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Assessment of Proinflammatory Th_1 Cytokines (IL_{18}-IFN γ) and Th_2 Cytokine (IL_{13}) Concentrations in patients with Autoimmune Rheumatic Diseases (Systemic Lupus Erythematosus, Rheumatoid Artharitis and Systemic Sclerosis)

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Abstract

Objective: Several cytokines play a role in the production of autoantibodies and the pathogenesis of rheumatic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SS). This study investigated serum concentration of the proinflammatory Th_1 cytokine; IL_{18} and its inducer IFNγ, the study also investigated serum concentration of proinflammatory Th_2 cytokine; IL_{13}, to explain the role of Th_1 and Th_2 in the pathogenesis of autoimmune rheumatic diseases (SLE, RA and SS)

Patients and methods: IL_{18}, IFNγ and IL_{13} levels were evaluated by enzyme linked immunosorbent assay (ELISA). Four groups were included in this study.

Group I: Comprised (15) patients of SLE. Group II: Comprised (15) patients of RA. Group III: Comprised (15) patients with SS. Group IV: Control group consisted of (15) sex and age matched healthy controls.

Results: Serum levels of IL_{18} was significantly higher in SLE (3138.200± 1413.096 pg/ml)& RA(3336.667± 921.839 pg/ml) than control group(86.647± 35.370 pg/ml), while IL_{18} in SS had no statistically significant difference between patients (103.634± 50.593 pg/ml) and control group (86.647± 35.370 pg/ml).The cut off level was 257.75 pg/ml .

IFNγ was significantly higher in SLE patients (5.439±1.430 IU/ml) and RA patients (2.973± 0.598 IU/ml) than control group(0.580 ± 0.234 IU/ml) ,while IFNγ in SS had no statistically significant difference (0.592± 0.245IU/ml) than control group (0.580 ± 0.234 IU/ml) .The cut off level was1.2 IU/ml .

As regard IL_{13} it was significantly higher in SLE patients (55.673±6.892 pg/ml) ,RA patients (59.587±12.183 pg/ml) and SS (61.550± 12.047 pg/ml) than control group (21.427± 7.274 pg/ml) .The cut off level was 44.4 pg/ml .There was significant positive correlation of IL_{18}/ IL_{13} and IFNγ / IL_{13} ratio in SLE and RA , while significant negative correlation of IL_{18}/ IL_{13} and IFNγ / IL_{13} ratio in SS.

Conclusion: There was a significant increase of both Th_1 cytokines (IL_{18} and IFNγ) and Th_2 cytokine (IL_{13}) in SLE and RA with Th_1 predominance,while predominance of Th_2 cytokine (IL_{13}) in SS than Th_1 cytokine (IL_{18} and IFNγ). This result suggests that IL_{18}, INFγ and IL_{13} could be involved in the pathogenesis of autoimmune rheumatic diseases.

Key words: SLE, RA ,SS, IL_{18}, IFNγ and IL_{13}

Introduction:

Rheumatic diseases are major cause of morbidity and long-term disability. They include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SS) and Sjogren's syndrome are those that affect connective tissue ***(Mosaad et al., 2003).*** The autoimmune phenomenon of these diseases might be caused by imbalance of T-helper cell cytokines ***(Wong et al., 2000).***

The balance of Th_1/Th_2 is essential for the normal human immunity and so changes in Th_1/Th_2 cytokines might be involved in the pathogensis of autoimmune diseases ***(Horwitz et al., 1998).*** Th_1 cells produce IL_2, IFNγ, IL_{12} and IL_{18} while Th_2 cells produce $IL_{4,5,6.10,13}$ ***(Jianxin et al., 2009).*** IL_{18} was initially described as IFNγ-inducing factor ***(Ewa et al., 2002).*** It is related to IL_1 family and produced by kupffer cells, activated macrophages, keratinocytes, intestinal epithelial cell, osteoblasts and adrenal cortex cells ***(Wong, 2000).***

IL_{18} production can be induced by IL_{12}, both have synergistic effect on the activation of natural killer (NK) cells and cytotoxic T lymphocytes (CTL). The primary function of IL_{18} include the induction of IFNγ production in IL_{12} activated T cells and NK cells, up-regulation of Th_1 cytokines including IL_2, M-CSF and IFNγ ***(Dinarello, 1999),*** stimulation of the proliferation of activated T cells and enhancement of fas ligand expression in NK and CTL ***(Dao et al., 1997).***

Moreover, IL_{18} can promote collagen induced inflammatory arthritis when produced by tissue macrophages ***(Yamamura et al., 2001).***

IL_{13} is protein secreted by activated Th_2 .It affects B-cell function and has the capability of inhibiting pro-inflammatory Th_1 cytokines such as IL_{12} and IFNγ, suggests that IL_{13} as well as IL_4 and IL_{10} could facilitate a Th_2 response and therefore modulate the immune response ***(Spadaro et al., 2002).***

The current study aimed to evaluate serum concentration of IL_{18} , IFNγ and IL_{13} levels as markers of Th_1 and Th_2 cytokines respectively and to detect the predominance of either Th_1 and Th_2 in the pathogenesis of autoimmune rheumatic diseases (SLE, RA and SS).

Material and Methods:

The study included 45 patients divided into three groups and fifteen sex and age matched healthy controls. They were selected from the inpatient and outpatient clinics of Internal Medicine, Dermatology and Rheumatology departments of Al-Zahraa University Hospital. Group I: consisted of fifteen patients with SLE; 3 males and 12 females with age range from 25 to 47 years, with disease duration 3-10 years.They were classified according to the updated American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus ***(Hochberg, 1997).***

Group II: consisted of fifteen patients with RA; they were 6 males and 9 females with age ranged from 35 to 52 years, with disease duration 5-11 years.They were classified according to American Rheumatism Association Criteria ***(Arnett et al., 1988).***

Group III: consisted of fifteen patients with SS; all of them were females with age ranged from 37 to 53 years, with disease duration 2-9 years. They were classified according to American College of Rheumatology (formerly, the American Rheumatism Association) criteria for the classification of systemic sclerosis (Scleroderma) **(LeRoy et al 1988).** Control group consisted of 15 healthy subjects. They were 9 males and 6 females; their age ranging from 29-48 years. All studied groups were subjected to complete history taking, general examination, evalution of the main laboratory parameters including renal function tests, liver function tests, complete blood picture (EDTA blood), ESR (citrated blood), CRP ,RF (latex test) ,anti-double stranded DNA (the standard indirect immunofluoescence technique) and anti –Scl 70

antibodies . 5 ml of venous blood were withdrawn from each subject. For cytokine estimation the sera obtained were divided into aliquots, and stored at – 70 until the time of assay. Measurement of serum level of , IL_{18} ,IFNγ and IL_{13}were done for all patients and control groups.
Determination of serum IL_{18} has been done using an enzyme linked immunosorbent assay (ELISA) kit. (Biosource International, Inc. 542 Flynn Road Camarillo, California 93012, USA).
Determination of serum interferon γ has been done using an immunoenzymometric assay kit. (Biosource IFNγ EASIA kit).Catalogue number: KAC_{1231}, Bio-source – Europe S.A. Nivelles Belgium.
Serum IL_{13} concentration were determined by using commercially obtained immunoassay . Quantitative Sandwich ELISA technique Bender Med systems GmbH compus Veinna. Biocenter 2A-1030 Vienna, Australia, Europe.

Statistical analysis:

Statistical analysis was done using statistical software package (SPSS) version 17. Quantitive analysis were presented as means and standard division (Mean ± SD). Standard t-test was used for comparison between means linear regration analysis with determination of correlation coefficient (r) was used for correlation between quantitative variable P-value of ≤ 0.05 was statistically significant.

Results

This study included 45 patients ,15 patients with SLE (3 males&12 females) with mean age 36.00 ± 7.39 and mean disease duration 6.367 ± 2.334 years ,15 patients with RA (6 males &9 females) with mean age 44.73 ± 6.03 and mean disease duration 8.200± 2.111 years, and 15 patients with SS (15 females) with mean age 45.06 ± 5.34 and mean disease duration 5.467±2.264 and 15 sex and age matched healthy control group (9 male& 6 female) with mean age 38.40 ± 6.43 (Table 1).

IL_{18} was significantly higher in patients with SLE (3138.200± 1413.096 pg/ml) than control group (86.647± 35.370 pg/ml),the cut off level was 257.75 pg/ml .

IL_{18} was significantly higher in patients with RA (3336.667± 921.839 pg/ml) than control group(86.647± 35.370 pg/ml), while IL_{18} in SS has no statistically significant difference between patients (103.634± 50.593 pg/ml) and control group (86.647± 35.370 pg/ml) (Table2&figure 1).

IFNγ was significantly higher in SLE patients (5.439±1.430 IU/ml) than control group (0.580 ± 0.234 IU/ml) ,the cut off level was 1.2 IU/ml . Also IFNγ was significantly higher in RA patients (2.973± 0.598 IU/ml) than control group(0.580 ± 0.234 IU/ml) , while IFNγ in SS had no statistically significant difference between patients (0.592± 0.245IU/ml) and control group (0.580± 0.234 IU/ml) (Table 3 &figure 2).

As regard IL_{13} it was significantly higher in SLE patients (55.673±6.892 pg/ml) ,RA patients (59.587±12.183 pg/ml) and SS (61.550± 12.047 pg/ml) than control group (21.427± 7.274 pg/ml) ,the cut off level was 44.4 pg/ml .(Table4 & figure 3).

There was significant positive correlation of IL_{18}/ IL_{13} ratio and significant positive correlation of IFNγ / IL_{13} ratio in SLE and RA (Figures 4&6),while there was significant negative correlation of IL_{18}/ IL_{13} and IFNγ / IL_{13} ratio in SS (figure 5&7).

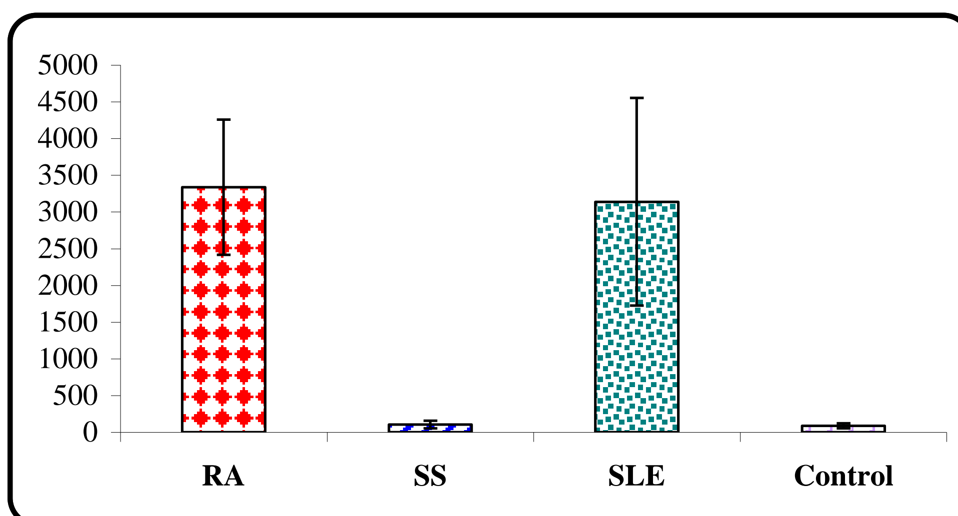
Table (1): Demographic data of all studied groups:

		SLE	RA	SS	control	Statistics value	P-value
Sex	**Female**	12 (80 %)	9(60%)	15 (100%)	6 (40%)	X^2=14.28	0.003
	Male	3 (20%)	6 (40 %)	0	9 (60%)		
Age	**Range**	47-25	52-35	53-37	48-29	F=7.739	0.000
	Mean±SD	36.00±7.39	44.73±6.03	45.06±5.34	38.40±6.43		
Duration	**Range**	3.0-10.0	5.0-12.0	2.0-9.0		F=5.811	0.006
	Mean±SD	6.367±2.33	8.200±2.111	5.467±2.264			

Table (2): The level of IL-18 in all studied groups:

	IL-18		ANOVA	
	Range	Mean ± SD pg/ml	f	P-value
RA	1966.0 - 4782.0	3336.667 ± 921.839	69.420	0.000
SS	40.0 - 223.1	103.634 ± 50.593		
SLE	1401.0 - 5463.0	3138.200 ± 1413.096		
Control	40.8 - 175.3	86.647 ± 35.370 1		

Tukey's test					
RA & SS	RA & SLE	RA & C	SS & SLE	SS & C	SLE & C
0.000	0.917	0.000	0.000	1.000	0.000



Figure(1): comparison of IL-18 level in all studied groups

Table (3): The level of IFNγ in all studied groups:

	IFNγ		ANOVA	
	Range	*Mean ± SD IU/ml*	f	P-value
RA	*1.3 - 3.8*	*2.973 ± 0.598*	128.201	0.000
SS	*0.3 - 1.2*	*0.592 ± 0.245*		
SLE	*3.2 - 7.6*	*5.439 ± 1.430*		
Control	*0.3 - 1.0*	*0.580 ± 0.234*		

Tukey's test					
RA & SS	*RA & SLE*	*RA & C*	*SS & SLE*	*SS & C*	SLE & C
0.000	*0.000*	*0.000*	*0.000*	*1.000*	0.000

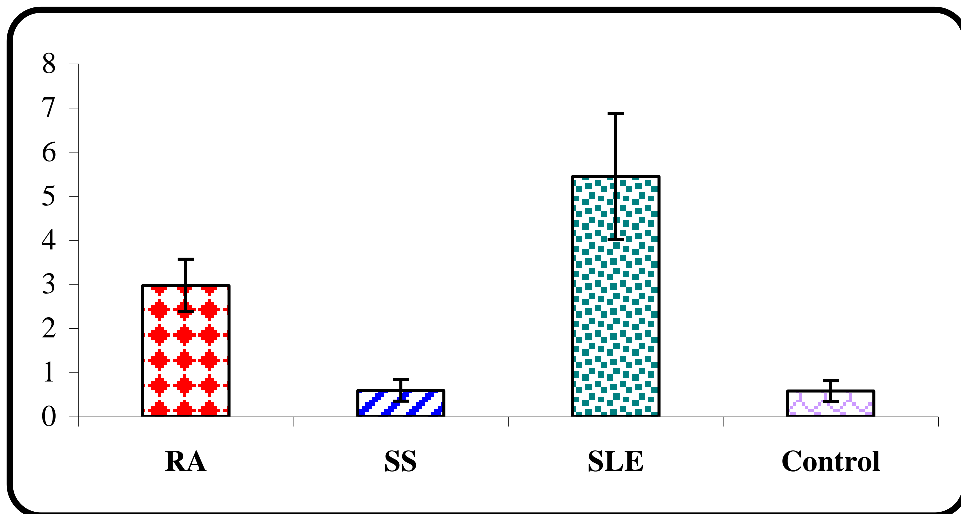


Figure (2): comparison of IFNγ in all studied groups

Table (4): The level of IL-13 in all studied groups:

	IL-13		ANOVA	
	Range	Mean ± SD pg/ml	f	P-value
RA	45.4 - 81.2	59.587 ± 12.183	54.475	0.000
SLE	44.7 - 65.3	55.673 ± 6.892		
SS	48.3 - 80.4	61.550 ± 12.047		
Control	9.1 - 33.1	21.427 ± 7.274		

Tukey's test					
RA & SS	RA & SLE	RA & C	SS & SLE	SS & C	SLE & C
0.703	0.948	0.000	0.375	0.000	0.000

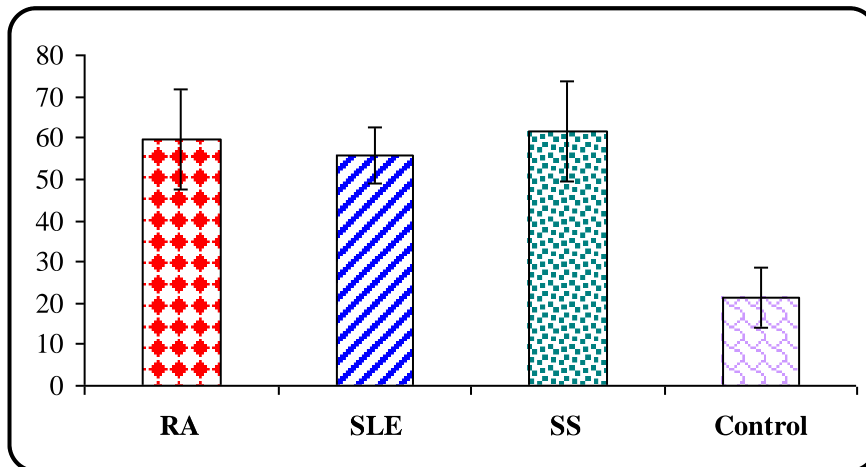


Figure (3): comparison of IL-13 level in all studied groups.

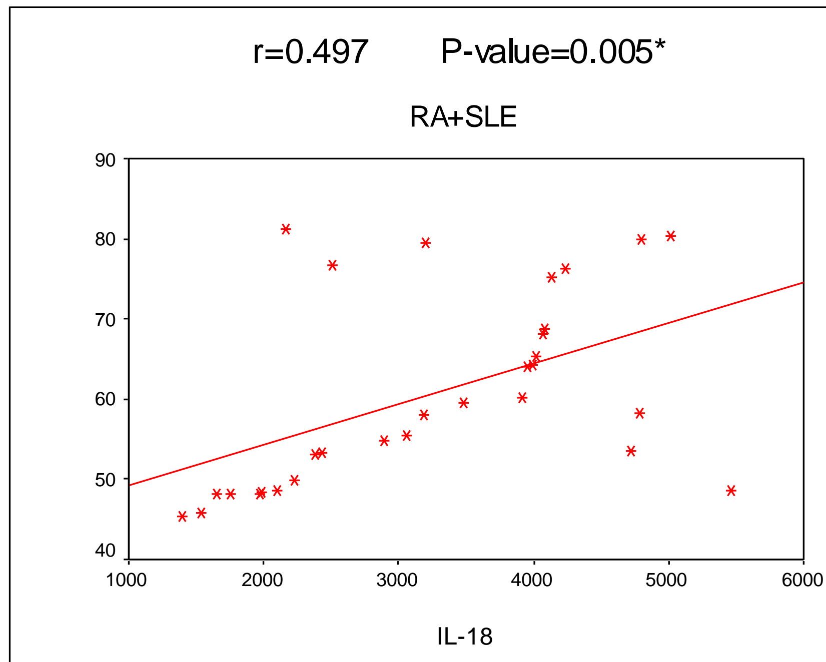


Figure (4): Significant positive correlation of IL18/ IL13 ratio in SLE and RA..

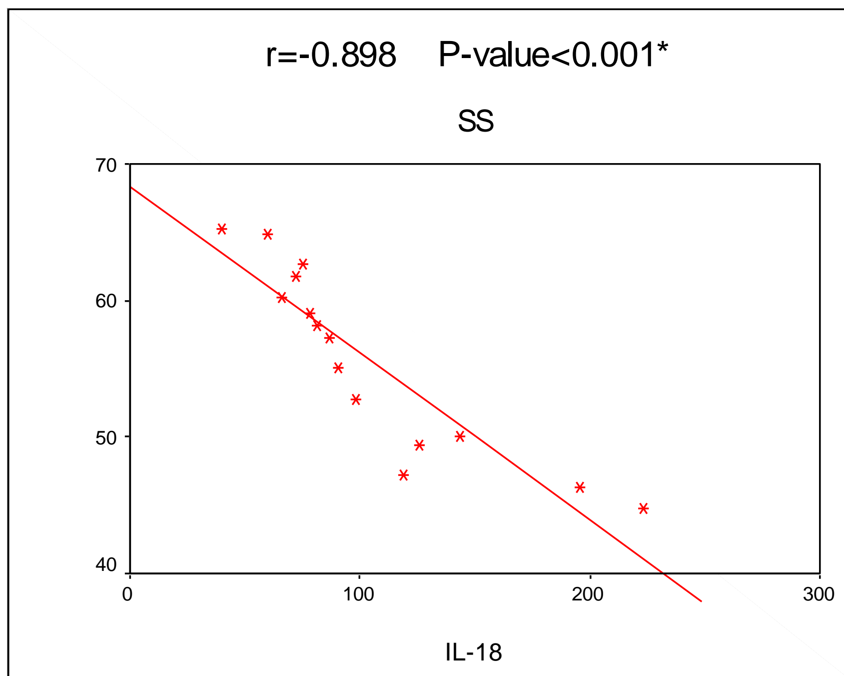


Figure (5): Significant negative correlation of IL18/ IL13 ratio in SS.

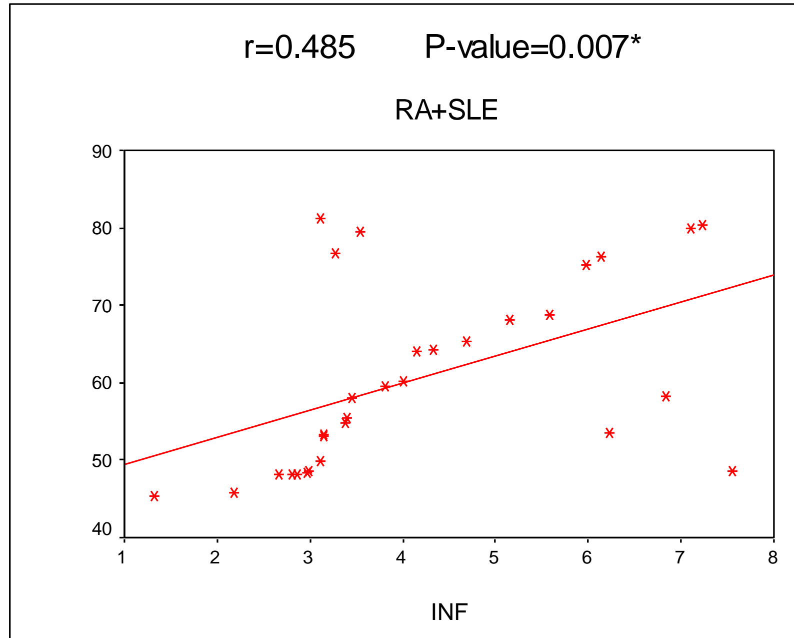


Figure (6): Significant positive correlation of INFγ/ I IL13 ratio in SLE and RA.

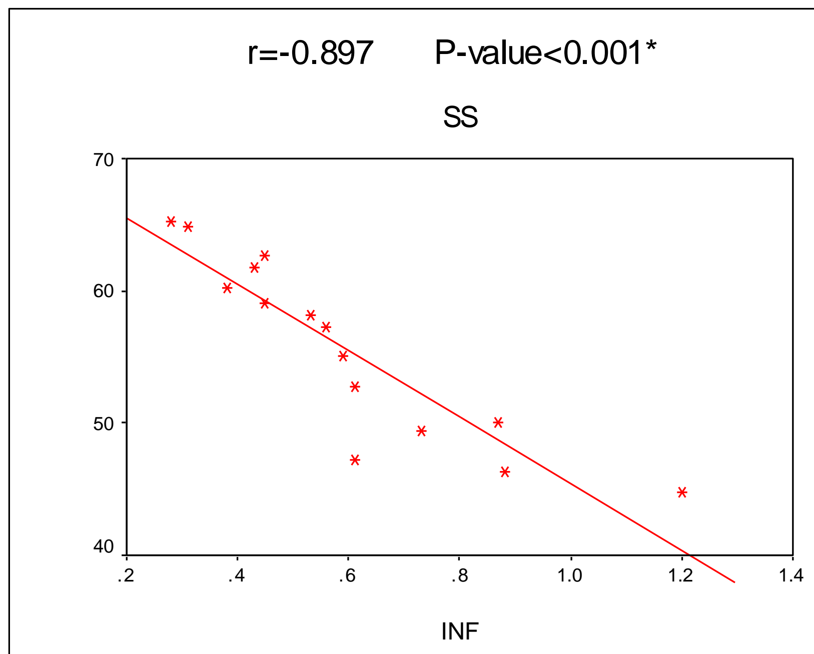


Figure (7): Significant negative correlation of INFγ/ IL13 ratio in SS.

Discussion

The balance between Th_1 and Th_2 cytokines plays an important role in the control of immune response **(Uhm et al 2003)** .Ratios of Th_1/Th_2 cytokines can reflect the cytokine homeostasis and indicate Th_1 or Th_2 predominance during the development of rheumatic diseases. Several studies have reported different results for the correlation of Th_1/Th_2 ratio and rheumatic disease activity (**El-Sayed et al 2008 &*Wong et al., 2000)***. The current study aimed to assess the predominance of Th_1 or Th_2 in the autoimmune rheumatic diseases (SLE, RA and SS) by investigating the serum level of Th_1 cytokines IL_{18} ,INFγ and Th_2 cytokine IL_{13}.

In the current study IL_{18} serum level was increased in SLE than control group. This result agreed with **Mosaad et al. (2003)** who found that increased serum level of IL_{18} and IL_{12} in immune rheumatic diseases (SLE, RA, SS, Behcet disease, dermatomyositis, mixed connective tissue diseases and Sicca syndrome). Also this result agreed with **Robak et al. (2002)** who found that increased serum levels of IL_{12} and IL_{18} in SLE and also agreed with **Wong et al. (2000)** who found that increased serum level of IL_{18}, IL_{17}, IL_{12} in SLE.

As regard the serum level of IL_{18} in RA the result of the current study showed significant higher serum IL_{18} level than control this result agreed with **Mosaad et al. (2003)** who found that increased IL_{18}, IL_{12} and ANA in RA patients than the control group. Also agreed with **Bresnihan et al. (2002)** who found significant higher serum IL_{18} level in RA than psoriatic arthritis they suggesting that IL_{18} has a role in pathophysiology of RA but it did not significantly correlate with clinical measures of disease activity or the response to treatment. In a study done by **Scola et al. (2002)** in juvenile RA they reported that increased expression of mRNA of IL_{12}, P35 and IL_{18}.

The result of the serum level of IL_{18} in SS had no statistically significant difference between patients and control group this was in contrast with **Scala et al (2004)** who observed high levels of IL_{18} in patients with SS compared to healthy subjects.

Significantly, elevated IL_{18} in SLE may be because IL_{18} enahnce the Fas lignad expression in NK and CTL, causing Fas-mediated apoptosis in epithelial cells and tissue damage in SLE ***(Dinarello, 1997).*** IL_{18} in combination with other proinflammatory cytokines, including IL_1 and TNFα must be an important cytokine for initiating and progressing the catabolic and inflammatory responses in SLE. Also, IL_{18} induce production of nitric oxide from macrophages that involved in tissue damage in SLE ***(Wong et al., 2000).*** In a study done by **Falvia et al. (2009)** they found that increased level of IL_{18} in both serum and plasma of SLE patients and correlate it with disease severity, they suggesting that the circulating IL_{18} levels are predictive for renal damage and could be used as a prognostic marker of renal involvement and useful to identify patients at risk of renal failure. Increased IL_{18} in RA may be explained by **Gracie et al (1999) study** who found that increased IL_{18} in RA induced Th_1 response and TNF-α production in short-term cultured cells from RA tissues and synovial fluid mono-nuclear cells. Furthermore, IL_{18} facilitated the erosive course in RA animal model of collagen induced arthritis.Moreover, **Olee et al. (1999)** reported that IL_{18} is involved in joint disease by its effect on cartilage destruction.

As regard IFN γ, the current study showed significant increase of IFN γ in SLE than control group. This result agreed with **EL- Sayed et al., (2008**) who found significant increase of IFN γ levels in SLE patients than contols. The main function of IFN γ in SLE is the activation of macrophages which stimulate proinflammatory cytokines production ***(Uham et al., 2003).***

The current study showed significant increase of IFN γ in RA than

control group this agreed with ***Canete et al 1999*** who found that significant higher level of IFN γ in RA than psoriatic arthritis. In study done by ***Bucht et al.,(2007***) they found that higher expression of IFN γ, IL_{18} and IL_{12} mRNA in RA synovial fluid mononuclear cells (SFMC) than peripheral blood mononuclear cells compared to healthy control group using a quantitative reverse transcriptase polymerase chain reaction (RT- PCR) assay.

In the current study IFN γ was decreased in SS patients with no statistically significant difference with healthy control group. This result agreed with ***Scala et al study (2004)*** who found reduced amounts of γ- IFN and macrophage derived chemokine (MDC) in SS patients. SS pathogenesis characterized by increase collagen production which may be due to decreased IFN γ level as IFN γ inhibit collagen synthesis by fibroblast ***(Serpier, 1997).***

In the current study IL_{13} serum level was increased in SLE ,RA and SS this result agreed with **Spadaro et al. (2002)** study who found increased IL_{13} levels in SLE ,RA and SS. Increased IL_{13} serum level could be explained by predominance of Th_2 response that stimulate B-cell and antibody production. IL_{13} affect B-cell through surface molecule modulation, the enhancement of proliferation, immunoglobulin production and isotopic switching (IgG and IgE) ***(Spadaro et al. 2002).***

The result of current study showed higher levels of both the Th_1 cytokines (IL_{18} and IFN γ) and Th_2 cytokine (IL_{13}) in both SLE and RA. This result agreed with **El-Sayed et al study (2008)** who found that significant increase of both Th_1 cytokines (IFN γ and TNFα) and Th_2 cytokines (IL_4 and IL_{10}) in SLE and **Wong et al (2000)** who also found an elevation of both Th_1 cytokines (IL_{18} , IL_{17} , IL_{12}) and Th_2 cytokine (IL_4) in patients with SLE. Elevation of both Th_1 and Th_2 cytokines in SLE and RA suggests an imbalance of cytokine profile supported by different cytokine patterns in different time-points to mediate the inflammatory response **(Wong et al 2000)**.

The current study showed significant elevation of Th_1/Th_2 ratio (IL_{18}/IL_{13} and IFN γ/IL_{13}) in both SLE and RA suggesting Th_1 predomennance . This result agreed with **wong et al (2000)**, who found an elevation of IL_{18} / IL_4 ratio in patients with SLE, and **El-Sayed et al study (2008)** who found that significant elevation of IFN/IL10 ,IFN/IL4, TNF/IL10 and TNF/IL4 ratios in patients with SLE. Clear –cut distinction between Th_1 and Th_2 patterns is not without complexity **(El-Sayed et al., 2008)**, this complexity may be due to many factors such as disease activity, treatment and organ involvement **(Nagy et al ., 2000).** So to determine the predominance of Th_1 or Th_2 in autoimune rheumatic diseases , it must not only dependant on evaluation of their serum levels but also supported by other sutdies such as gene polymorphism.

Conclusion: There was a significant increase of both Th_1 cytokines (IL_{18} and IFNγ) and Th_2 cytokine (IL_{13}) in SLE and RA with Th_1 predominance, while predominance of Th_2 cytokine (IL_{13}) in SS than Th_1 cytokine (IL_{18} and IFNγ). This result suggests that IL_{18}, IFNγ and IL_{13} could be involved in the pathogenesis of autoimmune rheumatic diseases.

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تقييم تركيز مفرزات الخلايا الناتج من الخلايا

الليمفاوية المساعدة- 1 (انترلوكين – 18، انترفيرون جاما)و مفرزات الخلايا الناتج من الخلايا الليمفاوية المساعدة- 2 (انترلوكين- 13) فى الامراض الروماتيزمية (الذئبة الحمراء- الروماتويد- تصلب الجلد الكلى).

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** قسم الطب الطبيعى- الروماتيزم والتاهيل الطبى
*** قسم الباطنة العامة
**** قسم الباثولوجيا العامة- كلية طب بنات جامعة الازهر

يلعب العديد من مفرزات الخلايا (السيتوكينز) دورا هاما فى انتاج الاجسام المضادة كذلك كمسببات للمرض فى الامراض الروماتيزمية مثل مرض الروماتيد ومرض الذئبة الحمراء ومرض التصلب الكلى. تقوم هذه الدراسة بدراسة نسبة تركيز مفرزات الخلايا الليمفاوية المساعدة (Th_1) (انترلوكين- 18، انترفيرون جاما) وكذلك نسبة مفرزات الخلايا الليمفاوية المساعدة (Th_2) (انترلوكين- 13) وذلك لتوضيح دور كلا من الخلايا الليمفاوية المساعدة -1 والخلايا الليمفاوية المساعدة- 2 كسبب لحدوث الامراض الروماتيزمية (الذئبة الحمراء- الروماتيد- التصلب الكلى).

المرضى والطريقة:

تشتمل هذه الدراسة على اربع مجموعات:
المجموعة الاولى:- 15 مريضا بالذئبة الحمراء
المجموعة الثانية:- 15 مريضا بالروماتيد
المجموعة الثالثة:- 15 مريضا بالتصلب الكلى
المجموعة الرابعة 15 من الاصحاء كمجموعة ضابطة
وقد تم قياس نسبة انترلوكين – 18، انترفيرون جاما، انترلوكين – 13 بواسطة جهاز انزيم لينكيد امبونوسوربنت اساي.

وكانت النتائج كالاتى:
كانت هناك زيادة ملحوظة فى كل من مفرزات الخلية الليمفاوية -1 انترلوكين- 18 فى كل من مرضى الذئبة الحمراء (3138.20 ± 1413.596) عن المجموعة الضابطة (86.647 ± 35.370) كذلك فى مرضي الروماتيد (3336.667 ± 921.839) عن المجموعة الضابطة (35.370 ± 86.647) بينما لم يكن هناك فارق احصائى فى مرضى التصلب الكلى (50.593 ± 103.634) عن المجموعة الضابطة (35.370 ± 86.647).
كذلك كانت هناك زيادة ملحوظة فى منشط الخلايا الليمفاوية انترفيرون جاما فى مرضى الذئبة الحمراء (5.439 ± 1.340) وفى مرضى الروماتيد (0.598 ± 2.973) عن المجموعة الضابطة (0.234 ± 0.580) بينما لم يكن هناك فارق احصائى فى مرضى التصلب الكلى (0.592 ± 0.245) عن المجموعة الضابطة (0.234 ± 0.580) اما بالنسبة لمفرز الخلايا اليمفاوية -2 (انترلوكين- 13) فقد كان هناك زيادة ملحوظة فى كل من مرضى الذئبة الحمراء (6.892 ± 55.673) ومرضى الروماتيد (59.587 ± 12.183) ومرضى التصلب الكلى (61.550 ± 12.047) عن المجموعة الضابطة (7.274 ± 21.427).
وتبين من النسبة بين مفرزات الخلايا الليمفاوية -1 ومفرزات الخلايا الليمفاوية-2 ان النسبة مرتفعة مما يدل على سيطرة الخلايا الليمفاوية -1 فى حدوث الامراض الروماتيزمية.

الخلاصة:-
هناك زيادة ملحوظة فى الدور الذى تلعبه مفرزات الخلايا الليمفاوية –1 (انترلوكين –18، انترفيرون جاما) عن مفرزات الخلايا الليمفاوية –2 فى مرض الذئبة الحمراء ومرض الروماتيد اما بالنسبة لمرض التصلب الكلى فتلعب مفرزات الخلايا الليمفاوية –2 دورا هاما عن مفرزات الخلايا الليمفاوية –1 مما يرجح ان مفرزات الخلايا الليمفاوية انترلوكين –18 انترفيرون جاما– انترلوكين –13 تلعب دورا هاما فى حدوث الامراض الروماتيزمية.