Interleukin-10, Interleukin- 16 and Interferon-γ in serum of patients with rheumatoid arthritis and correlation with disease activity

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Abstract

Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown etiology. The rheumatoid synovium is characterized by infiltration of T cells, macrophage, B cells, and proliferating fibroblasts which aggressively invade cartilage and bone, thus destroying joints' ability to function.

In rheumatoid arthritis (RA) both an imbalance between excessive production of the proinflamatory and ant-inflammatory cytokines and skewing of the T cell to a T helper like response.

Cytokines have been shown to play a modulatory role in the pathogenesis of RA. The imunoregulatory cytokine IL-10 increases autoantibody production by B cell stimulates its survival, proliferation and differentiation. Moreover IL-10 inhibits the generation of proinflamatory cytokines and proliferation of T helper lymphocyte.

Interleukin 16 might play a role in the pathogenesis of chronic inflammation in RA. It has a proinflammatory properties by promoting recruitment of T cells into the rheumatoid synovium. Also IFN-γ is of interest because of the role it plays in the initiation and perpetuation of T helper cell .

Serum level of IL-10, IL-16, and IFN-γ were determined in patients with rheumatoid arthritis in relation to disease activity.

All patients with RA (n=30) showed highly significant increase in ESR, CRP, IL-10, IL-16, IFNγ compared to control group (p<0.01).

Positive correlation were found between IL-10 and each IL-16 and IFN-γ (p<0.001) (r=0.63, 0.55) respectively, and highly significant correlation between IL-16 and IFNγ (p<0.001) (r=0.89)were determined.

Results showed positive correlation between ESR and each IL-10, IL-16, IFNγ (p<0.001) (r=0.67, 0.87, 0.75) respectively. And highly significant correlation between CRP and each IL-10, IL-16, IFNγ (p<0.001) (r=0.0.71, 0.83, 0.73) which indicate relation between increase level of cytokine with disease activity.

These data suggest that there is increased production of IL-10, IL-16, and IFN-γ in patients with rheumatoid arthritis, and that it is correlated with the disease activity. These cytokines are interesting for further research and novel therapeutic approach in this inflammatory disease.

Introduction

Rheumatoid arthritis (RA) is inflammatory disease of unknown etiology chara-- cterized by destruction of joints *(Verhoef et al;2001)*. Activation and infiltration of immunologic cells, including macrophage and lymphocytes, are prominent features of chronic inflammation in rheumatoid arthritis *(Scola et al;2002)*.

In RA, the cytokines resulting from this cellular infiltration greatly influence the outcome of disease. Macrophage generally express higher levels of cytokines than lymphocyte in RA, while the lymphocyte contribution to inflammatory and/or joint destructive process may be more indirect *(Panayi et al;1992)*.

Two subsets of T cells are recognized by their ability to produce different types of cytokines. Th1 cell activity characterized by IFN-γ production participates in macrophage activation and thereby causes joint destruction *(Verhoef et al;2001)*

Th2 cells selectively produces IL-4, IL-5, IL-6, IL-10 and IL-13, these cytokines mediate transformation of B- lymphocytes into antibody producing plasma cells *(Libula et al;1995)*.The balance between T1 and T2 cells regulates the production of pro- and anti-inflammatory cytokines *(Verhoef et al;2001)*

Systemic clinical signs of rheumatoid, such as the acute phase response (ESR, and CRP) in turn depend on the balance between these pro- and anti-inflammatory cytokines *(Littman et al;1995)*.

Interleukin-10(IL-10) one of the cytokines which had been shown to exert a number of immunoregulatory and anti-inflammatory effect in RA *(Cush et al;1995)*. The immunoregulatory cytokine IL-10 increases autoantibody production by B cells from RA patients *(Reparon-Schujt et al;1998 and 2001))*.

A side from this immunostimulatory function, IL-10 inhibits the activation and effectors functions of T cells, macrophage, and monocytes *(Lard et al;2003)*.As an anti-inflammatory cytokine IL-10 has been shown to inhibit the synthesis of IL-1α, IL-1B, and TNF- α, IL-6, IL-8, IL-12, and IL-18. IL-10 also inhibits the synthesis of gelatinase and collagenase *(Oberholzer et al;2002)*.

Interleukin -16 (IL-16) also known as lymphocyte chemoattractant factor, is generally considered to play a decisive role in most immune and inflammatory responses (Kaufmann et al;2001) in rheumatoid arthritis the presence of IL-16 has been described in synovial tissues from patients with RA. However the functional activity of this T cell derived cytokine in the pathogenesis of RA is not completely understood *(Blaschke et al;2001)*.

Interferon- gamma (IFN- γ) is a secretary product of activated T-cell of the Th1 subset and natural killer cells (NK). INF-γ is produced in response to specific and non-specific immunologic activation of lymphocyte, usually T-lymphocytes *(Boehm et al;1997)*. IFN- γ can down-regulate parameters of joint destruction such as IL-1, matrix metalloproteinase and proliferation of fibroblast- like synoviocytes (FLS) *(Moller et al;2003)*.

Aim of the work

Is to determine the level of IL-10, IL-16, and IFNγ in serum of patients with rheumatoid arthritis and assessing their role with disease activity.

Patients and methods
Subjects:

Our study included 30 patients with rheumatoid arthritis and 10 healthy controls. All patients were selected from patients attending internal medicine department, Al Zahraa university hospital
Subjects were divided into 2 groups:

Group I: (RA group): 30 patients were fulfilling The 1988 Revised American Rheumatism Association (ARA) criteria for adults RA *(Arnett, et al 1988))* 22 were female and 8 were males.

Their Age ranged from 17-50 years with a mean of (28.3± 9.7).

Duration of disease ranged between 2.5 and 9 years with mean (5.2 ±2).

Morning stiffness ranged between 18 and 90 minute, with mean (19 ± 2).

Articular index score (AIS) ranged between 22 and 27 with mean (24.8 ± 1.7)

Group II: (Control group): 10 healthy age and sex matched volunteers; they were selected from medical and paramedical staff of the hospital, 2 males and 8 females. Their Age ranged between 19-51 years with mean (31.7 ±9.7).

All patients and controls were submitted to the following:
1- Complete history taking and full clinical examination
2-Routine laboratory investigations including:
- Complete blood picture by automated blood counter.
- Assessment of ESR in the first hour according to Westergen method (1921)

- Latex rheumatoid factor
- C-reactive protein (CRP level)
- Fasting blood sugar, liver function tests and kidney function tests, using Bohringer Mannheim Company photometric kits West Germany on Hitachi 911 auto analyzer.

3- Specific laboratory investigations including:

1. Serum IL-10 by ELISA
(II) Serum IL-16 by ELISA
2. Serum INF-γ by ELISA

- For this purpose blood samples from patients and control were taken at the morning to avoid the influence of the time of the day on lymphocyte responses and cytokines. About 5cc of venous blood was drawn and centrifuged for about 10 minutes and serum was separated, taken and stored at-20c° until time of analysis.

Cytokines concentration were measured in serum using a commercially available monoclonal antibody based sandwich ELISA kit (Biosourse Europe S.A) for human IL-10,IL-16 and INF- γ. Briefly, standards, samples, and controls tested sera were pipetted into wells pre-coated with murin monoclonal antibodies raised against each parameter followed by addition of horse radish peroxidase antibodies to each parameter. After an incubation period allowing the formation of a sandwich, coated Mab1+Mab2 HRP.

The microtiter plate was washed to remove unbound enzyme labeled antibodies. Bound enzyme labeled antibodies were measured through a chromogenic reaction. Chromogenic solution (TMB+ H2O2) was added and incubated. The reaction stopped with the addition of stop solution(H2SO4) and the microtiter plate was then read at 450nm wave length. The level of IL-10, IL-16 and INF γ were calculated from standard curve corresponding to the measured optical densities. The results expressed as pg/ml.

All RA patients met the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA (Arnett *et al*; 1988). The disease activity comprised assessment of morning stiffness

(MS) duration in minutes, articular index scor (AIS) (joint tenderness) it is measured using The Ritchia articular index (Ritichia, *et al*, 1968), ESR in the first hours hemoglobin percentage (Hb%) and radiological examination of the affected joints.

Statistical analysis

Results were tabulated and statistically analyzed through Compaq computer. The value were given as mean ±SD. Comparison of the values were performed using the unpaired student T test and one tailed P value is considered significant when it is <0.05.

Results

Baseline clinical and laboratory characteristic of the studied groups is provided in table(1).

Table (1) show the criteria of RA (Age, duration of disease, morning stiff, tender joint, swollen joint count, articular index score (AIS).

Table(2) and fig(1,2,3) show that There was highly significant increase in ESR, CRP in patients with RA compared to control group (P<0.001) .Also there was highly significant increase in serum IL-10, IL-16, IFNγ in patients with RA compared to control group (P<0.001).

Table (3) shows correlation between serum IL-10 and each Hb, ESR, CRP, IL-16, IFNγ in group I (30 patients with RA). There was highly significant correlation between S. IL10 and each of ESR, CRP, IL-16, IFNγ (p=<0.001) (r=0.67, 0.71, 0.63, 0.55) respectively. Also there was negative significant correlation between S.IL-10 and Hb (p=<0.001) (r=0.74). Fig 4 show positive correlation between IL-10 and IL-16 among group 1.

Fig 5 show positive correlation between IL-10 and IFNγ among group 1

Table (4) show correlation between serum IL-16 and each Hb, ESR, CRP, IFNγ in group I (30 patients with RA). There was highly significant correlation between S. IL16 and each of ESR, CRP, IFNγ (p=<0.001) (r=0.87, 0.83, 0.89,) respectively. Also there was negative significant

correlation between S.IL-16 and Hb (p=<0.001) (r=0.89).

Fig 6 show positive correlation between IL-16 and IFNγ among group 1.

Table (5) show correlation between serums IFNγ and each Hb, ESR, CRP, in group I (30 patients with RA). There was highly significant correlation between IFNγ and each of ESR, CRP, (p=<0.001) (r=0.75, 0.73) respectively. And also there was negative correlation between IFNγ and Hb (p=<0.001) (r=0.80).

Table (1): Clinical and biochemical data for 30 patients with rheumatoid arthritis (group 1) and 10 control subject

parameter	Group I patients with RA N=30 mean ±SD	Group II control N=10 mean ±SD
Age (years)	28.3 ± 9.7	31.1 ±9.7
Duration of disease (years)	5.2 ± 2	_____
Morning stiff (minuets)	19 ± 3.2	_____
Tender joint	9.4 ± 2	_____
Swollen joint count	3.6 ± 1.4	_____
AIS	14.8 ±1.7	_____
Hemoglobin (g/dl)	10.5 ± 1.1	12.5 ± 4.7
ESR (mm/h)	60 ± 30	15± 4
CRP (mg/l)	34.1 ± 12.6	1.8 ± 0.4
IL-10 (pg/ml)	27.9 ± 5.6	2.27 ± 0.3
IL-16 (pg/ml)	60.7 ± 41.4	3.2 ± 0.6
IFN-γ (pg./ml)	83.5 ± 16.8	12.6± 2.8

Table 2:Mean values of laboratory variables in patients with RA(group I) as compared to control group (group II).

parameter	Group I mean ±SD	Group II mean ±SD	P value	T value	significance
Hemoglobin (g/dl)	10.5 ±1.1	12.5 ±4.7	<0.01	7.9	HS
ESR (mm/h)	60± 30	15±4	<0.01	3.8	HS
CRP (mg/l)	34.1 ±12.6	1.8 ±0.4	<0.01	1	HS
IL-10 (pg/ml)	27.9 ±5.6	2.27 ±0.3	<0.01	9.2	HS
IL-16 (pg/ml)	60.7± 41.4	3.2 ±0.6	<0.01	1.2	HS
IFN-γ (pg./ml)	83.5 ±16.8	12.6±2.8	<0.01	1.1	HS

Table (3): Correlation between IL-10 and each hemoglobin level, erythrocyte sedimentation rate, C reactive protein, IL-16, and IFNγ in (group I) 30 patients with RA

	parameter	R value	P value	significance
IL-10 (pg./ ml)	Hemoglobin (g/dl)	- 0.74	<0.001	HS
	ESR (mm/h)	0.67	<0.001	HS
	CRP (mg/l)	0.71	<0.001	HS
	IL-16 (pg/ml)	0.63	<0.001	HS
	IFN-γ (pg./ml)	0.55	<0.001	HS

Table 4): Correlation between IL-16and each of hemoglobin level, erythrocyte sedimentation rate, C reactive protein, and IFNγ in 30 patients (group I) with RA

	parameter	R value	P value	significance
IL-16 (pg./ ml)	Hemoglobin (g/dl)	- 0.89	<0.001	HS
	ESR (mm/h)	0.87	<0.001	HS
	CRP (mg/l)	0.83	<0.001	HS
	IFN-γ (pg./ml)	0.89	<0.001	HS

Table (5): Correlation between IFNγ and each hemoglobin level, erythrocyte sedimentation rate, C reactive protein in (group I) 30 patients with RA

	parameter	R value	P value	significance
IFN-γ (pg./ ml)	Hemoglobin (g/dl)	- 0.80	<0.001	HS
	ESR (mm/h)	0.75	<0.001	HS
	CRP (mg/l)	0.73	<0.001	HS
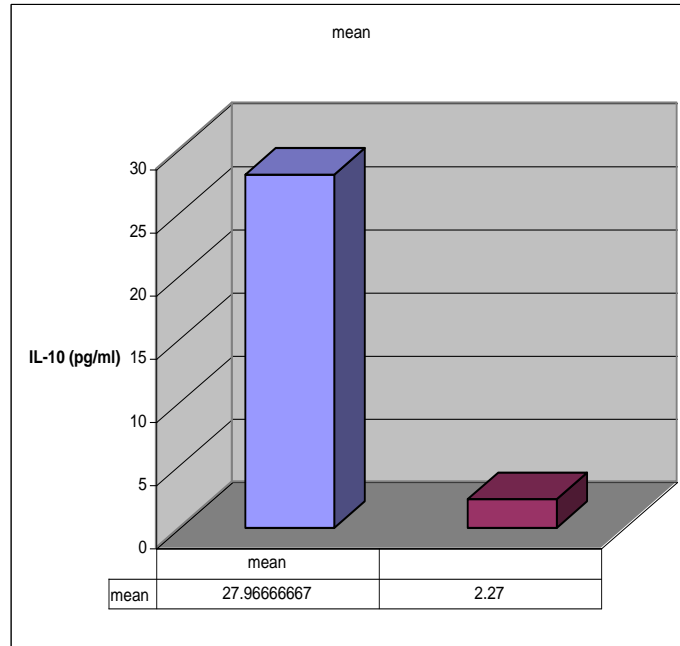
Fig(1) Mean values of IL-10 in rheumatoid arthritis group and control group
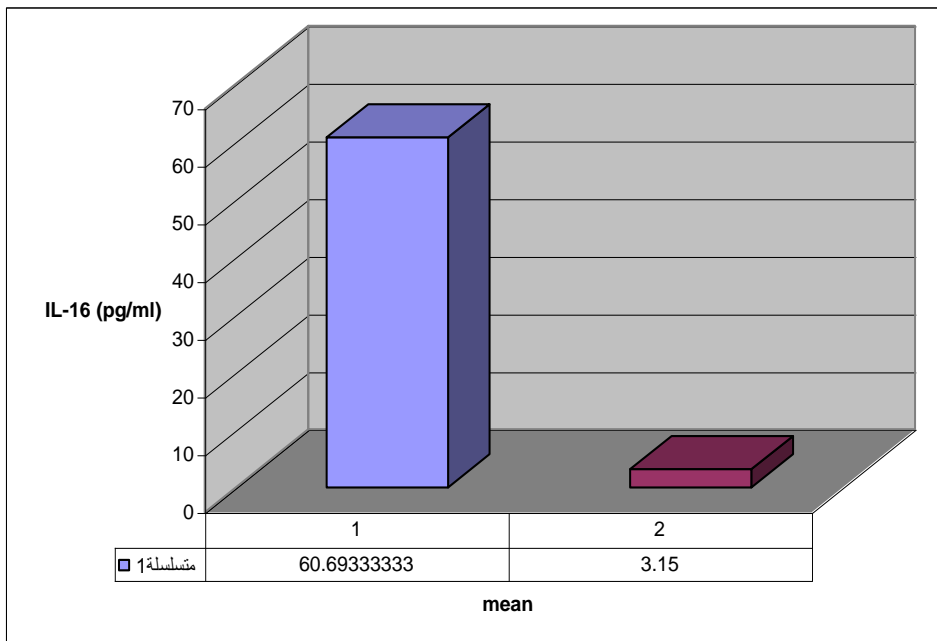
Fig (2) Mean values of IL-16 in patients with rheumatoid arthritis and control group.
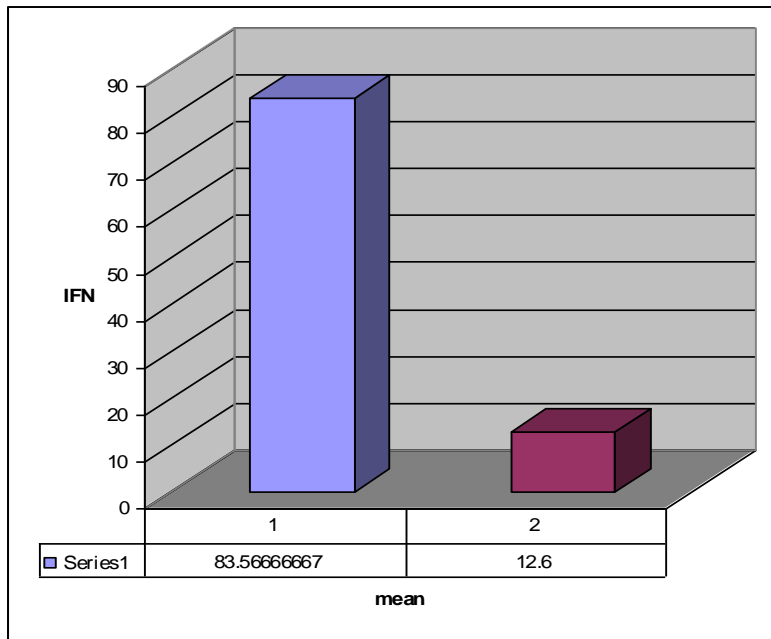
Interleukin-10, Interleukin- 16 and Interferon-γ……..

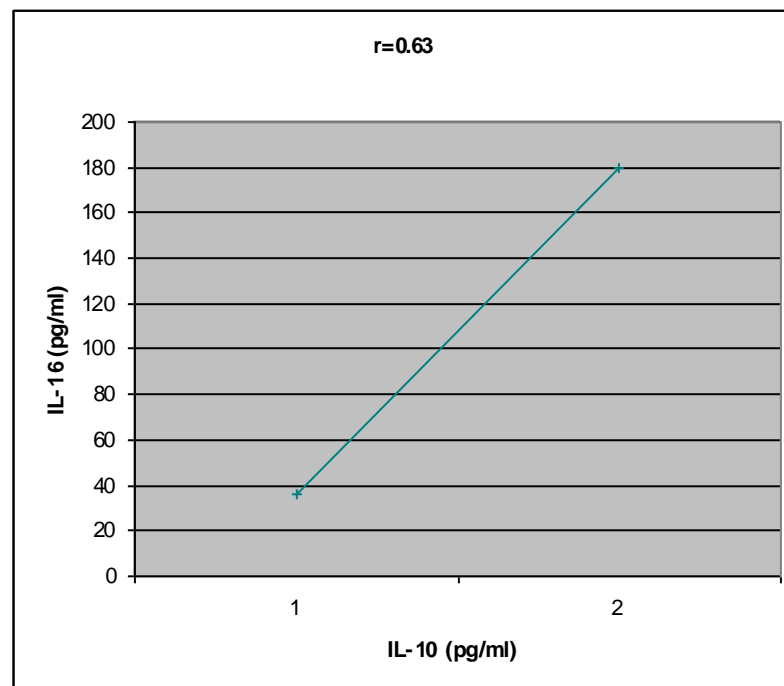**Fig (3) Mean values of IFNγ in patients with rheumatoid arthritis and control group**

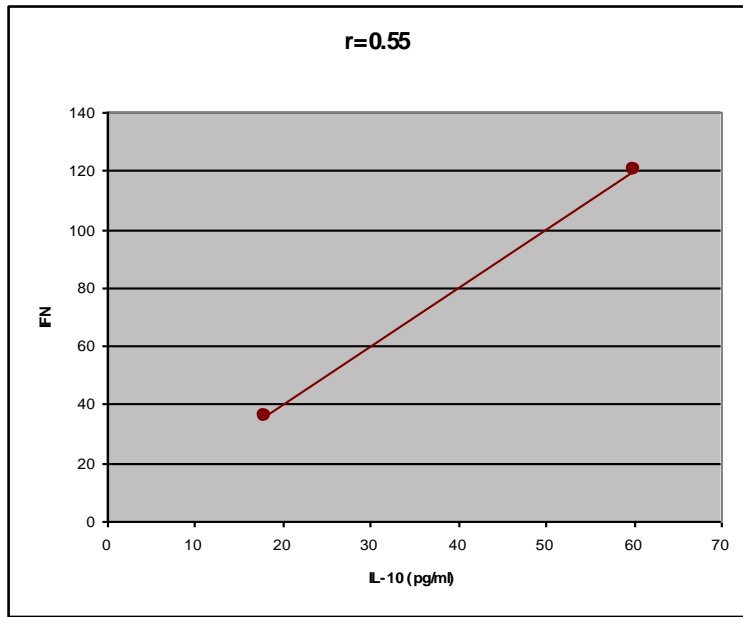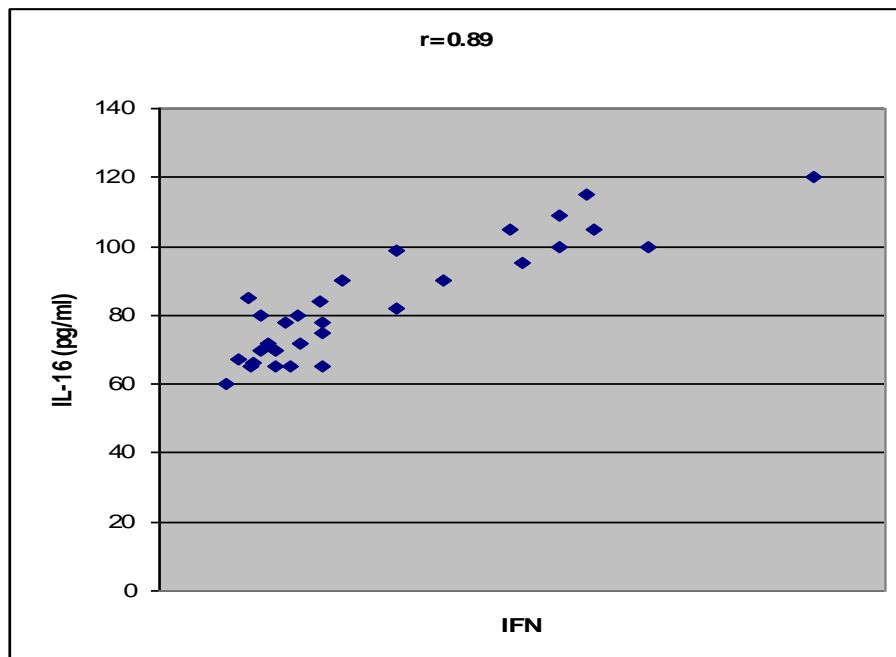**Fig (4) Positive correlation between IL-10 and IL-16 among group 1**

Fig (5) Positive correlation between IL-10 and IFNγ among group 1

Fig (6) Positive correlation between IL-16 and IFNγ among group 1

Discussion

Arthritis and joint destruction are the hallmarks of rheumatoid arthritis (RA). The progression of joint destruction varies considerably among patients with RA (Huizinga *et al;* 2000).

Proinflammatory cytokines play a significant pathogenic role in RA. Anti-inflammatory cytokines can also be found in the affected joints and it has been postulated that chronic synovitis may reflect an imbalance in pro- and anti-inflammatory cytokine production in RA (Weckmann *et al;* 1996). Consequently, the potential effect of anti-inflammatory cytokines such as IL-10 in RA is of great interest (Mackay *et al*; 2003).

Various lines of research suggest an important role of IL-10 in the pathogenesis of joint destruction in RA. Other studies show that IL-10 inhibits the generation of proinflammatory cytokines and the proliferation of Th1 lymphocytes.

IL-16 is a T cell derived cytokine originally identified and purified as lymphocyte chemoattractant factor.IL-16 acts via the CD4 molecule as its receptor and exert a broad spectrum of both pro- and anti-inflammatory biologic activities (Blaschke *et al*; 2001).

Interferon- gamma (IFN- γ) is a secretary product of activated T-cell of the Th1 subset and natural killer cells (NK). INF-γ is produced in response to specific and non-specific immunologic activation of lymphocyte, usually T-lymphocytes (Boehm *et al*; 1997).

In the present study plasma level of IL-10, IL-16, and IFN-γ were measured in 30 patients with rheumatoid arthritis comp-ared to 10 sex and age matched normal subjects.

Our results show highly significant increase in serum IL-10 in patients with RA compared to control group. Our results agree with Cush *et al;* (1995) who found serum and synovial fluid (SF) contained significantly elevated IL-10 level compared to control group. On other hand Verhoef *et al;* (2001) found IL-10 production was statistically higher in patients group with mild disease compared to severe disease.

Also our results show highly signif-icant positive correlation between serum IL-10 and each of ESR, CRP.This result disagree with Cush *et al*;(1995) who found no correlation was demonstrated between IL-10 levels and most clinical measures of disease activity (age, disease duration, morning stiffness, patients and physician global assessment, swollen or tender joint counts. Also they reported no significant difference was noted between those patients treated or not treated with prednisone. But Verhoef *et al;* (2001) found negative correlations between IL-10 production and ESR, CRP, and strong negative correlation with radiographic joint damage as well as progression of joint damage.

In the present study serum level of IL-10 show highly significant correlation with each serum level of IL-16 and IFNγ, this results show disagreements with the results of Verhoef et al; (2001) they reported no correlation between IL-10 and IFNγ.

Lard *et al*; (2003) reported that IL- 10 genotype was not associated with the incidence of RA, but instead ,correlated with disease progression, as determined by extent of joint destruction.

Our results show highly significant increase in serum IL-16 in patients with RA compared to control group. And also show highly significant positive correlation betw-een serum IL-16 and each of ESR, CRP.

Our data show agreements with that of Blaschke *et al*; (2001) who detect that IL-16 was significantly high in sera and synovial fluid of patients with RA in comparison to osteoarthritis and to normal control, also they reported the lack of significant correlation between IL-16 expression, clinical disease activity, and local inflammatory activity suggesting a regulatory rather a pro-inflammatory function for IL-16 in the pathogenesis of chronic synovial inflammation in RA.

These finding for IL-16 differ from cytokines with predominant proinflam-

matory activity in RA, such as TNF-α, IL1-B, and IL-6, also OKamoto *et al;* (1997) have described increased serum levels of these macrophage derived cytokines and significant correlation between serum cytokine concentration and disease activity in RA.

Kaufmann *et al;* (2001) found serum level of IL-16 in RA was increased significantly compared with non RA control, and in RA patients and controls, there were no significant differences in cytokine level with respect to age and sex. And also they reported that a level of IL-16 was correlated with ESR and C-reactive protein.

Our results show highly significant increase in serum IFNγ in patients with RA compared to control group. And also show highly significant positive correlation between serum IFNγ and each of ESR, CRP.

This result agree with Kanik et al; (1998) who found increased production of IFNγ in RA patients with new onset synovitis, in contrast to patients with chronic RA who had increased IL-16 production.

Verhoef *et al*; (2001) reported no correlation between IFNγ with disease activity variables (ESR, CRP) or joint damage and that may be due to use of medication, and also found negative correlation between IFNγ and age of RA patients.

Scola *et al;* (2002) found that juvenile RA (JRA) has generally been described as a type I disease with increased level of IFNγ and variably low IL-4 in study utilizing synovial fluid, and also confirm continued expression of IFNγ/IL-4 ratio compared to that of control tissue, but also they reported no significant difference in the expression of IL-10 in JRA from that controls, possibly indicating a loss of regulation in severe or long standing disease.

Bas *et al;* (2003) found SF concentrations of IL-10 were significantly lower in patients with reactive arthritis than RA patients. The SF level of IFNγ was not significantly different but the ratios of IFNγ to IL-10 were significantly higher in patients with reactive arthritis.

Conclusion

These data suggest that there is increased production of IL-10, IL-16, and IFN-γ in patients with rheumatoid arthritis, and that is correlated with disease activity. These cytokines are interesting for further research and novel therapeutic approach in this inflammatory disease.

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انترليوكين 10 و انترليوكين 16او انترفيرون جاما في مرض الرثيان المفصلي
وعلاقتها بالنشاط المرضى

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هناك العديد من الأسباب المحتملة لمرض الرثيان المفصلي ولكن الأسباب الحقيقية ليس مقطوعا بها حتى الآن، فقد لوحظ أن الخلايا الليمفاوية T و B و الميكروفاج تتخلل الغشاء الزليلى المفصلي، فتؤدى إلى ظهور الخلل التركيبى والوظيفي لهذا الغشاء وكذلك توثر على حالة الغضاريف والمفاصل وقد تبين أن هناك حالة من عدم التوازن بين الإنتاج المتزايد من مسببات الالتهاب ومضادات الالتهاب، فتلعب العشائر الخلوية مثل انترليوكين10 دورا هاما في التطور المرضى للمفاصل وكذلك التأثير على الجهاز المناعي.

ويلعب انترليوكين 16 دورا هاما في التطور المرضى المزمن في هذه الحالات حيث إن له خصائص منشطة لخلايا   T التي تؤثر على الأغشية الزليليه كما ان انترفيورن جاما يلعب دورا منشطا أيضا على خلايا T المساعدة.

وقد تم تحليل مستوى انترليوكين 10 و انترليوكين (16) وانترفيورن جاما في المرضى لتقييم درجة نشاط المرضى وقد أظهرت النتائج ارتفاع ذات دلالة إحصائية في كل من سرعة الترسيب وبروتين C النشط وانترليوكين 10 و انترليوكين 16 وانترفيورن جاما وثبت وجود علاقة ارتباطيه ذات دلالة إحصائية مرتفعة بين كل من انترليوكين 10 وانترليوكين 16 انترفيورن جاما كما يوجد أيضا علاقة ارتباطية بين انترليوكين 16او انترفيون جاما وكذلك بين سرعة الترسيب وكل من انترليوكين 10 وانترلوكين 16 وانترفيون جاما.

ووجود علاقة ارتباطية ذات دلالة احصائية بين بروتين C النشط وكل من انترليوكين 10 و**انترليوكين** 16 وانترفيرون جاما مما يشير إلى وجود علاقة بين ارتفاع مستوى العشائر الخلوية ودرجة نشاط المرض.