Research Article

Association between Inflammatory Cytokines and Liver Functions in Rheumatoid Arthritis Patients

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Abstract

Background: Rheumatoid arthritis (RA) is associated with abnormal liver tests, and the medications used for RA are often hepatotoxic. Therefore, this study aimed to investigate an association between pro-inflammatory and anti-inflammatory cytokines and liver function tests in RA patients.

Methods: In this descriptive cross-sectional study, 88 RA patients were included, 84 of them were women and 4 men, aged 21–81 years. Serum interleukin-10 (IL-10), interleukin-17 (IL-17), Osteopontin (OPN) were measured and liver function tests were conducted.

Results: The frequency of RA was higher among adults aged >41 years (72 [81.8%]) than young adults aged ≤41 years (16 [18.2%]). RA was more common in women (84 [95.5%]) than in men (4 [4.5%]) – approximately 21:1-fold. Young adults had higher abnormal IL-10 than adult RA patients (OR = 3.72, *p*-value 0.044). Abnormal IL-17 (OR = 5.67, *p*-value 0.034) was found to be increased in young-adult RA patients. No association was observed between age and OPN and between the duration of disease and IL-10, IL-17, and OPN. Similarly, no association was noted between the types of treatment and IL-10, IL-17, and OPN, nor between IL-10, IL-17, OPN and liver parameters (AST, ALT, ALP, ALB, TP, and GGT).

Conclusion: Pro-inflammatory and anti-inflammatory cytokines are not associated with abnormal liver functions, as has been demonstrated in RA patients.

Keywords: rheumatoid arthritis, interleukin, liver function tests, cytokines

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1. Introduction

Rheumatoid arthritis (RA) is a common autoimmune inflammatory disease. Although the prevalence of RA is lower globally (0.5–1%), it is associated with socioeconomic burden and higher risk of mortality rate [1]. Recent studies have demonstrated that the treatments used for RA improved outcome, and also accounts as a risk for hepatic complications [2]. The adverse effects of RA treatments include asymptomatic elevations of liver enzyme, fibrosis, and sometimes fatal hepatic necrosis [3]. On the other hand, liver disorders have been noted in untreated RA patients [4].

Increasing amounts of interleukin-10 (IL-10), a potent anti-inflammatory cytokine [5], can be detected in the synovium of RA patients. Additionally, considering that the activity of RA cannot be attenuated by IL-10 administration [6], many researchers suggest that IL-10 plays an important role in chronic liver diseases [7]. Interleukin-17 (IL-17), a pro-inflammatory cytokine, is upregulated in many autoimmune diseases such as RA; high levels of IL-17 have been reported to be produced in different samples of RA [8, 9]. Some investigators suggest that IL-17 plays a key role in many liver diseases and is also associated with the progress of the disease [10–12]. Osteopontin (OPN) is a pro-inflammatory cytokine that induces RA [13–15], and included in many liver diseases, despite its role in liver problems are still controversial [16]. Therefore, this study was carried out to find out the association between pro-inflammatory, anti-inflammatory cytokines and liver function tests among RA patients.

2. Materials and Methods

This descriptive cross-sectional hospital-based study was conducted on 88 RA patients who were clinically diagnosed according to the criteria of the American College of Rheumatology (ACR) 1987 and were examined at the common RA clinics in Khartoum State (military, Alamal hospital, and Zain clinic). All patients received treatment; the demographic data, type of treatment, and duration of disease for each patient were recorded – 4 men and 84 women aged 28–90 years. Non-Sudanese patients with RA and those with unclear diagnosis were excluded. Serum from each subject were centrifuged at 3000 g for 10 min after clotting for 30 min at room temperature and stored at –40°C until analysis. All samples were investigated for OPN, IL-17, and IL-10 by sandwich enzyme-linked immune sorbent assay (ELISA) (ELISA Development; Thermo Fisher scientific Systems, USA) according to the manufacturer's instructions. In addition, liver functions tests (TP, Albumin, AST, ALT, GGT, and ALP) were done using

fully automated Mindray chemistry analyzer (BS 200). Data were statistically analyzed by statistical software package, version 16. Results were expressed as numbers and percentages. Chi-square test was used to determine the level of significance (P-value of 0.05 was considered to be statistically significant).

3. Results

RA is more common in adults (72 [81.8%]) than young adults (16 [18.2%]), the frequency of RA was found to be higher in women (84 [95.5%]) than in men (4 [4.5%]). Moreover, 52 (59.1%) patients were receiving steroids while 36 (40.9%) were on non-steroid treatment. The duration of disease for 62 (70.5%) patients was ≤6 years and for 26 (29.5%) was >6 years. Abnormal IL-10 was found in 63 (71.6%) patients, while 25 (28.4%) had a normal percentage. The results of characteristic data show that while 80 (91%) RA patients had normal IL-17, 8 (9%) had abnormal. Normal OPN was observed in 76 (86.4%) RA patients and abnormal OPN in 12 (13.6%) (Table 1). Chi-square analysis revealed that young adults group had a higher abnormal IL-10 than adult RA patients (OR = 3.72, p-value 0.044). Also, abnormal IL-17 (OR = 5.67, p-value 0.034) was found to be increased in young adult RA patients while no association was seen between age and OPN (OR = 2.67, p-value 0.144; Table 2). Furthermore, no association was reported between the duration of the disease and IL-10, IL-17, and OPN with p-values 0.410, 0.176, and 0.502 and OR 0.77, 0.37, and 1.30, respectively (Table 3). Similarly, no association could be derived between the types of treatment and IL-10, IL-17, and OPN with p-value 0.246, 0.286, and 0.351 and OR 1.53, 2.21, and 0.65, respectively (Table 4). Pearson's correlation analysis revealed that there were no association between IL-10, IL-17, OPN and liver parameters (AST, ALT, ALP, ALB, TP, and GGT; Table 5).

4. Discussion

Abnormal liver functions were observed in RA patients. The researchers further attributed the abnormality to immune aggregations and others justified it by drugs toxicity. Accordingly, this study was carried out to assess whether the pro-inflammatory or anti-inflammatory cytokines are associated with liver functions in RA patients.

The current study revealed that there is no association between interleukins and liver function tests. In fact, abnormal liver tests were noted in patients with RA [17]. Concurrent with many previous studies, the frequency of RA is higher in elderly subjects [18, 19]. A possible explanation might be that the protective mechanisms in elderly population are

Table 1: Demographic and baseline characteristics of RA Patients.

Variables	Frequency (%)
Age (yr)	
≤41	16 (18.2%)
>41	72 (81.8%)
Sex	
Male	4 (4.5%)
Female	84 (95.5%)
Treatment	
Steroid	52 (59.1%)
Non-steroid	36 (40.9%)
Duration (yr)	
≤6	62 (70.5%)
>6	26 (29.5%)
Cut-off IL-10	
Abnormal	63 (71.6%)
Normal	25 (28.4%)
Cut-off IL-17	
Abnormal	8 (9%)
Normal	80 (91%)
Cut-off OPN	
Abnormal	12 (13.6%)
Normal	76 (86.4%)
Total	**88 (100%)**

Table 2: Association between interleukins IL10, IL17, OPN and age groups.

Variables	Age (yr)		OR	CI-Lower CI-Upper	P-value
	≤41	**>41**			
IL-10					
Abnormal	14 (23.0%)	47 (77.0%)	3.72	(0.78–17.7)	0.04
Normal	2 (7.4%)	25 (92.6%)			
IL-17					
Abnormal	2 (40.0%)	6 (60.0%)	5.67	(1.24–25.7)	0.03
Normal	12 (15.0%)	68 (85.0%)			
OPN					
Abnormal	4 (33.3%)	8 (66.7%)	2.67	(0.69–10.2)	0.14
Normal	12 (15.8%)	64 (84.2%)			

decreased, resulting in decreased immunotolerance and decreased cytokines synthesis and T cells proliferation [20]. The demographic data indicated that the prevalence of RA was found to be 21-fold higher in women than in men. In contrast to a previous study in Sudan, the female-to-male ratio was 9:1 [21]. Since the change in sex hormones after

TABLE 3: Association between interleukins IL10, IL17, OPN and duration of RA.

Variables	Duration (yr)		OR	CI-Lower CI-Upper	P-value
	≤6	>6			
IL-10					
Abnormal	42 (68.9%)	19 (31.1%)	0.77	(0.28–2.13)	0.41
Normal	20 (74.1%)	7 (25.9%)			
IL-17					
Abnormal	4 (50.0%)	4 (50.0%)	0.37	(0.08–1.65)	0.17
Normal	58 (72.5%)	22 (27.5%)			
OPN					
Abnormal	9 (75.0%)	3 (25.0%)	1.30	(0.32–5.25)	0.50
Normal	53 (69.7%)	23 (30.3%)			

TABLE 4: Association between interleukins IL10, IL17, OPN and types of treatment.

Variables	Treatment		OR	CI-Lower CI-Upper	P-value
	Steroid	Non-steroid			
IL-10					
Abnormal	38 (62.3%)	23 (37.7%)	1.53	(0.61–3.83)	0.24
Normal	14 (51.9%)	13 (48.1%)			
IL-17					
Abnormal	6 (75.0%)	2 (25.0%)	2.21	(0.42–11.6)	0.28
Normal	46 (57.5%)	34 (42.5%)			
OPN					
Abnormal	6 (50.0%)	6 (50.0%)	0.65	(0.19–2.21)	0.35
Normal	46 (60.5%)	30 (39.5%)			

puberty is associated with high prevalence of RA in women, a woman's immune system is potentially more reactive than that of a man. The current study reports that young adults are more likely to have abnormal IL-10 and IL-17. However, these results disagree with previous studies [22, 23]. No association was found between age and OPN level. Concurrent with this finding, a relationship between age and OPN has been previously reported [24]. Similar to other results, no associations between IL10, IL17, OPN levels and the duration of disease have been demonstrated [22, 23, 25]. Despite reducing IL-17 after the use of steroids therapy, IL-10 was increased [26]. The present study revealed no associations between IL-10, IL-17, OPN levels and the types of treatment. It has become clear that steroids directly modulate the pro-inflammatory cytokine or suppress cytokines-producing cells [26, 27].

TABLE 5: Association between cytokines and liver function parameters (Pearson's correlation results).

Parameters		P-value	R^2
IL-10	AST	0.62	0.12
	ALT	0.20	0.66
	ALP	0.80	0.05
	ALB	0.16	−0.13
	TP	0.56	0.02
	GGT	0.25	0.15
IL-17	AST	0.18	−0.15
	ALT	0.82	0.02
	ALP	0.82	−0.02
	ALB	0.23	0.12
	TP	0.59	0.05
	GGT	0.17	−0.14
OPN	AST	0.50	0.07
	ALT	0.25	0.12
	ALP	0.89	0.01
	ALB	0.29	−0.11
	TP	0.49	0.07
	GGT	0.98	−0.02

5. Conclusion

The data of present study shows that women are at a higher risk to have RA. Moreover, young adult RA patients are more likely to have abnormal IL-10 and IL-17. Furthermore, pro-inflammatory and anti-inflammatory cytokines are not associated with abnormal liver functions as has been demonstrated in RA patients.

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Ethical Considerations

Ethical permits for the study were obtained from the ethical review committees at the sites where patients were recruited, and all patients gave informed consent for their participation in the study.

Competing Interests

Availability of Data and Material

The study data are available with the author upon reasonable request

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