Research Article

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Evaluation of vascular endothelial growth factor levels in rheumatoid arthritis patients, with and without joint swelling; a comparison with erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor and anti-cyclic citruillnated protein

Eklem Şişliği Olan ve Olmayan Romatoid Artritli Hastalarda Vasküler Endoteliyal Büyüme Faktörü Düzeyleri ve Eritrosit Sedimantasyon Hızı, C-Reaktif Protein ve Anti-Siklik Sitrülinlenmiş Protein Düzeyleri ile Karşılaştırılması

DOI 10.1515/tjb-2016-0308
Received February 25, 2016; accepted October 11, 2016; previously published online February 17, 2017

Abstract

Introduction: The aim of our study was to investigate the vascular endothelial growth factor levels in joint swelling-positive and joint swelling-negative rheumatoid arthritis patients and to then examine the relationship between conventional parameters such as the erythrocyte sedimentation rate and the levels of C-reactive protein, rheumatoid factor, and anti-cyclic citrullinated protein.

Methods: Fifty-nine (52 women and seven men) rheumatoid arthritis patients and 25 (20 women and five men) healthy individuals volunteered for this study. The patient group was divided into two sub-groups based on whether or not they exhibited joint swelling.

Results: The levels of vascular endothelial growth factor in the joint swelling-negative group were significantly different from those in the joint swelling-positive group, but they were not different from those in the control group ($p = 0.001$ and $p = 0.72$, respectively). We investigated the correlation between vascular endothelial growth factor and C-reactive protein levels ($r = 0.37$, $p = 0.001$). We also evaluated the diagnostic adequacy of vascular endothelial growth factor and created a ROC curve. The area under the curve was calculated to be 0.767.

Conclusion: Vascular endothelial growth factor is an adequate diagnostic biomarker and can successfully be used to predict the occurrence of rheumatoid synovitis based on local inflammation.

Keywords: Vascular endothelial growth factor (VEGF); Erythrocyte sedimentation rate (ESR); C-reactive protein

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(CRP); Rheumatoid factor (RF); Anti-cyclic citrullinated protein (ACCP); Rheumatoid arthritis (RA).

Özet

Giriş ve amaç: Çalışmamızın amacı eklem şişliği olan ve olmayan romatoid artritli hastalarda Vasküler Endotelyal Büyüme Faktörü düzeylerinin araştırılması ve romatoid artrit tanı ve takibinde konvansiyonel parametreler olan Eritrosit Sedimantasyon Hızı, C-Reaktif Protein, Romatoid Faktör ve Anti-siklik Sitrülinlenmiş Protein düzeyleri ile ilişkisi olup olmadığının incelenmesidir.
Yöntem ve gereçler: Elli dokuz (52 kadın ve 7 erkek) romatoid artritli hasta ve 25 (20 kadın ve 5 erkek) sağlıklı kişi çalışmaya gönüllü olarak katıldı. Hasta grubu eklem şişliği olması ve eklem şişliği olmamasına göre alt gruplara ayrıldı.
Bulgular: Eklem şişliği negatif olan grup eklem şişliği pozitif olan gruptan anlamlı şekilde farklıyken, kontrol grubu ile aralarında istatistiksel olarak fark olmadığını gözlendi ($p = 0.001$ ve $p = 0.72$, sırasıyla). Vasküler Endotelyal Büyüme Faktörü ve C-Reaktif Protein düzeyleri arasında korelasyon olduğunu saptandı ($r = 0.37$, $p = 0.001$). Çalışmamızda Vasküler Endotelyal Büyüme Faktörü'nün tanısal yeterliği değerlendirilmesi için ROC eğrisi oluşturuldu. Eğri altında kalan alan 0.767 olarak hesaplandı.
Tartışma ve sonuç: Vasküler Endotelyal Büyüme Faktörü romatoid artrite bağlı olarak gelişen lokal enflasyonun belirlenmesinde kullanılabilecek bir biyobelirteçtir.

Anahtar Kelimeler: Vasküler Endotelyal Büyüme Faktörü (VEGF); Eritrosit Sedimantasyon Hızı (ESR); C-Reaktif Protein (CRP); Romatoid Faktör (RF); Anti-Siklik Sitrülinlemiş Protein (ACCP); Romatoid Artrit (RA).

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by uncontrolled inflammatory synovitis, hyperplastic synovium, joint swelling, cartilage and bone destruction, and autoantibody production [rheumatoid factor (RF) and anti–cyclic citrullinated protein antibodies]. It also has systemic features including cardiovascular, pulmonary, and skeletal disorders. RA severely affects quality of life and also has socioeconomic costs [1]. The prevalence of RA in Turkey is 0.36%–1% [2–4]. Angiogenesis is the formation of new capillaries from pre-existing vessels [5]. It is an essential event in the perpetuation of inflammatory and immune responses and in the support of the pannus growth and development of RA [6]. Vascular endothelial growth factor (VEGF) is a critical angiogenic factor that affects endothelial, inflammatory, and neuronal cells [7]. VEGF stimulates endothelial cell proliferation and migration and stabilizes newly formed blood vessels [8]. VEGF expression is increased in macrophages and fibroblasts in the synovial membrane of RA patients and is present in the synovial fluid and sera of RA patients [9]. VEGF-A is a 34–42 kDa dimeric, disulfide-bound glycoprotein that is a member of the VEGF family of angiogenesis-related proteins. The VEGF-A gene is located on the short (p) arm of chromosome 6 at position 12 [10]. The VEGF-A gene contains eight exons, which primarily give rise to five alternatively spliced isoforms (VEGF121, VEGF145, VEGF165, VEGF189, and VEGF206) [11]. Microvascular density is significantly higher in RA synovial tissues expressing VEGF 165. It has been shown that VEGF165 is the more specific isoform for RA [12]. In this paper, the term VEGF will refer only to isoform 165.

The erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP) are classical markers of inflammation that have long been used for the diagnosis and monitoring of RA [13]. Traditionally, the ESR has been the most widely used marker of inflammation in RA. The ESR is an indirect measure of inflammation and reflects the level of acute-phase plasma proteins (e.g. fibrinogen) in the blood that cause the red blood cells to settle more rapidly [14]. CRP is a member of the pentraxin family of proteins. It is composed of five 23-kDa subunits, and its expression can increase by 1000-fold or more with infection, inflammation, and tissue injury [15].

RF was the first antibody detected in RA patients and has been used as a biomarker of RA since 1940. Several different autoantibodies have been identified over time [16]. Recently, antibodies binding to citrullinated proteins have come into prominence. Activated peptidylarginine deiminases present in inflamed tissue citrullinate many peptides [17, 18]. Citrulline is the main antigenic epitope to which autoantibodies bind in RA [19]. The prevailing view is that anti-cyclic citrullinated protein (ACCP) has a higher specificity than RF, although it has a similar sensitivity [20, 21].

Laboratory tests for the diagnosis of RA have progressed significantly over the last decade. In contrast to the former criteria set forth by the American Rheumatism Association (ARA) in 1987, the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) of 2010 highlighted the importance of using CRP and RF as diagnostic criteria and described ACCP as a new diagnostic biomarker [22]. Thus, the use of ACCP, RF, ESR

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and CRP as a means of predicting the diagnosis and prognosis of RA has gained much more importance than ever before.

Swelling is considered to be one of the characteristics of inflammation. Joint swelling resulting from the inflammation of the synovial tissues of the joints is one of the symptoms of RA [23]. The clinical diagnosis of joint synovitis is based on inspection, palpation and range of motion [24]. The disease activity score uses 28 joint counts (DAS28) and has been widely used in clinical trials to monitor disease activity and to assess patients with RA. The DAS28 is calculated from four components: the tender and swollen joint counts (both of which are determined by the treating doctor), the visual analogue scale (VAS) score of the patient's global health and the laboratory parameter (ESR or CRP) [25, 26]. The DAS28 score is a single index calculated from several variables and is an indirect indicator of inflammation in RA. The search for a simple and direct method for the diagnosis, monitoring and treatment of synovitis in RA still continues. The number of studies focused on VEGF has gradually increased over the last decade, and VEGF has become a potential biomarker for RA.

We hypothesized that VEGF levels are higher in the joint swelling-positive patients than in the joint swelling-negative patients, and thus, VEGF levels may be a direct and quantitative indicator of synovitis in RA. To test the hypothesis, we divided the patient groups according to the presence of joint swelling. The presence of joint swelling was detected by a rheumatology specialist according to the ARA criteria. The aim of our study was to investigate the VEGF levels in joint swelling-positive and joint swelling-negative RA patients and to then examine the relationship between ESR, CRP, RF and ACCP levels.

Materials and methods

This study was conducted at the Medical Biochemistry Laboratory and Rheumatology Clinic of the Haseki Training and Research Hospital in Istanbul, Turkey. Fifty-nine (52 women and seven men) patients volunteered for this study. The control group (20 women and five men) was selected from healthy volunteers. All of the patients were questioned face-to-face regarding age, gender, time of diagnosis, the presence of joint swelling, the presence of joint tenderness, joint erosion, duration of treatment, history of smoking and the presence of other systemic diseases. People who had predisposing factors for angiogenesis, such as hypertension, a history of smoking and other inflammatory conditions, were excluded from the study. The groups were determined by the rheumatology specialist based on clinical evaluation. The patient group was divided into two sub-groups depending on the presence or absence of joint swelling. All of the patients were using disease-modifying anti-rheumatic drugs (a combination of methotrexate and sulfasalazine). This study was conducted in accordance with the Declaration of Helsinki (1964).

After the patients fasted for 12–16 h, venous blood samples were collected in gel-separated tubes without anticoagulant for VEGF, ACCP, CRP and RF analysis. In addition, whole-blood samples were collected in EDTA tubes for ESR analysis and studied from fresh samples. After 30 min, the blood samples were centrifuged at $1500 \times g$ for 10 min. Serum samples were stored at – 20°C for approximately 10–90 days.

VEGF analysis

A commercial human VEGF immunoassay kit (Biosource, CA, USA) was used for the analysis of VEGF levels. The ELISA kit is a solid-phase sandwich immunoassay that is designed for the detection of VEGF isoform 165. Its reported precision within each run (CV) is 4.3%.

ACCP analysis

A commercial CPA (citrullinatedprotein antibodies) ELISA kit (Genesis Diagnostics, Cambridgeshire, England) was used for the analysis of ACCP levels. The test was designed for the detection of IgG antibodies against citrullinated proteins. The reported precision within each run (CV) is 5.5%.

RF analysis

RF levels were measured using an immunonephelometric technique. A BN II nephelometer (Dade Behring, Hamburg, Germany) was used for the measurement of RF.

CRP analysis

CRP levels were measured using an immunonephelometric technique. A BN II nephelometer (Dade Behring,

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Hamburg, Germany) was used for the measurement of CRP.

ESR analysis

ESR analysis was carried out using the Westergren method.

The findings were evaluated using the SPSS (Statistical Package for Social Sciences) 17 package program (IBM, NY, USA). The mean, standard deviation (SD), median, minimum (min) and maximum (max) values were calculated as descriptive statistics. The quantitative data did not conform to normal distribution characteristics, and the groups were independent. Thus, the Kruskal-Wallis test was applied to investigate the differences between the groups in terms of the measured parameters with a 95% confidence interval. The probability value (p) was set at <0.05. The Mann-Whitney U-test was applied for one-to-one group comparisons with a 95% confidence interval, and the p-value was set at 0.017 for the three groups using the Bonferroni correction. The Spearman correlation analysis was applied to evaluate the relationship between the parameters. The power of this study was calculated using the PASS 12 package program (NCSS, UT, USA). The receiver operating characteristic (ROC) curve was used to evaluate the performance of VEGF values and to determine the optimal cut-off level.

Results

Descriptive analysis

The information for each group is given in Table 1. The descriptive statistics of the measured parameters are given in Table 2. The box plot graph illustrates the distribution of VEGF levels among the groups (Figure 1).

Power analysis

The power of this study with the current design, which contains three groups (one control and two patient) was calculated to be 0.82 using the Kruskal-Wallis test procedure for all pairs. The type I error (α value or p-value) was set at 0.05. The power of present study computed from results after the study is completed.

Group comparison

The three groups [control, joint swelling (–) and joint swelling (+)] were compared by Kruskal-Wallis analysis, and differences among the groups in terms of VEGF levels were observed ($p<0.001$). Mann-Whitney U-test was performed to specify the differing groups and the groups were compared with each other. A Bonferroni correction was applied, and the significance levels (p) were calculated to be 0.017. In terms of VEGF, there was no significant difference between the control group and the joint swelling (–) group ($p=0.72$). However, there were significant differences between the control group and the joint swelling (+) group ($p=0.001$) and between the joint swelling (–) and joint swelling (+) groups ($p<0.001$) (Table 3).

Correlation of evaluated parameters

Spearman correlation analysis was applied to evaluate the relationship among all of the parameters. We detected a significant positive relationship between VEGF

Table 1: Descriptive statistics for age, duration of illness, DAS28 scores and sex for three groups [standard deviation (SD), number of subjects (n)].

	Control group (n=25)		Joint swelling (–) group (n=28)		Joint swelling (+) group (n=31)	
	Mean	SD	Mean	SD	Mean	SD
Age	46.4	13.3	45.10	13.03	45.06	9.66
Duration of illness (years)	–	–	7.11	5.1	8.4	4.2
DAS28 score	–	–	2.1	0.8	4.7	1.5
Sex	n	%	n	%	n	%
Female	20	80.00	25	89.28	27	87.10
Male	5	20.00	3	10.72	4	12.90

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Table 2: The mean, standard deviation (SD), median, minimum (min) and maximum (max) values of ESR, CRP, RF, ACCP and VEGF measurements and the number of subjects (n) in three groups.

	Control group (n=25)	Joint swelling (–) group (n=28)	Joint swelling (+) group (n=31)
ESR (mm/h)			
Mean	12.36	39.07	35.73
SD	7.11	19.85	23.62
Median	12	26	30
min–max	2–25	8–84	8–105
CRP (mg/L)			
Mean	4.06	11.45	21.34
SD	1.67	11.43	21.00
Median	2.98	8.9	17.80
min–max	2.65–8.79	3–43.8	3–51
RF (IU/dL)			
Mean	18.83	113.43	108.83
SD	32.39	191.41	184.99
Median	9.5	12.6	23
min–max	9.5–165	9.5–859	9–624
Anti-CCP (U/dL)			
Mean	2.85	20.58	25.44
SD	3.49	31.84	34.12
Median	1.63	7.71	8.90
min–max	0.01–16.55	0.01–94.22	0.01–100.2
VEGF (pg/mL)			
Mean	63.03	69.29	155.70
SD	34.14	71.06	124.27
Median	66.23	50.16	128.41
min–max	2.66–111.6	1.26–278.6	20.1–523.8

Table 3: The results obtained from the statistical comparison of the groups using the Mann-Whitney U-test.

	Control group vs. joint swelling (–) group	Control group vs. joint swelling (+) group	Joint swelling (–) group vs. joint swelling (+) group
VEGF	0.72	0.001	<0.001
CRP	<0.001	0.001	0.75
ESR	<0.001	0.001	0.23
ACCP	0.082	0.048	0.625
RF	<0.001	0.001	0.73

The calculated p-values are listed in the table.

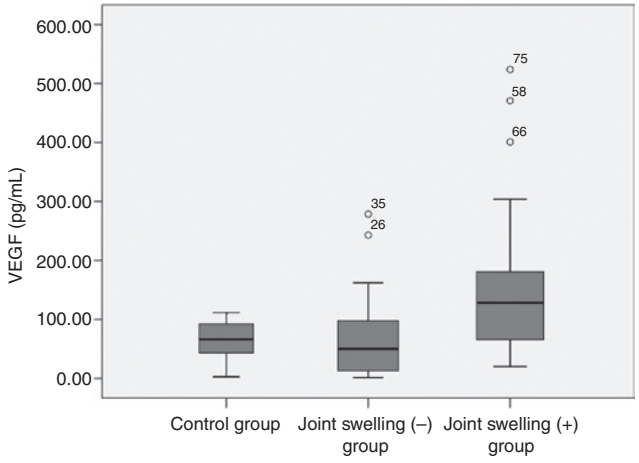

Figure 1: The distribution of the VEGF levels is depicted graphically by Box-plot graphic according to the groups. The median values, quartiles and outlier samples are demonstrated in the graphic.

and CRP levels (r=0.37, p=0.001), between VEGF and ESR levels (r=0.33, p=0.002) and between ACCP and RF levels (r=0.29, p=0.007). No significant relationship was observed between VEGF and ACCP levels (r=0.158, p=0.15).

Diagnostic adequacy of VEGF

We created a ROC curve to evaluate the diagnostic adequacy of VEGF. We created a two dimensional ROC curve. One is control the other is patient group. We combine the two patient groups [the joint swelling (–) and the joint swelling (+) group]. The diagnosis of the rheumatologist was considered the gold standard. The area under the curve was calculated to be 0.767. The ROC curve is shown in Figure 2. If the upper limit is set at 80 pg/mL, the sensitivity is 71% and the specificity is 67%.

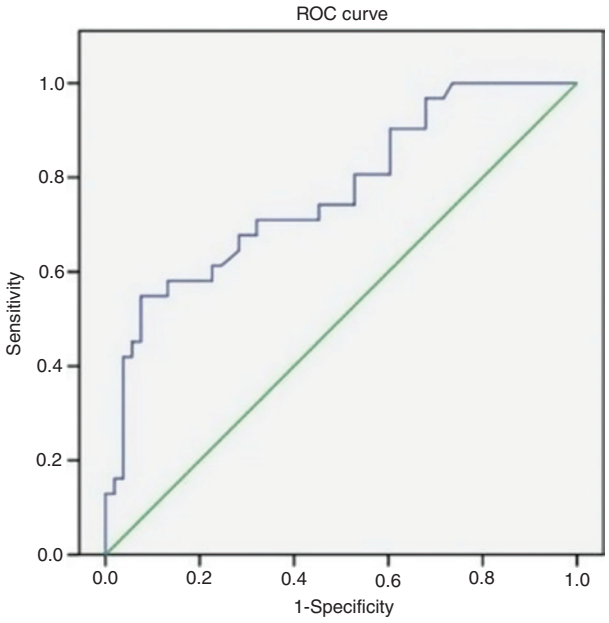

Figure 2: The ROC curve created from the analysis of VEGF levels. The area under the curve is 0.767.

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Discussion

The major finding of our study was that the level of VEGF in the joint swelling-negative group was significantly different from that of the joint swelling-positive group but not different from that of the control group ($p = 0.001$ and $p = 0.72$, respectively). CRP and ESR levels were significantly increased in both the joint swelling-negative and joint swelling-positive groups ($p < 0.001$, $p = 0.001$ and $p < 0.001$, $p = 0.001$, respectively) (Table 3). The microenvironment of an inflamed joint is characterized by a low partial pressure of oxygen [27]. HIF-1α is a hypoxia-induced transcription factor that stimulates the expression of VEGF in the inflamed synovium. HIF-1α-positive cells are strongly correlated with the number of blood vessels in RA synovial tissue and with inflammatory endothelial cell infiltration [28, 29]. During RA, hypoxia triggers angiogenesis, maintains a chronic inflammatory state by transporting inflammatory cells to the site of inflammation and induces hyperplasia by supplying nutrients and oxygen for the proliferation of the inflamed tissue. The increased endothelial surface area creates a capacity for the production of cytokines, chemokines, adhesion molecules and other inflammatory stimuli. Simultaneously, the development of new blood vessels in the synovial membrane allows for the invasion of this tissue and supports the active infiltration of synovial cells into cartilage resulting in the erosion and damage of the cartilage [30]. Emerging evidence suggests that fluid and serum VEGF levels are elevated in RA patients and by pro-inflammatory cytokines such as IL-1 and TNF-α [31]. This indicates that local and systemic inflammation are progressing simultaneously in RA. CRP and ESR are indicators of systemic inflammation, although VEGF seems to be more specific to the joints and to reflect the pathological condition of arthritic joints. Lee and Joo [32] reported that VEGF is correlated with disease activity and the swollen joint count. However, we were unable to reach any conclusion regarding the relationship between the conventional parameters and VEGF levels in RA patients with or without joint swelling.

We also calculated the correlation between VEGF levels and CRP or ESR levels measured in our study. ($p = 0.001$, $r = 0.37$ and $p = 0.002$, $r = 0.33$, respectively). This finding is consistent with those previously reported in the literature [9, 33].

Additionally, we tried to evaluate the diagnostic adequacy of VEGF using the data obtained from our study. We created a ROC curve and determined that the area under the curve was 0.767 (Figure 2). We aimed to select a cut-off level that would give the optimal sensitivity and specificity. If the upper limit was set at 80 pg/mL, the sensitivity was 71% and the specificity was 67%. The VEGF levels measured in this study are consistent with those reported in previous studies [9, 34–37]. The VEGF and cut-off levels determined in this study will contribute to the literature.

The presence of RF and ACCP are significant predictors of RA. We confirmed that ACCP and RF levels are significantly increased in RA patients. Our data have once again demonstrated the known relationship between RF and ACCP ($r = 0.29$, $p = 0.007$) [38]. We did not detect any significant relationship or correlation between the levels of VEGF and ACCP ($r = 0.158$, $p = 0.15$) [39–41].

In conclusion, VEGF is an adequate diagnostic marker for RA and can more successfully predict synovitis-based local inflammation. Additional studies should be performed to accumulate sufficient data on this subject.

Conflict of interest statement: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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