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Original Article

Serum Levels of IL-17A in Iraqi Female Patients with Endometriosis

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ABSTRACT

Endometriosis is a common disorder defined as the growth of endometrial tissue outside the uterine cavity. Cytokines have been implicated in the pathogenesis of endometriosis. Aim of the present study is to estimate serum levels of IL-17A, and to investigate whether IL-17A could be used as marker of susceptibility in endometriosis. Fifty female patients with endometriosis their age range (19 – 46) years and 30 apparently healthy females their ages were matched with patients were enrolled in this study. The diagnosis of patients was made by the consultant medical staff, which was based on clinical and ultrasonic laborscopy examinations. Serum level of IL-17A was measured in patients and controls by ELISA. The present findings showed that mean serum level of IL-17A was significantly elevated in females patient as compared with healthy females ($P<0.001$), On the other hand, there is high significant differences ($p<0.001$) in serum concentration of IL-17 among stages of disease, and high concentration was found in patients with stage 4 'sever endometriosis'. This study demonstrates that serum level of IL-17A could be used as marker of susceptibility in endometriosis, and may play an important role in pathogenesis of this disease.

Key words: *Endometriosis, Cytokines, IL-17A.*

INTRODUCTION

Endometriosis can be considered a chronic low grade inflammatory disease (Kobayashi *et al*., 2013). Chronic pelvic inflammation in endometriosis is associated with an abrogation of local and systemic immunity. Among the immunological abnormalities identified in patients with minimal and mild endometriosis include: abnormal natural killer (NK) cell function (Hernandez *et al*., 2002), reduced cytotoxic effect of lymphocytes and macrophage, imbalanced Th1/Th2 response (Podgaec, 2007) and high levels of cytokines in the peritoneal fluid (Candiani, 1991). It seems that these alterations contribute to the development and progression of endometriosis and infertility (Glitz *et al*., 2009). Within this context, several researches have been targeting the role of the cytokines in the pathogenesis of endometriosis (Chen, 2010, Ilie and Ilie, 2013). The dynamic interplay among cytokines may play a role in the creation of a microenvironment which favors the implantation of endometrial cells and the progression of the disease. IL-17A is proinflammatory cytokine has pleiotropic activities including the induction of TNF- α, IL-1, IL-6, IL-8 and monocyte chemoattractant protein-1 on various cell types (Iwabe *et al*., 1998). It has been shown that IL-17A can induce the expression of intracellular adhesion molecule (ICAM)-1 and enhance the proinflammatory responses induced by IL-1 and TNF- α (Maas *et al*., 2001). In addition, IL-17A has been implicated in several inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, systemic sclerosis, systemic lupus erythematosus and psoriasis (Albanesi *et al*., 1999). IL-17A up-regulates the peritoneal macrophage production and secretion of IL-6 and TNF-α, which are strongly implicated in the pathogenesis of endometriosis. It is a cytokine worth mentioning as it induces many factors related to the development and progression of endometriosis, such as ICAM-1, prostaglandin E2, cyclooxygenase- 2, nitric oxide (NO) synthase-2 and MMP-3. As IL-17 is pro-angiogenic, its increased concentrations during the initial stages of endometriosis may facilitate the implantation, proliferation, and formation of early endometriotic lesions (Gupta, et al., 2006).IL-17A increased the secretion of growth-regulated oncogene-α from

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endometrial stromal cells dose-dependently (Kalu *et al* ., 2007). This study was performed to estimate serum levels of IL-17A, and to investigate whether IL-17A could be used as marker of susceptibility in endometriosis and associated with infertility.

PATIENTS AND METHODS

Fifty female patients with endometriosis their age range (19 – 46) years and 30 females as control their ages were matched with the patients were enrolled in this study. They were from attendants to Kamal Al-Samari hospital and Baghdad medical city teaching hospital from June 2014 to January 2015. The diagnosis was made by the consultant medical staff, which was based on clinical and ultrasonic examinations. They were newly diagnosed and all of the cases had received no treatment with no complain of chronic or systemic diseases. Serum samples were separated from the whole blood, aliquated and stored at -20ºC until used. The level of IL-17A was determined by using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit and performed as recommended in leaflet with kit (IL-17A Boster/ USA). Statistical analyses were done using SPSS v19. The serum IL-17 was expressed as mean ± standard deviation, the significance of differences in mean was assessed using the student's t-test and ANOVA test. Analyses where the *P*-value was <0.05 were considered to be statistically significant.

RESULTS

The demographic characteristics of patients group and controls group included in this study are presented in table (1). There are no statistical significant differences (p>0.05) in age was existed between two study groups. The mean age of patients was 29.7 ± 0.94 years and for healthy controls was 29.6±1.40 year. Concerning the staging of endometriosis, stage 1 (minimal endometriosis) was found in 6 (12 %), stage 2 (mild endometriosis) consist of 13 (26 %), stage 3 (moderate endometriosis) was found in 26 (52%), while the rest 5 (10 %) were represented stage 4 (sever endometriosis). Regarding the family history of disease the current results showed that 3 (6%) of patients had positive family history of endometriosis, while 47 (94%) showed negative family history, as clearly observed in table (2).

Table (3) showed a highly significant elevation in mean serum level of IL-17A among females patients (59.19 ± 11.77 pg/ml) in comparison to that of healthy control (30.08±9.74 pg/ml), (p<0.01). In addition, there is high significant differences (p<0.001) in serum concentration of IL-17 among stages of disease, and high concentration was found in patients with stage 4 'sever endometriosis' (286.4±59.6 pg/ml), table (4).

Table -1: Age distribution of the studied groups

		Study groups		P-value
		Endometriosis Patients n=50	Healthy control n=30	
Age				
Age (years)	**Range**	(19-46)	(20-41)	
	Mean	29.7	29.6	0.947 NS
	SE	0.94	1.40	
	Median	30	29	

SE= Standard error; NS=Non significant (p>0.05).

Table-2: Distribution of patients according to infertility type, staging of disease and family history

Clinical Features		Endometriosis Patients n=50
Staging	Stage 1	6 (12 %)
	Stage 2	13 (26 %)
	Stage 3	26 (52%)
	Stage 4	5 (10 %)
Family History	Positive	3 (6%)
	Negative	47 (94%)

Table- 3: Differences in serum concentration of IL-17A between patients and healthy controls.

	patients	Control	P (T-test)
Serum IL-17A			
Range	(15.24-680)	(15.24-137.20)	
Mean	59.19	30.08	<0.001**
SE	11.77	4.341	
Median	22.7	23.13	
Total	50	30	

**Highly significant differences

Table-4: The difference in mean serum IL-17 level by stage of disease.

	Serum IL-17	
Stage1 N=6	Mean	21.923
	SE	4.414
Stage2 N=13	Mean	28.68
	SE	4.52
Stage3 N=26	Mean	38.57
	SE	8.61
Stage4 N=5	Mean	286.4
	SE	59.6
F-test		3.046
P-value		0.001
Sig.		S*

DISCUSSION

IL-17A is a potent pro-inflammatory cytokine involved in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis and psoriasis. Anyway, few data is available regarding endometriosis. Highly significant elevation in serum concentration of IL-17A among patients in comparison to control in this study is agreed with other studies (Zhang *et al*., 2005; Ahn *et al*., 2014). Zhang and colleagues found that IL-17 levels in peritoneal fluid were elevated in endometriosis than controls. Similarly, results reported by Ahn *et al.,* (2014) showed the presence of IL-17A in plasma samples and ectopic tissue samples from women with endometriosis. It is worthy to mention that surgical removal of lesions resulted in significantly reduced plasma IL-17A concentrations. Furthermore endometriotic lesions produce IL-17A and that the removal of the lesion via laparoscopic surgery leads to the significant reduction in the systemic levels of IL-17A (Ahn *et al.,* 2015). IL-17A plays a crucial in promoting angiogenesis and proinflammatory environment in the peritoneal cavity for the establishment and maintenance of endometriosis lesions (Gupta *et al.,* 2006; Ahn *et al.,* 2015). Conversely values of T-helper pathway related IL-17 levels were comparable between controls and endometriosis patients (Andreoli *et al.,* 2011), whereas other studies (Michael *et al*., 2014; Malutan *et al*., 2015) showed that IL-17 levels were not detected in serum and peritoneal fluid of patients with endometriosis. In addition the present study showed that high levels of IL-17 were found in patients with severe endometriosis (stage 4). In contrast other study reported that the patients with minimal/mild endometriosis had a significantly higher level of IL-17 in compared to those with moderate/severe endometriosis (Zhang *et al*., 2005). These results indicated that serum level of IL-17A could be used as marker of susceptibility in endometriosis, and may play an important role in pathogenesis of this disease.

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