

Association between Inflammatory Cytokines and Liver Functions in Rheumatoid Arthritis Patients

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Abstract

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

Materials and Methods: In a descriptive cross-sectional study, 88 RA patients were included, 84 were females and 4 were males, age ranged from 21 to 81 years old. Serum interleukin 10 (IL-10), interleukin 17 (IL-17), Osteopontin OPN and liver function tests were measured. **Results:** The frequency of RA is higher among adults >41 Years 72(81.8%) than young adults ≤41 Years 16(18.2%), RA is common in females 84(95.5%) than males 4(4.5%) approximately 21:1 fold. Young adults had higher abnormal IL-10 than adults RA patients (OR = 3.72, *p*-value 0.044). Abnormal IL-17 (OR= 5.67, *p*-value 0.034) were found to be increased in young adults RA patients. No association observed between age and OPN. No association between duration of disease and IL-10, IL-17 and OPN. No association found between types of treatment and IL-10, IL-17 and OPN. No association observed between IL-10, IL-17, OPN and liver parameters (AST, ALT, ALP, ALB, TP, and GGT). **Conclusion:** in conclusion proinflammatory and anti-inflammatory cytokines are not associated with liver functions as has been demonstrated in RA patients.

Keywords: Cytokines, Liver Functions, and Rheumatoid Arthritis

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Introduction:

Rheumatoid arthritis (RA) is common autoimmune inflammatory disease. Although the prevalence of RA is lower globally 0.5-1% it is still associated with socioeconomic burden, and higher risk of mortality rate (Kwan *et al.*, 2019). Recent studies have demonstrated that, the treatments used for RA improved outcome, and also account as risk for hepatic complications (Sundbaum *et al.*, 2019). The adverse effects of RA treatments includes asymptomatic elevations of liver enzymes, fibrosis and may be fatal hepatic necrosis (Conway and Carey, 2017). On the other hand liver disorders were noted in untreated RA patients (Rakuomi *et al.*, 2017).

Increasing amounts of IL-10 can be detected in the synovium of RA patients, a potent anti-inflammatory cytokine (Shikhpour *et al.*, 2018). Another fact is that the activity of RA cannot be attenuated by IL-10 administration (Holdsworth and Yi, 2015). Many researchers suggest that IL-10 plays an important role in chronic liver diseases (Zhang and Wang, 2006). IL-17 is a pro-inflammatory cytokine, which contributes and upregulates in many autoimmune diseases such as RA. A high level of IL-17 is produced in different samples of RA (Elvira *et al.*, 2018; Mengesha and Conti, 2017). Some investigators suggest that IL-17 plays a key role in many liver diseases, and also associated with the progress of disease (Du *et al.*, 2013; Tan *et al.*, 2013; Zheng *et al.*, 2013). Osteopontin (OPN) is a pro-inflammatory cytokine that induces RA (Shi *et al.*, 2018; Athanasiadou *et al.*, 2018; Luukkonen *et al.*, 2017). That OPN is included in many liver

diseases, beyond its roles, is still controversial (Iida *et al.*, 2018). Therefore this study carried out to find out the association between pro-inflammatory, anti-inflammatory cytokines and liver function tests among RA patients.

Materials and Methods

A descriptive cross sectional hospital based study on 88 RA clinically diagnosed according to the criteria of the American College of Rheumatology 1987 (ACR), were examined at the common rheumatoid arthritis clinics in Khartoum State (military, Almal hospital and Zain clinic). Ethical permits for the studies were obtained from ethical review committees at the sites where patients were recruited, and all patients gave informed consent for their participation in the studies. All patients received treatment, the demographic data, type of treatment and duration of disease for each patient were recorded, 4 male and 84 female, age range 28 -90 years, Non Sudanese patients with RA and the doubtful diagnosed patients were excluded. Serum from each subject were centrifuged at 3000g for 10 minutes after clotting for 30 minutes at room temperature and were stored at -40°C until analysis, All samples were investigated for OPN, IL 17 and IL10 by sandwich enzyme linked immune sorbent assay (ELISA) (ELISA Development; Thermo Fisher scientific Systems-USA) according to the manufacturer's instructions, also liver functions test TP, Albumin, AST, ALT, GGT, and ALP were analyzed using full automated Mindary Chemistry Analyzer (BS 200), Data was statistically analyzed by Statistical Software

Packages SPSS (version 16), Results were expressed as number and percent. *Chi square* was used to determine the level of significance (*P*-value of > 0.05 was considered to be statistically significant)

Results:

RA is more common in adults 72(81.8%) than young adults 16(18.2%), the frequency of the RA was found to be higher in female 84 (95.5%) than male 4 (4.5%). The patients receiving steroids was 52(59.1%) and the rest 36(40.9%) was on non steroids treatment. Moreover, 62(70.5%) was a duration of disease ≤6 and others 26 (29.5%) was >6 Years old. Abnormal IL-10 was found in 63(71.6%), was 25(28.4%) have normal percentage. The results of characteristic data shows, 80(91%) of RA patients had normal IL-17 whereas 8(9%) had abnormal. Normal OPN was observed in 76(86.4%) RA patients while 12(13.6%) was abnormal, the results presented in

table-1. Chi-square analysis revealed that, young adults group had higher abnormal IL-10 than adults RA patients (OR = 3.72, *p*-value 0.044). Also abnormal IL-17 (OR= 5.67, *p*-value 0.034) were found to be increased in young adults RA patients whereas no association observed between age group and OPN (OR= 2.67, *p* value 0.144), shows table-2. Furthermore no association reported between duration of disease and IL-10, IL-17 and OPN with *p*-value (0.410, 0.176, 0.502) and OR (0.77, 0.37, 1.30) respectively, the results noted in table-3. No association found between types of treatment and IL-10, IL-17 and OPN with *p*-value (0.246, 0.286, 0.351) and OR (1.53, 2.21, 0.65) respectively, shows table-4. Person correlation analysis revealed that there were no association observed between IL-10, IL-17, OPN and liver parameters (AST, ALT, ALP, ALB, TP, and GGT), results reported in table-5.

Table (1)

	Variables	Frequency (%)
Age	≤41 Years	16 (18.2%)
	>41 Years	72 (81.8%)
Sex	Male	4 (4.5%)
	Female	84 (95.5%)
Treatment	Steroid	52 (59.1%)
	Non-steroid	36 (40.9%)
Duration	≤6 Years	62 (70.5%)
	>6 Years	26 (29.5%)
Cut off IL10	Abnormal	63(71.6%)
	Normal	25(28.4%)
Cut off IL17	Abnormal	8(9%)
	Normal	80(91%)
Cut off OPN	Abnormal	12(13.6%)
	Normal	76(86.4%)
	Total	88 (100%)

Table (2)

Variables	Age		OR	CI-Lower CI-Upper	p-value
	≤41 Years	>41 Years			
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%)			

Table (3)

Variables	Duration		OR	CI-Lower CI-Upper	p-value
	≤6 Years	>6 Years			
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)

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%)			

Table (5)

Parameters		<i>p</i> - value	R ²
IL10	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
IL17	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

Discussion:

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

The current study revealed that there is no association between interleukins and liver function tests. In fact that, abnormal liver tests were noted in patients with RA (Dinic *et al.*, 2018). Concurrent with many previous studies indicated that, the frequency of RA is higher in elderly subjects (Mursal *et al.*, 2016; Elsedig *et al.*, 2014). Possible explanation might be that, in elder the protective mechanisms are decreased,

resulting in decreased immunotolerance, decreased cytokines synthesis and T cells proliferation (Kobak and Bes, 2018). The demographic data indicated that, the prevalence of RA was found to be 21 fold higher in females than males. In contrast with previous study in Sudan that, the ratio is 9:1 females to males (Abdelsalam *et al.*, 2011). Since the change in sex hormones after puberty associated with high prevalence of RA in females, moreover the female's immune system is potentially more reactive than males. Present study reported that, young adults more likely to have abnormal IL-10 and IL-17. These results disagreed with previous studies (Abd Elazeem *et al.*, 2018; Akdeniz *et al.*, 2018). Whereas no association found between age groups and OPN level. Concurrent with this finding a relationship between age and OPN has

previously reported (Iwadate *et al.*, 2013). Similar to other results, no associations between IL10, IL17, OPN level and duration of disease have been demonstrated (Abd Elazeem *et al.*, 2018; Akdeniz *et al.*, 2018; Al Zifzaf *et al.*, 2015). In spite of IL-17 has been decreased after used of steroids therapy, whereas IL-10 was increased (Negeera *et al.*, 2018). The present study revealed no associations between IL-10, IL-17, OPN levels and types of treatment. It have become clear that, steroids directly modulate the pro inflammatory cytokine, or through suppression of cytokines producing cells (Negeera *et al.*, 2018; Noack *et al.*, 2016).

Conclusion:

The data of present study concludes that, female at higher risk to have RA. Moreover, young adult RA patients are more likely had abnormal IL-10 and IL-17. Furthermore proinflammatory and antiinflammatory cytokines are not associated with liver functions as has been demonstrated in RA patients.

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