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Impact of Psoriasis Treatments on Serum Level of Vascular Endothelial Growth Factor and Its Soluble Receptors (Receptors 1&2) in Patients with Chronic Plaque Psoriasis

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Abstract:-
Psoriasis is a skin disease that is characterized by a chronic relapsing nature, although the clinical diagnosis of psoriasis is easy to make , it is hard to manage satisfactorily. dysregulated angiogenesis has been detected in inflammatory diseases and might be a cause of chronic cutaneous inflammation in psoriasis.
Narrowband ultraviolet B (NB-UVB) phototherapy is a first option treatment for severe psoriasis due to its efficacy and safety. It applied either as monotherapy or in combination with topical ointments, oral retinoids and/or biologic agents.
The objective of the study to evaluate the efficacy and impact of psoriasis treatment (narrowband UVB phototherapy and/or topical treatment) on serum concentrations of VEGF and its soluble receptors(VEGFR1 and VEGFR2) and compare post treatment levels of these parameters with the controls.
One hundred consenting psoriatic patients (males and females) aged 20-60 years who attended different medical centers including Al-Sadr Medical City and department of laser research in AL-Najaf city and Marjan Medical City in AL-Hilla -Iraq. Psoriasis area and severity index assessment was done for each patient. Blood samples was collected for vascular endothelial growth factor and its receptors (1&2) measurement**.**
Psoriasis is chronic disease as the majority of the patients had disease duration of more than two years. Serum VEGF, sVEGFR1 and sVEGFR2 are important in the pathogenesis of psoriasis, as their level are significantly elevated in severe form of psoriasis and both topical treatment and NB-UVB are effective in the management of psoriatic patients.
Keywords: Serum vascular endothelial growth factor, serum vascular endothelial growth factor receptor 1, Serum vascular endothelial growth receptor 2,Psoriasis area and severity index, Psoriasis, NBUVB.
List of abbreviation: sVEGFR= serum vascular endothelial growth factor receptor, PASI = Psoriasis area and severity index, SD=standard deviation , ECs=endothelial cells**.** ELISA= Enzyme Linked Immuno Linked Sorbant Assay. NB-UVB=narrow band ultra violet phototherapy.

Introduction

Psoriasis is a common, inflammatory, chronic and noncontagious skin disease, Although the precise cause of psoriasis is ambiguous, 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].

Narrowband ultraviolet B (NB-UVB) phototherapy is a first option treatment for severe psoriasis due to

its efficacy and safety. It applied either as monotherapy or in combination with topical ointments, oral retinoids and/or biologic agents[8]. Vascular endothelial growth factor (VEGF) is recognized as a pivotal factor responsible for angiogenesis in different tissues. Overexpression of VEGF can upregulate angiogenesis in psoriatic skin if it dominates the activity of antiangiogenic factors and account for the chronicity in psoriatic lesion [9 ,10]

The objective of the study to evaluate The efficacy and impact of psoriasis treatment (narrowband UVB phototherapy and/or topical treatment) on serum concentrations of VEGF and its soluble receptors(VEGFR1 and VEGFR2) and compare post treatment levels of these parameters with the controls.

Materials and Methods

This is a case-control study which included 150 subjects (100 patients and 50 controls) who attended different medical centers including Al-Sadr Medical City and department of laser research in AL-Najaf city and Marjan Medical City in AL-Hilla city from November/2013 to January /2015. Informed consents were gained from participant. The practical's parts of this study were done at the Biology Department / College of Science /Babylon University.

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.

After informed written consent, Psoriasis Area Severity Index (PASI) scoring was estimated [11].

The groups of the patients are as the following

1- Group I: Includes 20 males whose age ranged from 20 to 39 years old and they are divided into two subgroups according to type of treatment:-

A- Includes 10 males on topical treatment .

B- Includes 10 male on topical treatment and phototherapy .

2- Group II: Includes 33 females whose age ranged from 20 to 39 years old and they are divided into two subgroups according to type of treatment:-

A- Includes 16 females on topical treatment.

B- Includes 17 female on topical treatment and phototherapy.

3- Group III: : Includes 23 males whose age ranged from 40 to 60 years old and they are divided into two subgroups according to type of treatment:-

A- Includes 11 males on topical treatment .

B- Includes 12 male on topical treatment and phototherapy .

4- Group IV: Includes 24 females whose age ranged from 40 to 60 years old and they are divided into two subgroups according to type of treatment:-

A- Includes 13 females on topical treatment .

B- Includes 11 female on topical treatment and phototherapy .

Once taking informed consent and the history from the patients which includes age, gender, smoking history, disease duration and duration of present relapse, patients were exposed to whole body narrowband UVB radiation chamber.

sVEGF, sVEGFR1 and sVEGFR2 measurements: Eight to 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 xg for about 15 minutes, the serum was extracted and allocated into three parts ,and kept at (–20 C) till usage time. Serum aliquots were obtained to measure sVEGF, sVEGFR1 and sVEGFR2 before and after treatment with NB UVB phototherapy and / or topical treatment by sensitive Enzyme Linked Immuno Linked Sorbant Assay technique (ELISA) using ABCAM Human sVEGFR1 and sVEGFR2 ELISA Kits [12].

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 was used to estimate differences between two groups in continuous variables as well as the paired t-test was used to estimate the difference between the pre and post treatment levels of the measured parameters. the Pearson's product moment correlation was used. Results are reported as mean and standard deviation (mean ±SD) unless otherwise indicated. $P<0.05$, was considered statistically significant , $P<0.01$, was considered highly significant and $P<0.001$, was considered extremely significant [13].

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 mean duration of psoriasis was12.80± 12.45years (1month - 40 years) (table 1). About 89 % of the

patients had disease duration for more than 2 years.

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).

It was found that there was significant improvement in skin lesions (P<0.05) signified by reduction in PASI score in group A patients (on topical treatment alone) and significant improvement in skin lesions (P<0.01) for group B patients (on NB UVB phototherapy plus topical treatment) and there was significant difference between the two groups(P<0.05) (table 1). This means that patients on combined therapy responded better and had more reduction in PASI score than patients treated with topical treatment alone.

Table 1 : Psoriasis area and severity index(PASI) score (Mean ±SD) for both treatment groups before and after treatment.

Treatments groups	PASI score Before treatment (Mean ±SD)	PASI score After treatment (Mean ±SD)	P value	
Group A (Patients on topical treatment)	33.145± 9.124	15.225± 6.483	0.0162*	0.046*
Group B (Patients on NB UVB phototherapy plus topical treatment)	37.812± 10.82	7.172± 8.767	0.004**	

PASI : psoriasis area and severity index;*Significant difference between groups (P < 0.05);**Highly significant difference between groups (P < 0.01).

The serum level of vascular endothelial growth factor (VEGF) concentrations was significantly higher in both treatments groups and for all age groups of psoriatic patients when compared with the healthy controls (P<0.001). Concerning the serum level of vascular endothelial growth factor receptor 1, VEGFR1 was significantly higher in both treatments groups and for all age groups of psoriatic patients when compared with controls (P<0.001). About the serum level of vascular endothelial growth factor receptor 2, VEGFR2 statistically showed high significant elevation in both treatments groups (A&B) for all age groups of psoriatic patients when compared with the healthy controls (P<0.001). (table 2 ; table 3 ;table 4; table 5; table 6; table 7 ; table 8 and table 9) .

Firstly before we studied the effect of treatment, we compared the baseline serum level of VEGF, sVEGFR1 and sVEGFR2 between the two groups (A&B) and we found that there were no significant differences between the two groups for all ages groups regarding sVEGF, sVEGFR1 and sVEGFR2 (P>0.05)

In respect to the effect of treatment, it was found that in comparison to the pretreatment level there was highly significant improvement (P<0.01) in serum VEGF for group I (A&B) , group II(A), group III(A&B) and group V(B) while there was extremely significant improvement (P<0.001) for group II (B)and significant improvement (P<0.05) for group IV(A). However when we compared the post treatment level of VEGF in psoriatic patients with the controls there was still extremely significant elevation(P<0.001) for group IV(A) while highly significant elevation (P<0.01) in serum VEGF for group I (A&B) , group II (A), group III (A&B) and group IV (B) and there was significant elevation (P<0.05) for group II (B).

Similarly, it was noticed that there was there was extremely significant improvement (P<0.001) for group II(B) while highly significant improvement in VEGF R1 (P<0.01) compared to the baseline level for group I (A&B) , group II(A), group III(A&B) and group V(B) and significant improvement (P<0.05) for group V(A). As well as when we compared the post treatment level of VEGF R1 in psoriatic patients with the control there was still extremely significant elevation(P<0.001) for group I(A) , group III (A) and group V (A) as well as highly significant elevation (P<0.01) in serum VEGFR1 for group I (B) , group II (A), group III (B) and group V (B) while there was significant elevation (P<0.05) for group II (B).

Regarding VEGF R2, we noticed that there was significant reduction (P<0.05) in serum VEGFR2 for group I (A) , group III(A) and group V(B) while there was high significant reduction (P<0.01) for group IV(B)and extremely significant reduction (P<0.001) for group I(B) for group II (A&B) and group III (B).

Likewise, the comparison of the post treatment level of VEGFR2 in psoriatic patients with the healthy control showed that there was still significant increase (P<0.05) in serum VEGFR2 for group I (A&B) , group II (A), group III (A) and group V (A&B) while there was insignificant elevation (P>0.05) for group II (B) and group III (B).

Table 2: Mean (±SD) vascular endothelial growth factor (sVEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group IA patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patient	682.78± 206.99	448.50± 142.50	601.18± 102.63	359.61± 93.53	10956.58± 2694.18	8277.54± 2074.36
P value	0.0012**		0.0045**		0.037*	
Controls	210.61 ± 22.24		110.33 ± 30.56		7083.66± 1053.98	
P value	*** 0.0001	** 0.0032	*** 0.00012	*** 0.0004	** 0.0023	* 0.022

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2. *Significant difference between groups ($P < 0.05$); **Highly significant difference between groups ($P < 0.01$); ***Extremely significant difference between groups ($P < 0.001$).

Table 3 :Mean(±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group IB patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	705.96± 184.89	335.64± 137.16	622.45± 92.43	264.86± 82.66	11136.58± 2699.79	7743.64± 1529.56
P value	0.0013**		0.0001***		0.0001***	
Controls	210.61± 22.24		110.33±30.56		7083.66± 1053.98	
P value	*** 0.0001	** 0.0021	*** 0.0001	** 0.003	** 0.0019	0.084

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.
*Significant difference between groups ($P < 0.05$); **Highly significant difference between groups ($P < 0.01$).
***Extremely significant difference between groups ($P < 0.001$).

Table 4: Mean (±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group II A patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	673.95± 192.54	464.42± 229.16	585.32± 81.61	325.92± 115.52	11479.55± 2462.87	8810.66± 2981.45
P value	0.002***		0.0001***		0.001***	
controls	195.76 ± 36.77		122.13± 31.83		7672.90± 1743.12	
P value	*** 0.00035	** 0.0087	*** .00014	** 0.00431	*** 0.00156	* 0.0286

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.
*Significant difference between groups ($P < 0.05$);**Highly significant difference between groups ($P < 0.01$);
***Extremely significant difference between groups ($P < 0.001$).

Table 5: Mean (±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group II B patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	696.29± 182.81	316.61± 113.27	613.28± 121.52	184.32± 54.91	10893.36± 2378.63	7734.19± 2290.89
P value	0.0001***		0.0001***		0.0001***	
controls	195.765 ± 36.77677		122.131± 31.83233		7672.907± 1743.1227	
P value	*** 0.00098	*0.013	*** .000298	* 0.023	*** 0.00045	0.943

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2; *Significant difference between groups (P < 0.05);**Highly significant difference between groups (P < 0.01); ***Extremely significant difference between groups (P < 0.001).

Table 6: Mean (±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group IIIA patients before and after treatment in comparison with control.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2[pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	664.97± 198.63	465.55± 198.63	575.56± 135.82	407.33± 102.82	10287.53± 3966.17	8415.30± 2105.5
P value	0.0013**		0.021*		0.041*	
controls	184.83 ± 48.68		105.82 ± 15.63		7309.66± 1284.69	
P value	*** 0.0001	** 0.001	*** 0.0001	*** 0.0002	* 0.035	* 0.048

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.
*Significant difference between groups (P < 0.05); **Highly significant difference between groups (P < 0.01);***Extremely significant difference between groups (P < 0.001).

Table7: Mean (±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group IIIB patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	649.60± 199.84	378.22± 111.53	597.74± 117.04	289.34± 78.68	10928.34± 2615.96	7541.43± 2059.16
P value	0.0032**		0.0001***		0.0001***	
controls	184.83±48.68		105.82 ± 15.63		7309.66± 1284.69	
P value	*** .0001	** 0.006	*** 0.0009	** 0.003	*** 0.0002	0.761

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.
**Highly significant difference between groups (P < 0.01); ***Extremely significant difference between groups (P < 0.001).

Table 8: Mean (±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group IVA patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	667.92± 202.82	501.90± 154.47	558.77± 101.19	435.44± 130.59	11075.05± 2495.03	8807.11± 1773.40
P value	0.03*		0.028*		0.005**	
controls	200.53 ± 43.57		116.71 ± 19.59		7646.007± 1592.50	
P value	** 0.001	*** 0.00045	*** 0.00065	*** 0.000219	** 0.001	* 0.035

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.
* Significant difference between groups (P < 0.05); **Highly significant difference between groups (P < 0.01); ***Extremely significant difference between groups (P < 0.001).

Table 9: Mean (±SD) vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations in serum of group IVB patients before and after treatment in comparison with controls.

	VEGF [pg/mL]		sVEGF R1 [pg/mL]		sVEGF R2 [pg/mL]	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
patients	689.21± 210.86	405.22± 201.76	589.06± 133.62	318.73± 89.19	10676.33± 3702.27	8365.50± 2249.20
P value	0.003**		0.0002***		0.01*	
controls	200.53 ± 43.57		116.711 ± 19.59		7646.007±1592.50	
P value	*** 0.00021	** 0.005	*** 0.00023	** 0.0061	* 0.027	* 0.0413

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2. *Significant difference between groups (P < 0.05); **Highly significant difference between groups (P < 0.01); ***Extremely significant difference between groups (P < 0.001).

Baseline serum VEGF concentration increased in accordance with psoriasis activity demonstrated through PASI score. Statistically significant correlation was demonstrated between sVEGF serum concentration and PASI score while there were no associations between sVEGF levels and patients age, duration of present relapse and duration of whole disease (P>0.05).Also both sVEGF R1 and sVEGF R2 did not demonstrate significant association (P>0.05) with analyzed measures including PASI score (Table 10).

Table 10: Mean values (±SD) of ages, duration of the disease, its present relapse, psoriasis area severity index (PASI) and correlation (expressed as r-value) between these measures and serum vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations before start of the treatment

Parameters	(Mean ±SD)		sVEGF	sVEGFR1	sVEGFR2
Ages(years)	38.33±13.678	r	-.030	-0.16	-0.113
		P	0.091	0.117	0.312
Disease duration(years)	12.8075± 12.4579	r	-0.149	0.037	0.187
		P	0.089	0.132	0.58
Duration of present relapse (months)	6.6513±11.45049	r	0.103	-0.029	0.042
		P	0.756	0.112	0.314
PASI score	35.853 ± 9.453	r	0.784	0.116	0.065
		P	0.022*	0.087	0.176

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.

*Statistically significant (P < 0.05) correlation ; r correlation coefficient.

As shown in Table 11, there were no significant difference in sVEGF, sVEGF R1 and sVEGF R2 concentrations between patients with positive family history of psoriasis and patients with negative family history (P>0.05) as well as between smokers and non-smokers (P>0.05). Concerning the sex there were no significant changes in serum level of VEGF, VEGFR2 and VEGFR2between males and females in addition between patients in age group of 20-39 and in age group of 40-60 (P>0.05) .

Table 11: Mean values (±SD) of serum vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations according to the family history, smoking history, age and sex before start of the treatment.

Parameter		sVEGF (Mean ±SD)	P value	sVEGFR1 (Mean± SD)	P value	sVEGFR2 (Mean ±SD)	P value
Family history	Positive	649.919± 231.33	0.087	589.923± 132.415	0.668	1034.345± 2354.765	0.141
	Negative	696.714± 154.654		611.678± 123.6234		9954.376± 2875.132	
Smoking history	positive	653.5648± 178.736	0.287	575.3985± 123.986	0.498	10975.234± 2187.456	0.749
	Negative	694.1985±89.876		583.574± 98.835		11136.493± 2198.9376	
Sex	male	674.3598±191.869	0.836	598.6179± 111.10772	0.667	10819.412± 2959.88199	0.676
	female	682.4513± 190.35818		588.9640± 108.34053		11059.849± 2677.854	
Age(in years)	20-39	688.68± 185.687	0.587	604.1189± 99.36877	0.294	11132.66± 2465.189	0.499
	40-60	667.5213± 196.5		580.6765± 119.27579		10745.96± 3147.35457	

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.Statistically insignificant difference between groups (P > 0.05).

Additionally sVEGF, sVEGF R1 and sVEGF R2 did not demonstrate significant association (P>0.05) with family history, smoking history and sex (Table 12).

Table 12: Family history, smoking history, sex and correlation (expressed as r-value) between these measures and serum vascular endothelial growth factor (VEGF), sVEGF R1 and sVEGF R2 concentrations before start of the treatment.

Parameters		sVEGF	sVEGFR1	sVEGFR2
Family history	r	-0.051	0.151	0.174
	P	0.760	0.364	0.289
Smoking history	r	-0.119	-0.084	0.050
	P	0.463	0.612	0.759
Sex	r	0.021	-0.044	0.043
	P	0.836	0.667	0.676

sVEGF : serum vascular endothelial growth factor ; sVEGFR1: serum vascular endothelial growth factor receptor1; sVEGFR2: serum vascular endothelial growth factor receptor2.
Statistically insignificant difference between groups (P > 0.05).

In this study, narrow band UVB phototherapy plus topical treatment are used for treatment of psoriatic patients, for comparison, topical treatment was utilized as another therapy. With these therapies going on, all patients responded well without any uncomfortable complaints. Concerning the changes in the parameters studied with combination of NB-UVB plus topical therapies, we found that all parameters improved and that the

improvement was higher(more reduction) for the treatment with NB-UVB plus topical treatment than the treatment with topical treatment alone.

Starting with sVEGF, for group I, there was significant difference (P<0.05) between patients on topical treatment and patients on combination of topical treatment plus NB UVB phototherapy . Regarding group III, there was highly significant difference (P<0.01) between patients on topical treatment and patients on combination of topical treatment plus NB UVB phototherapy(figure 1).

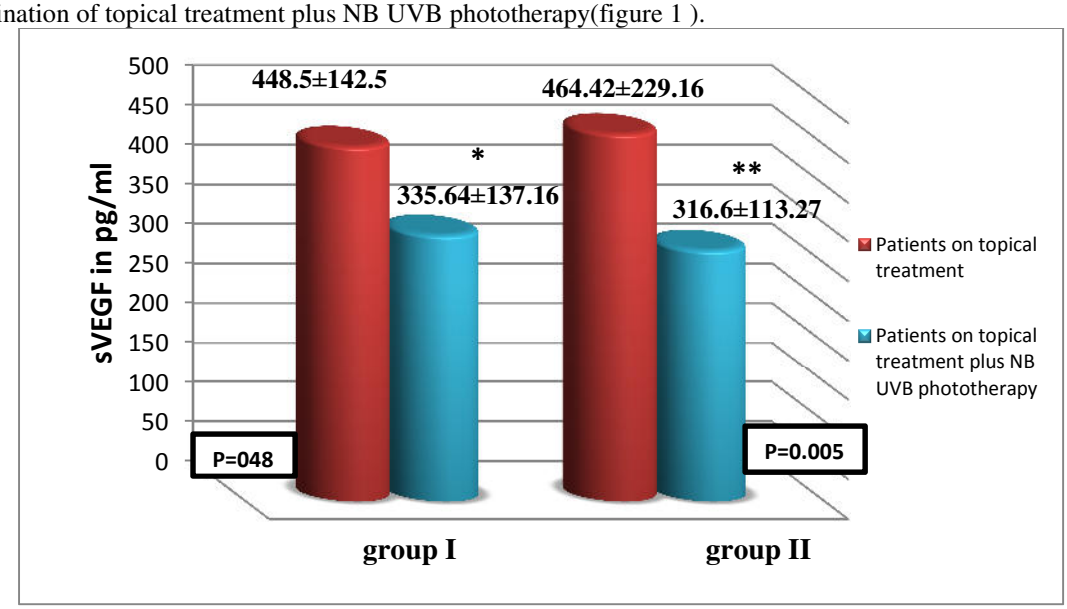

Figure 1: Post treatment level of vascular endothelial growth factor for males and females with age group of 20-39years (group I & group II).

sVEGF : serum vascular endothelial growth factor **.**

*Significant difference between groups (P < 0.05).

**Highly significant difference between groups (P < 0.01).

Concerning group III as well as group IV, there was significant difference (P<0.05) between patients on topical treatment and patients on combination of topical treatment plus NB UVB phototherapy (figure 2).

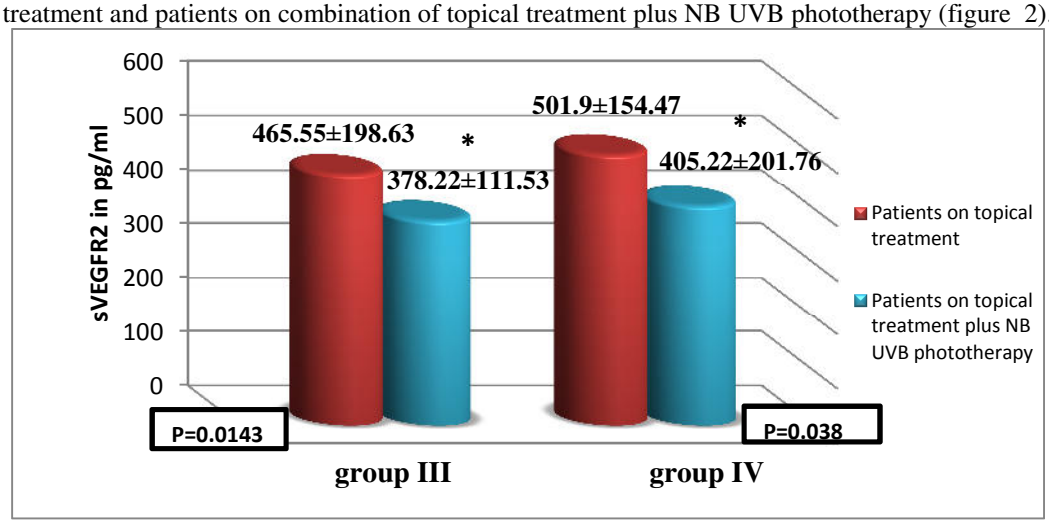

Figure 2: Post treatment level of vascular endothelial growth factor for males and females with age group of 40-60years (group III & group IV).

sVEGF : serum vascular endothelial growth factor **.**

*Statistically significant difference between groups (P < 0.05).

It means that patients on combination treatment of topical plus NB UVB phototherapy responded better and there was significant reduction in sVEGF concerning group I, group II and group IV and highly significant reduction regarding group III than patients on topical treatment alone. Concerning sVEGFR1, in group I, there was significant difference (P<0.05) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy. Regarding group II, there was highly significant difference (P<0.01) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy (figure 3).

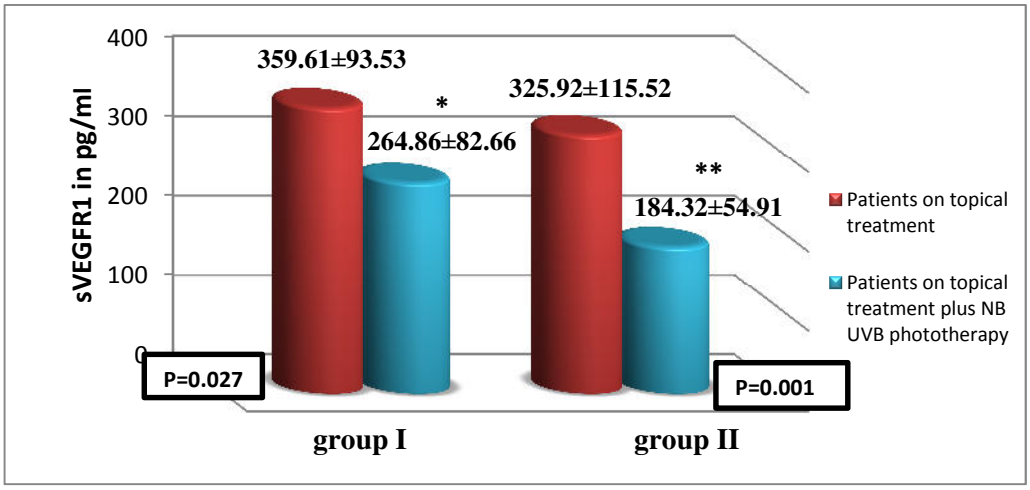

Figure 3: Post treatment level of vascular endothelial growth factor receptor1 for males and females with age group of 20-39years(group I & group II).

sVEGF : serum vascular endothelial growth factor ;*Significant difference between groups (P < 0.05).
**Highly significant difference between groups (P < 0.01).

Regarding group III, there was significant difference (P<0.05) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy. With regard to group IV, there was highly significant difference (P<0.01) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy (figure 4).

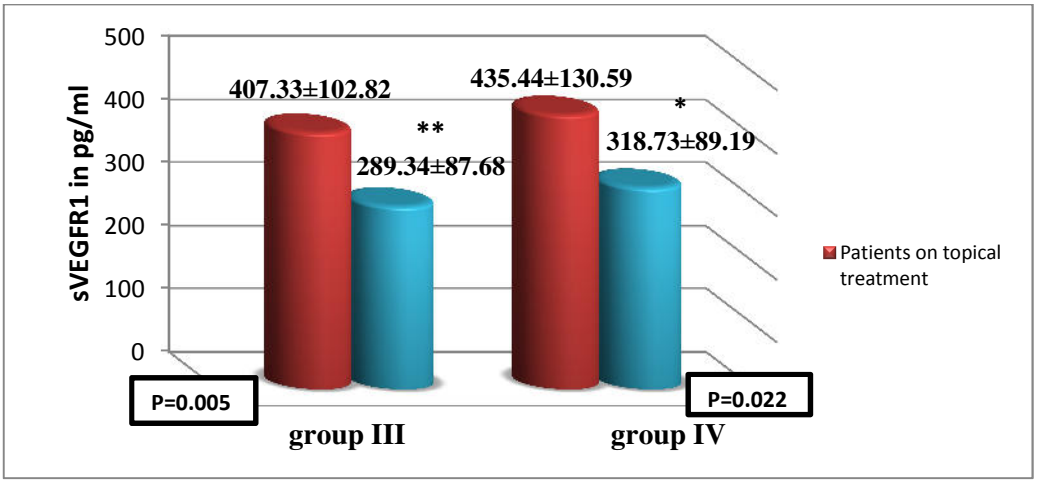

Figure 4: Post treatment level of vascular endothelial growth factor receptor 1 for males and females with age group of 40-60years60years (group III & group IV).

sVEGF : serum vascular endothelial growth factor **;***Significant difference between groups (P < 0.05).
**Highly significant difference between groups (P < 0.01).

Regarding the sVEGFR2 , for group I, there was insignificant difference (P>0.05) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy. Observing group II, there was significant difference (P<0.05) between patients on topical treatment and patients on topical treatment plus NB UVB photothera

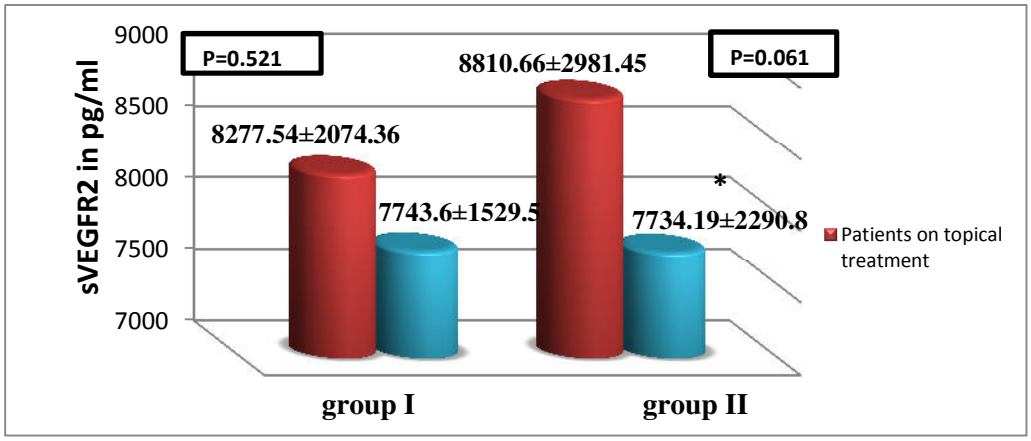

Figure 5: Post treatment level of vascular endothelial growth factor receptor2 for males and females with age group of 20-39years.

sVEGF R2: serum vascular endothelial growth factor receptor2 **;***Significant difference between groups (P < 0.05).

Regarding group III, there was significant difference (P<0.05) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy whereas there was insignificant difference (P>0.05) between patients on topical treatment and patients on topical treatment plus NB UVB phototherapy in group IV psoriatic patients(figure 6).

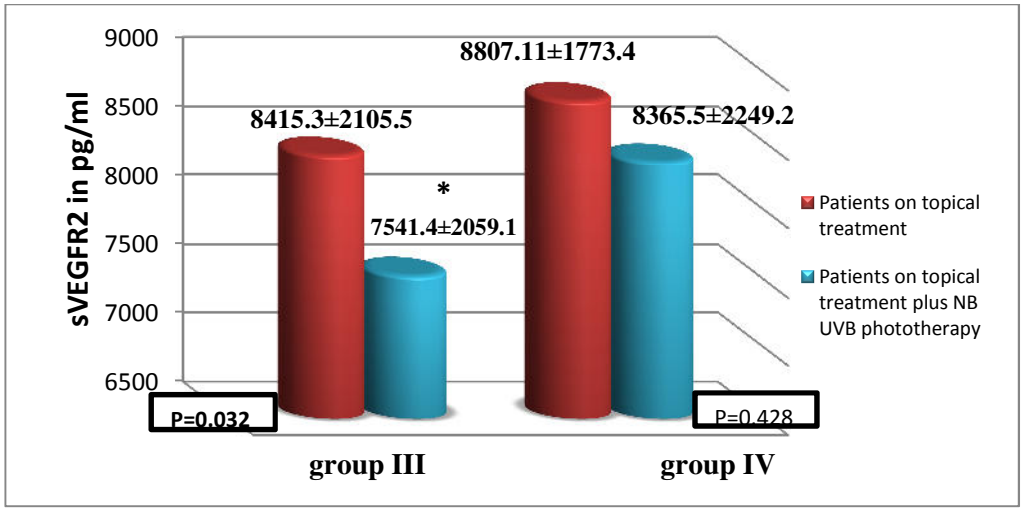

Figure 6: Post treatment level of vascular endothelial growth factor receptor 2 for males and females with age group of 40-60years.

sVEGFR2 : serum vascular endothelial growth factor receptor2.

*Significant difference between groups (P < 0.05).

Discussion

The mean duration of psoriasis was12.8± 12.45years (1month - 40 years) (table 1). About 63% of the patients had disease duration from 2-10 years.

In this study maximum (89%) of the patients were found suffering for more than two years duration. This indicate that the disease is chronic , tough in nature and resist to treatment. This finding is in accordance with the description given by Susan Burge and Dinny wallis[14].

Familial clustering in psoriasis had been observed for many years (15). A positive family history in 55%of the studied sample provided another support of this concept. Moreover, it confirmed the important role of genetics in the etiology of psoriasis especially in those with early onset (16).This figure was also in agreement with the figure reported few years ago in the same locality (Mosul city) which was 38.5% (17).

A large-scale observational study conducted in Spain, the authors showed that, as the age of onset of psoriasis increased, there was a progressive decrease in the incidence rates of a positive family history of psoriasis (16). Their results pointed towards two different psoriasis subtypes: a subtype with a strong genetic background for the disease (early onset psoriasis) and one in which genetic factors play a secondary role (late onset psoriasis) (18).

Association with smoking was seen in 44% of our patients which is consistent with a study of Al-Rubaiy &Rubiay (19) on Iraqi population and they found that about 40% of the patients are smokers and also consistent with Nisa &Qazi, (20) on indian population and they found that about 42% of the patients were smokers. Association with smoking may be partly explained by the action of nicotine in promoting Th1 mediated inflammation (21). Smoking induces an overproduction of IL-1β, TNF-α and TGF-β, which have been associated with psoriasis severity (22).

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).and regarding the effect of treatment, It was found that there was significant improvement in skin lesions signified by reduction in PASI score in all groups of psoriatic patient as compared to the baseline values. In the current work, our data confirmed that both NB-UVB plus topical treatment and topical treatment alone were able to induce a significant reduction in the PASI score after 12 weeks of therapy and the PASI score reduction was more with mixed treatment (topical plus NB UVB Phototherapy) than topical treatment alone(table 1).

As much as we know ,there was no matched study to our study and Flisiak and his coworkers (23) who used only topical treatment evaluated PASI before treatment and he found that PASI varied from 4.2 to 41.2 (mean 15.8 ± 1.3; median 15.1). After 14 days of topical treatment, PASI decreased to values between 0 and 4.3 (mean 1.2 ± 0.2). Another study done by Elghandour and his colleagues (24) and he found that there was significant reduction in PASI score for patients treated with narrow band UVB phototherapy alone as well as significant reduction for patients treated with methotrexate.

Our results also are agreed with the results of Zhou his colleagues (25) who used topical treatment and for comparison used NB-UVB phototherapy alone and they found that both of the two therapies were effective for clinical improvement showed by reduction in PASI score .

Concerning sVEGF, our results suggest that there is extremely significant increment in sVEGF in all psoriatic patients compared to the controls.

Our results are compatible with the finding of other several authors who reported that its levels are significantly high in plasma in the active stage of the disease (26,27,28 and29). Nonetheless, Shimauchi and his coworkers (2013) did not find significant differences in sVEGF levels between psoriasis patients and controls. Flisiak and his coworkers (30) and Flisiak and his co-workers (23) reported that the increment of serum VEGF became significant only in patients with medium and severe activity of the disease.

Dysregulated angiogenesis has been observed in inflammatory diseases and might be underly chronic cutaneous inflammation in psoriasis (31). Several experimental studies and clinical reports suggested that VEGF was involved in psoriasis pathogenesis, among those, transgenic over-expression of VEGF in keratinocytes in mice resulted in skin inflammation and a phenotype resembling human psoriasis. In different psoriasis models, anti-VEGF antibody treatment of mice, already displaying disease symptoms, resulted in an overall improvement of the cutaneous lesions (31). Additionally, a patient with psoriasis was reported to have complete remission of psoriasis during bevacizumab (a monoclonal antibody against VEGF) therapy for colon cancer (27). Therefore, VEGF is a pro-inflammatory factor in the pathogenesis of psoriasis.

Additional emerging evidence for a role of VEGF in the etiology of psoriasis comes from genetic analyses showing an association between VEGF promoter polymorphisms and the development of psoriatic symptoms (32).

Concerning sVEGFR1, our results suggest that there is extremely significant increment in sVEGFR1 in all psoriatic patients compared to control.

Our result are in agreement with the finding of Flisiak and his co-workers (30) and Flisiak and his co-workers (23) who reported that the increase of serum VEGFR1 becomes significant only in patients with severe psoriasis.

Young and his co-workers (33) also found significantly enhanced VEGF serum levels as well as increased levels of circulating (soluble) VEGFR-1 in psoriasis patients, although no direct correlation with disease severity as measured by the PASI score was found in this study .

Concerning the serum level of vascular endothelial growth factor receptor 2, our results suggest that there is extremely significant increment in sVEGFR2 in all psoriatic patients compared to control. Our finding disagrees with Flisiak and his co-workers (30) and Flisiak and his coworkers (23) who did not find significant differences in VEGFR2 levels between psoriatic patients and controls. Up to our knowledge no study till now supports our result regarding sVEGFR2 apart from experimental study done by Man *et al*., (34) and Zhou *et al*., (25) who measure epidermal VEGFR1 and VEGFR2 and they discovered that vascular endothelial growth factor receptors (VEGFR1 and VEGFR2) were found to be over-expressed in psoriatic epidermis compared to controls, implicating their pathological significance in the disease. Man *et al.*, (34) demonstrated that the overexpression of VEGFR-1/2/3 is in psoriatic epidermis at both mRNA and protein levels. Moreover, VEGFRs were strongly labeled in non-lesional, perilesional, and lesional psoriatic keratinocytes in all epidermal stratums *in vivo*. Furthermore, exogenous VEGF and calcium could enhance the expression of VEGFRs. These results provide

another prospective to understand the mechanism of VEGF 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(34).

Interestingly enough, hypoxia and oxidative stress also existed in the psoriatic lesions, which might be associated with overexpression of VEGFRs and subsequent hyperplasia of the epidermis(35 and 36).

Results of this study provide rationale for possible application of VEGF, sVEGF R1 and sVEGF R2 serum measurement as a biomarkers of psoriasis activity and predictor of possible exacerbation. As VEGF and its receptors are currently considered as possible targets of future psoriasis therapies, their measurement could also be useful in the evaluation of the treatment efficacy (31).

In addition, researches showed that VEGFRs were also overexpressed in psoriatic epidermis (25 and 34), but their real function in psoriasis remained unclear. Based on the findings that proliferation of keratinocytes could be promoted via VEGF/VEGFRs pathway (37 and 38), and that treatment with a VEGFR tyrosine kinase inhibitor could inhibit chronic and acute skin inflammation seen in psoriasis (39), and that the overexpressed VEGFRs in psoriatic epidermis might be involved in the pathological process of psoriasis (25).

TNF-α upregulates VEGFR-2 expression and has been shown to stimulate angiogenesis, enhance VEGF-mediated endothelial cell migration, and enhance wound healing (40).

TNF-α levels are elevated in psoriasis and play an important part in T-cell proliferation and disease pathogenesis (41). Treatment with the anti-TNF-α agent infliximab improves skin and joint disease and reduces VEGF expression in dermal and synovial tissue with corresponding reductions in tissue vascularity (42).

As shown in Table 10, there were no associations between VEGF levels and patients age, duration of present relapse and duration of whole disease ($P>0.05$).

Our results are in accordance with the finding of Flisiak and his co-workers (30). Nonetheless these findings disagree with the finding of Al-Shobaili (43) who found that the duration of disease showed significant positive correlations with VEGF ($r=0.35$, $P<0.01$).

Both sVEGF R1 and sVEGF R2 did not demonstrate significant association ($P>0.05$) with the duration of psoriasis, its present relapse, psoriasis area severity index (PASI). These findings are in accordance with the finding of Flisiak and his co-workers (23).

In respect to the effect of treatment, we found that in comparison to the pretreatment level of sVEGF, we noticed that there was significant improvement in serum level of VEGF in all group of psoriatic patients who treated with topical treatment as well as significant reduction in serum VEGFR1 .

Flisiak and his co-workers (23) found that the VEGF levels appear to be reduced by 14 days standard topical therapy in addition they found that VEGFR1 was significantly decreased after topical treatment only in severe form of psoriasis as well as these results are in accordance with the results of Zhou *et al*., (25) who measured epidermal level of VEGF and VEGFR1 and found that there were significant reduction in these parameters after topical treatment.

Regarding the serum VEGFR2, there was significant reduction in serum VEGFR2 after 12 weeks topical treatment, our results are inconsistent with the results of Flisiak and his co-workers (23) who found that the VEGFR2 levels appear to be not changed after standard topical therapy. In contrast this result are in accordance with the results of Zhou and his co-workers (25) who measured epidermal level VEGFR2 and found that there were significant reduction in its level after topical treatment.

So, by topical treatment, the conditions of lesional inflammation, hypoxia and oxidative stress were gradually relieved, which eventually brought about remission of the disease. In the meantime, the expression of VEGFRs declined spontaneously. So, we infer that although VEGFRs are not an initial factor, they really act as a key intermediate in psoriasis pathogenesis, and treatments targeting VEGFRs would be of potential significance for psoriasis.

Regarding the patients treated with topical treatment plus NB UVB phototherapy there were significant reduction in serum VEGF after 12 weeks of treatment, our results are in agreement with results of Andrys and his co-workers (44) who found that serum VEGF are significantly decreased after topical plus NB UVB phototherapy treatment.

Coimbra and his co-workers (28) confirmed that the levels of serum VEGF were significantly decrease in psoriatic patients after treatment with NB-UVB phototherapy alone. Nonetheless our findings disagree with the results of Akman and his co-workers (27) who found that the levels of serum VEGF were significantly increased in the groups of NB-UVB and Re-PUVA ($P<0.001$).

Phototherapy exerts anti-angiogenic effects. *In vitro*, it reduces endothelial cells proliferation and promotes apoptosis (Deng *et al*., 2004). Whether these effects also apply *in vivo* is unclear. However, it was observed in patients that PUVA and narrowband ultraviolet B (nbUVB) therapy reduced circulating level of VEGF (28).

Regarding serum VEGFR1 and serum VEGFR2 , There were significant reduction in serum concentration of both receptors. And up to our knowledge there were no study compatible to our study apart from study of Zhou and his co-workers (25) who measured epidermal level of VEGFR1 and VEGFR2 and found that there were significant reduction in their level after NB UVB phototherapy alone.

VEGFRs may be involved in the pathological process of psoriasis, and NB-UVB phototherapy is effective for psoriasis by directly down-regulating the overexpressed VEGFRs in psoriatic epidermis.

We propose that NB UVB phototherapy cause inhibition of IL-23, as well as TNFα, from DCs, which cause inactivation and proliferation of Th17 cells. Subsequently inhibition of IL-22 and IL-17, this lead to reverse keratinocyte hyperplasia and subsequent production of VEGF and its receptors contributing to inhibition of angiogenesis, characteristic of psoriasis lesions (34).

However when we compared the post treatment level of VEGF in psoriatic patients with the control there was still significant elevation in serum VEGF for patients treated with both treatment modalities.

These results are in agreement with the results of Coimbra *et al* ., (28) who found that VEGF was still significantly higher than the control in patients treated with NB-UVB irradiation as well as in accordance with the results of Flisiak and his co-workers (23) who found that the VEGF levels was still significantly higher than the control in patients treated with standard topical therapy.

Regarding the VEGF receptors (VEGFR1 and VEGFR2) when we compared the post treatment level of both receptors in psoriatic patients with the control there was still significant elevation in serum level of both receptors for patients treated with both treatment modalities.

As far as we know, there were no study compatible to our results.

NB-UVB irradiation is known to upregulate VEGF and its receptors (45). However, similar results were found for patients treated with topical treatment alone. Sustained high levels of VEGF, even at remission, as defined by PASI score, suggest that VEGF might be important in defining the time of remission, as VEGF is known to promote vascular permeability that enhances leucocyte traffic into the skin and alters the dermal capillaries to express leucocyte chemoattractant molecules (46). Moreover, in addition that a residual inflammation persists after treatment with topical treatment and NB-UVB, as CRP was still higher than the control (28). We wonder if this residual inflammatory stimulus, along with higher levels of VEGF and its receptors, could favour infiltration of inflammatory cells into the skin and, therefore, the development of lesions.

As shown in Table 11, there was no significant difference in sVEGF, sVEGF R1 and sVEGF R2 concentrations between patients with positive family history of psoriasis and patients with negative family history ($P>0.05$) as well as between smokers and non-smokers ($P>0.05$).

Up to our knowledge, there is no study compatible to our study and our explanation is that the psoriasis is a polygenic inheritance that comprises 36 chromosomal susceptibility loci (1). although some researcher identified that there was "angiogenetic constitution'' which could determine psoriasis susceptibility based on the analysis of single nucleotide polymorphisms of the VEGF gene in psoriatic and healthy individuals (33).

Regarding the smoking there was no significant difference between smokers and non-smokers ($P>0.05$). Also there was no compatible research with our finding and this result that the smoking not induce the production of VEGF, VEGFR1 and VEGFR2.

One research demonstrated that smoking induces an overproduction of IL-1β, TNF-α and TGF-β which have been associated with psoriasis severity and TGF-β is involved in neovascularization (22). This means that smoking affects neovascularization but not through the pathway of VEGF and its receptors.

Concerning the sex and age, there are no significant changes in serum level of VEGF, VEGFR2 and VEGFR2 between males and females along with between patients in age group20-39 and patients in age group 40-60 ($P>0.05$) (Table 11) , these results are in accordance with the results of Flisiak and his coworkers (30) and with the finding of Flisiak and his coworkers (23) . This findings mean that the level of VEGF and its receptors don't affected with age as well as with the sex of the patients. Nonetheless our finding disagrees with the finding of Creamer his coworkers (47) who said that high plasma levels of VEGF-A are associated with early onset psoriasis (onset before the age of 40 years) and psoriatic arthritis

We found that all parameters improved and that the improvement was higher for the treatment with NB-UVB plus topical treatment than the treatment with topical treatment alone.

There were significant difference in serum VEGF, sVEGFR1 and sVEGFR2 between patients treated with topical treatment alone and patients treated with topical plus NB UVB phototherapy and this means that combined treatment of topical plus NB UVB phototherapy was more effective in reduction serum VEGF, sVEGFR1 and sVEGFR2 than treatment with topical treatment alone. To the extent that we know there was no study compatible to our results. The extra effect is attributed to the effect of NB UVB phototherapy on reduction of serum VEGF and its receptors in addition to the effect of topical treatment.

Conclusion

Psoriasis is chronic disease as the majority of the patients had disease duration of more than two years. Serum

VEGF, sVEGFR1 and sVEGFR2 are important in the pathogenesis of psoriasis, as their level are significantly elevated in severe form of psoriasis and both topical treatment and NB-UVB are effective in the management of psoriatic patients.

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Author Contribution
The authors share the responsibility in preparing and completing this work.

Conflict of interest
The authors declare no conflict of interest.

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