Journal of Clinical & Experimental Dermatology Research

Jaworek et al., J Clin Exp Dermatol Res 2018, 9:6
DOI: 10.4172/2155-9554.1000471

Research Article Open Access

Serum Pro- and Antiangiogenic Factors in Patients with Types I and II of Rosacea

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Abstract

Introduction: Rosacea is a chronic inflammatory disease of the face's skin, characterized by erythema papules, pustules and phymatous changes. There are four types of this disease (erythematoteleangiectatic-ETR, papulo-pustular-PPR, ocular rosacea and type with domination of phymatous changes). The treatment of rosacea involved use of systemic and topical antibiotics, isotretinoin, metronidazole, and suitable dermocosmetics and sunscreens. The pathogenesis of rosacea is still unknown. The undesired angiogenesis and misbalanced ratio between proangiogenic (VEGF) and antiangiogenic (endostatin) factors could be among the pathomechnisms of this ailment.

Aim: To assess the serum concentrations of some factors affecting angiogenesis in patients with rosacea.

Method: 72 patients with type ETR and PPR of rosacea (28 men, 44 women) and 21 healthy volunteers were involved in the study (28 men, 44 women). Blood samples were taken to measure the concentrations of VEGF, endostatin, IL-6 and TNF-α by ELISA.

Results: Patients with rosacea have significantly higher serum level of VEGF than the control group (324.1 ± 33.0 *vs.* 21 238.6 ± 43,7pg/mL), whereas serum endostatin was reduced (261.2 ± 50.4 *vs.* 411.5 ± 40.2). Serum levels of IL-6 in rosacea patients was higher than in control group (2.82 ± 0.5 *vs.* 1.28 ± 0.25 pg/mL). No significant differences in the serum level of TNF-α in patients with rosacea have been noticed.

Conclusion: Increased production of proangiogenic factors; VEGF and IL-6 together with reduced antiangiogenic endostatin could be responsible, at least in part, for intensive angiogenesis and erythema in patients with rosacea. Further studies are needed to clarify the mechanism of this impaired angiogenesis to create the effective therapeutic strategy.

Keywords: Rosacea; TNF alpha; VEGF; IL-6; Angiostatin

Introduction

Rosacea is a chronic inflammatory disorder of face's skin with a course of remissions and exacerbations. It regards about 10-12% of population over 40 years old and involves more often women than men [1]. Typical changes are localized on the skin of the middle face area, precisely on convexities of the central face, i.e. cheek, nose, chin and forehead. Erythema is a primary symptom of the disease (paroxysmal at the beginning, nontransient afterwards) and it forms a base for papules, pustules and hypertrophic changes (phyma). It is commonly observed in patients with fair skin (Fitzpatrick scale: type I and II), but it also presents in Asians, Latin Americans and Africans. Four types (subtypes) of rosacea may be distinguished 1/erythematotelangiectatic rosacea (subtype I), 2/papulopustular rosacea (subtype II), 3/phymatous rosacea (subtype III), 4/ocular rosacea (subtype IV) [2-4]. Classification mentioned above may present also different stages of the disease. Most frequent subtypes of rosacea are subtype I and subtype II. Subtype I, erythematotelangiectatic rosacea (ETR) is characterized by persistent central facial erythema which underlies telangiectasia occurrence [1,2,5]. The predominant symptom of the papulopustular rosacea (PPR) subtype is a papule, often with pustule on it's top, accompanied by subtle epidermis exfoliation and skin protrusion induced by the edema. This variant concerns more often women and the chronic inflammation may become very intensive, leading to skin edema, which can transform into solid face's edema (Morbihan disease) and hypertrophic changes (phyma) [2,4-6].

The treatment of rosacea consists of topical metronidazole or azelaic acid, ivermectin, brimonidine tartrate and sometimes, calcineurin inhibitors as well. Also corrective make-up may be helpful, effective sun protection should be applied by every patient. Majority of patients (especially subtype II) must be treated with oral tetracyclines, macrolides or isotretynoin [7,8]. Recent reports indicate the pulsed-dye laser therapy as an effective way to treat ETR rosacea subtype [9]. Pathogenesis of rosacea is not clarified yet and its etiology is probably multifactorial, genetically motivated. Environmental factors (most notably UV radiation) impact on formation of rosacea, which on its own is increasingly associated with array of coexisting disorders such as arterial hypertension, dyslipidemia, coronary disease or migraine [10,11]. Also psychological components are considered as agents that exacerbate symptoms of rosacea, especially psychological stress [12]. Latest hypotheses emphasize importance of infectious factors (e.g. Helicobacter pylori, Demodex folliculorum, Bacillus oleronius, Chlamydia pneumoniae, Staphylococcus epidermdis) as well as Toll-like 2 receptor and antimicrobial peptide stimulation (particularly

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Received July 27, 2018; **Accepted** September 11, 2018; **Published** September 20, 2018

Citation: Jaworek A, Patuszczak M, Jaworek J, Zalewski A, Pelc AW (2018) Serum Pro- and Antiangiogenic Factors in Patients with Types I and II of Rosacea. J Clin Exp Dermatol Res 9: 471. doi:10.4172/2155-9554.1000471

cathelicidin hCAP-18/ LL 37, acting as a pro-angiogenic factor cathelicidin hCAP-18/ LL 37) [6,8,13-15]. It is highly plausible that angiogenesis (reorganisation of fully-grown blood vessels net) and vasculogenesis (blood vessels de novo formation) disfunction underlies the pathogenesis of rosacea. Symptoms such as erythema and teleangiectases are indicatives of this thesis [4,7,8]. Erythema relates to existence of increased blood vessels count or to their extended diameter and more superficial location within face's skin and subcutaneous tissue [16]. Remarkably complex process of the angiogenesis requires many factors which play regulative role in multistage phenomenon of blood vessels generation. Balanced pro- and anti-angiogenic agents ratio is responsible for vessels homeostasis and any disturbances may be the cause of pathogenetic changes in rosacea [17,18].

What is crucial for angio- and vasculogenesis is VEGF. It induces sprouting, migration and formation of new capillaries from endothelial cells [19]. Opposite function falls to endostatin, this belongs to endogenous angiogenesis inhibitors group. It is a molecule resulting from C-end section of type XVIII collagen [20]. During the inflammation in rosacea immunological cells are activated and pro-inflammatory cytokines are released. One of the most important of all cytokines is a tumor necrosis factor α (TNFα). It inhibits neoplastic cells division and stimulates their apoptosis, activates antigen presenting cells, increases lymphocytes T and B proliferation. TNFα performance effect depends on the balance between it's pro- and anti-inflammatory functions [21-23]. TNFα impels also production of other cytokines, including pro-inflammatory interleukin 6 (IL-6) [24]. The objective of this study was to assess concentration of elected angiogenesis modulating factors: VEGF and endostatin, as well as pro-inflammatory cytokines TNFα and IL-6 in rosacea (subtypes ETR and PPR) patients' blood. What was also attempted was to define the dependence between the intensity of skin lesions and levels of the above factors and cytokines in blood serum.

Methods

72 patients treated in Outpatient Clinic, Department of Dermatology, The University Hospital in Cracow were assessed: 44 patients with ETR subtype and 28 patients with PPR subtype (Table 1). The control group comprised of 21 healthy volunteers, chosen in terms of the age. Diagnosis of rosacea was made based on the Standard classification of rosacea (2002) published under the auspices of the National Rosacea Society. The intensity of skin lesions in the course of rosacea was evaluated in accordance with Standard grading system for rosacea. All subjects were informed about the purpose of the study and signed the consent to take part it this survey. The study was approved by JU MC Committee of Bioethics number KBET/76/B/2005. Blood samples from participants' ulnar veins were collected (a volume of ca. 15 mL) to determine the concentration of analyzed cytokines (VEGF, endostatin, TNFα, IL-6). Samples were taken early in the morning, between 6:30 A.M. and 8:00 A.M. After blood collection, test tubes were left for 2 hours at the room temperature, subsequently centrifuged. Obtained samples were divided into 4 even parts, which were stored at -80°C until tests were conducted.

The levels of IL-6, VEGF, endostatin and TNFα have been marked with ELISA method, using commercial tests purchased in R&D Systems Inc. (614 Mc Kinley Place NE, Minneapolis MN 55 413, USA). Analyzes were performed in Chair of Physiology JU MC in Cracow. Calculations were carried out using STATISTICA set. To describe evaluated groups, in case of continuous variables, mean value and standard deviation, median, the first and third quartiles, minimum and maximum were applied. For qualitative variables percentage description was used. The qualitative variables were compared by using c2 test, and in case of low abundance-Fisher's exact test. To analyze quantitive variables, while comparing two groups, Mann-Whitney test was applied, and the Kruskal-Wallis test when the number of groups was higher. Effects that were regarded to be relevant, were those for which the likelihood of a Type I error was lower than the established statistical significance level 0.05 ($p<0.05$).

Results

Percentage of presentations of rosacea in our patients was shown in Figure 1.

Serum VEGF concentration in patients with different subtypes of rosacea and in examined control group

In the control group mean serum VEGF concentration amounted to 238.6 ± 43.7 pg/mL (Figure 1) in both sexes. Mean serum VEGF concentration in all rosacea patients (subtypes ETR and PPR) was statistically significantly higher than in the control group and reached 324.1 ± 33.0 pg/mL (Figure 2). In the control group, amongst women, the mean level of VEGF in blood was equal to 245.1 ± 45.0 pg/mL, whereas in female patients with rosacea this value was much higher: 332 ± 43.7 pg/mL. In respective groups of men the VEGF levels were:

	ETR (n=44)	PPR (n=28)
Patients' age (years)	49.2 (± 12.3)	48.3 (± 13.8)
Patients' sex		
Female	26 (59.2%)	18 (64.3%)
Male	18 (40.8%)	10 (35.7%)
Severity of skin lesions	ETR 2 16 (36.3%) ETR 3 28 (63.7%)	PPR 2 15 (53.5%) PPR 3 13 (46.5%)
Duration of the disease	12.5 years (± 5.60)	11.5 years (± 6.07)

Table 1: Clinical data of patients participating in the study.

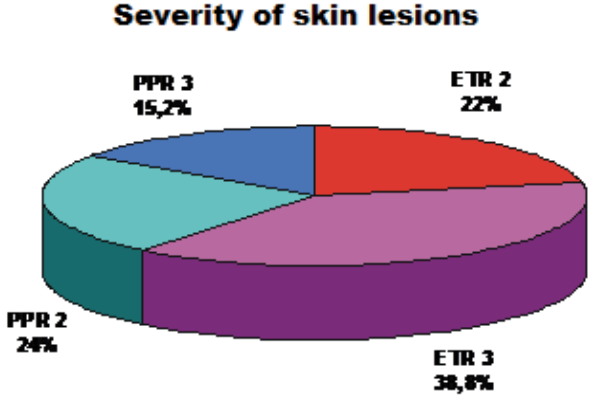

Figure 1: Severity of skin lesions (in patients with PPR general type) in patients with various subtypes of rosacea (number of patients: n=72, before treatment ETR 2: n=16; ETR 3: n=28; PPR 2: n=15; PPR 3: n=13, after treatment asymptomatic: n=4; ETR 1: n=36; ETR 2: n=27; ETR 3: n=5).

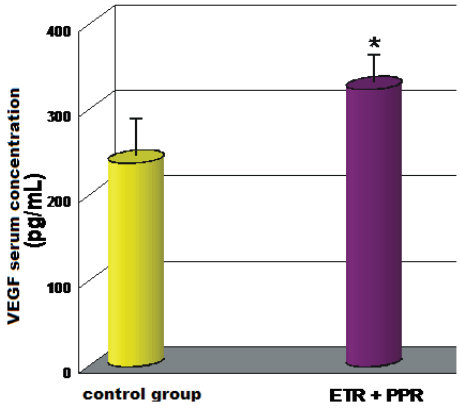

Figure 2: Serum VEGF concentration in the healthy volunteers group (n=21) and in the group of patients (n=72) with rosacea (mean values ± SEM of results obtained from 72 patients; the control group- mean values ± SEM of results obtained from 21 healthy volunteers). Mark (*) means statistically significantly higher VEGF level value in the group of patients before treatment comparing to the control group (p<0.05).

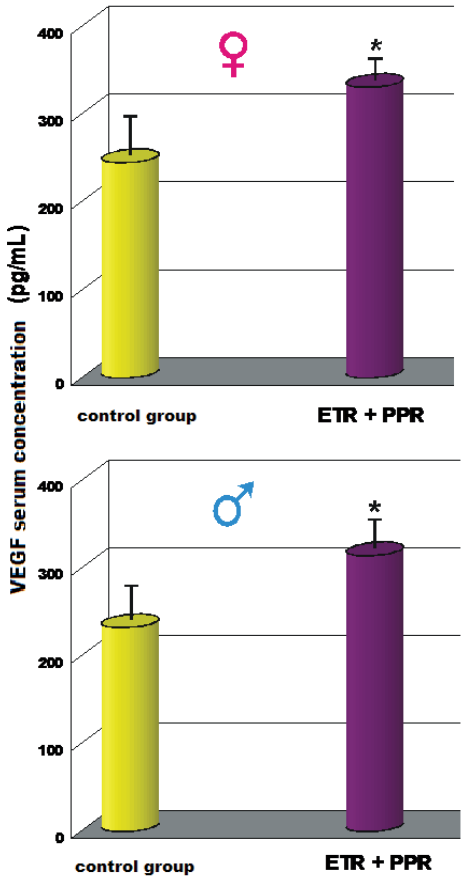

Figure 3: Serum VEGF concentration in the control group and in the group of patients (n=72) with rosacea according to patients' gender (mean values ± SEM of results obtained from 44 female and 28 male patients; the control group-mean values ± SEM of results obtained from healthy volunteers: 11 female and 10 male). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05).

232.2 ± 39.0 pg/mL (control group) and 314,0 ± 33,1 pg/mL (rosacea patients). There were no significant differences found between VEGF concentrations in male and female (Figure 3). VEGF level analysis (cumulatively in both sexes and separately in male and female groups) in different subtypes of rosacea patients blood serum was presented in Figures 4 and 5. The highest VEGF concentration was found in ETR 3 group and reached 370.2 ± 74 pg/mL (in the entire group, men and women concomitantly). In ETR 3 and PPR 2 rosacea patients concentrations of VEGF in blood serum was statistically significantly higher than in the control samples. The lowermost VEGF values were found in ETR 2 and PPR 3 rosacea groups. However, comparing patients with various forms of this disorder, the differences between the VEGF levels were not statistically significant.

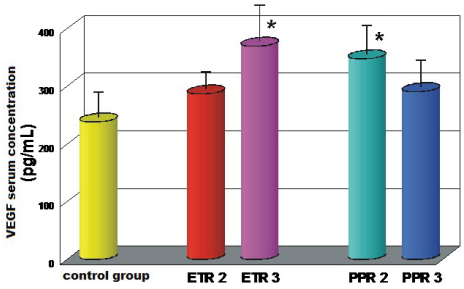

Figure 4: Serum VEGF concentration in the healthy volunteers group and in the group of patients with rosacea according to clinical subtype and severity of changes. Results present mean values ± SEM in particular groups (group abundance: ETR 2: n=16; ETR 3: n=28; PPR 2: n=15; PPR 3: n=13; control group: n=21). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05).

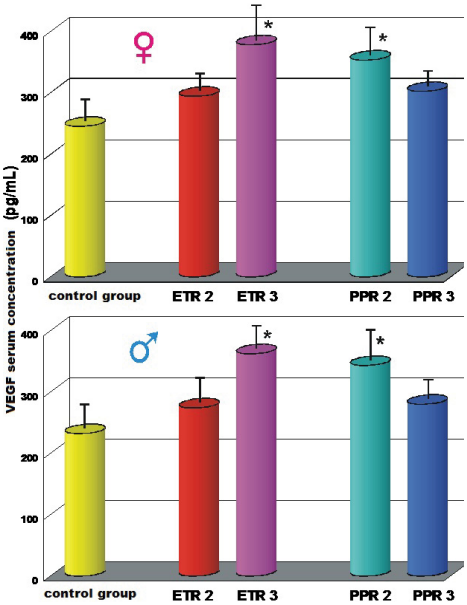

Figure 5: Serum VEGF concentration in the healthy volunteers group and in the group of patients with rosacea according to clinical subtype and severity of changes - divided to female and male. Results present mean values ± SEM in particular groups. Group abundance: female - ETR 2: n=10; ETR 3: n=16; PPR 2: n=9; PPR 3: n=9; control group: n=11; male - ETR 2: n=6; ETR 3: n=12; PPR 2: n=6; PPR 3: n=4; control group: n=10). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05).

Serum endostatin concentration in patients with different subtypes of rosacea and in examined control group

In the group of healthy volunteers mean level of endostatin amounted to 411.5 ± 40.2 pg/mL. In the whole group of rosacea patients (ETR and PPR collectively) mean endostatin level reached 261.2 ± 50.4 pg/mL and was statistically significantly lower than in the control group (Figure 6). According to obtained results, patients sex has no significant impact on endostatin level in control groups of female and male (399.0 ± 42.0 and 424.1 ± 45.1 pg/mL, respectively), as well as in rosacea patients (267.7 ± 50.1 and 254.7 ± 51.1 pg/mL, respectively) (Figure 7). Considering endostatin levels in blood collected from patients on different rosacea severity stages, it was found that in all investigated forms of the disease (ETR 2, ETR 3, PPR 2, PPR 3) concentration of the endostatin was far lower than in subjects from the healthy control group (Figure 8). There were no statistically significant differences between individual forms of rosacea (ETR 2, ETR 3, PPR 2, PPR 3), no substantial diversity was noted between female and male in whom the form of the disorder was alike.

Serum TNFα concentration in patients with different subtypes of rosacea and in examined control group

The TNFα concentration measured in the healthy group (control group) reached 2.62 ± 0.42 pg/mL, although there was no significant difference in this interleukin concentration between female and male groups (2.55 ± 0.46 and 2.69 ± 0.53 pg/mL, respectively). Mean TNFα value in the whole group of rosacea patients amounted to 3.08 ± 0.48 pg/mL, so it was not statistically significantly different from the control value assayed in healthy volunteers. There was also no statistically significant difference in TNFα blood concentration between female and male with rosacea (3.11 ± 0.42 and 3.03 ± 0.42 pg/mL, respectively) (Figures 9 and 10). In subtypes ETR 2, ETR 3, PPR 2 groups TNFα concentration does not deviate relevantly from control values. In patients with subtype PPR 3 this value was equal to 3.68 ± 0.49 pg/mL, therefore only in this form of rosacea TNFα concentration was statistically significantly higher than in healthy group (Figure 11). Signally higher, comparing to the control, TNFα concentration was found in female with PPR 3 rosacea and it reached 3.93 ± 0.7 pg/mL, whereas in corresponding male group this value was slightly higher than in the control, but it was not statistically significant (Figure 12).

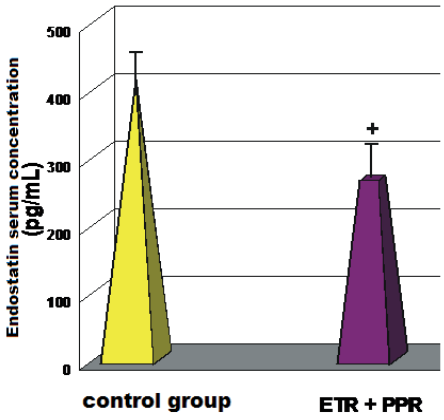

Figure 6: Serum endostatin concentration in the healthy volunteers group (n=21) and in the group of patients (n=72) with rosacea (mean values ± SEM of results obtained from 72 patients; the control group - mean values ± SEM of results obtained from 21 healthy volunteers). Mark (+) means statistically significantly higher endostatin level value in the group of patients before treatment comparing to the control group (p<0.05).

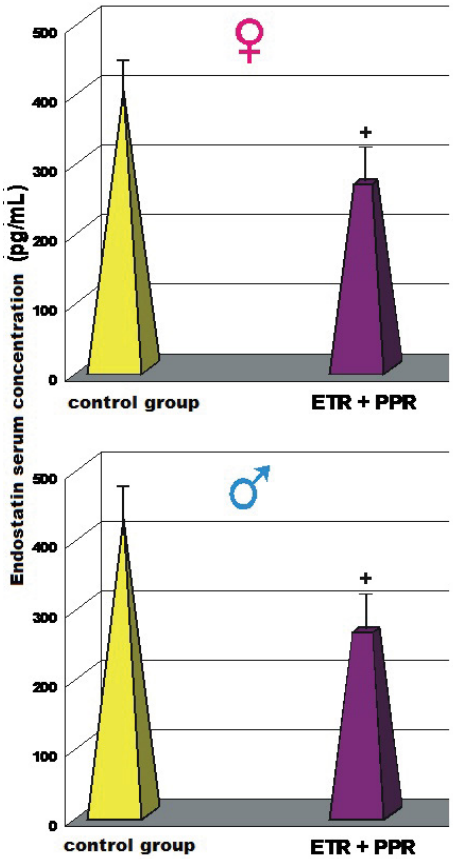

Figure 7: Serum endostatin concentration in the healthy volunteers group and in the group of female and male according to patients' gender (mean values ± SEM of results obtained from 44 female and 28 male patients; the control group-mean values ± SEM of results obtained from healthy volunteers: 11 female and 10 male). Mark (+) means statistically significantly higher value comparing to the control group (p<0.05).

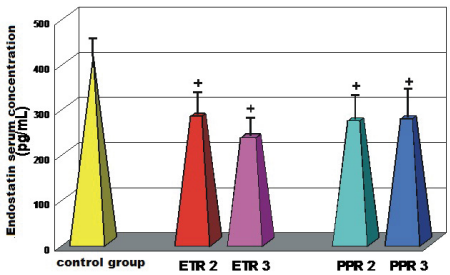

Figure 8: Serum endostatin concentration in the healthy volunteers group and in the group of rosacea patients according to clinical subtype and severity of changes. Results present mean values ± SEM in particular groups (groups abundance: ETR 2: n=16; ETR 3: n=28; PPR 2: n=15; PPR 3: n=13; control group: n=21). Mark (+) means statistically significantly higher value comparing to the control group (p<0.05).

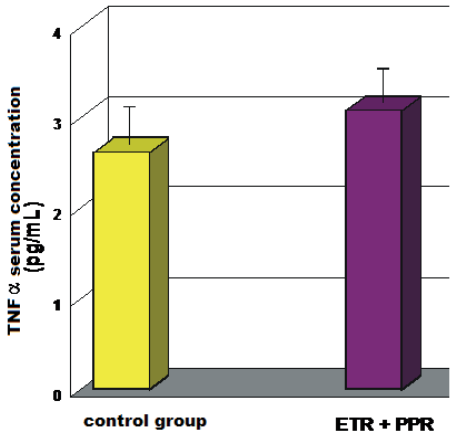

Figure 9: Serum TNFα concentration in the healthy volunteers group (n=21) and in the group of patients (n=72) with rosacea (mean values ± SEM of results obtained from 72 patients; the control group-mean values ± SEM of results obtained from 21 healthy volunteers).

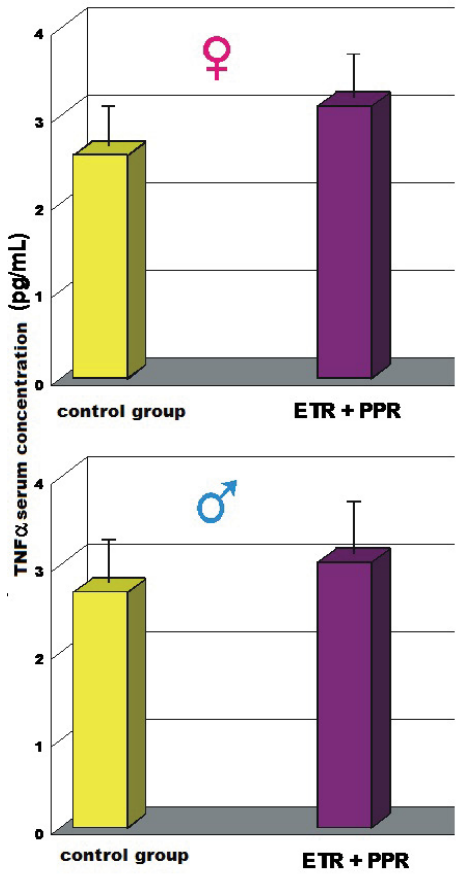

Figure 10: Serum TNFα concentration in the control group and in the group of patients with rosacea according to patients' gender (mean values ± SEM of results obtained from 44 female and 28 male patients; the control group-mean values ± SEM of results obtained from healthy volunteers: 11 female and 10 male).

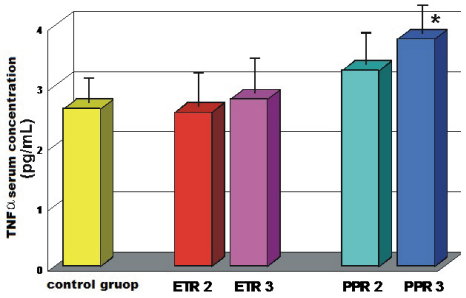

Figure 11: Serum TNFα concentration in the healthy volunteers group and in the group of rosacea patients according to clinical subtype and severity of changes. Results present mean values ± SEM in particular groups (groups abundance: ETR 2: n=16; ETR 3: n=28; PPR 2: n=15; PPR 3: n=13; control group: n=21).

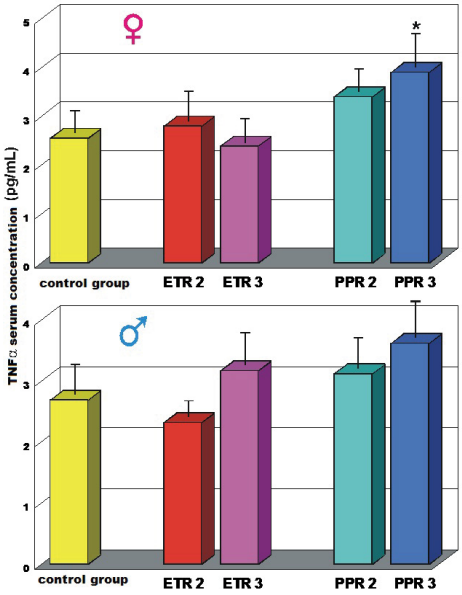

Figure 12: Serum TNFα concentration in the healthy volunteers group and in the group of patients with rosacea according to clinical subtype and severity of changes-divided to female and male. Results present mean values ± SEM in particular groups. Group abundance: female-ETR 2: n=10; ETR 3: n=16; PPR 2: n=9; PPR 3: n=9; control group: n=11; male - ETR 2: n=6; ETR 3: n=12; PPR 2: n=6; PPR 3: n=4; control group: n=10).

Serum IL-6 concentration in patients with different subtypes of rosacea and examined control group

In the control group (healthy volunteers) mean IL-6 concentration amounted to 1.28 ± 0.25 pg/mL. In the entire group of patients with rosacea (ETR and PPR) this value reached 2.82 ± 0.51 pg/mL and was statistically significantly higher comparing to the control group (Figure 13). No statistically significant differences in IL-6 levels among control groups was found: female (1.16 ± 0.25 pg/mL) and male (1.38 ± 0.45 pg/mL), as well as between female and male rosacea groups (2.88 ± 0.63 and 2.74 ± 0.4 pg/mL, respectively) (Figure 14). While considering IL-6 concentration in patients with rosacea separately, it was found that this interleukin levels were statistically significantly higher in both: ETR and PPR groups than in control group of healthy volunteers (Figure 15). The lowermost IL-6 concentration value occurred in patients with ETR 2 group (2.22 ± 0.45 pg/mL), and the top one was observed in PPR

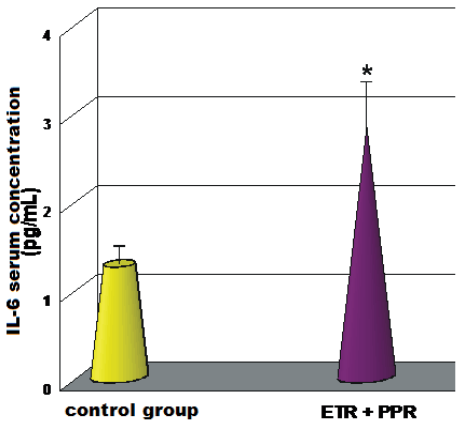

Figure 13: Serum IL-6 concentration in the healthy volunteers group (n=21) and in the group of patients (n=72) with rosacea (mean values ± SEM of results obtained from 72 patients; the control group-mean values ± SEM of results obtained from 21 healthy volunteers). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05).

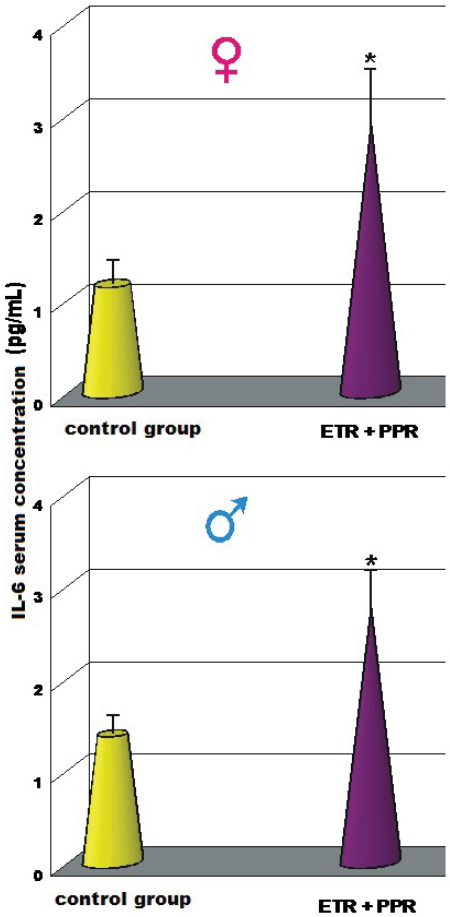

Figure 14: Serum IL-6 concentration in the healthy volunteers group and in the group of patients with rosacea according to patients' gender (mean values ± SEM of results obtained from 44 female and 28 male patients; the control group - mean values ± SEM of results obtained from healthy volunteers: 11 female and 10 male). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05). Mark (+) means statistically significant decline in tested cytokine level after treatment comparing to baseline (before treatment).

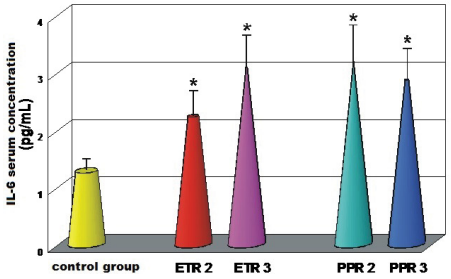

Figure 15: Serum IL-6 concentration in the healthy volunteers group and in the group of rosacea patients according to clinical subtype and severity of changes. Results present mean values ± SEM in particular groups (groups abundance: ETR 2: n=16; ETR 3: n=28; PPR 2: n=15; PPR 3: n=13; control group: n=21). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05).

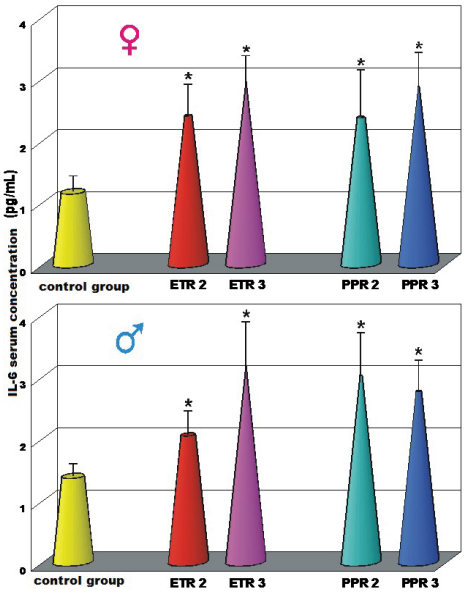

Figure 16: Serum IL-6 concentration in the healthy volunteers group and in the group of patients with rosacea according to clinical subtype and severity of changes - divided to female and male. Results present mean values ± SEM in particular groups. Group abundance: female - ETR 2: n=10; ETR 3: n=16; PPR 2: n=9; PPR 3: n=9; control group: n=11; male- ETR 2: n=6; ETR 3: n=12; PPR 2: n=6; PPR 3: n=4; control group: n=10). Mark (*) means statistically significantly higher value comparing to the control group (p<0.05).

2 patients (3.18 ± 0.63 pg/mL). IL-6 levels in patients of other groups (ETR 3, PPR 3) did not vary considerably. There were no statistically significant differences in IL-6 blood concentration between female and male groups with the same severity of rosacea (Figure 16).

Discussion

Conducted researches proved that angiogenesis stimulating VEGF blood serum concentration in patients with rosacea is statistically significantly higher than in healthy population, whereas anti-angiogenic endostatin level is decreased in this group. Elevated IL-6 value was also noted, while TNFα concentration does not differ from the control group of healthy volunteer's results. Observation concerning raised VEGF concentration in rosacea patients mentioned above, is related to other authors results, who believe that vascular endothelial growth factor is

responsible for angiogenesis stimulation [22,23]. As our investigation has shown, the maximum VEGF level presented in ETR 3 rosacea patients, so the subtype with the most severe vascular abnormalities. Typical vascular changes noted on the face's skin in patients with rosacea such as erythema and multitudinous telangiectasias indicate on the significantly increased (perhaps locally) pro-angiogenic activity of the system. In Smith et al. study [25] prominent enhancement of VEGF receptors (VEGF R1 and VEGF R2) in epithelial cells obtained from rosacea patients' skin biopsies was observed. Also on the surface of inflammatory cells (lymphocytes, macrophages, and plasmatic cells) collected from those patients' skin lesions numerous VEGF receptors appearance was demonstrated, what can substantiate our observations relating to this cytokine's involvement in rosacea pathogenesis.

Serum endostatin in rosacea patients was statistically significantly lower than in the group of healthy subjects, what points that its deficiency plays a role in rosacea pathogenesis. In previous studies [26] negative correlation between endostatin and bFGF (potent angiogenesis stimulating factor) concentration was noted. In current surveys a similar relationship was also described-the elevation of the serum endostatin after the treatment was accompanied by prominent decrease of the pro-angiogenic VEGF level. Endostatin belongs to the degradation products of XVIII collagen group and is one of the angiogenesis inhibiting connective tissue proteins. Moreover, endostatin is released by metalloproteinases. Their increased activity coexists with inflammation [27]. Recent research states that endostatin may play an important role in the pathogenesis of skin diseases. Raised serum endostatin concentration was observed in patients with the chronic urticaria [28]. Some scientists consider endostatin to be an early systemic sclerosis indicator, as its production increase in the early stages of this disorder [29]. In some studies significantly higher endostatin concentration was discovered in patients with psoriasis in remission what could be an expression of the compensation mechanisms mobilization in relation to intensified angiogenesis in the course of this disease [30]. In these surveys lower serum endostatin in rosacea patients than in healthy group was observed. It can be assumed that the endostatin production in rosacea patients is impaired; however, further investigation shall be performed to clarify mechanisms which lead to endostatin insufficiency.

One of the factors influencing the rosacea course is the inflammation which, according to many authors, underlies rosacea symptoms appearance such as: papules, pustules as well as nodules, fibrosis and hypertrophic changes [6,8]. In its initial period, inflammation development depends primarily on the granulocytes activation-cells of early stages of inflammation and cytokines released or activated by them, e. g. IL-6, TNFα, also reactive oxygen species or other inflammatory mediators [31]. TNFα has a particular prominence in the regulation of inflammation associated processes. TNFα, among others, secondarily stimulates pro-inflammatory cytokines as well as anti-inflammatory agents production [21,24,31]. In performed assays serum TNFα concentration in patients with various types of rosacea and in healthy volunteers were not relevantly different from each other. Statistically significantly higher serum TNFα was found only in female with most severe (inflammatory) changes in the course of the PPR rosacea-PPR 3. What is interesting, analogical male group has not shown similar relationship. This nonidentity between both sexes can be explained by the fact of more intensified inflammatory component in women. Many patients "manipulated" within lesions area (with their hands) what undoubtedly aggravated inflammation. Prior studies regarding to TNFα concentration in rosacea patients' tears also did not picture elevated level of this cytokine both in patients with ocular form of rosacea and in those without any ocular symptoms [32].

In the present paper, noticeable elevation of serum IL-6 concentration in patients with rosacea was noted. This interleukin is produced by monocytes and macrophages. It acts by lymphocytes T stimulation, lymphocytes B differentiation stimulation and is also associated with acute phase protein formation [33]. On the other hand, IL-6 inhibits retroactively TNFα production [34]. Furthermore, stimulative impact of IL-6 on angiogenesis was also demonstrated [35]. It enhances releasing VEGF from thrombocytes what rouses angiogenesis whilst inflammation [36]. Reported statistically significant raised serum IL-6 level in patients, compared to control group, may be one of the factors that are responsible for angiogenesis intensification in these subjects.

Conclusion

Results of conducted studies indicate on possible involvement of factors such as: VEGF, endostatin, TNFa and IL-6 in rosacea etiopathogenesis. It appears that the process of multiplied creation of new skin blood vessels in rosacea patients is associated, at least partially, with the disturbance of the balance between the pro-angiogenic VEGF and anti-angiogenic endostatin production. The increment in IL-6 generation relates to inflammation and potentiates angiogenesis. It is highly probable that explaining causes of the VEGF overproduction and the endostatin deficiency in the course of rosacea will enable the development of an effective strategy to prevent this disease.

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