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SERUM VISFATIN, RESISTIN LEVELS AND INFLAMMATION MARKERS IN PSORIASIS PATIENTS

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Psoriasis is a common chronic inflammatory skin condition that varies in severity. Psoriasis is associated with complex disorders, which incorporate metabolic syndrome, obesity and impaired glucose tolerance. Adipose tissue secretes several hormones and cytokines, in particular visfatin and resistin that could be involved in the development of psoriasis by acting as pro-inflammatory or immunoregulatory factors. The aim of this work was to evaluate the serum level of visfatin and resistin as well as of high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) in psoriatic patients. The study included 43 healthy individuals and 45 patients divided into three groups with mild, moderate and severe clinical degrees of disease assessed by the Psoriasis Area Severity Index (PASI). The results showed a significant increase in the concentration of serum visfatin, resistin, ESR and hs-CRP in patient groups in comparison with a control group. The highest increase in indicators was observed in the group of patients with severe disease compared with the mild and moderate patients groups. The significance of studied indicators as biomarkers of psoriasis disease severity is analyzed.

K e y w o r d s: psoriasis, visfatin, resistin, erythrocyte sedimentation rate, high-sensitivity C-reactive protein.

Psoriasis is derived from the Greek word psoriasis, which roughly translates to “itching condition” (psora “itch” and -sis “action, condition”) [1]. Psoriasis is a chronic, systemic immune-mediated disease characterized by the development of erythematous, indurated, scaly, pruritic and often painful skin plaques. Psoriasis pathogenesis is driven by proinflammatory cytokines and psoriasis is associated with increased risk for comorbidities, including, but not limited to, psoriatic arthritis, cardiovascular disease, diabetes mellitus, obesity, inflammatory bowel disease and nonalcoholic fatty liver disease compared with the general population. To explore the pathophysiological relationship between psoriasis and its common comorbidities and discuss the need for new treatment paradigms that include strategies to reduce systemic inflammation in patients with moderate to severe psoriasis [2]. Psoriasis is an inflammatory skin disease caused by the immune system that is characterized by epidermal hyperproliferation, keratinocyte dysfunction, excessive angiogenesis, and immunological dysfunction. Immunologic cells involved in the etiology of psoriasis that have received new attention include lymphocytes Th1, Th17, Th22, and regulatory T lymphocytes, in addition to lymphocytes Th1 (Treg). Langerhans cells and dermal dendritic cells are two immune cells that are equally significant (dDC) [3]. The association of psoriasis with metabolic syndrome and obesity has been described in several studies in the literature [4]. The exact mechanism is still unknown, but long-lasting chronic inflammation and inflammatory mediators are considered as the initiators of the development of metabolic syndrome. Moreover, hypertension, dyslipidemia, insulin resistance and obesity are described to be independently related to psoriasis other than as components of metabolic syndrome [5]. Adipose tissue is not only protecting the internal organs also it is a dynamic endocrine organ secreting multiple bioactive proteins - or adipocytokines - promoting inflammation and affecting glucose metabolism and vascular endothelial biology [6, 7].

It is estimated to have a worldwide prevalence of 2–4%. Males are twice as likely to be afflicted as females. Psoriasis has a significant influence on patients’ quality of life, treatment fulfillment and adherence, and socioeconomic stability since desquamate erythema can affect any skin location [8]. Psoriasis is a chronic, inflammatory, and proliferative

skin disease that manifests as persistent, strongly delineated, dull red, scaly plaques, especially on extensor prominences and the scalp[9]. After roughly a month, skin cells develop and shed. In psoriasis, however, the regular cycle of replacing old skin cells with new ones is disrupted [10]. Frequent locations are the elbows, knees, soles, lower back and scalp. Assessments of the prevalence of psoriasis vary from 0.5 to 4.6%, with rates varying between countries and races [11].

Visfatin is a newly discovered adipokine that is abundant in visceral fat. Obesity increases adipocyte visfatin expression and plasma concentrations in animals and humans [12]. Visfatin is a 52 kDa protein of 473 amino acids that is released primarily by hepatocytes, macrophages, and visceral adipocytes [13]. Some studies have indicated the involvement of visfatin in the pathogenesis of abdominal obesity, atherosclerosis, type 2 diabetes mellitus, and vascular and inflammatory diseases [14], because the protein has enzymatic, metabolic, inflammatory, and immunomodulatory properties [15]. As it causes chemotaxis and enhances the production of IL-1, IL-6, TNF-α, and stimulatory molecules by CD14+ monocytes, visfatin's effect in psoriasis might include regulation of the inflammatory or immunological response. Their capacity to generate proliferative responses is improved as a result of this [16]. Adipocytes produce resistin a dipocytokines, which are mostly produced by adipose tissue [17]. One of these adipocytokines is resistin, which was first discovered as a circulating mouse adipocyte gene product that is controlled by antidiabetic drugs [18]. In rodents, resistin is derived exclusively from adipocytes, circulates at increased levels in obese animals and causes dysregulated hepatic glucose production, leading to insulin resistance and seems to be a major determinant of hepatic insulin resistance induced by high-fat diet [19]. Resistin is a 12.5 kDa cysteine-rich polypeptide discovered in a screen for adipocyte gene products that are downregulated by antidiabetic thiazolidinedione drugs [20]. Resistin can involve in the development of psoriasis by acting as a pro-inflammatory factor leading to an increased mRNA expression of many chemokines and cytokines [21].

ESR is founded on the principle of deposition rate of RBC in the bottom of the test tube and separated from the yellow liquid (plasma)which will be in the top [22]. Physiological features that have an impact on sedimentation friction force on the red cell and change the surface of cells [21]. ESR helps in the diagnosis of those conditions related to acute and chronic inflammation, including cancers, autoimmune diseases, and infections [23].

The high-sensitivity C-reactive protein (hs-CRP) test is a blood test that finds lower levels of C-reactive protein (CRP) [24]. This protein measures general levels of inflammation in your body [25]. C-reactive protein (CRP) is a polypeptide and acute phase reactant synthesized mainly by the hepatocytes during inflammation in response to certain cytokines, such as interleukin (IL)-1, IL6, and tumor necrosis factor α-(TNF) [26], which play an important role in the pathogenesis of psoriasis. High sensitivity CRP can show small changes in CRP levels during inflammation; thus, it is a much more sensitive sign than CRP [27]. The aim of this work was to evaluate the serum levels of visfatin, resistin, ESR and hs-CRP in psoriasis patients and their relation to the severity of psoriasis.

Materials and Methods

This study has been conducted at the department of venereal and dermatology disease in Al-Nasiriyah teaching Hospital, in Thi-Qar Province, biochemistry laboratory in college of science/university of Thi-Qar at the period between (November 2021 - June 2022). It included (88) subjects, control (43) supposed healthy and patients (45). Age ranged from 12 to 50 years old. The study included patients with plaque psoriasis and nail psoriasis, patients had not received any topical or systemic therapy. The clinical diagnosis of patients was established by dermatologists physician. Patients were divided into three categories according to the severity of psoriasis, mild group, moderate and severe group, clinical severity of disease was assessed by an index called (psoriasis Area Severity Index PASI Score) which is the most commonly used measuring tool for psoriasis [28].

Methods. Venous blood (5.0 ml) were collected from patients and healthy controls, 2 ml of 5 ml were put in EDTA and the resting 3 ml drained slowly into disposable plane tube containing separating gel. Blood samples in the EDTA- tubes were used for (ESR) analysis. Whereas blood samples in the gel-containing tubes were allowed to clot at room temperature and then centrifuged for 10 min at (3200 g) then the sera were got and stored at freeze (-20°C). The serum was used for the estimation of visfatin and resistin hormones, the used reagents were supplied by (Bt lab, China), hs-CRP

was measured according to the method supplied by (Nipigon, Canada) kit, the value of erythrocyte sedimentation rate (ESR) was measured according to the method of Barbara et al. [29]. Body mass index (BMI) is a measure of someone's weight about their height, and then we put these measurements in the equation BMI = weight (kg)/height (m^2), BMI of patients group (29.93 ± 8.54), BMI of controls group (24.30 ± 6.27).

Excluding criteria. Patients are excluded with the following diseases: other chronic autoimmune/ inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases, hypertension, diabetes, cardiovascular disorders, cancers, overt infections, hematological diseases, chronic liver or kidney diseases, autoimmune disorders, genetic related, and bone marrow transplantation. As well as age under 12 and over 50 years old. Those who suffer from skin diseases other than psoriasis, patients under treatment or continuing treatment.

Ethical approval. The study was approved by research committee of the Thi-Qar health department/ training and human development center (Approval no:2022107). Written informed consent was obtained from each study participant. The study protocol conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical analysis. The statistical analysis was done using spss v 23. The results were expressed as mean ± standard deviation (mean ± SD). T-test was used to compare study groups, one-way ANOVA also used to compare subgroups. *P*-values ($P \leq 0.05$) were considered statistically significant.

Results

In this study, we measured the level of visfatin, resistin, erythrocyte sedimentation rate (ESR) and hs-CRP among patients and healthy individuals.

Table 1 shows significant increase in concentrations of serum visfatin, resistin and hs-CRP in patient groups in comparison with control group ($P \leq 0.05$). Also, the same table shows a significant increase in levels of blood ESR in patients group in comparison with control group ($P \leq 0.05$).

Table 2 shows a significant difference in the concentration of serum visfatin, resistin, ESR and hs-CRP in all patient age groups in comparison with the control age groups ($P \leq 0.05$). In the control age groups, there is no significant difference in the concentration of serum visfatin, resistin, ESR and hs-CRP between all control age groups ($P \leq 0.0$).

In the patients age groups there is no significant difference in the concentration of serum visfatin, resistin, ESR and hs-CRP between all patient age groups ($P \leq 0.05$).

Table 3 displays a significant difference in the concentration of serum visfatin, resisitin, ESR and hs-CRP in all patients gender groups in comparison with the controls gender group ($P \leq 0.05$). The present study shows no significant difference in the concentration of visfatin, resisitin, ESR and hs-CRP between control male group and control female group ($P \leq 0.05$). The results show a significant difference in the concentration of visfatin, ESR and hs-CRP between male patient groups and female patient groups ($P \leq 0.05$). The results show no significant difference in the concentration of serum resistin between patient male group and patient female group ($P \leq 0.05$).

Patients were divided according to the clinical severity of the disease measured by an index called (psoriasis Area Severity Index PASI Score) into three groups severe, moderate and mild and we measured the level of visfatin, Resistin, ESR, hs-CRP according to the severity of the disease.

Table 4 shows a significant increase in the concentration of serum visfatin in severe patient group in comparison with patient groups (moderate and mild) ($P \leq 0.05$). In the same Table 2, we notice a significant increase in the concentration of serum resistin in severe patient group in comparison with mild patients group ($P \leq 0.05$). It was found no significant difference between severe patients group and moderate patients group ($P \leq 0.05$). Also, it was found no significant difference between moderate

Table 1. Serum visfatin, resistin, ESR, hs-CRP of control and patients group

Groups	No	Visfatin (ng/l) (mean ± SD)	Resistin (ng/l) (mean ± SD)	ESR (mm/h) (mean ± SD)	hs-CRP (mg/l) (mean ± SD)
Patients	45	21.87 ± 5.61	922.44 ± 90.37	26.71 ± 5.07	4.22 ± 0.72
Controls	43	12.31 ± 2.88	580.42 ± 64.25	7.37 ± 1.47	0.62 ± 0.09
P-value		0.000	0.013	0.000	0.000

Table 2. Serum visfatin, resistin, ESR and hs-CRP for all age groups

Visfatin concentration (ng/l) (mean ± SD)						Resistin concentration (ng/l) (mean ± SD)				
Age groups	Control	No	Patients	No	*P*	Control	No	Patients	No	*P*
A	12.53±3.30[a]	16	21.94±5.64[a]	17	0.023	582.63±60.90[a]	16	939.32±89.98[a]	17	0.022
B	12.09±2.30[a]	12	23.07±5.05[a]	13	0.001	578.78±69.00[a]	12	903.38±96.96[a]	13	0.004
C	11.93±3.14[a]	15	20.60±6.21[a]	15	0.024	581.12±64.42[a]	15	924.61±86.40[a]	15	0.003
LSD	1.81		3.478			39.90		56.10		
ESR (mm/h) (mean ± SD)						hs-CRP concentration(mg/l) (mean ± SD)				
Age groups	control	No	Patients	No	*P*	Control	No	Patients	No	*P*
A	7.04±1.49[a]	16	27.27±5.23[a]	17	0.000	0.59±0.09[a]	16	4.36±0.73[a]	17	0.000
B	7.58±1.35[a]	12	25.53±4.35[a]	13	0.000	0.65±0.09[a]	12	4.25±0.64[a]	13	0.000
C	7.66±1.54[a]	15	27.33±5.70[a]	15	0.000	0.61±0.10[a]	15	4.05±0.80[a]	15	0.000
LSD	0.90		3.15			0.07		0.44		

None. Each value represents mean ± SD values with non-identical superscript (a, b or c … etc.) were considered significantly differences ($P \leq 0.05$) compare vertically. A: First age group (12-24 year). B: Second age group (25-37 year). C: Third age group (38-50 year). SD: Standard deviation. LSD: Least significant difference

Table 3. Serum visfatin, resistin, ESR and hs-CRP for all sex groups

Visfatin concentration (ng/l) (mean ± SD)						Resistin concentration (ng/l) (mean ± SD)				
Sex groups	Control	No	Patients	No	*P*	Control	No	Patients	No	*P*
Male	13.11±3.24	20	18.73±5.02	20	0.012	559.72±70.30	20	917.79±80.76	20	0.047
Female	11.62±2.45	23	23.59±6.89	25	0.000	596.81±55.10	23	936.15±98.88	25	0.002
P	0.259		0.045			0.090		0.036		
ESR(mm/h) (mean ± SD)						hs-CRP concentration (mg/l) (mean ± SD)				
Sex groups	Control	No	Patients	No	*P*	Control	No	Patients	No	*P*
Male	7.06±1.52	20	25.70±4.23	20	0.000	0.63±0.09	20	4.71±0.78	20	0.000
Female	7.62±1.40	23	28.62±6.62	25	0.000	0.61±0.10	23	3.83±0.53	25	0.000
P	0.918		0.044			0.865		0.048		

Table 4. Serum visfatin, resistin, ESR and hs-CRP in severity among psoriasis groups

Groups	No	Visfatin (ng/l)	Resistin (ng/l)	ESR (mm/h)	hs-CRP (mg/l)
Sever	15	27.21±5.03[a]	955.93±91.21[a]	30.07± 6.61[a]	4.83± 0.76[a]
Moderate	15	21.09±3.31[b]	913.26±88.27[ab]	26.67±3.55[b]	4.14±0.84[b]
Mild	15	17.38±4.12[c]	898.11± 56.94[b]	24.53± 4.24[b]	3.76±0.61[b]
LSD		2.95	49.39	2.70	0.50

None. Each value represents mean ± SD values with non-identical superscript (a, b or c … etc.) were considered significantly differences ($P \leq 0.05$) compare vertically.

patients group and mild patients group ($P \leq 0.05$). The study also showed an increase in the concentration of blood ESR in severe patients group in comparison with patients groups (moderate and mild) ($P \leq 0.05$). It was found no significant difference between moderate patients group and mild patients group($P \leq 0.05$). Also, there was increase in the concentration of serum hs-CRP in severe patients group in comparison with patients groups (moderate and mild) ($P \leq 0.05$). It was found no significant difference between moderate patients group and mild patients group.

Discussion

Psoriasis is a chronic, systemic, inflammatory disease, affecting mainly the skin and the joints [30]. It is measured to be an immune cell-mediated disease in which T-lymphocyte activation is of major importance. Although the precise atiology of psoriasis is unknown, it is widely known that the inflammatory response plays an essential role in the pathogenesis of psoriasis [31]. The IL-17 had a positive association with psoriasis as it was associated with the severity of psoriasis [32]. The last is indicated by cutaneous and systemic overexpression of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, IL-8, IL-12, IL-17, IL19, IL-20, IL-22, IL-23, IL-24, interferon-c, and other similar substances [33, 34]. This cascade of events eventually leads to the formation of the psoriatic lesion. Visfatin can induce cellular expression of inflammatory cytokines such as TNF-α, IL-1 and IL-6. It also increases cell surface expression of co-stimulatory molecules such as CD54, CD40, and CD80. Visfatin expression is up-regulated in a change of acute and chronic inflammatory diseases, including sepsis and rheumatoid arthritis, and plays a main role in the persistence of inflammation through its capacity to inhibit neutrophil apoptosis [35]. Recent literature data indicates that psoriasis can be included in the group of chronic inflammatory systemic diseases (CIDs). The presence of various mediators – including cytokines and adipokines responsible for systemic inflammation and its metabolic consequences has been demonstrated not only in the affected skin but also in peripheral circulation. Inflammatory mediators, also secreted by adipose tissue cells, participate in inducing vascular endothelial dysfunction and insulin resistance, increasing the concentration of thrombogenic factors and promoting oxidative stress and lipid oxidation disorders. Adipokines may be an important link connecting psoriasis with coexisting metabolic disorders [36].

Patients with psoriasis are more likely to develop obesity in the future than healthy people. With age, the percentage of fat and muscle size increases, as the increase in lipoproteins and fats is linked to the accumulation of fatty tissues. So there is an increase in the hormones visfatin and resistin with age between (patients and controls) all groups.

The role of visfatin in psoriasis might include modulation of the inflammatory or immune response, as it induces chemotaxis and increases the production of IL-1, TNF-α, IL-6, and costimulatory molecules by CD14+ monocytes. On the other hand, visfatin may be upregulated as response to proinflammatory cytokines during inflammation [37]. Recent studies have shown that resistin is involved in inflammation and immunity. Resistin participates in the regulation of proinflammatory cytokine expression [38] and can induce IL-6, IL-8, and TNF-α expression *in vitro* [39]. Resistin is considered to be involved in TNF-α related inflammation in psoriasis [40]. Resistin has been shown to stimulate the secretion of TNF-α and IL-12 from macrophages, and TNF-α and IL-1β, IL-6, or lipopolysaccharides strongly induce resistin expression [41, 42]. Previous studies have reported elevated levels of resistin in psoriasis patients [43]. Adipokines appear to drive metabolic alterations in obese people and seem to represent the pathophysiologic link between the skin inflammatory process and metabolic alterations in patients with psoriasis [44].

ESR is increased in patients with psoriasis. Evidence that it is an inflammatory marker that reflects the inflammatory state of the skin has been described in psoriasis independently of the presence of psoriatic arthritis [45, 46]. The hs-CRP is a highly sensitive biomarker of inflammation and much more sensitive than CRP. CRP is the most studied proinflammatory biomarker. CRP is produced in liver (hepatocytes) through action of IL-6 and IL-17 and other chemokines. CRP is an acute phase reactant protein which is an inflammatory through IL-6. CRP being a biomarker induced by TNF- reflection of systemic inflammatory pathway may guide treatment of the disease and prevention of mortality and comorbidities. hs-CRP is a very sensitive biomarker of inflammation [47]. In our study, criteria were measured according to disease severity measured by PASI. As we observed through statistical analy-

sis increase in the concentration of visfatin in patients with severe psoriasis than in those with mild and moderate psoriasis. Considering that the severity of inflammation worsens in severe psoriasis, and since the level of visfatin is regulated during inflammation and in response to inflammatory cytokines. Another explanation is that visfatin level might be upregulated during inflammation and in response to inflammatory cytokines [48, 35].

We also observed that resistin levels were significantly increased in patients with severe psoriasis than in those with mild and moderate psoriasis In severe cases of psoriasis, resistin can lead to the production of large amounts of CXCL8 and TNF-α by single-celled cells CXCL8, a strong neutrophil chemoattractant, is also known to stimulate the proliferation of keratinocytes which is characteristic for psoriasis. We also noticed an increase in concentration level of ESR in severe psoraisis compared with moderate and mild. It can be considered that the increase in the severity of psoriasis and the rate of association with systemic diseases leads to an increase in the severity of inflammation. Although the etiopathogenesis is not fully understood, chronic inflammation is thought to result in lipid-containing macrophage cell development, endothelial dysfunction and increased T helper-1 cytokine release [43, 49]. Increased concentrations of HS-CRP in severe psoriasis compared with mild and moderate psoriasis , as the inflammatory state in psoriasis releases pro-inflammatory cytokines, which stimulate liver to produce acute phase reactants. CRP is one such acute phase reactant. Raised CRP levels result from the interface between pro-inflammatory cytokines, namely IL-6, TNF-α and IL-1, their receptors and inhibitory factors. CRP concentrations in serum increase with increasing severity of psoriasis and show positive correlation with PASI [50]. These results are consistent with the characterization of psoriasis as an inflammatory response that worsens with increasing disease severity.

Conclusions. Age and gender have an effect on each of all the parameters studied. Elevated levels of visfatin and resistin are an important link between psoriasis and metabolism disorders and are a biological marker for systemic inflammation and severity of psoriasis. High levels of ESR and hs-CRP are useful markers of psoriasis severity and can be used to monitor psoriasis.

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РІВЕНЬ ВІСФАТИНУ, РЕЗИСТИНУ ТА МАРКЕРІВ ЗАПАЛЕННЯ В СИРОВАТЦІ КРОВІ ПАЦІЄНТІВ ХВОРИХ НА ПСОРІАЗ

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Псоріаз – це поширене хронічне запальне захворювання шкіри, яке відрізняється за ступенем тяжкості. Псоріаз часто супроводжується комплексними порушеннями, серед яких метаболічний синдром, ожиріння та порушення толерантності до глюкози. Жирова тканина секретує низку гормонів і цитокінів, зокрема вісфатин і резистин, які можуть впливати на розвиток псоріазу як прозапальні або імунорегуляторні фактори. Метою роботи було оцінити рівень вісфатину та резистину, а також високочутливого С-реактивного протеїну (hs-CRP) та швидкість осідання еритроцитів (ШОЕ) у сироватці крові пацієнтів хворих на псоріаз. У дослідженні брали участь 43 здорові особи та 45 пацієнтів, яких було розподілено на три групи відповідно до клінічного перебігу захворювання, а саме легкий, середній та важкий ступені за шкалою PASI (Psoriasis Area Severity Index). Одержані результати показали суттєве підвищення концентрації вісфатину, резистину, ШОЕ та hs-CRP у сироватці крові в групах хворих порівняно з контрольною групою. Найбільше підвищення показників спостерігалося в групі хворих із важким перебігом захворювання порівняно з групами пацієнтів з легким та середнім ступенем тяжкості. Проаналізовано важливість досліджених показників як біомаркерів тяжкості перебігу псоріазу.

Ключові слова: псоріаз, вісфатин, резистин, швидкість осідання еритроцитів, високочутливий С-реактивний протеїн.

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