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Roles of IL-17A and IL-23 in the Pathogenesis of Ulcerative Colitis and Crohn's Disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder, the etiology and pathogenesis of which have been suggested to be influenced by cytokines. Two main clinical types of IBD are recognized, namely ulcerative colitis (UC) and Crohn's disease (CD). The present study examined serum levels of two cytokines (IL-17A and IL-23) in 60 IBD patients (30 UC and 30 CD) and 30 healthy controls. The levels were correlated with age, gender, cigarette-smoking status, disease duration, family history, disease extension, symptoms, extra-intestinal manifestations, and medication. The results depicted that IL-17A level was significantly higher in UC and CD patients compared to control (45.2 ± 23.3 and 47.5 ± 34.4 vs. 15.6 ± 7.5 pg/ml, respectively; $p < 0.001$). Serum level of IL-23 was similarly increased in UC and CD patients compared to control (64.1 ± 23.7 and 62.5 ± 27.3 vs. 25.2 ± 11.1 pg/ml, respectively). However, the level of both cytokines showed no significant variation between UC and CD patients ($p = 0.713$ and 0.777 , respectively). Distributing UC and CD patients into subgroups according to some characteristics revealed that IL-17A level was significantly increased in UC male compared to female patients (57.3 ± 18.2 vs. 34.5 ± 22.5 pg/ml; $p = 0.005$). It was also significantly increased in smoker UC patients compared with non-smoker patients (51.9 ± 19.4 vs. 31.6 ± 25.5 pg/ml; $p = 0.022$). Smoker CD patients also showed a significantly increased level of IL-23 compared to non-smoker patients (72.7 ± 28.5 vs. 52.2 ± 22.6 pg/ml; $p = 0.038$). In the case of family history, IL-23 level was significantly decreased in UC patients with a family history of IBD compared to CD patients with a family history (84.5 ± 24.3 vs. 50.4 ± 17.0 pg/ml.; $p = 0.042$). In conclusion, the present data suggest a role for IL-17A and IL-23 in the etiology and pathogenesis of UC and CD.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; IL-17A; IL-23.

دور البين ابيضاض-17 والبين ابيضاض-23 بامراضية التهاب القولون التقرحي وداء كرون

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الخلاصة

يعد مرض الامعاء الالتهابي (Inflammatory bowel disease) من الامراض الالتهابية المزمنة، وقد وجد بان للحركات الخلوية تأثير على مسبباته وامراضيته. هناك نوعين سريريين لمرضى الامعاء الالتهابي وهما التهاب القولون التقرحي (Ulcerative colitis) وداء كرون (Crohn's disease). فحصت الدراسة الحالية المستوى المصلي لاثنتين من الحركات الخلوية (IL-17A و IL-23) في 60 عينة من مرضى الامعاء الالتهابي (30 عينة من مرضى القولون التقرحي و 30 من مرضى كرون) و 30 عينة لاشخاص اصحاء. وربطت هذه المستويات بالعمر والجنس وتدخين السجائر ومدّة المرض والتاريخ العائلي وامتداد المرض والأعراض والمظاهر خارج الأمعاء والعلاج. أظهرت النتائج ارتفاع المستوى المصلي للبين ابيضاض-17 (IL-17A) بشكل معنوي في مرضى القولون التقرحي وداء كرون مقارنة بالسيطرة (2.45 ± 23.3 و 34.4 ± 47.5 مقابل 15.6 ± 7.5 بيكوغرام/مل، على التوالي؛ الاحتمالية > 0.001). كما ارتفع ايضا المستوى المصلي للبين ابيضاض-23 (IL-23) في مرضى القولون التقرحي وداء كرون مقارنة بالسيطرة (23.7 ± 64.1 و 27.3 ± 62.5 مقابل 25.2 ± 11.1 بيكوغرام/مل، على التوالي). ولكن لم تظهر أي اختلافات معنوية في مستوى كلا الحركيين الخلويين بين مرضى القولون التقرحي وداء كرون (الاحتمالية = 0.713 و 0.777 على التوالي). وكشف توزيع مرضى القولون التقرحي وداء كرون الى مجاميع فرعية وفقا لبعض الخصائص التي بينت انفا بارتفاع المستوى المصلي للبين ابيضاض-17 وبشكل معنوي في ذكور مرضى القولون التقرحي مقارنة بالمرضى الإناث (18.2 ± 57.3 مقابل 22.5 ± 34.5 بيكوغرام/مل؛ الاحتمالية = 0.005). كما ارتفع وبشكل معنوي ايضا في مرضى القولون التقرحي المدخنين مقارنة بالمرضى غير المدخنين (19.4 ± 51.9 مقابل 25.5 ± 31.6 بيكوغرام/مل؛ الاحتمالية = 0.022). كما اظهر مرضى داء كرون المدخنين زيادة معنوية في المستوى المصلي للبين ابيضاض-23 مقارنة بالمرضى غير المدخنين (28.5 ± 72.7 مقابل 22.6 ± 52.2 بيكوغرام/مل؛ الاحتمالية = 0.038). وفي حالة التاريخ العائلي لمرض الامعاء الالتهابي، انخفض المستوى المصلي للبين ابيضاض-23 بشكل معنوي في مرضى القولون التقرحي مقارنة بمرضى داء كرون الذين لديهم تاريخ عائلي للمرض (24.3 ± 50.4 مقابل 17.0 ± 50.4 بيكوغرام/مل؛ الاحتمالية = 0.042). تستنتج الدراسة الحالية بان للبين ابيضاضين IL-17A و 23 دورا بالتسبب في مرض القولون التقرحي وداء كرون وامراضيتهما.

Introduction

Inflammatory bowel disease is a chronic inflammatory disorder with unexplained etiology. Two main clinical types of IBD are recognized, which are ulcerative colitis (UC) and Crohn's disease (CD) [1]. The inflammation in UC is restricted to the colon and rectum, while in CD it involves any part of the gastrointestinal tract in a non-continuous fashion [2]. Both types are chronic progressive inflammatory conditions that tend to have periods of relapses and remissions [3]. The pathogenesis of UC and CD is not well-understood, but complex interactions between genetic, environmental, immunological, and gut microbiomial factors have been suggested. Their interactions orchestrate a cascade of inflammatory responses in the intestinal mucosa [4]. It has been demonstrated that immune cells secrete active products that are associated with the initiation and maintenance of inflammation and result in damage of gut tissue. Excessive infiltration of immune cells into the colonic mucosa of IBD patients has also been found [5]. Further, altered regulations of several cytokines have been implicated in the pathogenesis of UC and CD. Among these cytokines are interleukin (IL)-17A and IL-23 [6, 7].

IL-17A is a proinflammatory cytokine and the main effector molecule that stimulates STAT3 (signal transducer and activator of transcription 3), which is involved in triggering strong immune responses during chronic inflammation [8]. It is a signature cytokine of T helper 17 (Th17) cells, while upregulated expression of IL-17 mRNA has been found in the inflamed mucosa of UC and CD patients; therefore, a pathogenic role for IL-17A in IBD has been suggested [9]. Besides that, murine studies depicted that IL-23 is a further cytokine that drives inflammation in the intestine of animal models of colitis [10]. IL-23 is mainly produced by antigen-presenting cells (APC) and its receptor is expressed by various innate and adaptive immune cells, including neutrophils, innate lymphoid cells

(ILC3), $\gamma\delta$ T cells, natural killer T (NKT) cells, and Th17 cells, to promote their functions [11]. IL-23 is also necessary for the maintenance, maturation, and expansion of Th17 cells; therefore, a correlated impact of IL-17A and IL-23 on the inflammatory response in UC and CD has been suggested [12]. Accordingly, this study sought to make a further understanding of the roles of IL-17A and IL-23 in the pathogenesis of UC and CD in Iraqi patients. Age, gender, cigarette-smoking status, disease duration, family history, disease extension, symptoms, extra-intestinal manifestations, and medication were targeted in this context.

Materials and Methods

Patients and control

During January – June 2019, a case – control study was conducted on 60 IBD patients (30 UC and 30 CD) and 30 healthy control subjects after obtaining the approval of the Ethics Committee at the Iraqi Ministry of Health and Environment. The patients attended the outpatient gastrointestinal clinics at Al-Kindy Teaching Hospital, Baghdad Teaching Hospital and Gastroenterology and Hepatology Teaching Hospital in Baghdad for diagnosis and treatment. The diagnosis was made by consultants at the clinics, based on standard clinical, radiological, endoscopic, and histopathological criteria [3]. Patients with indeterminate colitis or other related autoimmune diseases were excluded. The patients were characterized according to the following parameters: age, gender, cigarette- smoking, disease duration, family history, laboratory findings (hemoglobin; Hb, white blood cell count; WBC, and erythrocyte sedimentation rate; ESR), disease extension, symptoms, extra-intestinal manifestations, and medication (Table- 1). The control sample included blood donors who were healthy and their serum profile for anti-pathogen antibodies was negative (Central Blood Bank, Baghdad).

Blood sample collection

Four milliliters of venous blood were drawn from each participant in a plain tube. The blood was allowed to clot for 30 minutes at room temperature (18-25 °C). The tube was then centrifuged for 10 min at 3000 rpm in cooled centrifuge (4 °C). The obtained serum was kept in the freezer (-20 °C) until laboratory determination of IL-17A and IL-23.

Determination of IL-17A and IL-23 serum levels

Serum levels of IL-17 and IL-23 were determined using commercial ELISA kits for human IL-17A and IL-23 (Elabscience, USA) and the instructions of the manufacturer were followed. Absorbance was measured at a wavelength of 450 nm using a micro-plate reader (HumaReader HS, Germany). A standard curve was plotted (measured absorbance against the concentration of serially diluted standards) using an EXCEL sheet. According to the curve-fitting equation, cytokine levels were determined.

Statistical analysis

Data were statistically analyzed using the package IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp.). Categorical variables were given as numbers and percentages. Continuous variables were tested for normality distribution (Kolmogorov-Smirnov and Shapiro-Wilk tests). All continuous variables were normally distributed; therefore, they were presented as mean \pm standard deviation (SD). Pearson's Chi-squared and Fisher's exact tests were used to compare categorical variables, while analysis of variance (ANOVA) post-hoc by least significant difference (LSD) test were used to compare continuous variables. Receiver operating characteristic (ROC) was used to determine area under curve (AUC), sensitivity, specificity, and cut-off value. A probability (p) \leq 0.05 was considered significant.

Results

Baseline characteristics of populations studied

Regarding the characteristics given in Table- 1, there were no significant differences between IBD patients (UC and CD) and control.

Table 1-Comparison of the characteristics of ulcerative colitis and Crohn's disease patients and control.

Characteristics*		UC (N = 30)	CD (N = 30)	Control (N = 30)	<i>p</i>
Age (year)		31.4 \pm 9.8	29.8 \pm 8.7	32.5 \pm 9.8	0.540
Gender	Male	14 (46.7)	14 (46.7)	14 (46.7)	1.000

	Female	16 (53.3)	16 (53.3)	16 (53.3)	
Cigarette-smoking	Smoker	20 (66.7)	15 (50.0)	14 (46.7)	0.249
	Non-smoker	10 (33.3)	15 (50.0)	16 (53.3)	
Disease duration (year)	≤ 3	12 (40.0)	15 (50.0)	NA	0.604
	> 3	18 (60.0)	15 (50.0)	NA	
Family history	Yes	4 (13.3)	5 (16.7)	NA	1.000
	No	26 (86.7)	25 (83.3)	NA	
Hb (mg/dL)		10.3 ± 3.2	9.8 ± 4.1	NA	0.804
WBC (× 10 ⁹ /L)		7.6 ± 3.4	8.6 ± 3.0	NA	0.551
ESR (mm/hour)		59.0 ± 29.7	69.7 ± 44.5	NA	0.790
Disease extension	Ulcerative proctitis	13 (43.3)	NA	NA	
	Left-sided colitis	11 (36.7)	NA	NA	
	Extensive colitis	6 (20.0)	NA	NA	
	Ileocecal	NA	24 (80.0)	NA	
	Ileo-colonic	NA	6 (20.0)	NA	
Adalimumab or infliximab doses	0	5 (16.7)	5 (16.7)	NA	0.690
	1 – 10	14 (46.7)	10 (33.3)	NA	
	11 – 20	8 (26.7)	12 (40.0)	NA	
	21 – 30	3 (10.0)	3 (10.0)	NA	

*Data are either mean ± standard deviation or absolute number followed by percentage in parentheses; UC: Ulcerative colitis; CD: Crohn's disease; Hb: Hemoglobin; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; *p*: ANOVA (analysis of variance), LSD (least significant difference), Pearson's Chi-squared, or Fisher's exact test probability; NA: Not applicable.

Serum levels of IL-17A and IL-23

Serum level of IL-17A was significantly increased in UC and CD patients compared to control (45.2 ± 23.3 and 47.5 ± 34.4 vs. 15.6 ± 7.5 pg/ml, respectively; *p* < 0.001) (Figure- 1). Serum level of IL-23 was similarly increased in UC and CD patients compared to control (64.1 ± 23.7 and 62.5 ± 27.3 vs. 25.2 ± 11.1 pg/ml, respectively) (Figure- 2). However, the levels of both cytokines showed no significant variation between UC and CD patients (*p* = 0.713 and 0.777, respectively).

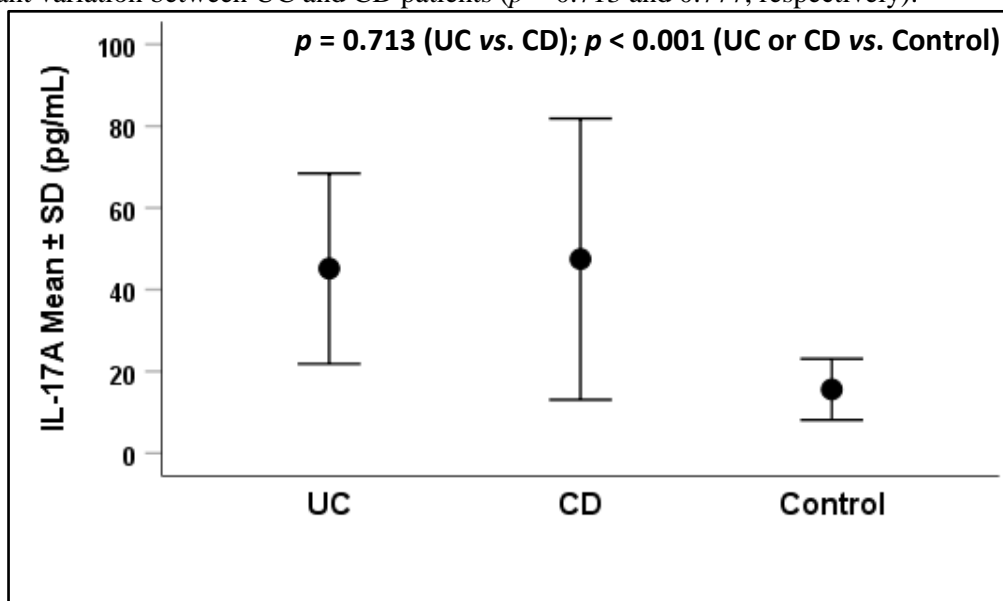


Figure 1-Mean serum level of IL-17A ± standard deviation (SD) in ulcerative colitis (UC) and Crohn's disease (CD) patients and control.

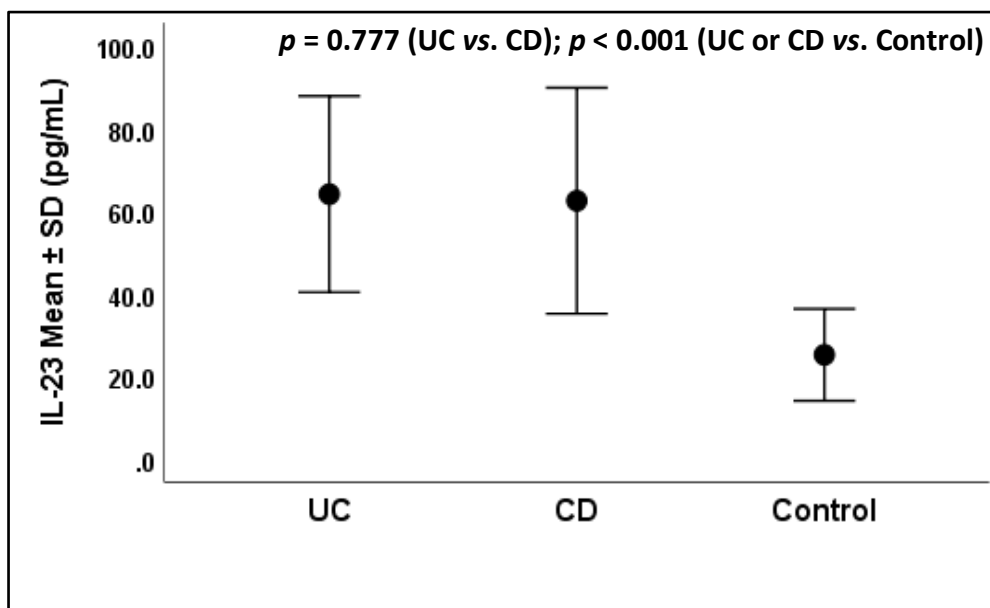


Figure 2-Mean serum level of IL-23 \pm standard deviation (SD) in ulcerative colitis (UC) and Crohn's disease (CD) patients and control.

ROC curve analysis revealed the predictive significance of IL-17A and IL-23. Both cytokines occupied a significant AUC in UC (IL-17A: AUC = 0.880; 95% CI: 0.795 - 0.965; $p < 0.001$; sensitivity = 76.7%; specificity = 76.7%; cut-off point = 21.7 pg/ml, and IL-23: 0.935; 95% CI: 0.874 - 0.996; $p < 0.001$; sensitivity = 83.3%; specificity = 83.3%; cut-off point = 37.6 pg/ml) and CD (IL-17A: AUC = 0.896; 95% CI: 0.810 - 0.981; $p < 0.001$; sensitivity = 80.0%; specificity = 80.0%; cut-off point = 22.9 pg/ml, and IL-23: AUC = 0.920; 95% CI: 0.854 - 0.986; $p < 0.001$; sensitivity = 83.3%; specificity = 83.3%; cut-off point = 36.3 pg/ml) (Table- 2 and Figures- 3 and 4).

Table 2-Receiver operating characteristic (ROC) curve analysis for IL-17A and IL-23 in ulcerative colitis and Crohn's disease patients.

Group	Cytokine	AUC	95% CI	p	Sensitivity; %	Specificity; %	Cut-off point; pg/ml
UC	IL-17A	0.880	0.795 - 0.965	< 0.001	76.7	76.7	21.7
	IL-23	0.935	0.874 - 0.996	< 0.001	83.3	83.3	37.6
CD	IL-17A	0.896	0.810 - 0.981	< 0.001	80.0	80.0	22.9
	IL-23	0.920	0.854 - 0.986	< 0.001	83.3	83.3	36.3

UC: Ulcerative colitis; CD: Crohn's disease; AUC: Area under curve; p : Probability; Significant p is bold-marked.

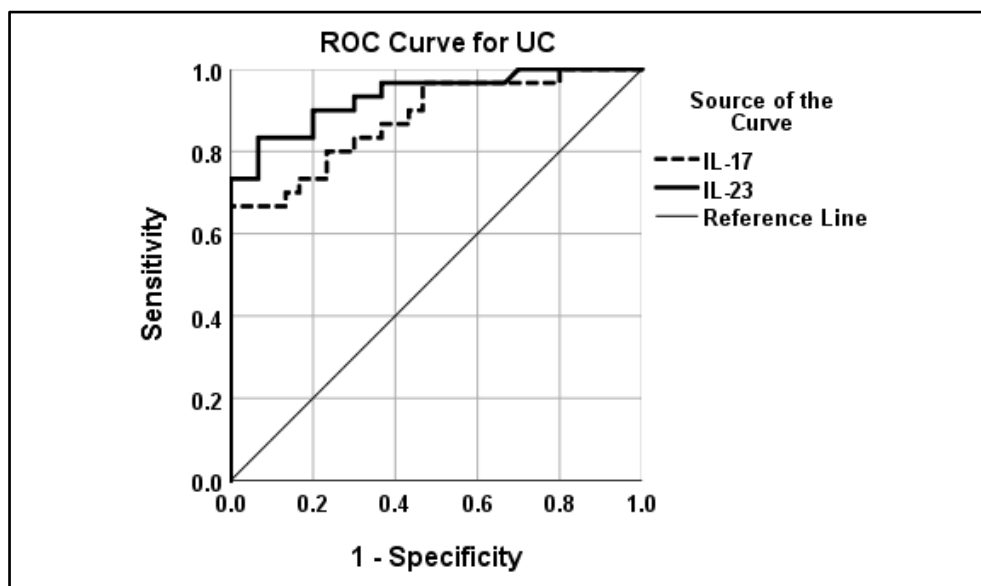


Figure 3- Receiver operating characteristic (ROC) curve for IL-17A and IL-23 levels showing area under curve (AUC) in ulcerative colitis (UC) patients.

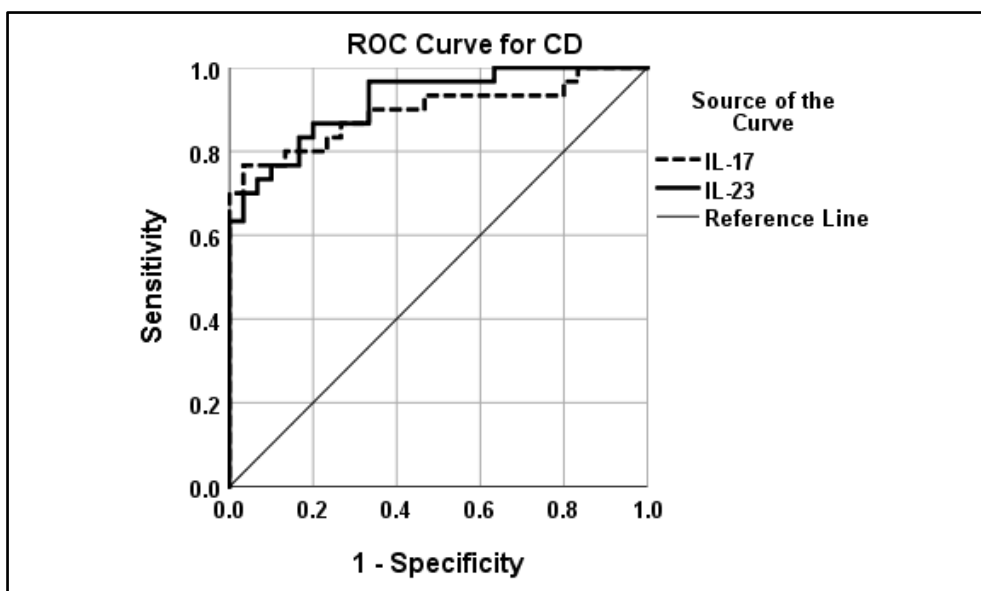


Figure 4- Receiver operating characteristic (ROC) curve for IL-17A and IL-23 levels showing area under curve (AUC) in Crohn's disease (CD) patients.

IL-17A and IL-23 Levels and characteristics of patients

Serum levels of IL-17A and IL-23 were first inspected in control subjects distributed according to gender and cigarette-smoking status. The mean levels of both cytokines showed no significant variation between males and females or smokers and non-smokers in the control group (Table- 3). However, distributing UC and CD patients into subgroups according to the characteristics presented in Table- 1 revealed some significant variations. Serum level of IL-17A was significantly increased in UC male patients compared to female patients (57.3 ± 18.2 vs. 34.5 ± 22.5 pg/ml; $p = 0.005$). It was also significantly increased in smoker UC patients compared with non-smoker patients (51.9 ± 19.4 vs. 31.6 ± 25.5 pg/ml; $p = 0.022$). Smoker CD patients also showed a significantly increased level of IL-23 compared to non-smoker patients (72.7 ± 28.5 vs. 52.2 ± 22.6 pg/ml; $p = 0.038$). In the case of family history, IL-23 level was significantly decreased in UC patients with a family history of IBD compared to CD patients with a family history (84.5 ± 24.3 vs. 50.4 ± 17.0 pg/ml.; $p = 0.042$) (Table-4).

Table 3- Serum levels of IL-17A and IL-23 in control subjects distributed according to gender and cigarette smoking status.

Characteristics		IL-17A mean \pm SD (pg/ml)	<i>p</i>	IL-23 mean \pm SD (pg/ml)	<i>p</i>
Gender	Male (N = 14)	15.3 \pm 7.1	0.860	25.4 \pm 11.3	0.923
	Female (N = 16)	15.8 \pm 8.1		25.0 \pm 11.1	
Cigarette-smoking	Smoker (N = 14)	14.4 \pm 6.9	0.406	23.8 \pm 11.2	0.533
	Non-smoker (N = 16)	16.7 \pm 7.9		26.4 \pm 11.3	

Table 4- Serum levels of IL-17A and IL-23 distributed according to some characteristics of ulcerative colitis and Crohn's disease patients.

Characteristics		IL-17A mean \pm SD (pg/ml)		<i>p</i>	IL-23 mean \pm SD (pg/ml)		<i>p</i>
		UC (N = 30)	CD (N = 30)		UC (N = 30)	CD (N = 30)	
Gender	Male	57.3 \pm 18.2	42.3 \pm 23.2	0.068	60.1 \pm 23.6	68.0 \pm 32.0	0.464
	Female	34.5 \pm 22.5	52.0 \pm 42.1	0.153	67.6 \pm 24.0	57.6 \pm 22.5	0.234
	<i>p</i>	0.005	0.450		0.397	0.307	
Cigarette-smoking	Smoker	51.9 \pm 19.4	47.9 \pm 44.8	0.722	60.6 \pm 20.5	72.7 \pm 28.5	0.153
	Non-smoker	31.6 \pm 25.5	47.1 \pm 21.1	0.111	71.0 \pm 29.1	52.2 \pm 22.6	0.082
	<i>p</i>	0.022	0.951		0.265	0.038	
Disease duration (year)	≤ 3	47.5 \pm 24.2	51.4 \pm 43.2	0.783	62.9 \pm 29.7	55.1 \pm 24.0	0.457
	> 3	43.6 \pm 23.2	43.6 \pm 23.4	1.000	64.9 \pm 19.7	69.9 \pm 29.2	0.563
	<i>p</i>	0.661	0.544		0.826	0.141	
Family history	Yes	38.1 \pm 21.4	48.2 \pm 27.6	0.568	84.5 \pm 24.3	50.4 \pm 17.0	0.042
	No	46.2 \pm 23.8	47.3 \pm 36.1	0.898	60.9 \pm 22.5	64.9 \pm 28.6	0.581
	<i>p</i>	0.527	0.959		0.063	0.337	
Disease extension	Ulcerative proctitis	42.5 \pm 17.7	NA		55.3 \pm 22.3	NA	
	Left-sided colitis	46.5 \pm 31.9	NA		70.4 \pm 23.4	NA	
	Extensive colitis	48.5 \pm 17.9	NA		71.5 \pm 25.1	NA	
	Ileocecal	NA	49.6 \pm 37.5		NA	60.1 \pm 28.1	
	Ileo-colonic	NA	39.1 \pm 16.8		NA	72.1 \pm 23.4	
	<i>p</i>	0.857	0.513		0.213	0.344	
Adalimumab or Infliximab doses	0	60.3 \pm 25.7	50.4 \pm 23.0	0.539	48.6 \pm 32.7	43.1 \pm 22.1	0.763
	1 – 10	40.0 \pm 21.9	27.9 \pm 15.4	0.148	69.4 \pm 20.7	69.1 \pm 27.8	1.000
	11 – 20	48.9 \pm 23.6	62.1 \pm 43.9	0.449	64.3 \pm 22.1	68.2 \pm 28.4	0.747

	21 – 30	34.0 ± 21.9	49.6 ± 34.8	0.547	64.6 ± 27.0	49.6 ± 18.6	0.472
	<i>p</i>	0.307	0.138		0.436	0.237	

UC: Ulcerative colitis; CD: Crohn's disease; *p*: ANOVA (analysis of variance), LSD (least significant difference); NA: Not applicable; Significant *p* is bold-marked.

Discussion

The results of this study enhance the concept that IL-17A and IL-23 play significant roles in the etiology and pathogenesis of UC and CD. The serum levels of both cytokines were markedly elevated in both groups of patients. On the contrary, no significant variation was noticed between UC and CD patients. This may suggest that IL-17A and IL-23 are involved in a common pathway of inflammatory responses that shape the pathogenesis of both IBD phenotypes. ROC analysis confirmed that both cytokines occupied a significant AUC in UC and CD; thus, the potential of IL-17A and IL-23 in the progression of UC and CD is augmented. Consistent with these findings, previous studies demonstrated the significance of IL-17A and IL23 in the pathogenesis of IBD [6, 9–12].

The pro-inflammatory cytokine IL-17A is produced by TH17 cells. It has been demonstrated that these cells show a marked infiltration in the inflamed gastrointestinal mucosa of IBD patients, with upregulated expression of TH17-related cytokines in both UD and CD tissues. Also, RNA transcripts of *IL17A* and *IL17F* genes were upregulated in inflamed mucosa of the patients. Thus, IL-17A has been proposed to have a key pathogenic role the intestine of UD and CD patients [13, 14]. A positive correlation between the levels of IL-17A and disease activity has also been reported in UC patients. Further, various studies have reported elevated production of other Th17-related cytokines in the inflamed mucosa of IBD patients; for instance, IL-21, IL-22, IL-23 and IL-26, which in turn exaggerate the inflammatory response in the gut [12, 15]. A more recent study investigated serum level of IL-17A in 68 children with IBD (43 UC and 25 CD) and 20 healthy children. It was found that IL-17A level was significantly increased in IBD children [16]. Case-control studies provided further insights into the genetic influence of IL-17A and its serum level in UC and CD pathogenesis [17, 18]. Accordingly, there has been converging evidence from human observational and population genetic studies that supports the significance of IL-17A in the regulation of mucosal inflammation in the gut of UC and CD patients [19]. However, patients with plaque psoriasis, psoriatic arthritis, or ankylosing spondylitis treated with Secukinumab, an anti-IL 17A monoclonal antibody, were at risk to develop IBD [20]. Further, the same antagonist was associated with exacerbation of CD and increased risk to develop new-onset fulminant colitis [21]. This is reasoned by the fact that using IL-17A antagonist to counteract the increased level of IL-17A may disturb the integration of the cytokine network due to a high synergistic potential with other inflammatory stimuli [22, 23].

In addition to IL-17A, IL-23 also showed a significantly increased serum level in UC and CD patients. Observational, genetic, and functional studies in human and laboratory animal models share the same outcome that IL-23 is a key pathway in IBD pathogenesis and suggest that IL-23 and its receptor (IL-23R) are important targets for immunotherapy in intestinal inflammations. Genome-wide association studies further linked UC and CD to a number of genes in the IL-23 axis [11, 24]. In this context, it has been suggested that IL-23 synthesis may contribute to mucosal homeostasis in the intestine via influencing specific intestinal target cells carrying the IL-23R [25]. In healthy mice, a high production of constitutive IL-23 p19 was noted in the intestine, being more expressed in the terminal ileum. Such elevated production of IL-23 may create a local environment of specific cytokines that target IL-23 sensitive cells in the intestine, and TH17 is among these cells [26, 27]. This may explain the increased levels of both cytokines in the present UC and CD patients, where their functional roles are accordingly suggested. In this regard, it has been identified that IL-23 is a key activator of TH17 cells in the mucosa of UC and CD patients, promoting these cells to produce interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), and IL-17A. A suppression of IL-10 production is a further effect of IL-23 on immune cells in the intestinal mucosa [28–30]. These findings suggest that overproduction of IL-23 may suppress IL-10 and other related cytokines and, by such pathway, IgA production is reduced and consequently the mucosa function against intestinal pathogens is impaired in IBD patients [25].

A consistent observation in UC and CD patients depicted that cigarette-smoking was associated with elevated serum levels of IL-17A and IL-23, while such variation was not observed between smoker and non-smoker control subjects. Based on numerous observational studies, cigarette-smoking has been described to have divergent roles in UC and CD, by protecting against UC but increasing the risk of CD, whereas former smoking elevates the risk of both diseases. However, the evidence is not conclusive and inconsistent observations have also been made [31, 32]. With respect to the impact of cigarette-smoking on IL-17A and IL-23 levels in IBD patients, there is no direct evidence supporting the present findings. However, it has been demonstrated that rats exposed to cigarette smoking exhibited multiple inflammatory responses that were associated with upregulated gene expression of several cytokines in brain sections, including IL-17A and IL-23 [33].

The study demonstrated further that IL-17A level was significantly increased in UC male patients compared to female patients, while IL-23 level was significantly decreased in UC patients with a family history of IBD compared to CD patients with a family history. No previous study has targeted gender and family history in UC and CD patients regarding IL-17A and IL-23 serum levels. Therefore, further studies are required to confirm or refute these findings.

In conclusion, the present data suggest a role for IL-17A and IL-23 in the etiology and pathogenesis of UC and CD. However, the study was limited by sample size, and increasing the number of patients and controls will certainly make a better understanding of the association between IL-17A and IL-23 and risk potential in both phenotypes of IBD.

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