ORIGINAL ARTICLE

Interleukin 17A -197 G/A Gene Polymorphism and Interleukin-17 Serum Level in Patients with Spondyloarthropathy

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ABSTRACT

Background*: Although the exact cause of spondyloarthropathy (SpA) is unknown, evidence points to the importance of interleukin-mediated immune responses 17A (IL-17A) in the progression of the condition.* ***Objective:*** *is to assess how IL17A gene polymorphism in the -197 G/A promoter region affects IL17 levels, disease severity, and treatment response in spondyloarthropathy patients.* ***Methodology:*** *A total of 65 Egyptians, 35 of them are patients with SpA, have been registered at the Aswan University Clinical Rheumatology department. Thirty healthy volunteers whose ages and sexes are matched to those of the patient group. Demographic information was given to each participant. Clinical examination, as well as a laboratory evaluation that included measuring the level of IL-17A in their serum using ELISA, Additionally, Extracted DNA was used for genotyping.* ***Results****: Of our cases, 17 patients (48.57%) were females and 18 were males (51.43%) In our investigation, the serum IL-17A levels of the patients and the controls differed significantly. The patients' levels of IL-17 were significantly higher in SpA than the controls'. The level of IL-17A in SpA was significantly correlated with either its active state (AS or PsA) or its sub-tyes, with a distinct cutoff point. The genotyping results for IL 17A -197 G/A in patients and the control group did not differ significantly.****conclusion****, our research suggests that IL-17A is a low-cost valued, and practical biomarker for identifying SpA in patients without symptoms and helps in early diagnosis of the disease to prevent development of disabilities.*

INTRODUCTION

Spondyloarthropathy (SpA) is an inflammatory illness of the immune system that affects the spine, peripheral joints, and extra-articular organs such the skin, intestines, and eyes.[1]

The early clinical symptoms and signs of the SpA disease are frequently non-specific, radiological sacroiliitis develops later in the illness, and human leukocyte antigen (HLA)-B27 which has strong relation to the SpA disease, all those are not very specific because they can appear in healthy individuals.[2]

While the precise causes of psoriatic arthritis (PsA) remain somewhat unclear, there is growing evidence indicating that interleukin 17A (IL-17A)-related immune responses is important in the illness. The significant therapeutic advantages of IL-17A inhibitors in the treatment of PsA serve to highlight this.[3].

Although the exact disease mechanisms underlying psoriatic arthritis (PsA) remain unclear, evidence suggests that interleukin 17A (IL-17A)-mediated immune responses play a critical role. This idea is strongly supported by the notable clinical success of IL-17A inhibitors in the treatment of PsA.[4]

Interleukin 17A (IL-17A) in the illness. IL-17A inhibitors' remarkable clinical efficacy in treating SpA.[5]

Diagnosis of SpA in its early stages greatly enhances treatment response. Early intervention with anti-inflammatory medications or immune-modulating treatments notably enhances disease outcomes and prevents the progression of complications and disabilities.[6]

Th17 and IL-17, a potent pro-inflammatory cytokine, has shed light on the function of Th17 cells in RA as well as other immune-mediated illnesses like multiple sclerosis, psoriasis, and Crohn's disease.[7]

TNF-α and IL-1, are essential cytokines in destructive arthritis, IL-17 contributes significantly to the additive and synergistic effects that are produced.[8]

Elevated level of IL-17A in both blood and synovial fluid have been associated with the severity of SpA, suggesting a more intense disease progression.[9]

Moreover, genetic variations in genes linked to inflammation, particularly those involving cytokines and their receptors, may cause an upregulation of IL-17 expression.[10]

new genetic associations beyond HLA-B27 have been shown by extensive genome wide association studies, indicating the involvement of mechanisms involving inflammatory cytokines in the development of ankylosing spondylitis (AS) and other human SpA subtypes. Additionally, these results point to the possible therapeutic application of inflammatory cytokines in the management of SpA.[11]

METHODOLOGY

This study was approved by the Ethics Committee of the Faculty of Medicine at Aswan University. Every participant provided a written consent after being fully informed. (Asw. U./301/10/18)

A case-control study was carried out on 65 Egyptians, of whom 35 patients were diagnosed with SpA using the 2009 ASAS (Axial Spondyloarthritis Classification) Criteria and were registered at the Aswan University Hospital's Division of Clinical Rheumatology[12] and the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria in patients with PsA, as well as the ASAS Criteria 201112 for peripheral SpA[13], to supplement the ASAS criteria and enhance confidence in the gathered data, aging between 18 and 80 years old. Control group consists of 30 healthy volunteers' age and sex matched as the patient group. Written, informed consent was given to each participant, along with a questionnaire containing social and demographic information (age, sex, age of disease onset, length of disease, and therapy).

Exclusion criteria

Pregnancy or lactation; coexistence with other connective tissue systemic diseases other than RA; alcohol misuse; hepatotropic virus infection; infections resistant to treatment; continued cancer history if a cure is not obtained; uncontrolled diabetes; patient unwillingness or incapacity to cooperate.

Clinical and laboratory assessment

Every individual underwent a thorough medical history assessment, covering personal details, family background, and past drug usage. They all received detailed local and general physical examinations. For both the patients and the control group, laboratory evaluations included tests for erythrocyte sedimentation rate (ESR) and a full blood count (CBC). Furthermore, C-reactive protein levels were checked, and IL-17 levels in the blood were measured using an enzyme-linked immunosorbent assay (ELISA) method.

From each participant had five milliliters of venous blood were drown and centrifuged at 4000x g for 20 minutes in sterile flat-bottom tubes. The separated serum was promptly stored at -20°C until analysis. The concentration of IL-17 in the serum was determined using a commercial Interleukin 17 ELISA Kit, Bioassay Laboratory Technology (96 wells), China, A semi-automated ELISA reader system (Tecan, Infinite F-50 microplate absorbance reader, Czech Republic) was used to process the ELISA and to determine optical densities of final products. following the manufacturer's guidelines to measure IL-17 levels.

Assay producers:

- All reagents are bought to room temperature before use. The assay is performed at room temperature.
- The strips were inserted in the frames for use.
- 50µl standard was added to standard well.
- 40µl sample was added to sample wells and then 10µl anti-IL-17 antibody was added to sample wells, then 50µl streptavidin-HRP were added to sample wells and standard wells (Not blank control well, Mixed well. the plate was Covered with a sealer and Incubated 60 minutes at 37°C.
- The sealer was removed and the plate was washed 5 times with wash buffer. Wells were Soaked with at least 0.35 ml wash buffer for 30 seconds to 1 minute for each wash. For automated washing, aspirating all wells and wash 5 times with wash buffer, overfilling wells with wash buffer. Then Blot the plate onto paper towels or other absorbent material.
- 50µl substrate solution A was added to each well and then 50µl substrate solution B added to each well. Plate Incubated covered with a new sealer for 10 minutes at 37°C in the dark.
- 50µl Stop Solution was added to each well, the blue color will change into yellow immediately.
- The optical density (OD value) of each well was Determine immediately using a microplate reader set to 450 nm within 30 min after adding the stop solution.
- Calculation of results, a standard curve Constructed by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and draw a best fit curve through the points on the graph.

Every individual had 5 milliliters of peripheral venous blood taken aseptically using sterile tubes, both with and without ethylene diamine tetra acetic acid (EDTA). The first part was collected and stored in EDTA tubes at -80°C until the DNA was extracted and used in additional genetic study. Thermo Scientific GeneJET Whole Blood Genomic DNA Purification kit Mini Kit #K0781 was used to isolate DNA. The identification of polymorphisms in the promoter region of IL-17A rs2275913 (-197 G/A) was achieved through a polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) approach, utilizing specific

primers as previously reported by Zandi *et al.*[23] These included:

IL-17A -197 G/A forward–TM=72, nucleotide sequence: 5'AACAAG TAAGAATGAAAAGAGGA CATGGT3', and IL-17A -197 G/A reverse – TM = 75, nucleotide sequence: 5'CCCCCA ATGAGG TCATAGAAGAATC3', (Thermo Fisher Custom Primers, USA). Table-1

Table 1: Size of IL-17A 197 G/A products before and after digestion

IL-17A	Primer sequence	Size of PCR product (bp)	Size of restriction fragments
IL-17A 197 G/A (rs2275913)	**Forward:** 5'AACAAGTAAGAATGAA AAGAGGACATGGT3'. **Reverse:** 5'CCCCCAATGAGG TCATAGAAGAATC3'.	102bp	AA = 102 bp AG = 102, 68, 34 bp GG= 68, 34 bp

Statistical analysis

Statistical Package for the Social Sciences, version 22, was installed on a personal IBM computer, which was used for data collection, tabulation, and statistical analysis (SPSS Inc.). Based on their normal distribution, quantitative data were summarized using statistics like mean, standard deviation (mean ± SD), range, median, and interquartile range (IQR). The Chi-square test ($\chi 2$) was used to compare qualitative data that were expressed as numbers and percentages. A Spearman's correlation coefficient (r) and the Student's t-test were used to compare and correlate quantitative data, specifically IL-17A levels. By choosing the value from the receiver operating characteristic (ROC) curves with the highest accuracy, diagnostic cutoff points were established. Multiple regression analysis was used to identify independent risk factors, which are shown as odds ratios (ORs). A level of significance of P <.05 was applied for statistical significance.

RESULTS

Table 2 presents demographic details, clinical data, and lab findings for both the patient and control groups. Age and gender showed no significant variations, with patients categorized into 23 individuals (65.7%) diagnosed with Ankylosing Spondylitis (AS) and 38 individuals (34.3%) diagnosed with Psoriatic arthritis (PsA). The IL-17A -197 G/A genotyping outcomes revealed no significant distinctions between patients and controls in terms of genotype distribution

A noteworthy contrast was observed between patients and controls concerning IL-17A levels in the serum, indicating significantly elevated levels in the patients compared with controls with a p-value of 0.0001. SpA: Spondyloarthropathy, PsA: Psoriatic arthritis, AS: Ankylosing Spondylitis, SD: standard deviation.

Table 2: Demographic and laboratory characteristics of studied groups

		SpA	SpA subtypes		Controls	P value
			AS	PsA		
		N=35	N=23	N=12	N=30	
Age (years)		40.06±8.41	40.43±9.39	39.33±6.43	41.3±13.63	0.52
Gender	Male	18 (51.43%)	18 (78.26%)	0	14 (46.67%)	0.70
	Female	17 (48.57%)	5 (21.74%)	12 (100%)	16 (53.33%)	
IL-17 (pg./dL)	Mean±SD	207569.7±530765.4	289163.8±632213.4	51181±175377	127.96±164.07	<0.0001
	Median	480.7	480.7	342.3	96.5	
	range	28.5:25703	28.5:2570355	80:608075	7.1:761	
IL-17A -197 G/A genotype	GG	4 (11.43%)	1 (4.35%)	3 (25.00%)	5 (16.67%)	0.58
	GA	19 (54.29%)	14 (60.87%)	5 (41.67%)	18 (60.00%)	
	AA	12 (34.29%)	8 (34.78%)	4 (33.33%)	7 (23.33%)	

Serum levels of IL17 and the IL17A-197 G/A polymorphism in spondyloarthropathy patients

CDAI Disease Activity Index, SD: standard deviation Anti-TNF a: anti tumor necrosis factor alpha

IL-17serum level was significantly higher in active PsA (**clinical Disease Activity Index** ,**CDAI**), (CDAI>22) group than the non-active (CDAI≤22) group with p value 0.01, IL-17 serum level was significantly lower in ankylosing spondylitis patients receiving anti-TNF for treatment than others not receiving anti-TNF for treatment with p value 0.001 (Table 3).

Table 3: Relation between IL-17 level and features of SpA patients

		Mean ± SD and median of IL-17			
		SpA	SpA subtypes		P value
			AS	PsA	
		N=35	N=23	N=12	
IL-17A -197 G/A genotype	GG	904.8±946.5	1761	619.3±924.6	0.85
	GA	349782.5±682796	474528±762785	495.3±367.5	
	AA	51287.82±175.343.9	701.9±772	152459.5±303744.3	
CDAI	≤22	28.5:5628.5	28.5:5628.5	80:932.7	0.001
	>22	146.7:2370355	146.7:2570355	1452:608075	
Anti-TNF	Yes	50:480.7	50:480.7		**0.001**
	No	28.5:22570355	28.5:2570355		

We utilized Receiver Operating Characteristic (ROC) curves (Figure 1) to evaluate the efficacy of serum IL-17 concentration in detecting SpA, Ankylosing Spondylitis, and Psoriatic Arthritis (PsA). For SpA, IL-17 demonstrated a sensitivity of 77.14%, specificity of 73.33%, and an area under the curve of 0.815 at a cutoff value > 118.1 (pg/ml); p < 0.0001, CI 95% = 0.700±0.901. In identifying Ankylosing Spondylitis, IL-17 showed a sensitivity of 65.22%, specificity of 86.67%, and an area under the curve of 0.806 at a cutoff value > 157 (pg/ml); p < 0.0001, CI 95% = 0.674±0.902. For Psoriatic Arthritis, IL-17 exhibited a sensitivity of 83.33%, specificity of 73.33%, and an area under the curve of 0.833 at a cutoff value > 118.1 (pg/ml); p < 0.0001, CI 95% = 0.686±0.930 (Table 4).

Table 4: The cutoff point, sensitivity, and specificity were determined to assess how well serum IL-17 levels could detect Spondyloarthritis (SpA).

	Area under curve	P-value	cut off	CI 95%	sensitivity	specificity
SpA	0.815	<0.001*	>118.1 pg/ml	0.700±0.901	77.14%	73.33
AS	0.806	<0.001*	>157 pg/ml	0.674±0.902	65.22%	86.67%
PsA	0.833	< 0.0001*	>118.1 pg/ml	0.686±0.930	83.33%	73.33%
The ability of serum IL-17 level in discerning between active and non-active stages of the disease						
SpA	0.948	<0.001*	>932.7 pg/ml	0.815±0.9994	92.31%	95.45%
AS	0.931	< 0.0001*	>671 pg/ml	0.744±0.996	90.00%	92.31%
PsA	1.00	< 0.0001*	>932.7 pg/ml	0.735±1.00	100%	100%

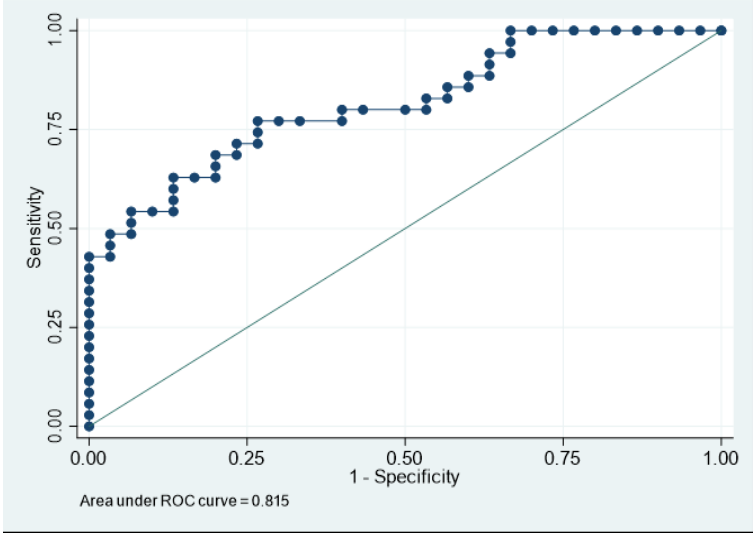

Fig. 1: ROC curve study to evaluate the performance of serum IL-17 **concentration** in detecting SpA. **The area under the ROC curve is 0.815; p < 0.0001, CI 95% =0.700±0.901. For a 73.33% specificity, sensitivity was about 77.14% at a cutoff value of > 118.1 pg/ml.**

Using a cutoff value of > 932.7 (pg/ml), we employed the ROC curve (Figure 2) to assess the ability of serum IL-17 levels to differentiate between active and non-active SpA. The findings indicated a sensitivity of 92.31%, specificity of 95.45%, and an area under the curve of 0.948; p < 0.0001, CI 95% = 0.815±0.9994. Another ROC curve, with a cutoff value of > 671 (pg/ml), was utilized to determine the sensitivity and specificity of serum IL-17 to differentiate between active and non-active AS . It demonstrated a sensitivity of 90.00%, specificity of 92.31%, and area under the curve of 0.931; p < 0.0001, CI 95% = 0.744±0.996. Additionally, an ROC curve was employed to evaluate serum IL-17 levels' ability to distinguish between active and inactive PsA. At a cutoff value of > 932.7 (pg/ml), IL-17 exhibited a sensitivity and specificity of 100%, with an area under the curve of 1.000; p < 0.0001, CI 95% = 0.735±1.00. The analytical findings of IL-17A -197 G/A polymorphism are presented in (Table 5).

Table 5: Comparison of the three genotypes in SpA patients.

Variable	G/G N=4	G/A N=19	A/A N=12	P value
Age/ year				
Mean ± SD	43±5.94	40.26±9.56	38.75±7.37	0.66
Median (range)	43(36:50)	40(24:54)	39(24:48)	
Gender				
Female	3 (75.00%)	8 (42.11%)	6 (50.00%)	0.49
Male	1 (25.00%)	11 (57.89%)	6 (50.00%)	
ESR				
Mean ± SD	40.0±24.59	47.42±23.53	47.5±27.56	0.88
Median (range)	33(19:75)	45(12:96)	40(10:112)	
IL-17				
Mean ± SD	904.8±946.5	349782.5±682796.9	51287.8±175343.9	0.85
Median (range)	889(80:1761)	495.6(28.5:2570355)	478.7(62:608075)	
CDAI				
Mean ± SD	45.0±30.99	25.53±9.67	24.04±11.05	0.45
Median (range)	37.25(20.5:85)	20.5(15:46)	21.5(14:56.5)	
CDAI				
≤22	2 (50.00%)	13 (68.42%)	7 (58.33%)	0.73
>22	2 (50.00%)	6 (31.58%)	5 (41.67%)	
DMARDS				
No	1 (25.00%)	11 (57.89%)	7 (58.33%)	0.46
Yes	3 (75.00%)	8 (42.11%)	5 (41.67%)	
NSAID				
No	2 (50.00%)	4 (21.05%)	3 (25.00%)	0.48
Yes	2 (50.00%)	15 (78.95%)	9 (75.00%)	
Anti-TNF a				
No	4 (100%)	14 (73.68%)	10 (83.33%)	0.46
Yes	0	5 (26.32%)	2 (16.67%)	

ESR: erythrocyte sedimentation rate**.** CDAI Disease Activity Index , SD: standard deviation **,** DMARDS: Disease modifiying anti rheumatic drugs, NSAID:nonsteroidal anti inflammatory drugs, Anti-TNF a:anti tumor necrosis factor alpha

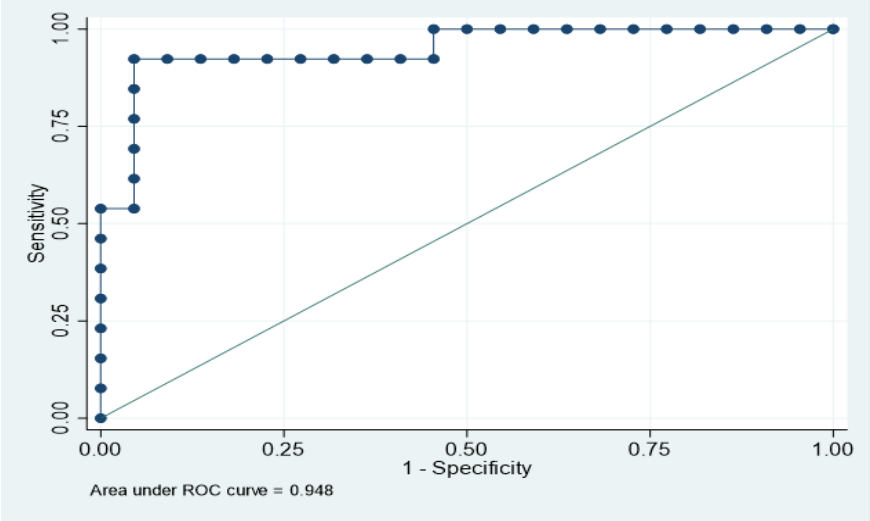

Fig. 2: ROC curve to assess the ability of serum IL-17 level in **discerning** between active and non-active SpA. **The area under the ROC curve is 0.948; p < 0.0001, CI 95% = 0.815 ±0.9994. For a specificity of 95.45%, the sensitivity was about 92.31% at a cutoff of >932.7 pg/ml.**

DISCUSSION

Pathophysiology of PsA and psoriasis has been linked to IL-17A, [14]. Moreover, it has been observed that the progression of Spondyloarthropathy (SpA), a diverse set of inflammatory immune-related conditions characterized by shared clinical traits, genetic susceptibilities, and disease mechanisms, is notably influenced by the IL-17A pathway. This condition may appear as ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, or arthritis linked to inflammatory bowel illness. and it can also present as undifferentiated arthritis. [15] Therefore, this study aims to illustrate the predictive value of IL-17A in identifying SpA, AS, and PsA. Our study revealed no significant differences in the distribution of IL-17A -197 G/A genotypes and allele frequencies between SpA patients and controls. In SpA patients, the frequency of G/G genotype was 11.43% compared to 16.67% in controls, G/A genotype was 54.29% compared to 60.00% in controls, and A/A genotype was 34.29% compared to 23.33% in controls, with a P-value of 0.58. Similarly, in PsA patients, the frequencies were G/G (11.43%), G/A (60.87%), and A/A (34.78%), with a P-value of 0.31. For AS patients, the frequencies were G/G (25.00%), G/A (41.67%), and A/A (33.33%) (Table 1). Our findings align with Erkol-İnal E. *et al*., [16], who also found no significant differences in IL-17A G197A polymorphism genotype distribution and allele frequencies between AS patients and healthy controls. This suggests that there is no substantial association between susceptibility to and severity of AS disease and IL-17A G197A polymorphisms.

Neves J.S.F. *et al.* [17] examined the impact of IL17, TNF, and VDR gene polymorphisms in SpA patients who were HLA-B*27negative, which contradicts our findings.PsA patients had a higher frequency of the IL17A A/A genotype than controls. Additionally, it was examined whether patients with higher levels of vitamin D deficiency and clinical disease activity had IL17 and TNF genotypes linked to SpA. Patients with SpA who had a vitamin D deficiency and a BASDAI of less than 4.0 had higher frequencies of IL17A G/G and TNF-308 G/G.

Loures *et al.*[18] revealed Significant associations of genetic polymorphisms were confirmed between IL17A (rs2275913) genotype frequencies with the development of the SpA and its clinical forms (AS and PsA) in a mixed Brazilian population regardless of gender or the presence of HLA-B27. IL17A (rs2275913) AA/GA was associated with PsA, SpA and AS. Yang *et al.*[19] revealed that allele G on SNP (rs2275913G>A) on IL-17A was significantly associated with AS susceptibility.

We noted that IL-17serum level was significantly higher in the SpA group (207569.7±530765.4) than the control group (127.96±164.07). IL-17serum level was significantly higher in active SpA (CDAI>22) group (557984.5±765868) than the non-active (CDAI≤22) group (506.47±1173.39). In SpA patients we found positive correlation between IL-17 level and CDAI values. No correlation between the IL-17A polymorphism with serum IL-17 values. The same as regard AS and PsA where IL-17 serum level was significantly higher in them than the control group. (289163.8±632213.4) and (51181±175377) respectively showing significant association with disease activity in AS where 17serum level was significantly higher in active AS (CDAI>22) group (664258.5±836925.6) than the non-active (CDAI≤22) group (629.51±1515). IL-17serum level was significantly lower in AS patients receiving Anti-TNF for treatment (165.4±155.9) than in

patients not receiving Anti-TNF for treatment (415600±728141.2).

In earlier research Jansen *et al.*,[20] Patients with early active axial SpA exhibited a larger percentage of CD4+ T cells that generated IL-17 as compared to healthy controls. Results of Mei *et al.*[21] indicated that patients with AS had significantly higher serum levels of IL-17 and IL-23. However, there was no significance difference between more active AS and less active AS in terms of blood IL-17 or IL-23 levels.

There was no correlation found in the correlation study between the serum levels of IL-17 and IL-23 and the BASDAI. According to Shen *et al.* [22] following stimulation with anti-CD3/CD28, patients with AS had significantly higher concentrations of IL-17 in supernatants and a percentage of IL-17 positive CD4+T cells in peripheral blood mononuclear cells (PBMCs) than healthy controls. Additionally, there was a significant positive correlation between the frequency of CD4+ cells displaying intracellular staining for IL-17 and IL-17 production. This implies that the main source of IL-17 in peripheral blood is CD4+ T cells. These results are in line with the hypothesis that IL-17-producing cells play a part in the pathogenesis of inflammatory arthritis and appear to apply to both AS and RA. RA levels and disease activity showed a substantial association; in AS, no such correlation was observed. Nevertheless, patients who had minimal disease activity after anti-TNF medication treatment nevertheless exhibited high Th17 cell percentages.

CONCLUSION

According to our research, IL-17 is a cheap, practical, and valuable biomarker for identifying SpA in patients without symptoms. It can aid in early treatment and help stop disabilities from worsening.

Declaration of Conflicting Interests

Regarding the research, writing, and publication of this article, the author(s) have stated that they have no potential conflicts of interest.

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Ethical approval

The Aswan University Faculty of Medicine's Ethics Committee Board examined and approved the study's procedure. (Ref. No. Asw.U. /301/10/18).

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