

Resistin serum levels in psoriasis patients and association with disease severity in Iraqi population

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Abstract

Psoriasis is a disorder with genetic and immunologic background. Psoriasis is associate with many metabolic disorders like insulin resistance. Resistin can involve in development of psoriasis by acting as a pro-inflammatory factor leading to an increased mRNA expression of many chemokines and cytokines . Our primary goals is to study the serum level of Resistin in psoriasis patients, and relation between the Resistin serum levels and psoriasis severity. The study involved 60 patients with psoriasis and 40 healthy controls. We analyzed plasma levels of Resistin in psoriasis patients and compared them with those of healthy control. Evaluation of plasma levels of Resistin was performed by enzyme immune sorbent assay (ELISA) . also we study the relation between Resistin serum with the severity of psoriasis that evaluated by psoriasis area and severity index (PASI) score. psoriasis patients have considerably higher serum levels of Resistin than heathy control. Resistin serum levels were 12.9 ± 4.1 ng/ml , 7.2 ± 2.1 ng/ml in patients and control group respectively .Also the Resistin levels were association with severity of psoriasis where serum levels of Resistin were 14.68 ± 4.20 ng/ml and 10.87 ± 2.9 ng/ml in severe and mild to moderate cases respectively . our results suggests that the Resistin has important role in development of psoriasis

Introduction

Psoriasis is a common inflammatory T-cell mediated skin disorder, affect in 2-3% of the population .⁽¹⁾ in which the most prominent microscopic abnormality is hyperproliferation and altered differentiation of keratinocyte . while the disease has several phenotypes,⁽²⁾ plaque psoriasis affects about 90% of patients . although the precise pathomechanism remains unknown various cytokines and growth factors are assumed to be involved . the etiology of psoriasis is not clear yet but the disease is believed to have an

autoimmune basis and s strong genetic component⁽³⁾

As in the case of many autoimmune diseases its real cause remains poorly defined .Resistin is considered to be important modulator of chronic inflammation contributing to the development of many disorders . High insulin concentration significantly upregulated Resistin and the other cytokines⁽⁴⁾.

Resistin could stimulate the expression of the proinflammatory cytokines TNF- α and IL-6 of both human macrophages via the NF- κ B-dependent pathway while intravenous

administration of endotoxin and activation of this inflammatory cascade could result in hyperresistinemia in humans, indicating the importance of this signalling pathway in the resistin-mediated inflammation^(5,6).

Resistin is a 12 kDa cysteine-rich polypeptide which is produced in humans predominantly by stromal macrophages and monocytes of the visceral adipose tissue⁽⁷⁾. Elevated resistin levels are found in obesity and inflammation, and may play a significant role in the pathogenesis many inflammatory diseases⁽⁸⁾. More importantly, resistin acts as a pro-inflammatory factor leading to an increased mRNA expression of twenty chemokines and cytokines including TNF- α , IL-1, IL-6, IL-12, chemokine ligand CXCL8, monocyte chemoattractant protein-1 and resistin itself via the nuclear factor-kappa B (NF-k B)⁽⁹⁾.

In recent years, more has been learned about psoriasis and its disease associations, and physicians were recognized that psoriasis is a disease that affects much more than just the skin. Patients with moderate or severe psoriasis have increased rates of obesity^(10,11) additionally psoriasis has also been linked to the metabolic syndrome. there is now a growing body of evidence that insulin resistance is also more prevalent in patients with psoriasis⁽¹²⁾.

In the majority of studies exploring the association of resistin with psoriasis, hyperresistinemia characterized untreated psoriatic patients and correlated with disease severity and nail psoriasis severity index⁽¹³⁾.

Resistin was originally discovered as an adipokine with a possible link

between obesity and insulin Resistance⁽¹¹⁾. human resistin is synthesized in cells other than adipocytes, predominantly in macrophages and monocytes characterized by a high metabolic turnover. Resistin is expressed primarily in inflammatory cells and has been shown to be involved in obesity-related subclinical inflammation, atherosclerosis, and CVD⁽¹⁴⁾.

Aim of study

Our primary aims is to study the serum level of Resistin in psoriasis patients, and relation between the Resistin serum levels and psoriasis severity.

Material and Methods

patients with psoriasis who had not received any prior local or systemic treatment within two months were included in the study (Dec 2013 to Jan 2014). The diagnosis was made clinically, based on characteristics of psoriatic . patients with psoriatic arthritis were excluded. The severity of psoriasis was assessed by the psoriasis area and severity index (PASI) for each patient. The control group was comprised of healthy, non psoriatic volunteers with no family history of psoriasis. A total of 60 patients (35 males, 25 females), and 40 healthy subject (19 male ,21 female) were included in this study , 5 ml blood sample were taken from patient and control group.

Sample collection and Resistin measurements of Blood samples were prospectively collected with the appropriate Ethical Committee permissions, from patients attending dermatology Outpatients Clinics at Tikrit Teaching Hospital in Iraq. Each sample had been collected in a one tube for ELISA where serum was

separated within 1 h of blood collection after spinning for 15 min at 1500 g. The serum was stored without preservative at -20°C and then thawed just prior to testing. Serum Resistin concentrations were determined using the commercially available enzyme-linked immuno-sorbent assay (ELISA Ultra sensitive), kit supplied by BOSTER Immunoleader (USA). The assays employ the quantitative sandwich enzyme immunoassay technique using recombinant human Leptin with antibodies raised against the recombinant proteins .

Result

Our study observed that there were no significant differences in Resistin serum levels according on age and gender in patients and control groups ($P > 0.05$). as shown in tables (1,2).

In this study we show that serum Resistin is elevated in patients with psoriasis compared with age-, sex- and BMI matched healthy controls and also confirm that Resistin correlates with disease severity.

In this study we observed a significant increase in The mean levels of Resistin of the patients than those of the control ($p \leq 0.001$) . Resistin serum levels were 12.9 ± 4.1 ng/ml , 7.2 ± 2.1 ng/ml in patients and control group respectively as shown in table (3) .also there were a significant increase in Resistin levels in severe cases of psoriasis than those of mild to moderate cases ($p \leq 0.001$) where serum levels of Resistin were 14.68 ± 4.20 ng/ml and 10.87 ± 2.9 ng/ml in severe and mild to moderate cases respectively table (4).

Discussion

In this study, serum Resistin levels were investigated by the ELISA technique aiming at studying the suggested relationship between Resistin levels and the severity of psoriasis vulgaris. All patients included in the study did not receive any topical or systemic steroid therapy for four weeks before taking serum , in order not to disturb any cytokine production. In this study we found that serum resistin is elevated in psoriasis patients compared with age, sex and BMI matched healthy controls .Also serum Resistin levels were find to be associated with the severity of the disease, we found that the serum Resistin levels are significantly higher in patients with severe psoriasis than patients with mild to moderate psoriasis , severity of psoriasis was measured by the Psoriasis Area and Severity Index (PASI) this could be explained on the basis of previous studies which demonstrated that Resistin has an important role in the pathogenesis of immune - mediated inflammatory diseases ⁽¹⁵⁾ . Also is totally agree with the most of previous studies which indicate that the plasma levels of resistin were significantly increased in psoriasis as compared with those of healthy controls^(16,17)

This study and recently others observe a positive correlation between psoriasis disease severity and serum Resistin levels ^(15,16) human Resistin is synthesized in cells other than adipocytes, predominantly in macrophages and monocytes particularly in the visceral adipose tissue characterized by a high metabolic turnover⁽¹⁸⁾. Elevated resistin levels caused by genetic or environmental factors such as obesity and inflammation may play a pivotal role in the pathogenesis of insulin

resistance metabolic syndrome and diabetes mellitus, this results may be due to that Resistin could induce CXCL8 and tumour necrosis factor-alpha production by blood monocytes. CXCL8, a strong neutrophil chemoattractant, is known to stimulate the proliferation of keratinocytes⁽¹⁹⁾. elevated CXCL8 levels in the serum of patients with psoriasis and that resistin can induce the production of CXCL8 by blood monocytes. Given that keratinocytes may both respond to and secrete CXCL8, this chemokine is likely to contribute to the keratinocyte hyperproliferation in psoriasis. TNF- α has different effects on the cellular level, which correlate with the pathophysiological mechanisms of the disease. It has been shown that TNF- α is capable of increasing production of several pro-inflammatory cytokines synthesized by activated lymphocytes or keratinocytes, exerting specific effects⁽²⁰⁾.

Resistin induces the expression of adhesion molecules, such as vascular cellular adhesion molecule-1 and intercellular adhesion molecule-1 and that adiponectin inhibit the effect of resistin in vascular endothelial cells⁽²¹⁾.

Resistin may be involved in the pathogenesis of psoriasis in overweight individuals, possibly by augmenting the cytokine expression by the inflammatory infiltrate. resistin promotes foam cell formation via the dysregulation of scavenger receptors macrophages⁽²²⁾.

Resistin correlated to elevated proinflammatory cytokines such as IL-1 β , IL-6 and IL-6R. An association between resistin and inflammation has been reported in several different diseases, including RA⁽²³⁾ and inflammatory bowel disease, but is very weak or nonexistent in studies of

apparently healthy individuals. Other study found that current glucocorticosteroid dose correlated positively to resistin levels and remained a significant variable of resistin in multiple regression analyses⁽²⁴⁾.

the severity of psoriasis, as measured by the Psoriasis Area and Severity Index PAS correlated with insulin resistance, as determined by the OGTT and HOMA-IR⁽¹²⁾. Other studies have also supported this finding. patients who had psoriasis for more than two years were at a significantly increased risk of developing diabetes and therefore insulin resistance⁽²⁵⁾

In agreement with most experimental data, serum resistin concentrations are significantly elevated in patients with severe inflammatory disease. Several studies have reported that metabolic syndrome and insulin resistance are more prevalent in patients with psoriasis than normal population. also demonstrate that exogenous resistin can induce monocytes to produce the inflammatory cytokines CXCL8 and TNF- α in vitro⁽²⁶⁾. increases in IL-6 and TNF- α in the culture medium of PBMC cultures stimulated with 1000 ng mL⁻¹ resistin. Resistin has also been shown to increase the expression by human endothelial cells of the vascular cell adhesion molecule-1, CCL2 and endothelin-1⁽²⁷⁾.

Resistin has furthermore been reported to promote proliferation and migration of cultured endothelial cells and to increase the expression of vascular endothelial growth factor receptors and matrix metalloproteinases-1 and -2⁽²⁸⁾. all these various activities of Resistin make it an important effector cytokine in psoriasis.

Conclusions

These findings suggests that the Resistin has important role in development of psoriasis lesion because these cytokines have important role in inflammation process.

Overexpression of Resistin in patients with psoriatic may explain features of psoriasis that link keratinocyte proliferation with immune activation and insulin resistance .so the possibilities of the presence of a relation between the psoriasis and diabetes mellitus has increase .

References

1. Christophers E. Psoriasis – epidemiology and clinical spectrum. *Clin Exp Dermatol* 2001; 26 :314–20.
2. Griffiths CE, Christophers E, Barker JN et al. A classification of psoriasis vulgaris according to phenotype. *Br J Dermatol* 2007;156:258–62.
3. Valdimarsson H. The genetic basis of psoriasis. *Clin Dermatol* 2007;23:563–7.
4. Stepan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. *Nature* 2001; 409: 307-312
5. Gisondi P, Ferrazzi A, Girolomoni G (2010) Metabolic comorbidities and psoriasis. *Acta Dermatovenerol Croat* 18 (4), 297–304.
6. Tobin AM, Veale DJ, Fitzgerald O et al. (2010) Cardiovascular disease and risk factors in patients with psoriasis and psoriatic arthritis. *J Rheumatol* 37 (7), 1386–94..
7. Schwartz DR, Lazar MA. Human resistin: found in translation from mouse to man. *Trends Endocrinol Metab* 2011; 22: 259-265
8. Dalamaga M, Sotiropoulos G, Karmaniolas K, Pelekanos N, Papadavid E, Lekka A. Serum resistin: a biomarker of breast cancer in postmenopausal women? Association with clinicopathological characteristics, tumor markers, inflammatory and metabolic parameters. *Clin Biochem* 2013; 46: 584-590
9. Filková M, Haluzík M, Gay S, Senolt L. The role of resistin as a regulator of inflammation: Implications for various human pathologies. *Clin Immunol* 2009; 133: 157-170
10. . Bremmer S, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Young Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol.* 2010 63:1058-69 ٦٩-١٠٥٨.
11. Sterry W, Strober BE and Menter A. Obesity in psoriasis: the metabolic clinical and therapeutic implications. Report of an interdisciplinary conference and review. *Br J Dermatol.* 2007; 157:649-55
12. -Boehncke S, Thaci D, Beschmann H, Ludwig RJ, Ackermann H, Badenhop K

- and Boehncke WH. Psoriasis patients show signs of insulin resistance Br J Dermatol. 2007; 157:1249-51
13. Ozdemir M, Yüksel M, Gökbel H, Okudan N, Mevlitoğlu I. Serum leptin, adiponectin, resistin and ghrelin levels in psoriatic patients treated with cyclosporin. J Dermatol 2012; 39: 443-448 [PMID: 22300284]
14. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol 2011; 20: 81-87 [PMID: 21255085]
15. Boehncke S, Thaci D, Beschmann H et al. Psoriasis patients show signs of insulin resistance. Br J Dermatol 2007; 157:1249
16. Takahashi H1, Tsuji H, Honma M, Ishida-Yamamoto A, Iizuka H. Increased plasma resistin and decreased omentin levels in Japanese patients with psoriasis. Arch Dermatol Res. 2013 Mar;305(2):113-6
17. Robati RM1, Partovi-Kia M2, Haghghatkhah HR3, Younespour S2, Abdollahimajd F2. Increased serum leptin and resistin levels and increased carotid intima-media wall thickness in patients with psoriasis: is psoriasis associated with atherosclerosis? J Am Acad Dermatol. 2014 Oct;71(4):642-8
18. Ferraroni NR, Geloneze B, Mansour E et al. Severe hypoleptinaemia associated with insulin resistance in patients with common variable immunodeficiency. Clin Endocrinol (Oxf) 2005; 63:63-5.
19. Johnston, A.* S. Arnadottir, J.E. Gudjonsson Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation British Journal of Dermatology 2008 159, pp342-350
20. Bokarewa M, Nagaev I, Dahlberg L et al. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005; 174:5789-95
21. Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y, Manabe I, Utsunomiya K, Nagai R. Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun 2004; 314: 415-419
22. Lee TS, Lin CY, Tsai JY, Wu YL, Su KH, Lu KY, Hsiao SH, Pan CC, Kou YR, Hsu YP, Ho LT. Resistin increases lipid accumulation by affecting class A scavenger receptor, CD36 and ATP-binding cassette transporter-A1 in macrophages. Life Sci 2009; 84: 97-104
23. Senolt L, Housa D, Vernerová Z, Jirásek T, Svobodová R, Veigl D, Anderlová K, Müller-Ladner U, Pavelka K, Haluzík M: Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. Ann Rheum Dis 2007, 66:458-463.

24. Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalis EA: Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflamm Bowel Dis* 2006, 12:100-105.
25. Brauchli YB, Jick SS and Meier CR. Psoriasis and the risk of incident diabetes mellitus: a population-based study. *Br J Dermatol.* 2008; 159:1331-7
26. Bokarewa M, Nagaev I, Dahlberg L et al. Resistin, an adipokine with potent proinflammatory properties. *J Immunol* 2005; 174:5789-95.
27. Verma S, Li SH, Wang CH et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation* 2003; 108:736-40
28. Mu H, Ohashi R, Yan S et al. Adipokine resistin promotes in vitro angiogenesis of human endothelial cells. *Cardiovasc Res* 2006; 70:146-57.

Table (1) the mean and St.D of Resistin serum levels in psoriasis patients and healthy control groups depend upon age groups

Age	Resistin levels	
	Patients mean ± SD N	Control mean ± SD N
Less than 40 years	12.93 ± 4.03 ng/ml N=29	7.01 ± 2.26 ng/ml N=22
More than 40 years	12.92 ± 4.3 ng/ml N=31	7.64 ± 2.21 ng/ml N=18
P Value	0.99	0.373

Table (2) the serum levels of Resistin in both female and male of patients and control groups.

Gender	Resistin levels	
	Patients mean ± SD N	Control mean ± SD N
Female	13.35 ± 4.06 ng/ml N=31	6.93 ± 2.16 ng/ml N=21
Male	12.47 ± 4.23 ng/ml N=29	7.69 ± 2.21 ng/ml N=19
P Value	0.416	0.283

Table (3) the serum levels of Resistin in patients with psoriasis and control group.

Cytokine	Psoriasis patients No: 60 mean ± SD	Control N0: 40 mean ± SD	value
Resistin	12.9 ± 4.13 ng/ml	7.29 ± 2.19 ng/ml	≤ 0.001

Table (4) the serum levels of Resistin in mild and sever cases of psoriasis

Cytokine	severity		P Value
	Mild and Moderate N0: 27 mean ± SD	Sever N0: 33 mean ± SD	
Resistin	10.87 ± 2.9 ng/ml	14.68 ± 4.20 ng/ml	≤ 0.001