THE CORRELATIONS OF CYTOKINES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Objectives: Rheumatoid arthritis is the most common chronic arthritis. Although its etiology remains unclearly, various cytokines are known to play key roles as mediators that induce abnormality. **Subjects and Methods**: Determine the correlation between levels of serum *IL-1α,IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, MCP1, EGF* which clinical factors: disease duration, the number of damaged joint , DAS 28 as well as clinical factor: CRP,VS in patients whith rheumatoid arthritis. Subject and methods: The research in 76 patients with rheumatoid arthritis was diagnosed according to ACR/EULAR 2010, were examined to determine the disease duration as well as the number of damaged joints, take quantitative blood and serum concentrations of cytokines (*IL-1α,IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, MCP1, EGF),* CRP, and VS. **Result:** The average of cytokines serum concentrations in patients with rheumatoid arthritis are *(IL-1α,IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, MCP1, EGF),* (5,09; 10,73; 33,08; 6,62; 31,95; 79,92; 12,67; 549,21; 16,68; 15,90; 243,23; 115,17). Disease duration correlated with IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, MCP1. Was correlated the number of damaged joint were correlated with IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α. DAS 28 was correlates with IL-1α, IL-1β, IL-2, IL-4 , IL-6, IL-8, IL-10, IFN-γ, TNF-α . CRP correlated with IL-1α, IL-1β, IL-2 , IL-4 , IL-6, IL-10, IFN-γ , TNF-α.VS correlates with IL-1α, IL-1β, IL-2 , IL-4, IL-6, IL-10, IFN-γ, TNF-α . EGF wasn't correlated with disease duration, the number of damaged joint, DAS 28 as well as clinical factor: CRP,VS.

Key words: *Rheumatoid arthritis, chronic arthritis, IL-1α,IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, MCP1, EGF*

1. BACKGROUND

Rheumatoid arthritis is an autoimmune, chronic arthritis. The pathogenesis of this disease is very complex. Currently we can only restrict or stop the progression of the disease rather than cure, so the number of patients significantly increased. In recent years, there have been a better understanding of the inflammatory response and tissue destruction mechanisms of rheumatoid arthritis, in which the role of the cytokines had been increasingly asserted. The current target for new treatments to prevent or slow the bone destruction is directed at T lymphocytes and oriented to cytokines and tumor necrosis factor-α (TNF α). While medicine has not found a way to cure patients with rheumatoid arthritis, we can say that the understanding of the role of cytokines in the pathogenesis of rheumatoid arthritis is an important basis for the treatment of rheumatoid arthritis with biological drugs. Every year, new studies on this issue are bringing unexpected findings and increase hope for patients with rheumatoid arthritis. In Vietnam, in the field of cytokine, there have been inadequate studies. So we made this theme aims to:

Evaluate the correlation of cytokines with disease duration, number of inflamed joints, disease activity, CRP, erythrocyte sedimentation rate in patients with rheumatoid arthritis treated at Cho Ray Hospital.

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2. SUBJECTS AND METHODS

2.1. Study subjects

Study subjects are patients with rheumatoid arthritis treated at rheumatology department – Cho Ray hospital from June 2013 to April 2014 with the diagnosis of rheumatoid arthritis according to the diagnostic criteria of American Rheumatism Association and European League against Rheumatism 2010 (ACR/EULAR 2010).

Cases group include 76 patients

2.2. Exclusion criteria

- Patients with confusion, loss of consciousness, can not ask medical history
- The patients did not consent to participate in the study
- The patients with other kinds of autoimmune arthritis apart from rheumatoid arthritis such as: Multiple sclerosis, Systemic lupus erythematosus...
- Patients with ongoing infectious diseases
- Patients treated with biopharmaceutical
- Patient being treated with NSAIDS or corticoid

2.3. Methods

Descriptive cross-sectional Case-control study

Patients were asked about medical history, given clinical examination to diagnose rheumatoid arthritis according the criteria of ACR/EULAR 2010

Check the comorbidities to exclude

Patients were examined to identify disease duration, number of affected joints, and assessed the disease activity by DAS28 scale

The first day after admission, patients had blood drawn for cytokines testing simultaneously with RF, CRP, ESR.

Quantification of cytokine by the method of immunized luminescence

3. RESULTS

3.1. General characteristics of patients with rheumatoid arthritis

3.1.1. Duration of the disease

Most patients had the disease with the duration <5 years (67.1%). The average duration of the disease is 57.57 months (SD = 70.31), the shortest is 2 months, longest is 29 years.

3.1.2. Number of the affected joints

Average number of affected joints are 23.34 (SD =5.45). The minimun is 6 joints, maximum is 30 joints.

3.1.3. Assess the disease activity by DAS 28

Average value of DAS28: 7.175 ± 0.892; the lowest is 3,556; the highest was 8.559. high disease activity in 75 cases accounted for 98.7%, moderate disease activity in 1 cases accounted for 1.3%, no case with low disease activity.

3.2. Cytokine tests

Table 3.1. Mean, median of cytokines in patients with rheumatoid arthritis

Cytokin	Mean *(X± SD)*	Median
IL-1α (pg/mL)	57.36 ± 196.43	5.09
IL-1β (pg/mL)	123.77± 532.51	10.73
Il-2 (pg/mL)	279.93 ± 945.04	33.08
IL-4 (pg/mL)	41.62 ± 945.04	6.62
IL-6 (pg/mL)	91.35 ± 170.52	31.95
IL-8(pg/mL)	270.84 ± 445.45	79.92
IL-10(pg/mL)	134.58 ± 496.14	12.67
VEGF(pg/mL)	638.87 ± 540.18	549.21
IFN-γ (pg/mL)	136.43 ± 338.68	16.68
TNF-α (pg/mL)	106.27 ± 265.57	15.90
MCP1 (pg/mL)	292.34 ± 265.52	243.23
EGF (pg/mL)	152.62 ± 123.64	115.17

Comments: The average concentration of the cytokine highly increased in patients with rheumatoid arthritis. The highest is VEGF (638.87 ± 540.18), with the median of 549.21.

3.3. Relationship between cytokines and some clinical, laboratory manifestations in studied patients

3.3.1. IL-1α

Table 3.2. The relationship between levels of serum IL-1α with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL1-α		r*	p
	Increase	No increase		
Duration of the disease	96.52±82.49	30.78±44.48	0.648	<0.01
Number of the affected joints	26.06±2.81	21.47±6.02	0.526	<0.01
DAS 28	7.66±0.53	6.840±0.93	0.450	<0.01
CRP	94.2±67.8	41.99±44.33	0.447	<0.01
ESR	82.35±32.24	51.18±33.92	0.542	<0.01

**: Spearman's rank correlation*

IL-1α has a moderately positive correlation with the disease duration, number of affected joints, DAS 28, CRP, ESR (p <0.01).

3.3.2. IL1-β

Table 3.3. The relationship between levels of serum IL-1 β with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL1-β		r*	p
	Increase	No increase		
Duration of the disease	89.78±78.83	27.05±43.55	0.644	<0.01
Number of the affected joints	25.89±3.239	20.92±6.02	0.501	<0.01
DAS 28	7.64±0.54	6.732±0.93	0.502	<0.01
CRP	94.2±67.7	33.9±32.6	0.553	<0.01
ESR	82.95±28.97	45.82±33.75	0.621	<0.01

**: Spearman's rank correlation*

IL-1 β has a moderately positive correlation with disease duration, number of affected joints, DAS 28, CRP, ESR (p <0.01).

3.3. IL-2

Table 3.4. The relationship between levels of serum IL-2 with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL-2		r*	p
	Increase	No increase		
Duration of the disease	101.44 ±89.68	36.10±46.01	0.586	<0.01
Number of the affected joints	26.48 ±2.85	21.80±5.76	0.508	<0.01
DAS 28	7.62± 0.44	6.95±0.975	0.475	<0.01
CRP	109.45 ±62.04	40.65±45.28	0.522	<0.01
ESR	87.44±33.06	52.35±32.49	0.689	<0.01

**: Spearman's rank correlation*

IL-2 has a positive correlation with disease duration, number of affected joints, DAS 28, CRP, ESR in moderate levels (p <0.01).

3.4. IL4

Table 3.5. The relationship between levels of serum IL-4 with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL-4		r*	p
	Increase	No increase		
Duration of the disease	85.55±78.46	26.53± 42.89	0.648	<0.01
Number of the affected joints	25.75±3.152	20.68±6.21	0.429	<0.01
DAS 28	7.54±0.61	6.76±0.97	0.416	<0.01
CRP	85.54±66.59	36.32±38.41	0.453	<0.01
ESR	82.95±29.85	42.72±31.29	0.547	<0.01

**: Spearman's rank correlation*

IL-4 correlated moderately with: disease duration (r = 0.648; p <0.01), the number of affected joints (r = 0.429; p <0.01), DAS 28 (r = 0.416; p <0.01), CRP (r = 0.453; p <0.01), ESR (p <0.01).

3.5. IL-6

Table 3.6. The relationship between levels of serum IL-6 with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL-6		r*	p
	Increase	No increase		
Duration of the disease	57.59±70.28	-	0.392	<0.01
Number of the affected joints	23.34±5.44	-	0.353	<0.05
DAS 28	7.17±0.89	-	0.352	<0.05
CRP	63.28±60.48	-	0.275	<0.05
ESR	63.89±36.45	-	0.333	<0.01

**: Spearman's rank correlation*

IL-6 has a moderately positive correlation with disease duration, number of affected joints, DAS 28, ESR in moderate levels, weak positive correlation with CRP ($r = 0.275$, $p < 0.05$).

3.6. IL-8

Table 3.7. The relationship between levels of serum IL-8 with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL-8		r*	p
	Increase	No increase		
Duration of the disease	62.40±81.32	54.46±62.819	0.062	<0.01
Number of the affected joints	23.37±81.32	23.33±5.37	0.046	<0.01
DAS 28	7.16 ±0.87	7.17 ±0.91	0.092	<0.01
CRP	62.12 ±62.32	64.04±59.93	-0.068	>0.05
ESR	57.77±39.55	67.89±34.14	-0.096	>0.05

**: Spearman's rank correlation*

IL-8 positively correlated with: disease duration ($r = 0.062$), number of affected joints ($r = 0.046$) and DAS 28 ($r = 0.092$) with statistical significance ($p < 0.01$).

3.7. IL-10

Table 3.8. The relationship between levels of serum IL-10 with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IL-10		r*	p
	Increase	No increase		
Duration of the disease	67.97 ±73.98	11.64±5.69	0.619	<0.01
Number of the affected joints	24.89±3.71	16.50±6.67	0.502	<0.01
DAS 28	7.37±0.68	6.28±1.14	0.473	<0.01
CRP	70.68±62.55	30.50±36.38	0.452	<0.01
ESR	70.18±35.51	36.07±26.99	0.517	<0.01

**: Spearman's rank correlation*

IL-10 has a positive correlation with: disease duration, number of affected joints ($r = 0.502$), DAS 28 ($r = 0.473$), CRP ($r = 0.452$), ESR ($r = 0.517$)

3.8. VEGF

Table 3.9. The relationship between levels of serum VEGF with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	VEGF		r*	p
	Increase	No increase		
Duration of the disease	59.64±52.83	55.43±85.65	0.261	<0.05
Number of the affected joints	23.87 ±5.11	22.78±5.79	0.152	>0.05
DAS 28	7.20 ±0.81	7.14±0.97	0.086	>0.05
CRP	69.54 ±48.54	56.69±71.03	0.187	>0.05
ESR	67.87 ±36.97	59.70±35.93	0.070	>0.05

**: Spearman's rank correlation*

VEGF has a weak positive correlation with the disease duration ($r = 0.261$, $p < 0.05$). The correlation between VEGF and number of affected joints, DAS 28, CRP, ESR, RF, CRP has no statistical significance.

3.9. IFN-γ

Table 3.10. The relationship between levels of serum IFN-γ with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	IFN-γ		r*	p
	Increase	No increase		
Duration of the disease	75.22±77.57	21.64±29.90	0.567	<0.01
Number of the affected joints	25.51±3.23	18.92±6.37	0.447	<0.01
DAS 28	7.46±0.67	6.57±0.99	0.340	<0.05
CRP	79.39±64.58	30.41±32.63	0.513	<0.01
ESR	78.24±32.53	34.64±24.89	0.534	<0.01

**: Spearman's rank correlation*

IFN-γ have a moderate positive correlation with the disease duration (r = 0.567; p <0.01), the number of affected joints (r = 0.447; p <0.01), CRP (r = 0.513; p <0.01), ESR (r = 0.534; p <0.01), weak correlation with DAS 28 (r = 0.340; p <0.05).

3.10. TNF-α

Table 3.11. The relationship between levels of serum TNF-α with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	TNF-α		r*	p
	Increase	No increase		
Duration of the disease	80.53±77.69	20.41±31.62	0.635	<0.01
Number of the affected joints	25.62±3.30	19.66±6.22	0.506	<0.01
DAS 28	7.54±0.60	6.58±0.96	0.469	<0.01
CRP	86.38±63.29	25.84±29.46	0.611	<0.01
ESR	82.81±28.82	33.24±24.93	0.588	<0.01

**: Spearman's rank correlation*

TNF-α is moderately correlated with the disease duration (r = 0.635; p <0.01), the number of affected joints (r = 0.506; p <0.01), DAS 28 (r = 0.469 ; p <0.05), CRP (r = 0.661; P <0.01), ESR (r = 0.588; p <0.01).

3.11. MCP1

Table 3.12. The relationship between levels of serum MCP1 with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	MCP1		r*	p
	Increase	No increase		
Duration of the disease	75.61±60.37	49.77±73.33	379	<0.05
Number of the affected joints	2.00±3.92	22.62±5.87	0.160	>0.05
DAS 28	7.23±0.75	7.15±0.95	0.057	>0.05
CRP	76.42 ±58.91	57.58 ±60.80	0.263	>0.05
ESR	74.65±36.69	59.23±35.69	0.119	>0.05

**: Spearman's rank correlation*

MCP1 is weakly correlated with the disease duration (r = 0.379; p <0.05). The correlation between MCP1 and the disease duration, rheumatoid quantity, DAS 28, CRP, ESR is not statistically significant.

3.12. EGF

Table 3.13. The relationship between levels of serum EGF with clinical and laboratory manifestations of rheumatoid arthritis patients

Clinical, laboratory tests	EGF		r*	p
	Increase	No increase		
Duration of the disease	34.37±27.99	72.74±84.46	-0.114	>0.05
Number of the affected joints	22.07±5.58	24.17±5.25	-0.150	>0.05
DAS 28	7.10 ±0.83	72.21±0.93	-0.038	>0.05
CRP	43.06 ±52.84	76.47±62.01	-0.182	>0.05
ESR	54.23±37.78	70.20±35.53	-0.140	>0.05

**: Spearman's rank correlation*

No correlation was found between EGF and surveyed factors.

4. DISCUSSIONS

Our study subjects are patients diagnosed with rheumatoid arthritis according to the diagnostic criteria of American Rheumatism Association and European League against Rheumatism 2010 (ACR/EULAR 2010).

About some clinical characteristics, the shortest disease duration is 2 months, the longest is 29 years (348 months), the average is 57.57 months (SD = 70.31). Of these, 15 patients affected within 1 year, which is accounted for 19.7%. Our results are similar to findings of the study by Nguyen Thi Mong Trang at Cho Ray Hospital in 2006 [2]: the average disease duration is 5 years, of which 32.43% patients affected within a year. The average number of affected joints at the time of the study is 23.34 (SD = 5.44). The minimum is 6 joints, and maximum is 30 joints. This result is also consistent with the literature, in acute attacks of rheumatoid arthritis, the inflammation usually occurs in many joints. Assess the disease activity by DAS28: 7.44; the lowest is 3.5, the highest was 8.5. High disease activity in 75 cases, accounted for 98.7%, moderate disease activity in 1 cases, accounted for 1.3%, no cases with low disease acitivity. According to the study in other countries, this index is from 3.9 to 6.2 [5], [7], [11]. Thus, our results are significantly higher. This may be due to the fact that patients with rheumatoid arthritis in our country were not treated promply. However, high disease activity at one point does not reflect the stage of the disease.

Cytokine tests, in this study we examined 12 cytokines. Results obtained from Table 3.10 shows that: the increased concentration of cytokines in the serum of patients with rheumatoid arthritis is accounted for a high proportion. Especially IL-6 (100%). Followed by IL-10 (81.6%), IFN-γ (67.1%), TNF-α (61.8%) ... according to the study by CutuKculer N. et al, the concentration of the cytokine IL-1α, IL-2, IL-4, IL-6 and TNF-α in patients with rheumatoid arthritis are higher than healthy people [9]. According to Table 3.11, average levels of IL-1α is 196.43 ± 57.36, IL-6 is 91.35 ± 170.52, TNF-α is 106.27 ± 265.57. According to the study by N. et al KutuKculer in 22 patients in Turkey, the levels of these cytokines are IL1-α (3.24 ± 2.14), IL-6 (60.1±109.2), TNF-α (11.5 ± 13.2) [9], our results were significantly higher, this may result from the fact that our study was conducted in many rheumatoid arthritis patients at advanced stages so the cytokine levels are very high.

Relationships between cytokines and some clinical and laboratory manifestations in patients with rheumatoid arthritis

IL-1α derived from monocyte and macrophages is an endogenous pyrogen. In this study, we found that IL-1α has a moderate positive correlation with the disease duration, number of affected joints, DAS 28, CRP, ESR ($p < 0.01$, $|r| = 0.4$ to 0, 8). This result is consistent with studies of N. Kutuculer et al, in which there is no correlation between IL-1α and ESR ($r = 0.0168$, $p > 0.05$) [9].

IL-1β is also produced by macrophages. This is also an important mediator of inflammation in rheumatoid arthritis. It was found that IL-1β concentrations in patients with rheumatoid arthritis is higher than healthy people. In this study, we found that IL-1β is positively correlated with both the duration of diabetes, number of affected joints, DAS 28, CRP, ESR, RF ($p < 0.01$). Study of P.F.Zangerlecho found that IL-1β is also correlated with CRP ($p = 0.007$, $r = 0.09$).

According to Suenaga Y, concentrations of IL-2 receptor in serum of patients with rheumatoid arthritis is higher than healthy controls [12]. In this study, from the results in Table 3.14, we found that IL-2 is correlated with the disease duration, number of affected joints, DAS 28, CRP, ESR.

The role of IL-4 in rheumatoid arthritis is not well understood. In this study we noted that IL-4 is moderately correlated with the disease duration ($r = 0.648$; $p < 0.01$), the number of affected joints ($r = 0.429$; $p < 0.01$,), DAS 28 ($r = 0.416$; $p < 0.01$), CRP ($r = 0.453$; $p < 0.01$), ESR ($p < 0.01$), RF ($p < 0.01$, $r = 0.447$).

From the results of Table 3.5, we found that IL-6 is correlated with the disease duration, number of affected joints, DAS 28, CRP, ESR, RF and anti-CCP with statistical significance ($p<0.05$). IL-6 is seen as a very important role in rheumatoid arthritis. IL-6 have a high concentration in serum and synovial fluid of patients with rheumatoid arthritis and IL-6 concentrations are related to disease activity of rheumatoid arthritis [8]. Considering the correlation between CRP levels and IL-6 in serum of patients with rheumatoid arthritis, we found that serum IL-6 levels have a positive correlation with CRP, $r = 0.331$, with statistical significance ($p < 0.05$). The results of our study are similar to a number of studies in other

countries. According to the study by M. Yilmaz et al, IL-6 and CRP are correlated very closely . In Soo Jin Chung study, IL-6 has a positive correlation with CRP (r = 0.45, P = 0.007) [5]. Considering the correlation between serum IL-6 and erythrocyte sedimentation rate of patients with rheumatoid arthritis, we noticed a positive correlation between these two factors. This result is consistent with the findings of Phan Thi Thu Tram on the same subjects [3].

IL-8 concentrations is weakly correlated with the disease duration (r = 0.062), number of affected joints (r = 0.046) and DAS 28 (r = 0.092) with highly statistical significance (p<0.01). We found no correlation between IL-8 and CRP, ESR, RF and Anti-CCP. This result is consistent with the findings of M. Yilmaz et aL.

IL-10 increased in most patients with rheumatoid arthritis (81.6%), along with other cytokines such as IL-1, IL-6, TNF-α, IL-10, it also plays a central role in the process of joint synovitis. From the results in table 3:18, we found that IL-10 had a positive correlation with disease duration, number of affected joints (r = 0.502), DAS 28 (r = 0.473), CRP (r = 0.452) , ESR with statistical significance (p <0.01). When studying the effect of leflunomide on clinical parameters and serum levels of IL-6, IL-10, MMP-1 and MMP-3 in patients with refractory rheumatoid arthritis, Irena Litinsky et al found a correlation between the concentration of IL-10 with the number of affected joints (p = 0.0039) and the ESR (P = 0.0022) [10].

VEGF is produced by fibroblasts in the joints synovium. The proinflammatory cytokines such as TNF-α and IL-1 stimulates fibroblasts in the synovium and other cells to produce VEGF. In this study, from the results of Table 13.9, VEGF has a weak positive correlation with the disease duration (r = 0.261; p <0.05). This is also consistent with the literature. The production of VEGF in patients with rheumatoid arthritis significantly increased compared with healthy individuals. Patients with longer disease duration have a significantly higher VEGF concentration compared to patients with rheumatoid arthritis at early stages. The increased production of VEGF is related to prolonged disease duration [12]. In addition, we found no correlation between VEGF and the number of affected joint, DAS 28, CRP, ESR.

IFN-γ is produced mainly by T cells and natural killer cells activated by antigens. The main biological activity of IFN-γ is immunomodulatory, different to other interferon which are mainly antiviral. IFN-γ has been shown to be effective in the treatment of rheumatoid diseases. In this study, the results of Table 3.20 showed that IFN-γ is moderately correlated with disease duration (r = 0.567; p <0.01), the number of affected joints (r = 0.447; p <0.01), CRP (r = .0,513; p <0.01), ESR (p <0.01); weak correlation with DAS 28 (r = 0.340; p <0.05)

Recently, there are a lot of research going into the role of TNF-α. From the results of table 3.10, we found that TNF-α is moderately correlated with the disease duration (r = 0.635; p <0.01), the number of affected joints (r = 0.506; p <0.01) , DAS 28 (r = 0.469; p <0.05), CRP (r = 0.661; p <0.01), ESR (p <0.01). TNF-α have a moderate correlation. This result is similar to the study of N. Kutuculer: TNF-α is correlated with DAS 28 (r = 0.5024, p <0.05) and CRP (r = 0.05, p <0.05). However, in this study, the authors found no correlation between TNF-α and ESR (r = 0.0808, p> 0.05) [9].

MCP1 have a role in conditioning the immune response related to the inflammatory process in rheumatoid arthritis. However, the role of MCP1 in rheumatoid arthritis has not been studied much. From the results of Table 3.11, we find a weak correlation between MCP1 and the disease duration (r = 0.379; p <0.05), we did not find any correlation between MCP1 with disease duration, number of inflamed joints, DAS 28, CRP, ESR.

Finally EGF is epidermal growth factor. In this study we did not find any correlation between EGF and surveyed factors.

5. CONCLUSIONS

- Duration of the disease is correlated with IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, MCP1.
- Number of affected joint is correlated with IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α.
- DAS 28 is correlated with IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α.
- Number of joint inflammation is correlated with IL-1α,, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α.
- ESR is correlated with IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α
- In this study we did not find any correlation between EGF with surveyed factors.

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