INTRODUCTION

Angiogenesis plays an important role in the pathogenesis of chronic inflammatory joint diseases. Increased angiogenesis stimulates the formation of new vessels in the articular synovium in patients with rheumatoid arthritis (RA). Moreover, angiogenesis participates in endothelial dysfunction in patients with RA and those with chronic kidney disease. Synovial angiogenesis is regulated by a combination of tissue hypoxia, upregulation of endothelial growth factors, and downregulation of the inhibitors of angiogenesis. Vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic and acidic fibroblast growth factors (FGFb and FGFa) are cytokines that play a key role in the initiation of angiogenesis.

In chronic inflammatory joint diseases, inflammation may regulate the expression of VEGF. In patients with psoriatic arthritis (PsA), it has been confirmed that vascular morphological changes are present in the skin and nail fold. It has also been suggested that similar vascular lesions are present in the synovial membrane in PsA. Ellevated serum levels of VEGF are correlated with disease activity and radiographic damage in RA, Wegener’s granulomatosis, systemic lupus erythematosus, and spondyloarthopathies. On the other hand, the +936 T allele in the VEGF gene may protect against the development of PsA.

The potential roles of VEGF, EGF, FGFb, and FGFa in angiogenesis and correlations with disease activity in PsA and SAPHO syndrome (the acronym stands for synovitis, acne pustulosis,
Serum was stored at –70°C until the analysis of VEGF, EGF, FGFb, and FGFa using a sensitive sandwich enzyme-linked immunosorbent assay (Human VEGF Immunoassay Quantikine® ELISA kit, Human EGF Immunoassay Quantikine® ELISA kit, Human FGF basic Immunoassay Quantikine® ELISA kit and Human FGF acidic Immunoassay Quantikine® ELISA kit, R&D System, United States). The system uses microplates with the walls coated with a monoclonal antibody and an enzyme-linked polyclonal antibody specific for VEGF, EGF, FGFb, or FGFa. All analyses and calibrations were performed in duplicate and were read using BioTek PowerWaveXS (Biotek Instruments, United States).

Data distributions were assessed using the Shapiro–Wilk test. Data were described as mean ± standard deviation and median (Q1, Q3). We used the rank Spearman’s test to calculate correlations. The r values of correlations were determined and corresponding P-values of less than 0.05 were considered significant. The groups were compared using the Mann–Whitney U test and Kruskal–Wallis test. The statistical analysis was performed using the STATISTICA software, version 6.0.

RESULTS The clinical and laboratory characteristics of the patients and controls are presented in the TABLE. Serum VEGF, EGF, FGFb, and FGFa levels were similar between the patient groups and controls (P > 0.05) (FIGURES 1 and 2). In the study group, 75 patients were treated with disease-modifying antirheumatic drugs (37 received methotrexate, 2 received methotrexate in combination with cyclosporine A, and 36 received sulfasalazine) and 23 received only

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Psoriatic arthritis (n = 80)</th>
<th>SAPHO syndrome (n = 18)</th>
<th>Healthy controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, y</td>
<td>50.1 ±12.0</td>
<td>51.0 ±11.1</td>
<td>48.1 ±14.0</td>
</tr>
<tr>
<td>sex, n (female/male)</td>
<td>43/37</td>
<td>17/1</td>
<td>12/8</td>
</tr>
<tr>
<td>disease duration, y</td>
<td>4.5 (2.0, 10.0)</td>
<td>2.0 (2.0, 4.0)</td>
<td>0</td>
</tr>
<tr>
<td>VAS pain, mm</td>
<td>45.0 (31.0, 67.0)</td>
<td>38.5 (34.0, 48.0)</td>
<td>0</td>
</tr>
<tr>
<td>PASI</td>
<td>3.0 (0.3, 8.0)</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>3.9 (1.6, 9.2)</td>
<td>3.7 (1.2, 8.7)</td>
<td>–</td>
</tr>
<tr>
<td>hemoglobin, mmol/l</td>
<td>8.5 ±0.8</td>
<td>8.1 ±0.6</td>
<td>–</td>
</tr>
<tr>
<td>WBC, G/l</td>
<td>7.2 (5.9, 9.0)</td>
<td>7.0 (6.0, 9.0)</td>
<td>–</td>
</tr>
<tr>
<td>platelets, G/l</td>
<td>245.0 (224.0, 307.0)</td>
<td>254.9 ±71.1</td>
<td>–</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>10.0 (6.0, 21.0)</td>
<td>13.0 (6.0, 30.0)</td>
<td>–</td>
</tr>
<tr>
<td>VEGF, pg/ml</td>
<td>288.6 (193.2, 551.0)</td>
<td>333.1 (205.0, 375.0)</td>
<td>300.1 (217.0, 437.6)</td>
</tr>
<tr>
<td>EGF, pg/ml</td>
<td>110.0 (60.0, 162.0)</td>
<td>138.0 (70.0, 228.0)</td>
<td>93.0 (45.0, 192.5)</td>
</tr>
<tr>
<td>FGFb, pg/ml</td>
<td>0 (0, 0)</td>
<td>0</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>FGFa, pg/ml</td>
<td>0 (0, 0)</td>
<td>0</td>
<td>0 (0, 0)</td>
</tr>
</tbody>
</table>

Data are presented as number or mean ± standard deviation (Q1, Q3). Abbreviations: CRP – C-reactive protein, EGF – epidermal growth factor, ESR – erythrocyte sedimentation rate, FGFa – acidic fibroblast growth factor, FGFb – basic fibroblast growth factor, PASI – Psoriasis Area and Severity Index, SD – standard deviation, VAS – visual analogue scale, VEGF – vascular endothelial growth factor, WBC – white blood count.
Serum levels of angiogenic cytokines in psoriatic arthritis and SAPHO syndrome

EGF levels were found between patients with the peripheral and axial forms of the disease ($P = 0.56$ and $P = 0.28$, respectively). In the group of 64 patients with peripheral arthritis, there were no differences between the subgroups of patients with polyarthritis, oligoarthritis, and distal arthritis in terms of ESR, CRP, VEGF, EGF, FGFB, and FGFA levels ($P > 0.05$).

In the PsA group, serum VEGF levels were positively correlated with CRP levels ($P = 0.04$), the BASFI score ($P = 0.03$), and disease duration ($P = 0.007$). There were no correlations between serum VEGF levels and PLT, ESR, BASDAI, BASMI, BASG, VAS, or age ($P > 0.05$).

No correlations were found in the PsA group between EGF and CRP, ESR, PLT, BASDAI, BASFI, BASMI, BASG, VAS, age, or disease duration ($P > 0.05$). Moreover, no differences were found in this group between the subgroups of patients receiving different treatments in terms of VEGF and EGF levels ($P > 0.05$).

Only 9 patients (11.3%) with PsA had measurable FGFB levels (above 0 ng/ml) and only 18 (22.5%) had detectable FGFA levels (above 0 ng/ml).

In patients with SAPHO syndrome, 17 patients had palmoplantar pustulosis and 1 patient had severe acne. No significant correlations were observed between VEGF and EGF levels and CRP, ESR, PLT, BASDAI, BASFI, BASMI, BASG, VAS, age, or disease duration ($P > 0.05$). We did not calculate correlations for FGFB and FGFA in the SAPHO group because only 1 patient (5.6%) had FGFB levels over 0 ng/ml and only 4 patients (22.2%) had FGFA levels over 0 ng/ml. No differences were found in this group between the subgroups of various treatment regimens in terms of VEGF ($P = 0.99$; **FIGURE 3**) and EGF levels ($P = 0.80$; **FIGURE 4**).

**DISCUSSION** There are scarce data in the literature regarding a potential role of serum VEGF in disease pathogenesis and its correlations with disease activity in patients with PsA. Moreover, no data have been found for the serum levels of VEGF or other angiogenic cytokines in SAPHO syndrome. On the other hand, there are data available on serum VEGF levels in RA patients. Serum VEGF may be derived from a number of sources including neutrophils, synovial fluid, inflamed synovial tissue, and platelets. The presence of VEGF has been demonstrated in serum, synovial membrane, and synovial fluid in patients with RA. In these patients, VEGF is produced by neutrophils and its concentration in the synovial fluid is correlated with disease activity. However, no correlations have been shown between VEGF concentrations in the synovial fluid and those in serum in patients with RA. In these patients, serum VEGF is correlated with the markers of acute disease and the number of swollen and tender joints. Previous studies reported higher serum VEGF levels in early disease in patients with RA.
the differences in their concentrations in serum and synovial fluid.

The formation of new vessels plays an important role in the inflammatory process in the course of sacroilitis and enthesitis in ankylosing spondylitis. Angiogenesis also plays a role in bone formation, especially in diseases characterized by bone formation. Angiogenesis is stimulated by VEGF. Goldberger et al. reported a positive correlation between serum VEGF levels and the BASMI in patients with ankylosing spondylitis. The absence of differences in serum VEGF levels in PsA patients with peripheral arthritis and axial disease could suggest the potential role of VEGF in synovitis and enthesitis.

In the PsA group, the lack of correlations between the markers of angiogenesis and the PASI score could be partly explained by low severity of skin lesions (mean PASI score, 7.1).

No differences between the patient groups and controls in terms of serum concentrations of angiogenic cytokines could be explained by low activity of the disease following treatment that might have affected serum concentrations of angiogenic cytokines and resulted in a decrease of their levels.

No differences between the subgroups of various treatment regimens in terms of VEGF and EGF levels could be explained by the effectiveness of treatment.

We were unable to demonstrate a relationship between the concentrations of various angiogenic cytokines and the parameters of disease activity in the SAPHO group. This may due to the small size of the group.

Our study has several limitations including a small number of study patients (especially in the SAPHO group) and no group of patients without treatment.

In conclusion, our data suggest a role of VEGF in PsA. Further studies are required to better understand the role of angiogenic cytokines in PsA.

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REFERENCES

Serum levels of angiogenic cytokines in psoriatic arthritis and SAPHO syndrome


Ocena stężeń w surowicy cytokin angiogennych u chorych na łuszczycowe zapalenie stawów i zespół SAPHO

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ARTYKUŁ ORYGINALNY

STRESZCZENIE

Angiogeneza bierze udział w patogenezie zapalenia stawów.

Celem pracy była ocena stężen w surowicy wybranych angiogennych cytokin i ich związku z obrazem klinicznym u chorych na łuszczycowe zapalenie stawów (ŁZS) i zespół SAPHO.

Badaniami objęto 98 chorych: 80 chorych na ŁZS i 18 chorych na SAPHO. Zebrano następujące dane: wiek, płeć, czas trwania choroby, zajęcie stawów, typ łuszczycy, łuszczyczne zmiany paznokci oraz leczenie. Oceniano następujące wskaźniki aktywności ŁZS i SAPHO: PASI, BASDAI, BASFI, BASMI, BASG i VAS. Oznaczono OB, stężenie białka C-reaktywnego (C-reactive protein – CRP) oraz płytki krwi. Metodą ELISA w surowicy badanych oznaczono: czynnik wzrostu śródbłonka naczyń (vascular endothelial growth factor – VEGF), naskórkowy czynnik wzrostu (epidermal growth factor – EGF), zasadowy i kwasowy czynnik wzrostu fibroblastów (basic and acidic fibroblast growth factors – FGFb i FGFa).

U chorych na ŁZS wykazano dodatnią korelację między stężeniem VEGF i CRP (p = 0,04), wartością BASFI (p = 0,03) i czasem trwania choroby (p = 0,007). Nie wykazano różnic między grupą chorych z łuszczycą paznokci a bez niej w stężeniu VEGF (p = 0,32) i EGF (p = 0,85). Nie wykazano różnic między grupą chorych z obwodową a osiową postacią zapalenia stawów w stężeniu VEGF (p = 0,56) i EGF (p = 0,28). Nie wykazano istotnych korelacji między stężeniem EGF i FGF a obrazem klinicznym ŁZS. U chorych na SAPHO nie wykazano istotnych korelacji między stężeniem angiogennych cytokin a obrazem klinicznym.

Wyniki sugerują, że VEGF bierze udział w patogenezie ŁZS. Konieczne są dalsze badania, żeby lepiej zrozumieć rolę angiogennych cytokin w ŁZS.

SŁOWA KLUCZOWE

czynnik wzrostu fibroblastów, czynnik wzrostu śródbłonka naczyń, naskórkowy czynnik wzrostu, łuszczyczne zapalenie stawów, zespół SAPHO

WPROWADZENIE

angiogeneza

CELE

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