (DM) have low levels of irisin. Moreover, irisin level has been found to be decreased in nonalcoholic fatty liver disease and heart failure.[8]

The association between psoriasis and insulin resistance is known, and many studies in have been published in this area.[9,10] However, none of these studies has evaluated irisin levels in patients with psoriasis. Our study is the first study to examine irisin levels in psoriasis aimed at understanding etiopathogenesis of the disease. In our study, by measuring irisin levels in patients with psoriasis, which is a disease associated with increased insulin resistance, we evaluated whether irisin levels show any correlation with severity of the disease. We hope our results would also aid in establishing a protocol aimed at understanding the etiopathogenesis and treatment of psoriasis.

Materials and methods

This study was conducted by the Dermatology Department of Mugla Sitki Kocman University Faculty of Medicine. The study included patients diagnosed with psoriasis vulgaris ($n = 30$), who presented to the dermatology outpatient clinic and were not receiving systemic treatment (receiving topical therapy). The control group included voluntary participants who did not have any disease ($n = 30$). Individuals in both groups were informed about the study protocol, and all participants provided written consent.

The study exclusion criteria were as follows: (1) other forms of psoriasis such as pustular psoriasis or erythrodermic psoriasis; (2) presence of any systemic disease (coronary artery disease, hepatic failure, renal failure, malignancy, etc.); (3) pregnancy; (4) breastfeeding; (5) younger than 18 years of age; and (6) receiving systemic treatment.

All participants provided a detailed history. Age, duration of disease, presence of any other family member with psoriasis, smoking status, and current treatment methods were questioned and noted on patient forms. Extent and severity of psoriasis were assessed using the Psoriasis Area and Severity Index (PASI) scoring method and by calculating the affected body surface area percentage.

Individuals in both the patient and control groups provided 3 mL of venous blood and 0.5 mL of saliva samples following 8–12 hours of fasting. Saliva samples were collected in sterile urine cups. Blood and saliva samples were centrifuged at 4000 rpm for 10 minutes. The samples were then transferred to small-volume tubes, and stored at −80°C until further analysis. Irisin levels were analyzed using enzyme linked-immunosorbent assay. In addition to venous and salivary irisin levels, we also measured glucose, triglyceride, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein levels in both patient and control groups. Insulin resistance was calculated according to the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula: fasting glucose (mmol/L) × fasting serum insulin (μIU/mL)/22.5. In addition, body mass index (BMI) and Dermatological Life Quality Index (DLQI) values were calculated.

Comparison of parameters between the two groups were made with Kolmogorov–Smirnov test and Student t test. Correlation of parameters were analyzed with Spearman correlation test and p values less than 0.05 was accepted as the level of significance.

Results

There were 15 males (50%) and 15 females (50%) in the patient group, and 15 males (50%) and 15 females (50%) in the control group. There was no statistically significant difference between the two groups in distribution of sex ($p > 0.05$). Mean age was 39.67 ± 9.30 years in the patient group, whereas it was 39.76 ± 15.74 years in the control group. Mean BMI was 27.73 ± 4.17 kg/m^2 in the patient group, and 26.17 ± 3.81 kg/m^2 in the control group. There was no statistically significant difference between the patient and control groups regarding mean age and BMI ($p > 0.05$). PASI scores in the patient group varied between 0.4 and 15.8, and the mean PASI score was 4.71 ± 3.52. The DLQI value in the patient group varied between 0 and 26. The mean DLQI value was 10.73 ± 7.82. Table 1 summarizes biochemical parameters, insulin and hemoglobin A1c (HbA1c) levels, and HOMA-IR scores in the patient and control groups.

Serum irisin and salivary irisin levels were significantly lower in the patient group when compared with the control group ($p < 0.05$; Figure 1).

The patient group had significantly higher serum glucose and triglyceride levels, and significantly lower HDL levels when compared with the control group ($p < 0.05$; Figure 2).

The patient group had significantly higher HbA1c levels and HOMA-IR scores when compared with the control group ($p < 0.05$; Figure 3).

In the patient group, serum irisin levels showed a positive correlation with salivary irisin levels ($r = 418$; $p = 0.022$) and a negative correlation with PASI ($r = -437$; $p = 0.016$) and DLQI ($r = -424$; $p = 0.02$) values. Salivary irisin levels had a negative correlation with PASI, but these correlations were not statistically significant ($r = -351$; $p = 0.058$). In addition, serum irisin levels had a negative correlation with serum triglyceride levels and HOMA-IR scores and a positive correlation with serum HDL levels; however, these correlations were also not statistically significant.

Discussion

Although the pathogenesis of psoriasis is not fully understood, activation of T lymphocytes and keratinocyte hyperproliferation are given particular emphasis in pathogenesis. In addition, there is evidence indicating a role of endothelial cells in pathogenesis in the early period of psoriasis. The most commonly emphasized mechanism concerning pathogenesis of psoriasis involves activation of T cells of the immune system. Activated T cells release cytokines such as interferon-γ or tumor necrosis factor-α (TNF-α), and increase concentration of other immune effector cells, including neutrophils, in the inflammation site.[11] TNF-α additionally stimulates vascular endothelial cell growth factor production in keratinocytes, and induces secondary proliferation of epidermal and vascular cells.[12] Various studies have been performed to determine the pathogenesis of psoriasis; however, its etiology is not yet clear. Many studies have emphasized chronic inflammation in psoriasis.[13,14] Recently, a strong association has been suggested to exist between psoriasis and metabolic syndrome as well as one of its components, insulin resistance.[15,16] It has been suggested that cytokines that are released during the chronic inflammation in psoriasis may lead to the development of metabolic syndrome. One study emphasized the presence of a strong correlation between severity of psoriasis and insulin resistance. Furthermore, it drew attention to psoriasis not only as a disease of the skin, but also as a metabolic disease.[17]

Adipocytes are described as newly introduced members of the immune system, as they release cytokines such as interleukin 6 and TNF-α in addition to adipokines such as irisin, adiponectin, and

Table 1 Sociodemographic characteristics and biochemical parameters of the patient and control groups.

	Psoriasis ($n = 30$)	Control ($n = 30$)	p
Age (y)	39.67 ± 9.30	39.76 ± 15.74	>0.05
Sex (female/male)	15/15	15/15	>0.05
Body mass index (kg/m^2)	27.73 ± 4.17	26.17 ± 3.81	>0.05
Glucose (mg/dL)	93.06 ± 10.85	87.03 ± 7.62	**<0.05**
Hemoglobin A1c (%)	5.52 ± 0.53	5.17 ± 0.51	**<0.05**
Cholesterol (mg/dL)	214.56 ± 34.77	201.8 ± 35.22	>0.05
High-density lipoprotein (mg/dL)	44.46 ± 8.27	49.47 ± 9.51	**<0.05**
Low-density lipoprotein (mg/dL)	134.4 ± 23.89	123.07 ± 28.22	>0.05
Triglyceride (mg/dL)	181.5 ± 79.45	146.43 ± 49.02	**<0.05**
Insulin (μIU/mL)	7.39 ± 1.85	6.55 ± 2.01	>0.05
Homeostasis Model Assessment of Insulin Resistance	1.87 ± 1.05	1.44 ± 0.41	**<0.05**
Serum irisin (ng/mL)	257.12 ± 67.33	292.39 ± 31.81	**<0.05**
Salivary irisin (ng/mL)	333.52 ± 81.08	381.07 ± 78.75	**<0.05**

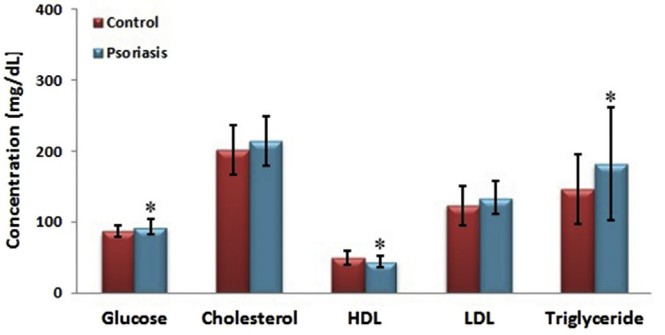

Figure 2 Serum glucose, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels of the patient and control groups. * $p < 0.05$ compared with the control group.

leptin.[18] Discovered by Boström et al, irisin is made up of 112 amino acids, and is synthesized in the muscular tissue. White adipose tissue also secretes FNDC5/irisin; therefore, irisin also behaves as an adipokine and induces the browning of white adipose tissue and protects against diet induced obesity and diabetes.[5,19] Interestingly, the concentration of irisin rises remarkably following exercise in both mice and humans. Some animal model studies have shown that irisin prolongs life span, reduces body weight by increasing total energy expenditure, and decreases insulin resistance caused by diet-induced obesity.[5]

By contrast, one study involving patients with polycystic ovary syndrome, which is a disease associated with increased insulin resistance, reported significantly increased irisin levels in these patients. This result was interpreted as a protective mechanism against development of DM in patients with polycystic ovary syndrome.[8] In addition, Park et al[20] found increased levels of irisin in patients with metabolic syndrome. In Behçet's disease, which is characterized by endothelial dysfunction and atherosclerosis that are triggered by hyperglycemia and chronic inflammation, irisin levels were found to be low. It was stated that lower irisin levels could be related to atherosclerosis. A negative correlation was observed between irisin levels and HOMA-IR scores.[21] In our study, although we also found a negative correlation between irisin levels and HOMA-IR scores, this was not statistically significant.

There is a strong association between psoriasis and insulin resistance, suggesting a possible role for irisin in etiopathogenesis of psoriasis, as irisin is known to reduce weight by increasing total energy expenditure, and decrease insulin resistance caused by diet.[22] The serum irisin levels were found to be decreased in patients with type 2 DM, and this was associated with insulin resistance.[23,24] One study involving 581 patients with psoriasis found a significant association between psoriasis and type 2 DM.[25] Another study found significantly increased insulin levels and HOMA-IR scores in patients with psoriasis vulgaris.[26] Naldi et al[27] observed a significant association between BMI and psoriasis. In our study, there was no significant association between psoriasis and BMI; however, there was a significant association between psoriasis and levels of glucose and HbA1c, as well as HOMA-IR scores.

Some studies have found a positive correlation between irisin and low-density lipoprotein cholesterol.[24] Wen et al[28] detected a positive correlation between irisin and HDL levels in patients with chronic renal failure. Similar to our results, Icli et al[21] did not find any correlation between irisin and lipid profile.

Cytokines such as TNF-α have important roles in the pathogenesis of psoriasis. As is already known, TNF-α is an important cytokine for inflammatory, infectious, and malignant states. TNF-α has been found to be elevated in the serum of patients with psoriasis, and in psoriatic skin. Furthermore, TNF-α level has been shown to decrease in serum and skin lesion following treatment. Moreover, TNF-α antagonists are effectively used in the treatment of psoriasis.[29] In one study with mice model, following short-term administration of the cytokines TNF-α and interleukin-1β to mice, an inflammatory state was induced, which reduced the release of irisin from skeletal muscle.[30] Signaling pathways leading to psoriasis development are, however, not fully clear yet; one study has

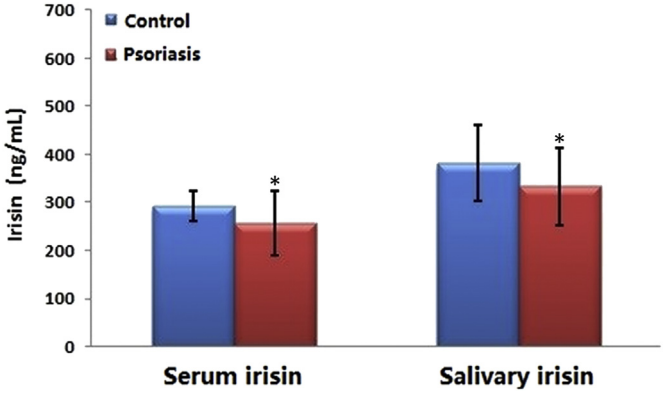

Figure 1 Serum and salivary irisin levels of the patient and control groups.* $p < 0.05$ compared with the control group.

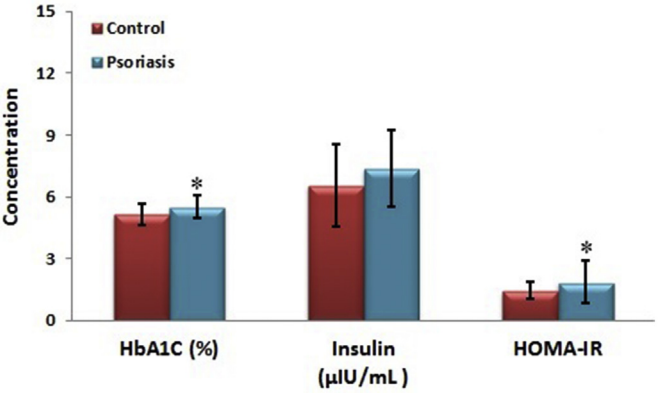

Figure 3 Levels of serum hemoglobin A1c (HbA1C) and insulin, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) scores of the patient and control groups. * $p < 0.05$ compared with the control group.

emphasized that peroxisome proliferator-activated receptor-γ might cause development of metabolic syndrome in patients with psoriasis.[31] Moreover, peroxisome proliferator-activated receptor-γ coactivator α plays a primary role in lipid and carbohydrate metabolism and inflammation, and irisin synthesis is regulated through its activation.[30,32]

Previous studies showed that parotid, sublingual and submandibular glands produce and release irisin into saliva.[33] Salivary irisin levels were found to be elevated in patients with Prader–Willi syndrome, whereas they were found to be reduced and correlated with serum irisin levels in patients who had acute myocardial infarction.[33,34] In our study, salivary irisin levels were low. Our study demonstrates that rather than using invasive methods, irisin levels can also be measured in the saliva of patients with psoriasis.

Conclusion

Pathogenesis of psoriasis and its relationship with insulin resistance are not clearly understood. There are many studies demonstrating insulin resistance in patients with psoriasis. However, no previous study has evaluated irisin levels and its association with insulin resistance in patients with psoriasis. Our study is the first study to examine irisin levels in patients with psoriasis. We found lower serum and salivary irisin levels in these patients, which indicate that irisin levels can also be measured in saliva, rather than in serum. We also found a negative correlation between serum irisin levels and the severity of psoriasis.

In conclusion, our results suggest that irisin may have a role in the pathogenesis of psoriasis, and may be a marker showing the severity of psoriasis, which could warn us against development of insulin resistance and DM. There is a need for future large-scale studies that investigate the association of irisin with the immune system and metabolic parameters in patients with psoriasis.

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