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Role of vascular endothelial growth factor receptors in the pathogenesis of psoriasis

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Abstract:-

Background : Psoriasis is a chronic immune-inflammatory-mediated disease characterized by epidermal hyperplasia and angiogenesis. Recently, vascular endothelial growth factor receptors (VEGFRs, including VEGFR-1, VEGFR-2 and VEGFR-3) were found to be expressed in normal human epidermis and associated with proliferation and migration of keratinocytes.

Objective: The purpose of this study is to investigate the serum level of vascular endothelial growth factor receptors (sVEGFR1 and sVEGFR2) in psoriatic patients

Methods: 100 consenting psoriatic patients(males and females) aged 20-60 years who attended out patients clinic of dermatology in Al-Sadr Medical City in AL-Najaf city -Iraq. Psoriasis area and severity index assessment was done for each patient. Blood samples was collected for vascular endothelial growth factor receptor 1 and receptor 2 measurement**.**

Result: The serum level of vascular endothelial growth factor receptor 1 in addition to receptor 2 were significantly increased in all group of psoriatic patients compared to healthy controls ($P<0.001$) .

Conclusion: The serum level of vascular endothelial growth factor receptor 1 in addition to receptor 2 had significant role in evolution of psoriatic plaque.

Keywords: Serum vascular endothelial growth receptor 1, Serum vascular endothelial growth receptor 2,Psoriasis area and severity index, Psoriasis.

List of abbreviation: sVEGFR= serum vascular endothelial growth receptor, PASI = Psoriasis area and severity index, SD=standard deviation , ECs=endothelial cells**.** ELISA= Enzyme Linked Immuno Linked Sorbant Assay.

Introduction

Psoriasis is a chronic inflammatory skin disease characterized by epidermal hyperplasia, impaired epidermal differentiation, and accumulation of distinct leukocyte subpopulations. Although the precise cause of psoriasis is indistinct, psoriasis may be the consequence of two main mechanisms: a polygenic inheritance that comprises 36 chromosomal susceptibility loci, and the other, a strong immunological component(1). New researches have been identified that the hyperproliferation and altered differentiations of keratinocytes that occurred in psoriasis may link the pathways of angiogenesis and inflammation. Vessels expansion looks to show a significant role in the development of psoriatic plaques (2).

Vascular endothelial growth factor is a chief factor of neoangiogenesis (3). The influence of VEGF is intermediated by VEGF receptors (VEGFRs, comprising VEGFR-1,VEGFR-2 which are principally expresses by vascular endothelial cells (ECs)). Vascular endothelial growth factor attaching one of the receptor results in receptors stimulation and intracellular signals transductions (4). There are inadequate information about the probable role of soluble VEGF receptors in psoriasis (5)

The psoriatic lesion is distinguished by sharply marginated erythematous plaque with a white silvery scale that spread in a roughly symmetrical fashion on the trunk and limbs (6).

When scales are entirely scrapped off, the basement membrane is exposed and perceived as a red moist surface (Membrane of Bulkeley), through which dilated capillaries are noticed as red spots. Characteristically, the amplified vascularization could be confirmed clinically by “Auspitz sign” wherever rubbing scales of psoriatic plaque result in pinpoint bleedings. On the other hand, Auspitz sign is not sensitive or specific for psoriasis (7). The objective of study is to evaluate serum level of vascular endothelial growth factor receptors (sVEGFR1 and sVEGFR2) in psoriatic patients .

Materials and Methods

This is a case-control study which included 150 subjects (100 patients and 50 controls) who attended who attended out patients clinic of dermatology in Al-Sadr Medical City in AL-Najaf city –Iraq from November/2013 to January /2015. Informed consents were gained from participant.

The inclusion criteria include consenting patients having chronic plaque psoriasis with PASI score > 20 aged between 20 to 60 years with no co morbid illness or any medications. The groups of the patients are as the following:-

1- **Group I:** Includes 20 males whose age ranged from 20 to 39 years .
2- **Group II:** Includes 33 females whose age ranged from 20 to 39 years old .
3- **Group III: :** Includes 23 males whose age ranged from 40 to 60 years .
4- **Group IV:** Includes 24 females whose age ranged from 40 to 60 years old .

After informed written consent, Psoriasis Area Severity Index (PASI) scoring was estimated (8).
A uniformed cases sheets were assigned for every participant in the study which includes:

1. Age of the patient.
2. Gender of the patient.
3. Disease duration.

sVEGFR1 and sVEGFR2 measurements: Ten milliliters of blood were collected in plane tube without anticoagulants , the tubes were left for 30 minute at room temperatures. After coagulation, tubes were centrifuge at 1000 rpm for about 15 minutes and then kept at (–20 C) till usage time. Serum aliquots were obtained to measure sVEGFR1 and sVEGFR2 by sensitive Enzyme Linked Immuno Linked Sorbant Assay technique (ELISA) using ABCAM Human sVEGFR1 and sVEGFR2 ELISA Kits (9).

Statistical Analysis:-

Statistical analysis were done by SPSS 20.0 (SPSS Inc, Chicago, I L, U S A).

The normal distribution was confirmed for all analyzed measures. For correlation analysis, independent t-test is utilized to evaluate difference between two group in continuous variable (10).

Results

Of 100 patients included in the study ,43(43%) males and 57 (57%) females. The males to females ratio was 1:1.3. The patients presented severe form of disease as revealed by psoriasis areas and severity index (PASI) score (mean ±SD) of 35.85 ±9.45 with range (20.76-51.97).

Serum level of vascular endothelial growth factor receptor 1 (sVEGFR1):

The serum vascular endothelial growth receptor 1 showed significant increment in all groups of psoriatic patients when compared to the healthy controls(P<0.001). For males and females in the age group 20-39years, the P values were 0.0001 and 0.00021 respectively while in age group 40-60years, the P values are 0.00013and 0.00011for males and females respectively (figure1and figure 2).

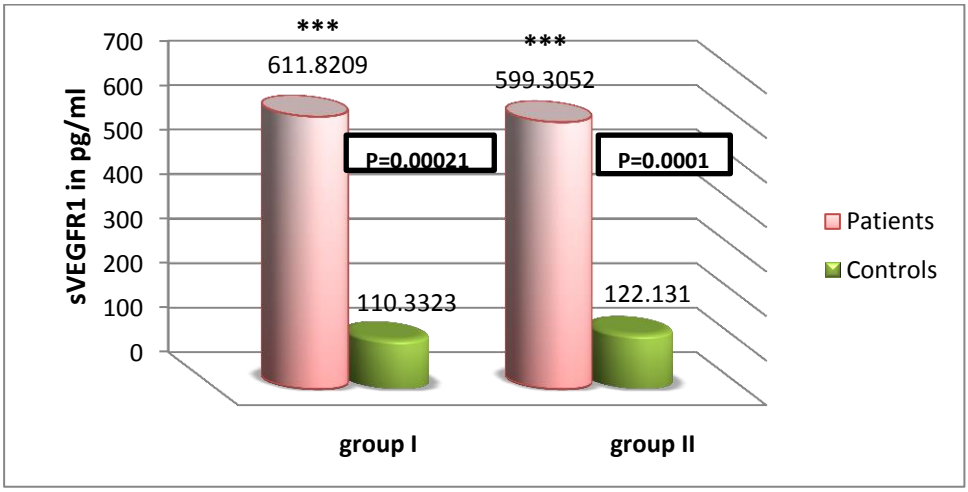

Figure 1: vascular endothelial growth factor receptor1 for males and females with age group between 20-39years (groups I and II).

sVEGF : serum vascular endothelial growth factor.

*** significant differences at P<0.001.

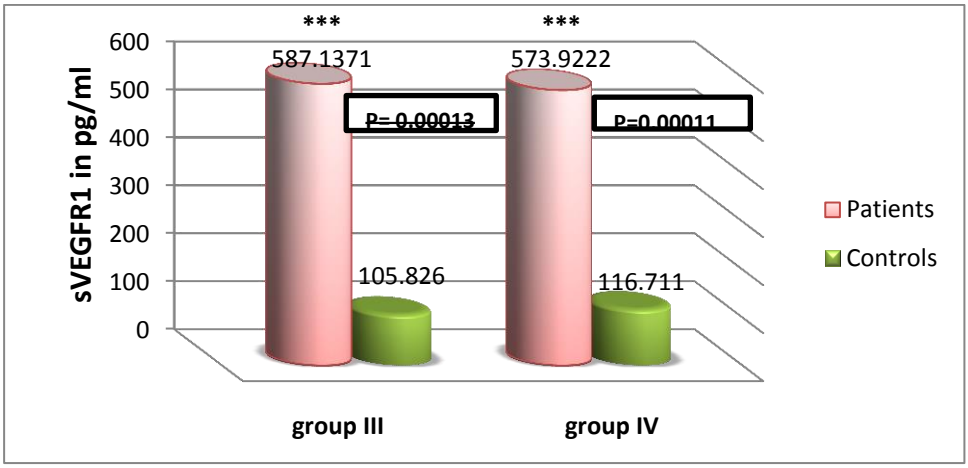

Figure 2: vascular endothelial growth factor receptor1 for males and females with age group between 40-60years (groups III and IV).

sVEGF : serum vascular endothelial growth factor.

*** significant differences at P<0.001.

Serum level of vascular, endothelial growth factor receptor2 :-

The serum vascular endothelial growth receptor 2 displayed significant increment in all groups of psoriatic patients when compared to the healthy controls(P<0.001). For males and females in the age group 20-39years, the P values were 0.00024 and 0.0001 respectively while age group 40-60years, the P values are 0.0005and 0.0002for males and females respectively (figure3and figure 4).

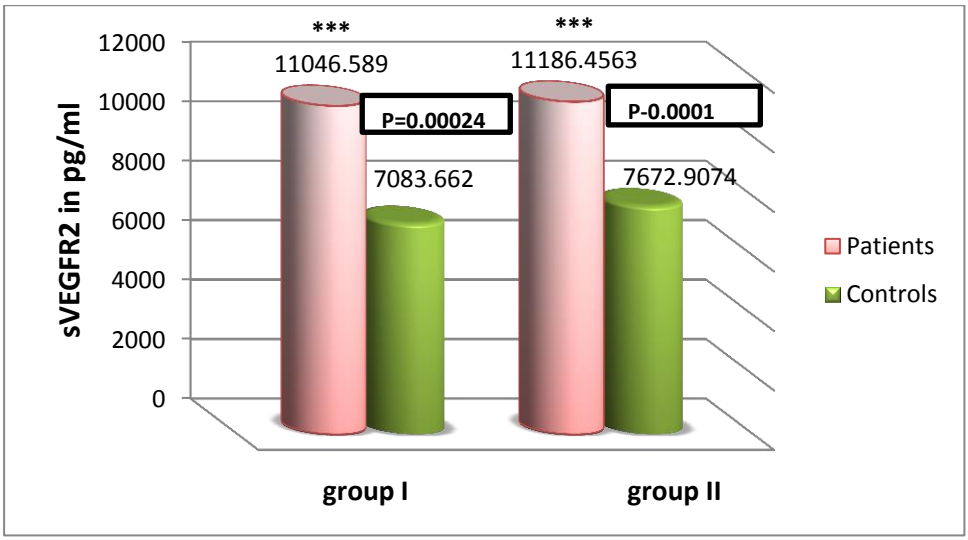

Figure (3): Vascular endothelial growth factor receptor2 for males and females with age group between 20-39years (groups I and II).

*** significant differences at P<0.001. sVEGF : serum vascular endothelial growth factor.

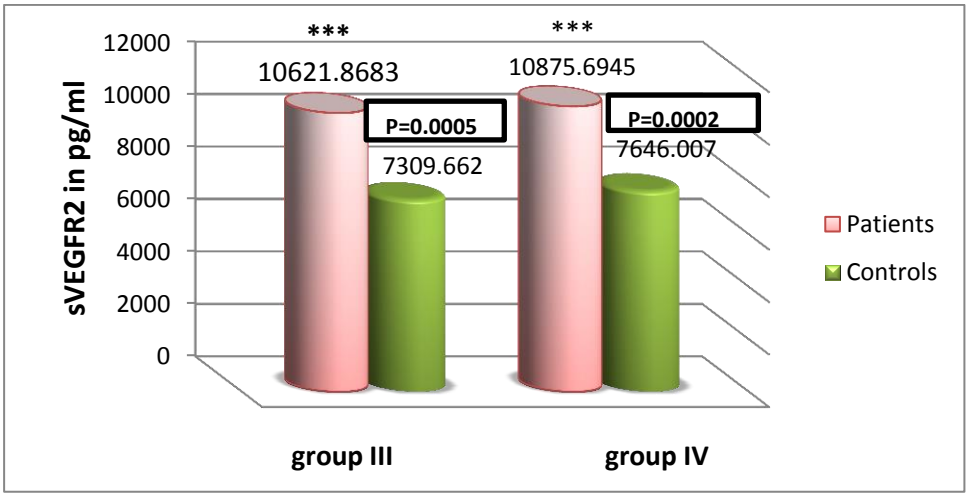

Figure (4): Vascular endothelial growth factor receptor2 for males and females with age group between 40-60years(groups III and IV).

*** significant differences at P<0.001. sVEGF : serum vascular endothelial growth factor

Discussion

The present study showed a slightly female predominance (male/ female ratio approximately 1:1.3) which yet again may reflect a sex related preference in psoriatic patients (figure 4.1). This was in accordance to Mallbris *et al*., (2005) who found a female dominance (approaching 1.3:1) as compared with the male.

Several researcher reported that psoriasis occurs in any gender or race with equal amount of male and female (Smith *et al* .,1993 and Kerkhof, 2003). There is remaining controversy regarding psoriasis gender preponderance and it lies between no difference (Chandaran & Raychaudhuri , 2010) to male preponderance (Raychaudhuri & Farber, 2001). In one research, no gender difference were observed in the frequency of items related to appearance and socialization (Gupta and Gupta, 1995).

Psoriasis can manifest at any age from infancy to old age (Langely *et al* ., 2011). More than 50% of the patients experienced their reportedonset before the age of 40 years(Naldi and Gambini, 2007). Accurate determination of the age of onset of psoriasis is problematic as studies, which do so typically rely on a patient's recall of the onset of the lesion or determine the onset from the physician's diagnosis as recorded on the initial visit. Data based on patient's recall can be inaccurate; determining onset based on first visit to the physician could under estimate the time of disease occurrence, as minimal disease may be present for years before a consultation is sought (Ferrandiz *et al* ., 2002and Naldi , 2004). In this study, psoriasis was found to be higher in patients of age groups 20-39 years old; the number of the patients in this age group 53/100(53%) as shown in figure 4.2 . This result corresponds to an Iraqi study which mentioned that psoriasis was higher in individuals of age group 18-40 years old (62.8%) (Lafi *et al* ., 2010). This finding was also in accordance with what was detected by Hwerta and his coworkers (2007) and Zieve and his co-workers (2008) who recognized that the highest incidence of psoriasis was in the second decade or in the reproductive age group. On the other hand, present result disagree with the finding of Abdullah and his co-workers (2007) who reported that psoriasis particularly psoriasis vulgaris was higher and common in individual within 40-50 years old.

In the present study the youngest patient was 20 years old and oldest was 60 years old.

Papp and his co-workers (2011) also found the prevalence of psoriasis was developed in older Canadian population (more than 70 years). While, Bell and his co-workers (1991) revealed that psoriasis tend to appear at an earlier age among females than males.

Concerning sVEGFR1, our results suggest that there is highly significant increment in sVEGFR1 in all psoriatic patients compared to control (figure 1 and figure 2).

Our results are in agreement with the finding of Flisiak and his coworkers (2010) and Flisiak and his coworkers (2012) who reported that the increase of serum VEGFR1 becomes significant only in patients with severe psoriasis(12,13).

Young *et al* (2004) also found that in psoriatic patients, the serum VEGF are significantly increased in addition to serum circulating (soluble) VEGFR-1, although no direct correlation with disease severity as measured by the PASI score was found in this study (14).

Additionally, our results suggest that there is highly significant increment in sVEGFR2 in all psoriatic patients compared to controls (figure 3 and figure 4). Our finding disagree with Flisiak and his coworkers (2010) and Flisiak and his coworkers (2012) who did not find significant differences in VEGFR2 levels between psoriatic patients and controls (12,13). Up to our knowledge no study presents till now supports our result regarding sVEGFR2 apart from experimental study done by Man et al., (2008) and Zhou *et al*., (2013) who measure epidermal VEGFR1 and VEGFR2 and they discovered that VEGFR1 and VEGFR2 were established to be overexpressed by epidermal psoriatic skin compared to controls, supporting their pathological importance in the development of psoriatic lesion. These results provide another prospective to understand the mechanism of VEGF and VEGFR in psoriasis. That is to say, VEGF participates in the pathogenesis of psoriasis through two manners. One is that keratinocytes-derived VEGF induces angiogenesis to provide essential nutriments, energy, and cells to support the hyperproliferation of epidermis in a paracrine manner indirectly; the other one is that VEGF directly stimulates the proliferation of keratinocytes via VEGFRs expressed on epidermis in an autocrine manner(15,16).

Remarkably adequate, hypoxias and anoxidative stress likewise occurred in psoriasis lesions , that could be linked to over-expression of vascular endothelial growth factor receptors and consequent hyperprofileration of epidermal layers(17,18).

Bhusan*et al*., (1999) established that vascular endothelial growth factors and it's receptors are upregulated by keratinocytis of the supra basal epidermal layer and fibroblasts, indicating a dermally resulting impact on neoangiogenesis(19).

Yang et al (2006) and Man et al (2009) revealed that the proliferations of keratinocytes can be stimulated via VEGF/VEGFRs pathways and management with aVEGFR tyrosine kinases inhibitors can impede chronic or acute skin inflammations like that of psoriasis (20,21).

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