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Cytokines and autoantibodies profile during systemic lupus erythematosus and psoriasis diseases in Egypt

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Abstract

Objective: Cytokine, a small secreted protein, is secreted from one cell types to exert a particular effect on other cell types and/or on itself. Cytokines are characterized by their redundancy in the function; they are secreted in a cascade and can work synergistically and/or antagonistically. Cytokines have an important role in the pathogenesis of autoimmune diseases like systemic lupus erythematosus (SLE) and psoriasis (PS). Due to their crucial roles in the immune cells' development, differentiation and regulation; any dysregulation in their production and/or action can lead to the development of autoimmune diseases. The study population was composed of healthy control volunteers, SLE patients that were diagnosed as lupus nephritis (LN) patients or non-LN patients with developed atherosclerosis (As), and psoriasis patients that were diagnosed as psoriasis patients without arthritis (Ps) or psoriatic arthritis patients (PsA). **Methods:** The current study aimed to measure and compare the levels of T helper (h)1, Th2 and Th17 cytokines (IFN-γ, TNF-α, IL-17, -1β, -12, -10, -4, -2, -23, -18, -34 and -6) among Egyptian SLE and Ps patients. In addition, the pathway and type of Th cells involved in autoimmune-mediated tissue injury was examined. Detection of autoantibodies (ANA, anti-dsDNA, anti-sm, anti-histone, anti-ribosomal, APLA and anti-Ro/SSA) was performed to find if there is a relation between disease development and their presence. **Results:** Detection of autoantibodies and complement proteins were

beneficial in the diagnosis of SLE and psoriasis. ANA and anti-dsDNA autoantibodies were a good marker for the diagnosis of SLE and monitoring disease activity; however, other autoantibodies like APLA, anti-sm, anti-histone and anti-ribosomal can be used to indicate the disease activity. **Conclusions:** Cytokines can be used to determine the disease activity and autoimmune-mediated tissue injured in both SLE and psoriasis. Where, IL-17 recorded the highest level in LN and PsA patients; while the highest levels of IL-34, -23 and -6 were recorded in PsA patients and IL-1β was a characteristic cytokine in As patients.

Key words: systemic lupus erythematosus, psoriasis, interferon-γ, interleukin-6, interleukin -17.

1. Introduction

Autoimmune disorders, which affect 3–8% of the population, are a major source of morbidity and mortality (Patrikiou *et al.,* 2020). Systemic lupus erythematosus (SLE) and psoriasis (Ps) are examples of these autoimmune disorders that are activated when the immune system's self-tolerance is disrupted; a process that is still poorly understood and includes many distinct components (Paquissi and Abensur, 2021). Although treatment protocols have been significantly progressed, a deeper understanding of these disorders' pathogenesis is required (Patrikiou *et al.,* 2020; Koga *et al.,* 2021). SLE is a genetically predisposed autoimmune disease (Nath *et al.,* 2004); where there is a sexual predominance, with women accounting for more than 80% of SLE cases (González *et al.,* 2004; Juneblad *et al.,* 2018). SLE affects numerous internal organs, including the kidney, heart, joints, and central nervous system. Furthermore, blood abnormalities in SLE patients include lymphopenia, leucopenia, thrombocytopenia and complement deficiency (C1q, C2, and C4) (Patrikiou *et al.,* 2020). Autoantibodies and immune complex deposition are the main causes of SLE; where the development of excessive levels of autoantibodies is caused by the increased apoptosis along with the poor clearance of apoptotic cells (Herrmann *et al.,* 2000). The immune dysfunction is exacerbated by dysregulated cytokine production, which also plays a role in tissue inflammation and organ damage (Budagyan *et al.,* 1998). When T and B

cells are activated, they produce a wide range of cytokines, as well as autoantibodies, which add to the disease's characteristics (Zian *et al.,* 2021).

Psoriasis is a multiple gene inheritance skin disease that is characterized by chronic skin inflammations (Juneblad *et al.,* 2018). In a large number of patients, joint involvement has been reported leading to joint deterioration and substantial functional disability. In recent years, evidence has accumulated that psoriasis is a multisystem disorder including even coronary arteries and the heart (Ludwig *et al.,* 2007). In a study of thirty-two psoriasis patients and a control group of the same size, researchers discovered that psoriasis patients have a higher prevalence and severity of coronary artery calcification (Ludwig *et al.,* 2007). Both epidermal inflammatory T cells and keratinocytes play a pivotal role in psoriasis pathogenesis, secreting a diversity of inflammatory mediators that activate antigen-presenting cells (APCs), T cells, B cells, macrophages and epidermal keratinocytes (Nickoloff, 2007). Psoriasis has become increasingly recognized as an autoimmune disease in recent years, despite the lack of a particular autoantigen. The review of Nickoloff (2007) reported cytokines that are implicated in the disease aetiology, concentrating on the IL-23/Th17 pathway and its function in psoriasis skin inflammation. Where, IL-23 promotes the growth of pro-inflammatory, IL-17-secreting CD4+ memory T cells (Th17 cells).

When comparing the two diseases, SLE is associated with the production of high levels of autoantibodies from activated B cell and the activation of Th2 cells to produce IL-6 and IL-10 (Tan *et al.,* 2017). On the other hand, Ps is mediated by Th17, Th1 cells and their secreted cytokines (IL-2, -12, -17, -23 and IFN-γ); in addition to T regulatory (reg) cells which destroy autoreactive lymphocytes. However, the common distinctive feature in the two disorders is the

presence of elevated number of Th17 cells and high serum levels of IL-17 and -23 (Dybowska-Gołota *et al.,* 2020).

The immune response involves a three-way balance of Th1, Th2 and Th17 cells; in addition to regulatory cells that control the extra load. APCs activate naïve Th cells through the interaction between peptide-MHC class II complex and T cell receptor; leading to the production of effector cell clones (Kaiko *et al.,* 2008). Th cells are classified as ThI, Th2 and Th17 with characteristic cytokines secretion phenotype. Th1 cells are effective against intracellular infection and cancer cells and secret IFN-γ, TNF-β (Kidd, 2003). Th2 cells are involved in asthma development, activate the production of antibodies through IL-4 secretion, IL-5 induced eosinophilia and stimulate proliferation of mast cells by IL-13. Th17 cells have an important role in development of tissue inflammation and neutrophils activation. Treg cells, secret IL-10 and TGF-β, suppress the activity of other Th cells. This means that cellular immunity is mediated by Th1 cells, while humoral immunity is mediated by Th2 cells (Kaiko *et al.,* 2008). Inflammatory cytokines and chemokines play a critical role in the pathophysiology of many autoimmune diseases, many of which have been only recently identified (Juneblad *et al.,* 2018). Kikly *et al.* (2006) reported the importance of IL-12 family during autoimmune diseases; where APCs produce IL-12 leading to CD4+ cells differentiation to Th1 cells and secretion of IFN-γ. But in the existence of IL-4, the same cell develops into Th2 which secrets IL-4, -5 and -13. On the other hand, IL-17 and -17F are not secreted from Th1 or Th2 but secreted from Th17 cells (Aggarwal *et al.,* 2003). Th17 cells are stimulated by IL-23 resulting in the secretion of granulocyte-macrophage colony-stimulating factor, IL-6 and TNF-α. Previously, autoimmune diseases like SLE and psoriasis were attributed to Th1 immune response; nowadays, it becomes very clear the role of Th17 in their pathophysiology (Kikly *et al.*, 2006). Also, IL-21 is a modulator of acquired immune

response during autoimmune diseases like SLE, type I diabetes, Multiple sclerosis and Rheumatoid arthritis (Vogelzang and King, 2008).

Therefore, the current study aimed to measure and compare the levels of Th1, Th2 and Th17 cytokines (IFN-γ, TNF-α, IL-17, -1β, -12, -10, -4, -2, -23, -18, -34 and -6) among Egyptian SLE and psoriasis patients. In addition, the pathway and type of Th cells involved in autoimmune-mediated tissue injury were examined.

2. Patients and methods:

2.1 Study design:

The study population was composed of six groups: 250 healthy control volunteers who matched the patients in both sex and age (group I), 350 lupus patients (group II) from which 152 patients were suffering from lupus nephritis (LN, group III) and 161 non-LN patients developed atherosclerosis (As, group IV); and 340 psoriasis patients (Ps, group V) from which 173 were diagnosed as psoriatic arthritis patients (PsA, group VI). Healthy control volunteers had no history of lupus, psoriasis, psoriasis arthritis or rheumatoid arthritis. For patients and healthy control volunteers, the exclusion criteria were: 1- the history of cancer, diabetes or any inflammatory disease; 2- treatment by steroids, biological therapy or phototherapy, for one month before the study; 3- smokers were excluded. Ps patients were chosen from the Dermatology Outpatient Clinics of Cairo University Hospitals. Psoriasis diagnosis was clinically based on characteristic lesions. The Psoriasis Area and Severity Index (PASI) scores were utilized to express the psoriasis severity in regard to erythema (E), infiltration (I) and desquamation (D) according to Fredriksson and Pettersson (1978). PsA patients fulfilled the diagnostic criteria defined according to the Classification Criteria for Psoriatic Arthritis

(CASPAR). Lupus patients were selected from the outpatient of the Rheumatology clinic of Cairo University Hospitals. Patients were selected according to the revised criteria of the American College of Rheumatology (ACR) for SLE classification. Patients were defined as having SLE if they fulfilled four of the 1997 American College of Rheumatology revised criteria (Hochberg, 1997). Disease activity was evaluated by the SLE disease activity index (SLEDAI) according to Bombardier *et al.* (1992) and damage assessed using the Systemic Lupus International Collaborative Clinics (SLICC) damage index according to Stoll *et al.* (2004). Lupus diagnostic features were malar rash, discoid rash, photosensitivity, presence of antiphospholipid antibodies (APLA), seizures, oral ulcers, serositis, proteinuria, anemia, leucopenia, thrombocytopenia, hemolytic anemia and positive autoantibodies. The study was conducted in accordance with the World Medical Association Declaration of Helsinki for human subjects and approved by the ethics committee of Cairo University (N72020) and all participants gave an informed written consent. Patients were subjected to full history taking and thorough clinical examination including hair, skin, mucous membranes and joints examination. Patients with high levels of total cholesterol (≥ 240 mg/dl), LDL-C (160-189 mg/dl) and triglycerides (200-499 mg/dl) are considered hyperlipidemic according to the National Cholesterol Education Panel's/Adult Treatment Program-3 (NCEP/ATP-III) guidelines. Individuals with sustained high blood pressure (140/90 mmHg) are suffering from hypertension according to the International Society of Hypertension. Body mass index (BMI) ≥ 30 is used to classify obese patients. Five ml of venous blood sample were collected from all patients groups and the healthy volunteers; followed by centrifugation for sera collection. Serum samples were stored at -20^{o}C until analysis.

2.2 Serology:

Different autoantibodies (ANA, anti-dsDNA, anti Ro/SSA, APLA, anti-sm, anti-histone and anti-ribosomal) were screened in the serum of both patients and controls by human ELISA kits [MBS702970 (MyBioSource, USA), MBS269122 (MyBioSource, USA), MBS265301 (MyBioSource, USA), MBS739746 (MyBioSource, USA), MBS494673-ORG 510 (MyBioSource, USA), MBS723888 (MyBioSource, USA) and Rip-P Ab (elisakits, UK) ELISA Kit, respectively]. Also, complement proteins (C3 and C4) were measured by human ELISA kit [ab108822 (abcam, USA) and MBS2502561 (MyBioSource, USA), respectively].

2.3 Cytokines measurements:

Serum was screened for levels of different cytokines by human ELISA kits [IL-17 (RAB0262), IL-1β (ab214025, abcam, USA), IL-12 (MBS763918, MyBioSource, USA), IL-10 (ab185986, abcam, USA), IL-4 (ab215089, abcam, USA), IL-2 (ab270883, abcam, USA), IL-23 (ab221837, abcam, USA), IL-18 (ab215539, abcam, USA), IL-34 (ab213797, abcam, USA), IL-6 (ab178013, abcam, USA), IFN-γ (ab48490, abcam, USA) and TNF-α (ab181421, abcam, USA)] according to the manufacturer's instructions.

2.4 Statistical analysis:

The data have been collected, revised, and analyzed by GraphPad Prism version 10 (GraphPad Software, San Diego CA). Results were expressed as mean ± standard deviation (mean ± SD) or median and range or, n (%) as appropriate. Student's T test and Mann–Whitney U test have been used for normally and non-normally distributed data, respectively. Pearson correlation test and Spearman correlation coefficients have been used for the parametric and nonparametric distributed data, respectively. Duncan's Multiple Range test (DMRT) has been used to measure the specific differences between pairs of means.

3. Results

3.1 Demographic data:

The demographic data was presented in table (1). It was noticed that 315 lupus patients, from 350, were females. On the other hand, psoriasis patients (340) were composed of 198 male and 142 female patients. The number of male psoriatic arthritis patients (98) was higher than female ones (39). Psoriasis duration was seven years for group V (Ps) and thirteen years for group VI (PsA). The mean PASI for group VI (PsA) was higher than that of group V (Ps); 21.4 and 16.2, respectively. Nail involvement was found in 24 Ps patients and 85 PsA patients (7.05 and 49.13 %, respectively). No significant difference was noticed in BMI among different groups. The highest percent of hyperlipidemia, hypertension and obesity was found in group IV (lupus patients with developed atherosclerosis). The occupation and residence of different groups were presented in table (1). Occupation and residence information, of the patients and control group, have been included in the demographic data to clarify that the study population included all categories of the community. The difference between male and female was significant in patients with systemic lupus erythematosus. SLE usually affects females at far greater rates than males.

3.2 Serology:

Serum levels of complement proteins (C3 and C4) were significantly reduced in LN (43.4 and 8.5, respectively) and As (56.4 and 22.5, respectively) patients when compared to the healthy control group (123.2 and 43.8 mg/dl for C3 and C4, respectively). ANA and anti-dsDNA autoantibodies were the most dominant autoantibodies in the serum of the five patients groups (table 2). APLA, anti-sm, anti-histone and anti-ribosomal autoantibodies were detected in the serum of large numbers of LN and As patients more than in Ps and PsA patients (table 2). Anti

Ro/SSA was detected in a few numbers of patients (7, 4, 3, 5, and 3 patients from group II, III, IV, V and VI, respectively). According to table (3), autoantibodies titers were highly elevated in all patients groups. ANA, anti-dsDNA, APLA, anti-sm and anti-ribosomal levels were significantly higher in SLE patients (LN and As groups) more than psoriasis patients.

3.3 Cytokine profile:

Table (6) showed that all cytokines levels were significantly higher in PsA patients than in Ps patients; except IL-10 that showed the opposite. LN patients showed significant high levels of IL-17, -10, -4, -2, -23, -18 and -34 when compared to As patients (table 5). On the other hand, level of IL-1β was higher in As patients (183.4 mg/ml) more than that of LN patients (175.6 mg/dl). No significant difference, between LN and As patients, was observed in levels of IL-12, -6, -18, IFN-γ and TNF-α. Lupus patients, either LN or As, showed significant higher levels of IL-17, -1β, -12, -10 and -4 when compared to Ps patients. The opposite was observed with IL-23 which recorded 194.3 and 223.7 mg/ml in Ps and PsA patients, respectively (table 4). IL-34, -6, IFN-γ or TNF-α level was close between patients groups (LN, AS, Ps and PsA). Serum IL-17 recorded the highest level in LN patients followed by PsA patients, in comparison to control group. The highest level of IL-34 and -6 was observed in PsA patients.

3.4 Correlation between disease severity indices (SLEDAI in SLE patients and PASI in psoriasis patients) and hematologic levels of autoantibodies, complement proteins (C3 and C4) and cytokines:

Strong positive correlation was found between SLEDAI (in SLE patients) and levels of autoantibodies (ANA, anti-dsDNA, APLA and anti-ribosomal antibodies); and levels of cytokines (IFN-γ, TNF-α, IL-17, -1β, -12, -4, -2, -23, -34 and -6). Also, PASI (in psoriasis patients) showed strong positive correlation with autoantibodies levels (ANA, anti-dsDNA, and

anti-ribosomal antibodies) and with cytokines levels (IFN-γ, TNF-α, IL-17, -1β, -12, -4, -2, -23 and -34). Both of C3 and C4 levels were negatively correlated with SLEDAI and PASI.

Table 1: Demographic data in different groups:

	Group I: Control (n= 250)	Group II: Lupus (n= 350)	Group III: Lupus nephritis (LN) (n= 152)	Group IV: Lupus with atherosclerosis (As) (n= 161)	Group V: Psoriasis (Ps) (n= 340)	Group VI: Psoriasis arthritis (PsA) (n=173)
Age (years; mean±SD)	43.5±13.5	49.3±21.2	48.1±16.6	41.5±24.5	42.5±12.5	48.7±11.6
Median (range)	49 (39-53)	43 (33-54)	44 (35-52)	40 (41-51)	44 (39-51)	47 (41-50)
Sex (male/female)	32/218	35/315	15/137	16/145	198/142	98/39
Duration (years)	-	4	9	8	7	13
PASI (mean±SD)	-	-	-	-	16.2±6.9	21.4±10.3
Nail involvement n (%)	-	-	-	-	24 (7.05%)	85 (49.13%)
SLEDAI (mean±SD)	-	9.8±5.6	12.6±6.1	11.6±7.2	-	-
BMI (mean±SD)	23.1±9.9	26.4±19.1	25.1±13.5	27.5±11.1	24.5±16.4	26.7±21.4
Hyperlipidemia n (%)	134 (53.60%)	211 (60.28%)	90 (59.21%)	144 (89.44%)	233 (68.52%)	115 (66.47%)
Hypertension n (%)	83 (33.20%)	190 (54.28%)	80 (52.63%)	116 (72.04%)	134 (39.41%)	98 (56.64%)
Obesity n (%)	53 (21.20%)	252 (72.00%)	77 (50.65%)	143 (88.81%)	231 (67.94%)	112 (64.73%)
Occupation						
Farmers n (%)	101 (40.40%)	171 (48.85%)	49 (32.23%)	43 (26.70%)	201 (59.11%)	72 (41.61%)
Workers n (%)	91 (36.40%)	111 (31.71%)	64 (42.10%)	73 (45.34%)	87 (25.58%)	63 (36.41%)
Unemployed n (%)	58 (23.20%)	68 (19.42%)	39 (25.65%)	45 (27.95%)	52 (15.29%)	38 (21.96%)
Residence						
Urban n (%)	118 (47.20%)	140 (40.00%)	90 (59.21%)	89 (55.27%)	150 (44.11%)	80 (46.24%)
Rural n (%)	132 (52.80%)	210 (60.00%)	62 (40.78%)	72 (44.72%)	190 (55.88%)	93 (53.75%)

Results were expressed as mean ± standard deviation (mean ± SD) or median and range or, n (%) as appropriate.

Table 2: Autoantibodies positivity in different groups:

	Group I: Control (n= 250)	Group II: Lupus (n= 350)	Group III: Lupus nephritis (LN) (n= 152)	Group IV: Lupus with atherosclerosis (As) (n= 161)	Group V: Psoriasis (Ps) (n= 340)	Group VI: Psoriasis arthritis (PsA) (n=173)
ANA	0 (0%)	342 (97.71%)$^{\&}$	152 (100.00%)$^{\&*\#}$	160 (99.37%)$^{\&*\#}$	303 (89.11%)$^{\&}$	160 (92.48%)$^{\&*\#}$
Anti-dsDNA	0 (0%)	339 (96.85%)$^{\&}$	123 (80.92%)$^{\&*\#}$	149 (92.54%)$^{\&*\#}$	287 (84.41%)$^{\&}$	159 (91.90%)$^{\&*\#}$
anti Ro/SSA	0 (0%)	7 (2.00%)$^{\&}$	4 (2.63%)$^{\&}$	3 (1.86%)$^{\&}$	5 (2.89%)$^{\&}$	3 (0.88%)$^{\&}$
APLA	0 (0%)	98 (28.00%)$^{\&}$	35 (23.02%)$^{\&*\#}$	59 (36.64%)$^{\&\#}$	4 (1.17%)$^{\&*}$	2 (1.15%)$^{\&*}$
Anti-sm	0 (0%)	103 (29.42%)$^{\&}$	23 (15.13%)$^{\&*\#}$	43 (26.70%)$^{\&*\#}$	8 (2.35%)$^{\&*}$	5 (2.89%)$^{\&*}$
Anti-histone	0 (0%)	98 (28.00%)$^{\&}$	49 (32.23%)$^{\&*\#}$	69 (45.39%)$^{\&*\#}$	11 (3.23%)$^{\&*}$	8 (4.62%)$^{\&*}$
Anti-ribosomal	0 (0%)	123 (35.14%)$^{\&}$	53 (34.86%)$^{\&*\#}$	63 (39.13%)$^{\&*\#}$	9 (2.64%)$^{\&*}$	6 (3.46%)$^{\&*}$

Results were expressed as n (%); ANA: *antinuclear antibodies,* Anti-dsDNA: anti-double strand DNA, anti Ro/SSA: anti–Sjögren's-syndrome-related antigen A autoantibodies, APLA: Antiphospholipid antibody and *Anti-sm: anti-Smith.*

$^{\&}$ represents a significant difference by Fisher exact test in comparison to control group (P <0.05).

* represents a significant difference by Fisher exact test in comparison to group II (P <0.05).

$^{\#}$ represents a significant difference by Fisher exact test in comparison to group V (P <0.05).

Table 3: Titers of autoantibodies in different groups.

	Group I: Control (n= 250)	Group II: Lupus (n= 350)	Group III: Lupus nephritis (LN) (n= 152)	Group IV: Lupus with atherosclerosis (As) (n= 161)	Group V: Psoriasis (Ps) (n= 340)	Group VI: Psoriasis arthritis (PsA) (n=173)
ANA (IU/ml)	0.2±0.1^{a}	3.1±0.3^{c}	7.1±0.2^{e}	6.4±1.2^{d}	2.4±0.9^{b}	3.7±5.3^{c}
Anti-dsDNA (IU/ml)	11.1±2.1^{a}	294.6±2.4^{e}	356.2±3.6^{f}	225.7±5.6^{d}	34.9±4.1^{b}	69.7±8.7^{c}
anti Ro/SSA (U/ml)	0.2±0.01^{a}	2.1±0.6^{b}	1.9±0.4^{b}	1.8±0.1^{b}	0.5±0.01^{a}	0.1±0.01^{a}

APLA (U/ml)	3.1±0.3[a]	110.2±2.9[d]	99.3±6.1[c]	115.4±4.1[d]	6.4±1.1[b]	5.4±2.3[b]
Anti-sm (U/ml)	1.6±0.2[a]	34.4±6.4[c]	43.4±9.4[d]	39.4±5.4[d]	2.3±0.2[b]	3.5±4.1[b]
Anti-histone (IU/ml)	0.6±0.1[a]	1.9±0.9[c]	2.1±0.4[c]	1.8±0.3[c]	1.1±0.3[b]	0.9±0.03[b]
Anti-ribosomal (U/ml)	0.9±0.1[a]	21.3±3.3[c]	32.4±4.2[d]	26.6±2.4[c]	6.4±2.7[b]	5.9±0.7[b]
C3 (mg/dl)	123.2±23.4[e]	53.4±55.4[b]	43.4±26.7[a]	56.4±19.6[b]	103.8±18.4[d]	96.6±44.4[c]
C4 (mg/dl)	43.8±37.6[e]	12.5±32.1[b]	8.5±16.4[a]	22.5±46.7[c]	33.4±55.7[d]	23.5±37.1[c]

The results were presented as m±SD. In each row, the mean values marked with the same superscript letter are similar (insignificant, P>0.05) whereas those with different ones are significantly differed (P<0.05) using Duncan's Multiple Range test (DMRT).Normal values: ANA 0.9 IU/ml; anti dsDNA 17.7 IU/mL; anti Ro/SSA 10 U/mL; APLA 10 U/ml; anti-Sm 10 U/mL; anti-histones 1.5 IU/mL; anti-ribosomal 10 U/mL.

Table 4: Cytokines levels in psoriasis patients compared to healthy controls.

	Group I: Control	**Group V: Psoriasis (Ps) (n= 340)**	**Group VI: Psoriasis arthritis (PsA) (n=173)**	***P* value**	
				Group V versus group I	**Group VI versus group V**
IL-17 (pg/ml)	12.1 (10.2-29.4)	41.7 (30.7-49.7)	62.4 (47.1-74.5)	**0.04**	**0.01**
IL-1β (pg/ml)	53.4 (45.7-88.7)	110.1 (88.7-128.7)	119.4 (98.4-131.4)	**0.002**	0.21
IL-12 (pg/ml)	98.7 (78.9-121.4)	151.4 (122.6-167.5)	167.4 (139.7-181.1)	**0.02**	0.09
IL-10 (pg/ml)	44.1 (35.7-55.7)	99.4 (72.6-105.8)	87.1 (55.7-98.7)	**0.006**	0.05
IL-4 (pg/ml)	49.4 (33.4-61.7)	59.7 (41.3-66.7)	71.1 (54.2-87.1)	0.11	0.10
IL-2 (pg/ml)	10.4 (9.7-13.7)	49.4 (37.1-57.2)	67.4 (46.7-72.4)	**0.009**	0.09
IL-23 (pg/ml)	34.8 (22.4-49.7)	201.7 (187.9-219.7)	234.4 (204.6-241.7)	<**0.001**	0.20
IL-18 (pg/ml)	69.8 (55.7-89.7)	112.1 (87.1-124.7)	134.7 (119.7-139.5)	**0.01**	0.10

IL-34 (pg/ml)	17.4 (12.9-27.8)	71.8 (58.4-89.6)	113.4 (91.4-126.7)	**<0.001**	0.06
IL-6 (pg/ml)	19.7 (12.7-29.7)	32.4 (48.2-53.7)	111.4 (84.3-126.4)	**0.03**	**0.03**
IFN-γ (pg/ml)	5.3 (4.7-7.9)	35.6 (19.4-39.4)	47.2 (30.7-54.7)	**0.02**	0.30
TNF-α (pg/ml)	11.7 (7.4-18.7)	26.7 (18.1-31.4)	46.1 (22.4-50.9)	**0.03**	0.08

Results were expressed as median and range, where bold values indicated significance ($p < 0.05$). IL: interleukin, IFN: interferon and TNF: tumor necrosis factor.

Table 5: Cytokines levels in psoriasis patients compared to healthy controls.

	Group I: Control	**Group II: Lupus**	**Group III: Lupus nephritis (LN)**	**Group IV: Lupus with atherosclerosis (As)**	***P* value**		
					Group II versus group I	**Group III versus group II**	**Group IV versus group II**
IL-17 (pg/ml)	12.1 (10.2-29.4)	66.7 (49.7-81.7)	76.9 (55.7-89.7)	62.7 (51.7-84.7)	**0.03**	0.1	0.27
IL-1β (pg/ml)	53.4 (45.7-88.7)	169.7 (153.9-197.8)	159.7 (144.4-189.4)	171.8 (167.4-198.7)	**0.001**	0.08	0.60
IL-12 (pg/ml)	98.7 (78.9-121.4)	199.7 (189.4-275.2)	201.7 (194.3-251.7)	215.7 (188.7-259.7)	**0.02**	**0.04**	0.07
IL-10 (pg/ml)	44.1 (35.7-55.7)	139.7 (121.4-151.7)	147.9 (134.7-172.4)	144.7 (129.7-179.4)	**0.007**	0.09	**0.04**
IL-4 (pg/ml)	49.4 (33.4-61.7)	119.7 (99.7-127.4)	122.7 (107.4-143.8)	119.7 (97.4-135.7)	**0.004**	**0.01**	**0.01**
IL-2 (pg/ml)	10.4 (9.7-13.7)	36.4 (21.4-49.7)	35.7 (33.7-36.7)	27.8 (19.9-31.7)	**0.001**	0.24	**0.02**
IL-23 (pg/ml)	34.8 (22.4-49.7)	71.8 (45.9-87.3)	93.7 (59.7-110.7)	83.7 (69.7-97.7)	**<0.001**	0.30	0.23
IL-18 (pg/ml)	69.8 (55.7-89.7)	149.7 (129.7-159.7)	159.7 (137.8-176.4)	157.4 (124.7-187.4)	**0.04**	0.41	0.06
IL-34 (pg/ml)	17.4 (12.9-27.8)	87.1 (54.2-91.7)	97.1 (41.2-101.7)	84.7 (56.7-101.4)	**0.006**	0.31	0.22
IL-6 (pg/ml)	19.7 (12.7-29.7)	47.5 (21.9-51.4)	42.1 (19.7-44.5)	39.6 (22.8-43.7)	0.09	0.97	0.37
IFN-γ (pg/ml)	5.3 (4.7-7.9)	31.4 (18.7-41.5)	29.9 (22.7-36.7)	23.4 (17.4-29.7)	**0.01**	0.11	0.13
TNF-α (pg/ml)	11.7 (7.4-18.7)	37.8 (29.8-42.6)	59.7 (37.8-64.7)	49.7 (30.1-59.7)	0.07	0.08	0.20

Results were expressed as median and range, where bold values indicated significance ($p < 0.05$). IL: interleukin, IFN: interferon and TNF: tumor necrosis factor.

Table 6: Cytokines profile in different groups:

	Group I: Control (n= 250)	**Group II: Lupus (n= 350)**	**Group III: Lupus nephritis (LN) (n= 152)**	**Group IV: Lupus with atherosclerosis (As) (n= 161)**	**Group V: Psoriasis (Ps) (n= 340)**	**Group VI: Psoriasis arthritis (PsA) (n=173)**
IL-17 (pg/ml)	16.5 ± 9.4^{a}	56.7 ± 16.1^{c}	66.7 ± 14.7^{d}	58.4 ± 10.6^{c}	34.9 ± 9.4^{b}	58.4 ± 18.4^{c}
IL-1β (pg/ml)	71.6 ± 22.4^{a}	180.2 ± 31.1^{d}	175.6 ± 18.6^{d}	183.4 ± 16.8^{e}	98.5 ± 61.4^{b}	110.5 ± 33.8^{c}
IL-12 (pg/ml)	102.4 ± 18.7^{a}	234.1 ± 41.6^{d}	244.5 ± 26.7^{e}	250.4 ± 26.8^{e}	134.6 ± 76.4^{b}	145.5 ± 43.6^{c}
IL-10 (pg/ml)	45.8 ± 44.7^{a}	143.6 ± 16.4^{d}	162.4 ± 13.8^{f}	154.2 ± 33.4^{e}	88.6 ± 16.4^{c}	78.2 ± 51.7^{b}
IL-4 (pg/ml)	52.1 ± 12.7^{a}	112.3 ± 32.9^{c}	135.4 ± 11.9^{e}	121.7 ± 19.7^{d}	58.7 ± 11.3^{b}	64.7 ± 13.8^{b}
IL-2 (pg/ml)	11.4 ± 6.3^{a}	35.6 ± 9.8^{c}	43.6 ± 8.6^{d}	23.2 ± 9.8^{b}	43.5 ± 13.2^{d}	56.6 ± 20.1^{c}
IL-23 (pg/ml)	32.8 ± 11.4^{a}	68.4 ± 10.1^{b}	88.9 ± 5.4^{d}	76.4 ± 10.4^{c}	194.3 ± 27.5^{e}	223.7 ± 36.8^{f}
IL-18 (pg/ml)	78.6 ± 23.9^{a}	134.2 ± 8.7^{c}	146.7 ± 6.4^{d}	133.1 ± 22.9^{c}	109.7 ± 32.8^{b}	121.8 ± 40.5^{b}
IL-34 (pg/ml)	15.5 ± 16.6^{a}	67.8 ± 11.3^{b}	77.5 ± 11.4^{c}	66.7 ± 12.1^{b}	64.1 ± 24.1^{b}	95.6 ± 19.1^{d}
IL-6 (pg/ml)	22.3 ± 42.9^{a}	39.6 ± 8.8^{b}	33.6 ± 5.6^{b}	32.1 ± 19.3^{b}	45.9 ± 8.7^{c}	96.4 ± 16.7^{d}
IFN-γ (pg/ml)	6.4 ± 5.8^{a}	25.4 ± 6.4^{b}	21.1 ± 6.7^{b}	20.6 ± 38.4^{b}	21.1 ± 9.9^{b}	32.4 ± 22.6^{c}
TNF-α (pg/ml)	17.6 ± 3.6^{a}	34.5 ± 3.1^{c}	42.4 ± 5.9^{d}	39.4 ± 17.3^{c}	23.4 ± 11.4^{b}	33.7 ± 10.4^{c}

The results were presented as m±SD; in each row, the mean values marked with the same superscript letter are similar (insignificant, $P>0.05$) whereas those with different ones are significantly differed ($P<0.05$) using Duncan's Multiple Range test (DMRT). IL: interleukin, IFN: interferon and TNF: tumor necrosis factor.

Table 7: Correlation between disease severity indices (SLEDAI in SLE patients and PASI in psoriasis patients) and hematologic levels of autoantibodies, complement proteins (C3 and C4) and cytokines.

Parameter	SLEDAI		PASI	
	r	*P* value	r	*P* value
ANA	0.73	**0.005**	0.62	**0.03**
Anti-dsDNA	0.54	**0.04**	0.56	**0.006**
anti Ro/SSA	0.21	0.06	0.23	0.21
APLA	0.41	0.05	0.12	**0.01**
Anti-sm	0.21	**0.002**	0.34	0.06
Anti-histone	0.32	0.08	0.11	0.31
Anti-ribosomal	0.46	**0.03**	0.64	**0.02**
C3	-0.22	**0.001**	-0.34	**0.03**
C4	-0.14	**0.002**	-0.44	**0.009**

Parameter	SLEDAI		PASI	
	r	*P* value	r	*P* value
IL-17	0.61	**0.01**	0.53	**0.02**
IL-1β	0.57	0.05	0.67	**0.002**
IL-12	0.47	0.06	0.41	**0.04**
IL-10	0.21	**0.007**	0.22	0.23
IL-4	0.66	0.06	0.64	**0.007**
IL-2	0.89	**0.001**	0.50	0.08
IL-23	0.78	**0.005**	0.90	**0.003**
IL-18	0.21	0.12	0.09	0.11
IL-34	0.71	0.54	0.82	**0.02**
IL-6	0.43	**0.01**	0.16	0.05
IFN-γ	0.59	**0.02**	0.40	**0.01**
TNF-α	0.73	**0.04**	0.70	**0.06**

Bold values indicated significance at $p < 0.05$.

4. Discussion

Generally, in autoimmunity, CD4+ Th cells are essential in the development of immune responses. Th cells are classified into Th1, Th2, Th17, follicular helper T (Tfh) cells and Treg cells according to their secreted cytokines. Th1 cells secret primarily IFN-γ that activates cytotoxic T lymphocyte (CTL), macrophage and natural killer (NK) cells; in addition to TNF- α, IL-2, -10, -12 and -1β. On the other hand, Th2 cells secret cytokines like IL-4 and -10 in addition to B lymphocyte activation. However, the pathogenesis of autoimmune disorder cannot depend on the Th1 and/or Th2 immune responses alone; Th17 cells, which secret IL-17, and Treg cells play a central role in the development of tissue injury (Koga *et al.*, 2021). In addition to T cells, B cells are considered a major factor in autoimmunity pathogenesis; where hyperactivated B cells produce autoantibodies against self-antigens. This dysregulation of B cells activates T cells, recruits dendritic cells, inhibits Treg cells and induces Th1 and Th17 phenotype activation.

Detection of autoantibodies can be beneficial in the diagnosis of certain autoimmune diseases like SLE and psoriasis. Most SLE patients have positive ANA, which is a category of autoantibodies that target nuclear antigens. ANA, anti-Sm, and anti-dsDNA antibodies, for example, are part of the American College of Rheumatology's SLE diagnostic criteria. With a cutoff titer of 1/80, ANA by indirect immunofluorescence test is extremely sensitive and specific for SLE. In this study, detection of autoantibodies (ANA, anti-dsDNA, anti-sm, anti-histone, anti-ribosomal, APLA and anti-Ro/SSA) was performed to find if there is a relation between disease development and their presence.

According to our results, the sera of all patients' groups were positive for ANA and anti-dsDNA antibodies. APLA, anti-sm, anti-histone and anti-ribosomal autoantibodies were detected in sera

of large numbers of LN and As patients more than in Ps and PsA patients. Serum levels of complement proteins (C3 and C4) were significantly reduced in LN and As patients when compared to the healthy control group. Anti Ro/SSA was detected in a few numbers of LN and As patients. From our results, we can conclude that although, ANA and anti-dsDNA are suggested to be a good marker for the diagnosis of SLE and monitoring disease activity, however, other autoantibodies like APLA, anti-sm, anti-histone and anti-ribosomal can be used to provide a better indicator for disease activity. Moreover, levels of ANA, anti-dsDNA, APLA, anti-sm and anti-ribosomal can be used in differentiating between SLE and psoriasis diseases due to their elevated levels in SLE patients (LN and As groups) more than psoriasis patients (Ps and PsA). On the other hand, anti-histone levels showed no significant difference between SLE and psoriasis patients; therefore, it can be used as a diagnostic markers between them. Bigler *et al.* (2008) were in agreement with our results; they reported a good association between anti-nucleosome and LN. González *et al.* (2004) revealed a contradictory outcome regarding anti-histone antibodies; they considered it as a specific marker for SLE diagnosis with an equivalent diagnostic value to anti-dsDNA while other studies revealed that anti-histone is sensitive but not specific for SLE. On the other hand, Patrikiou *et al.* (2020) reported that ANA was frequently detected in Ps and PsA patients, but their target autoantigens remain unknown. According to this study, although APLA, anti-sm, anti-histone and anti-ribosomal antibodies were detected in a few number of Ps patients, the predominant autoantibodies in Ps and PsA patients were ANA and anti-dsDNA. Also, Anti Ro/SSA was detected in a few numbers of Ps and PsA patients. Wilhelm and Major (2012) reported that elevated concentrations of autoantibodies have contributed to SLE accelerated atherosclerosis; they added that a high concentration of APLA was associated with an increased risk of cardiovascular disease.

This study evaluated the clinical consequences of different cytokines secreted from CD4+ Th cells [Th1 (IFN-γ, TNF- α, IL-2, -10, -12 and -1β); Th2 (IL-4 and -10) and Th17 (IL-17)] in Egyptian SLE and psoriasis patients. In addition, the potential role of these cytokines as factors involved in disease activity and autoimmune-mediated tissue injured was investigated.

Although several cytokines have been reported in Ps patients where they coordinate inflammation leading to endothelial cells damage, IL-17 and -23 have an important role in psoriasis development (Farid *et al.*, 2020). Also, TNF- α potentiate the effect of IL-23 and -17 by maintaining the cells that produce these cytokines (Yamanaka *et al.*, 2021). According to our results, PsA patients have high levels of all measured cytokines except IL-10, which was higher in Ps patients. IL-17 recorded the highest level in LN and PsA patients, while the highest levels of IL-34, -23 and -6 were recorded in PsA patients. Our results were in agreement with many studies that reported IL-17 as the maestro cytokine in psoriasis. IL-17 facilitates abnormal keratinocytes proliferation and induces inflammatory mediators' release. The synergetic effect of IL-17 and TNF-α leads to gene transcription of other inflammatory cytokines such as IL-1β, -8 and -6 (Farid *et al.*, 2020). IL-23 facilitates the production of IL-17, through the IL-23/Th17 axis, where the maintenance of Th17 is directly linked to IL-23 (Yamanaka *et al.*, 2021). In addition, our study showed that although IL-34 and -6 levels were significantly elevated in all patients' groups, they achieved the highest level in PsA patients. This was in agreement with many studies that revealed the significant role of IL-34 in the development of psoriasis arthritis (Farid *et al.*, 2020). IL-34 is secreted from epidermal keratinocytes in the skin, where it has a role in homoeostasis of the skin. It is, also, involved in macrophage differentiation and osteoclastogenesis. Mice injected with IL-34 showed an elevation in the osteoclast precursor's number and activated the resorption of bone. IL-34 acts as an inflammatory cytokine by the

activation of monocytes and chemokines upregulation. TNF-α and IL-1β stimulates the expression of IL-34 that in turn elevated IL-17 production (Tian *et al.*, 2013). IL-6, a single glycoprotein chain, secreted from monocyte and endothelial cell and has a significant role in arthritis development in psoriasis patients (Juneblad *et al.*, 2018). Furthermore, the IL-6 targeted drug was effective in the amelioration of PsA symptoms in clinical trials. Our study showed that an elevated level of IL-18 was observed in SLE patients, either LN or As, more than in Psoriasis patients. Xiang *et al.* (2021) reported a high IL-18 level in SLE patients. IL-18 is a pro-inflammatory cytokine that has been classified as an element of the IL-1 superfamily; it shares several similar physiological functions with IL-1α and IL-1β. It recruits MyD88 leading to NF-κB activation, upon its binding with its receptor. The activation of this signaling pathway leads to IFN-γ production and Th1 immune response. Bossù *et al.* (2003) found that MRL/lpr mice model treated with anti-IL-18 showed alleviated lupus; on the contrary, exogenous IL-18 administration worsens the severity of the disease. Umare *et al.* (2019) reported the correlation between IL-18 levels and the severity of LN.

In this study, the results showed that the levels of IL-17, -10, -4, -2, -23, -18 and -34 were higher in LN patients when compared to their corresponding levels in As patients. On the other hand, IL-1β was a characteristic cytokine in As patients. Studies showed that inflammatory cytokines (IL-6, 1β and TNF-α) and immunomodulatory IL-10 played an important role in SLE development. Also, IL-2 maintains the function and homeostasis of Treg cells; in addition to the inhibition of IL-17 production. As a consequence IL-2 can be considered as a crucial cytokine for the prevention of autoimmunity. Our results showed that IFN-γ was significantly elevated in lupus patients, either LN or As. This observation was in agreement with Ohl and Tenbrock (2011) who reported that serum levels of SLE patients showed a high level of IFN-γ; and

Bengtsson *et al.* (2000) showed that a high IFN-γ level was correlated to anti-dsDNA production and SLE activation. Moreover, IFN therapy led to the production of autoantibodies and SLE like syndrome. Moreover, Buono *et al.* (2003) found reduced atherosclerosis in mice lacking IFN-γ and considered IFN-γ as a pro-atherogenic cytokine. McLaren and Ramji (2009) showed that IFN-γ, secreted from activated T cells, has been associated with atherosclerotic plaques instability.

LN is among the most concerning intrinsic SLE manifestations, as well as one of the greatest indicators of a bad prognosis in SLE, accounting for the majority of the disease's burden, particularly in low-income communities (Paquissi and Abensur, 2021). In LN, Th17 is hyperactivated and correlated to the fatality of the disease. Several studies found expressed IL-17 receptors on kidney cells such as renal endothelial cells, mesangial cells and podocytes (Krohn *et al.*, 2018). They added that IL-17 is involved in the maintenance of an inflammatory environment in the kidney, nephron morphological and function disruption, fibrosis activation, architecture loss and finally kidney function loss.

Urowitz *et al.* (1976) showed the increased risk of cardiovascular disease in lupus patients. They reported that early death (less than one year after diagnosis) in lupus disease was attributed to nephritis development, while the cardiovascular disease was associated with later deaths. Nowadays, atherosclerosis in SLE patients is considered a main cause of death; after the appearance of effective therapeutic approaches for lupus nephritis. Several factors are involved in the accelerated atherosclerosis process. Dysregulation of T and B cells and the elevated levels of circulating inflammatory cytokines were the most dominant factors. Wilhelm and Major (2012) reported that T cells play many roles in SLE and atherosclerosis development; and added that T cells dysregulation has participated in the cardiovascular diseases observed in lupus

patients. CD4+ Th1 cells are the primary T cell subset found in the atherosclerotic lesion. Zhou *et al.* (2000) reported that Th1 cells played a pathogenic role in atherosclerosis; where they found that the transfer of CD4+ T cells in immune-deficient *SCID/SCID* (ApoE−/− mice) led to an increased atherosclerosis. Th1 secreted inflammatory cytokines, like IFN-γ, activate macrophages in the atherosclerotic lesion. In addition to the role of T cells in atherosclerosis development, cytokines play an important role in the pathogenesis of SLE. Dawisha *et al.* (1994) found that Th cells in SLE disease are hyperactive with a decreased activation threshold. In addition, Budagyan *et al.* (1998) found that T cells in SLE disease have an elevated survival rate and resistance to apoptosis; and produce many inflammatory cytokines like IL-17 and IFN-γ. Schulte *et al.* (2008) examined Th1/Th2 relation in atherosclerotic mice model; they found that Th1 phenotype was related to increased atherosclerosis and Th2 was associated with decreased atherosclerosis.

On the other hand, Treg cells suppress T cell activation, induce apoptosis, prevent effector T cell response, and inhibit the function of B cells leading to important regulatory roles in the development of both SLE and atherosclerosis. Wilhelm and Major (2012) reported the role of Th17 cells in SLE accelerated atherosclerosis; where Th17 cells were found in human and mice atherosclerotic plaque. Shah *et al.* (2010) added that Th17/Th1 ratio was dysregulated in lupus patients with an elevation in Th17 percent. And Ma *et al.* (2010) reported the decreased Treg/Th17 ratio in lupus patients. Critical roles for IL-17, TGF-β and IL-10 have been associated with Th17, Treg and Breg cells.

In conclusion, detection of autoantibodies and complement proteins were beneficial in the diagnosis of SLE and psoriasis. ANA and anti-dsDNA autoantibodies were a good marker for the diagnosis of SLE and monitoring disease activity, however, other autoantibodies like APLA,

anti-sm, anti-histone and anti-ribosomal can be used to indicate the disease activity. Cytokines can be used to determine the disease activity and autoimmune-mediated tissue injured in both SLE and psoriasis. Where, IL-17 recorded the highest level in LN and PsA patients, while the highest levels of IL-34, -23 and -6 were recorded in PsA patients. IL-1β was a characteristic cytokine in As patients. There were two major limitations in the study that should be addressed in the future research. First, the study focused on small-size population and second the time of blood sample collection. However, we suggest addressing these limitations by increasing the population size (>500 individual in each group) and collect blood samples frequently during 24 hour period to validate the results.

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