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Safaa Muhsin Khudheir

Thekra Abdullah Mahmoud

ORIGINAL STUDY

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Serum Transforming Growth Factor-Beta (TGF-β) as Diagnostic Biomarker for Ulcerative Colitis: An Association Study With ABO Blood Group and Extra Intestinal Symptoms

Safaa Muhsin Khudheir *, Thekra Abdullah Mahmoud

Dept. of Medical Microbiology, College of Medicine, University of Kufa, Najaf, Iraq

Abstract

Background: Ulcerative colitis (UC) is a recurrent and remitting inflammatory bowel disease (IBD). Anti-inflammatory cytokines such as transforming growth factor-beta (TGF-β) are part of the pathophysiology of UC; these cytokines set off a specific immune response. Extra-intestinal manifestations (EIMs) reported occurrence differs from 14% to 47%, and accounts for the majority of related conditions in UC. This study aims to find the correlation of ulcerative colitis with TGF-β, ABO blood group and EIMs.

Objectives: To determine the serum level of TGF-β in both groups by sandwich ELISA, determine blood group by agglutination slide method, identify extra intestinal manifestation in UC patients.

Methods: enzyme linked immune-sorbent assay was used to assessment serum levels of TGF-β in compliance with the manufacturer's instructions. Agglutination slide method used to detect ABO and rhesus (Rh) group.

Results: non-significant difference in apparently healthy individual compared to UC patients regarding to occupation, smoking, blood group and Rh group as P-value for them was >0.05. UC patients exhibited significant lower concentration mean TGF-β (31.57 ± 23.86 pg/ml) compared to control group (42.93 ± 25.35 pg/ml) (P-value = 0.02).

Conclusion: The findings indicate a decreased serum concentration of TGF-β in UC patient compared to seeming healthy individual with no significant link to clinical symptoms or ABO blood group. These results suggest that TGF-β play role in the pathogenesis of UC independent of clinical presentation or blood type.

Keywords: Ulcerative colitis, Transforming growth factor-beta, Extra intestinal manifestation

1. Introduction

Ulcerative colitis (UC) is recurrent and remitting inflammatory bowel disease (IBD), characterized by mucosal inflammation begins distantly from the rectum and can spread proximally to encompass the entire colon, which is a hallmark of UC [1]. The incidence of UC has a bimodal age distribution the first peak in the age period (15–30) years and a second peak between (50–80) years [2]. The common symptoms of UC include abdominal discomfort, diarrhea, weight loss, rectal bleeding and urgency [3]. Some data indicated an increasing incidence of UC in newly industrialized countries in Asia, specially China and India, each with populations above one billion, the rapid increases in the prevalence of IBD are not fully understood The reasons for it [4]. Dysregulated expressions of pro- and anti-inflammatory cytokines such as IL-12, IFN-γ, TNF-α, IL-6, as well as IL-10 and TGF-β, are part of the pathophysiology of UC, these cytokines directly damage tissue and mucosa, and some of them set off a specific immune response [5]. Extra-intestinal manifestations (EIMs) reported occurrence differs from 14% to 47%,

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* Corresponding author.
E-mail addresses: safaam.almaqsosy@student.uokufa.edu.iq (S. M. Khudheir), thikra.almayah@uokufa.edu.iq (T. A. Mahmoud).

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and accounts for the majority of related conditions in UC. EIMs most commonly affect joints (axial and peripheral arthropathies), the skin (erythema nodosum, Sweet syndrome, pyoderma gangrenosum, aphthous stomatitis), primary sclerosing cholangitis (PSC), and the eye (uveitis, episcleritis). Less frequently, EIMs as well attack other organs [6, 7]. The pathophysiology of EIMs in UC may be arise from the translocation and extension of immune complexes from the colon to further organs or may perhaps happen as independent inflammatory proceedings [8]. One important cytokine that regulates cellular immunity and homeostasis is transforming growth factor-beta (TGF-β). It is a member of the TGF-β superfamily, which also consist of TGF-β1, TGF-β2, and TGF-β3. These molecules are latent in the extracellular matrix and need to be stimulated in order to start signaling through both conventional and non-canonical routes [9, 10]. TGF-β secreted by leukocytes, epithelial, and stromal cells, it modulates intestinal dendritic cells, retaining immune tolerance and preventing UC [11]. TGF-β directs T cell activation, differentiation, and survival, stimulating Th17/Th9 while suppressing Th1/Th2 subsets [12]. Additionally, TGF-β1 controls B cell functions by inducing IgA class switching [13]. Smad7 is an intracellular protein that blocks TGF-β/Smad signaling via binding to the TGF-βreceptor. Silencing Smad7 with an antisense oligonucleotide reestablishes TGF-β signaling, this restoration decreases inflammatory cytokines, proposing a treatment strategy for UC [14].

2. Materials and methods

2.1. Studt question and objectives

Does the serum level of TGF-β differ among apparently healthy group and UC patients? Can baseline serum TGF-β level predict association with disease symptoms or extra-intestinal manifestation? Does the blood type have association with UC?

The study objectives are to determine the serum level of TGF-β in both groups by sandwich ELISA, to determine blood group by agglutination slide method, and to identify extra intestinal manifestation in UC patients.

2.2. Design

This study is a case- control study, established on previously published regional studies [15, 16]. This present study involved (50 patients with UC and 50 appearently healthy controls). This sample size is regarded adequate for pilot valuation of potential associations between (immunologic, hematological and environmental risk factors) and UC in the Iraqi population in Wasit province. A standardized questionnaire covering sex, age, occupation, smoking, and any history of chronic illness or inflammation was used to gather sociologic and clinical data, along with any pertinent data.

2.3. Inclusion and exclusion criteria

Inclusion criteria included all patients between the ages of 15 and 70 who have been diagnosed with UC by a gastroenterologist are eligible to participate. The American Gastroenterological Association's (AGA) 2024 Living Guideline and the British Society of Gastroenterology's (BSG) 2024 IBD Guidelines will agreement with clinical targets. Exclusion criteria included a systematic random selection of individuals who do not meet the UC criteria and are between the ages of 15 and 70.

2.4. Setting

This study covered 100 participants in total, comprising 50 patients, ages 15 to 70, who were hospitalized to the gastrointestinal center at AL-Zahraa Teaching Hospital in Wasit province between February 2025 and July 2025. Fifty (50) Volunteers who appeared healthy and ranged in age from 15 to 70 were examined since they had no clinical evidence of ulcerative colitis, no history of the disease, and no visible abnormalities.

2.5. Sample

Both the patients and the healthy control group had a 5 ml venous blood sample taken. Each sample of blood was separated into two tubes:

- Two milliliters of EDTA tubes for the blood group test

For enzyme-linked immunosorbent tests (ELISA), the last 3 milliliters of the blood sample were transported to a sterile gel tube: Before centrifugation, the serum was collected by permitting the gel tube to coagulate at 37°C for 30 minutes. Five minutes of centrifuging the tubes at 5000 rpm, the serum was extracted and stored in a deep freezer at –80°C until it was needed.

2.6. Techniques of investigations

Commercial ELISA kits (SunLong Biotech, Cat.No :SL1736Hu; China) were used to measure the serum levels of TGF-β in accordance with the manufacturer's instructions (supplementary file Section 1 & Figure 1). Using a micro-plate reader (BioTek, USA),

Table 1. Distribution of participants according to Sociodemography and blood group in UC patients and control.

	Age interval (years)	Patients N (%)	Control N (%)	chi-square	*p*-value
Age group	15 to 22	6(12)	6(12)	2.798	0. 833
	23 to 30	14(28)	14(28)		
	31 to 38	10(20)	7(14)		
	39 to 46	6(12)	7(14)		
	47 to 54	5(10)	8(16)		
	55 to 62	3(6)	5(10)		
	63 to 70	6(12)	3(6)		
Genus	Male	31(62)	26 (52)	1.019	0.312
	Female	19(38)	24 (48)		
Occupation	Employee	15 (30)	17 (34)	0.713	0.700
	Winner	19 (38)	15 (30)		
	Housewife	16 (32)	18 (36)		
Smoking	Smoking	8 (16)	12 (24)	2.099	0.350
	Non-smoking	37 (74)	36 (2)		
	Past-smoking	5 (10)	2 (4)		
Blood group	A	9 (18)	10 (20)	1.961	0.580
	B	15 (30)	17 (34)		
	AB	10 (20)	5 (10)		
	O	16 (32)	18 (36)		
Rh group	Positive	38 (76)	35 (70)	0.456	0.499
	Negative	12 (24)	15 (30)		

absorbance was measured at 450 nm. Using an Excel document, a standard curve was created by plotting the absorbance versus the concentration of serially diluted standards. The levels of TGF-β were determined using the curve-fitting equation.

Red blood cells have been created to respond with commercially available antisera (Spanclone, India) that include known agglutinins in order to identify each participant's blood type with. After that, the slide is viewed under a microscope to determine whether or not red cell clumping and hemolysis (agglutination), which are caused by an antigen-antibody response, are present.

2.7. stat method

IBM SPSS Statistics software, version 20, was used to analyze the data. Both the Shapiro-Wilk and Kolmogorov-Smirnov tests were used to estimate the normality of continuous variables which afforded P-value<0.05, demonstrating that the data were not normally distributed. For categorical variables, descriptive statistics were displayed as frequencies and percentages; for continuous variables, they were displayed as mean ± standard deviation. The Chi-square test was used through the Legacy dialog to assess relationships between categorical variables. To determine the diagnostic performance of particular parameters, a Receiver Operating Characteristic (ROC) curve analysis was conducted. The degree and direction of relationships between non-parametric variables were evaluated using the Spearman's correlation coefficient. Statistical significance was defined as a p-value of less than 0.05.

3. Results

This study was performed on 50 UC patients and 50 apparently healthy individual without signs and symptoms of any systemic disease. The participant's age of both groups ranged from 15 to 70 years with a mean± standard deviation (SD) of UC patients (38.16 ± 15.46) years versus control group was (38.48 ± 14.78). Results showed as in Table 1 large portions of UC patient located in the age period between 15 to 38 years, despite there no significant difference as compared to apparently healthy group ($X^2 = 2.798$, $P = 0.833$), statics displayed no significant difference between the patients and control groups concerning to genus (($X^2 = 1.019$, $P = 0.312$) and despite this most UC patient were from male 31(62) of total 50 patients. Also Table 1 revealed non-significant difference in apparently healthy individual compared to UC patients regarding to occupation, smoking, blood group and

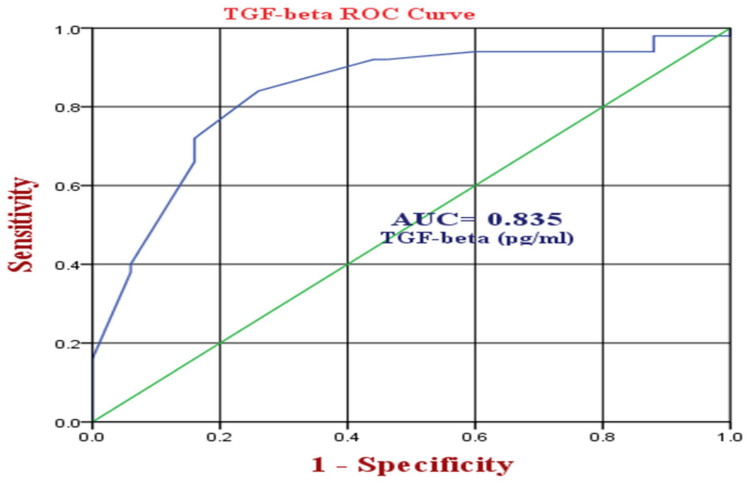

Fig. 1. Receiver operating characteristic curve for TGF-β in UC patients.

Table 2. Frequency distribution of UC patients according to some clinical symptoms in UC patients (N = 50).

variable	Present No.(%)	Absent No.(%)
Blood in stool	48 (96%)	2 (4%)
Vomiting	2 (4%)	48 (96%)
Abdominal pain	44 (88%)	6 (12%)
Weight loss	25 (50%)	25 (50%)
Appetite loss	23 (46%)	27 (54%)
Fever	23 (46%)	27 (54%)

Data described as frequency and percentage.

Rh group as P-value for them was >0.05 ($X^2 = 0.713$, $P = 0.700$; $X^2 = 2.099$, $P = 0.350$; $X^2 = 1.961$, $P = 0.580$ and $X^2 = 0.456$, $P = 0.499$) respectively.

The statistic finding regarding UC patients in Table 2 demonstrated that most patients were have blood in stool and abdominal pain, while 50% of patients were suffered from weight loss, there are no clear or high percentages between the rest of the symptoms like (fever, vomiting and appetite loss) and UC.

The finding of extra-intestinal manifestation among UC patients expressed significant differences ($X^2 = 114.2$, $P = 0.001$), 80% of UC patients did not experience any manifestation while 12% of them had Skin manifestation, other manifestation were presented in very small proportions.

The current result showed that UC patients exhibited significant lower mean anti-inflammatory TGF-β levels (31.57 ± 23.86 pg/ml) compared to control group (42.93 ± 25.35 pg/ml) (P-value = 0.02). ROC Fig. 1, was performed to revealed diagnostic accuracy of using TGF-β concentration to distinguish UC patients from control group, reflected as accurate and acceptable marker with sensitivity 84%, specify 74% and AUC of 0.835 (95%Confidence interval: 0.752–0.917) for cutoff more than 32.16 fold.

The results in (Table 4) showed non-significant correlations found between TGF-β serum level and any of the considered clinical symptoms, extra-intestinal manifestation and blood group types among UC patients P-value > 0.05 for each one. This indicates that serum TGF-β level was not affected by loss of weight or appetite, blood in stool, fever, vomiting, EIMs or blood group types in this study.

4. Discussion

Continuous inflammation of the colonic mucosa and submucosa is a hallmark of ulcerative colitis (UC), a chronic, nonspecific IBD [17]. Globally, its incidence is increasing, particularly in newly industrialized countries adopting Western lifestyles. Symptoms such as bloody diarrhea need to defecate and weight loss significantly affect the quality of life for patients [18]. This study encompassed of 50 UC patients and 50 controls. The participants' ages ranged from 15 to 70 years old. The average age of those with UC was 38.16 ± 15.46 years, while the control group's mean age was 38.48 ± 14.78 years. The average age of UC patients in Wasit, Iraq, is 35.3 years, which is consistent with the Alahmed and Al-Rubaee study in Basrah, Iraq [19], and another study conducted in Kurdistan, Iraq, by Alshekhani *et al*. (35.41) [20]. There is no noticeable age difference between the two groups. According to Alkaraawi and Kadhim at Al-Najaf Al-Ashraf [21], the majority of UC patients were between the ages of 15 and 38. Mohammed and Amin's study from 2022 indicated that the majority of UC patients were between the ages of 21 and 29 [22]. The data results revealed highly percentage of male compared to female in UC patients which agreed with study in Iran [23], but differ slightly with observation

Table 3. Prevalence of EIM categories among UC patients (N = 50).

Finding	No. (%)	Chi-square	P-value
No thing	40 (80%)	114.2	0.001*
Skin manifestation	6 (12%)		
Ocular manifestation	1 (2%)		
Musculoskeletal manifestation	2 (4%)		
Ulcer around mouth	1 (2%)		

Table 4. The association between UC and some symptoms, EIMs and blood groups.

	TGF-β	
	r	p-value
Weight loss	–0.109	0.450
Appetite loss	–0.144	0.316
Fever	0.074	0.607
Blood in stool	0.189	0.187
Vomiting	0.089	0.538
EIM	–0.051	0.722
Blood group	–0.086	0.550
Rh group	0.245	0.086

R = Spearman's Correlation Coefficient.

of study in Baghdad when the male with UC was 47.7% while female was 52.3% [24], this may be due to the sample size studied or a slight difference in lifestyle. The researches have attributed the increased of UC in male to sex-related hormones and variation in the gut microbiota between male and female especially in Asian-Pacific and western countries and the male above 45 years old established higher risk of occurrence UC than females [25]. Inspire of non-significant variances between control versus patients group, most UC patients distributed between winner and housewife and slightly portion was employee this agreed with local study in Al-Najaf [26].

The current finding showed non-significant differences regarding smoking and most UC patients were nonsmokers, this confirmed by other Iraqi study which reported that smoking may prevent ulcerative colitis from developing and is not a risk factor for it; these findings lend confidence to the idea that smoking protect from UC [20]. Nicotine could decrease the inflammatory response in UC by suppressing immune cells like macrophages and T-helper cells. Moreover, smoking can deteriorate immunological response and intestinal motility, which reduces gut tissue responsiveness and, in turn, diminishes the severity of inflammation in UC patients [27]. Regarding blood group and Rhesus (Rh) group the results showed non- significant differences, blood types (O) and (B) were the most common in patients this results were consisted with a study conducted in Taiwan, which showed that neither nether blood groups nor Rh group have effect on the risk of developing UC [28].

The outcome of this study showed that most UC patients had rectal bleeding (blood in stool) and abdominal pain in addition to most of them were have weight loss, while other local study recorded small portion of their IBD patients were have this symptoms [29]. Another study in Egypt reached similar results to this current study [30]. The persistent inflammation damaged the colon mucous layer, particularly affecting the rectum, which led to bleeding and impaired nutrient absorption, resulting in weight loss for patients with ulcerative colitis (UC).

There is significant correlation between UC and EIMs in this study; 6 (12%) of UC patients had skin manifestations, while 20 (40%) of them did not suffer from any EIMs. The other manifestations represent a minimal proportion of UC patients. A local study in Kurdistan found comparative results regarding some of EIMs [20], a meta-analysis study reported that dermatological manifestation occurs in about 10% of IBD patients, while joint manifestations occurs in about 4% to 11% and ocular manifestations approximately 2% of IBD patients [31]. However, in fact Long-term monitoring is necessary for the development of these characteristics, besides some of which do not correspond with disease activity.

The investigation results of anti-inflammatory TGF-β serum level showed a significant high concentration in the control group compared to UC patients, which contrasts with most studies that recorded an increase in the level of TGF-β in untreated IBD patients compared to healthy individuals [32]. In the current study the decrease in serum level of TGF-β in UC patients suggests that treatment procedures as 92% of our UC patients had been undergoing therapeutic administration (e.g., 5-aminosalicylates, corticosteroids, or immunosuppressant) or disease modulated regulatory mechanisms may suppress TGF-β expression and this agrees with a study in Buenos Aires/ Argentina which found the level of TGF-β was decreased after 42 days of conventional treatment in UC patients [33]. A given the high discriminatory ability detected (ROC = 0.835), TGF-β could be considered a prospective biomarker for monitoring therapeutic response in UC or quiescent disease.

The statistic displayed a non-significant correlation between TGF-β serum level and UC patients clinical

symptoms or blood groups and EIM, suggesting that its systemic level may not reflect disease severity. This finding agrees with previous studies demonstrating that TGF-β acts mainly at the mucosal level rather than in circulation [34].

5. Conclusion

Our finding indicate a decreased serum concentration of TGF-β in UC patient compared to seeming healthy individual with no significant link to clinical symptoms or ABO blood group. These results suggest that TGF-β play role in the pathogenesis of UC independent of clinical presentation or blood type.

6. Study limitations and recommendation

The main limitation of this study was inability to conducts assessments on tissue samples and the restriction of the study period. Further studies with large sample size and extended timeframes should search for the underlying mechanisms responsible for this reduction and its specific relation to disease activity. Future studies must focus on following serum TGF-β longitudinally before and after introducing therapy to confirm its effectiveness as a reliable marker for monitoring treatment response and defining disease remission.

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Authors' contribution

S.M.K and T.A.M: conceptualization, resources, writing (original-draft, review and editing), data collection, investigation, statistical analysis and discussion.

Ethical approval

The ethics committees of the Wasit province's health directorate and Kufa Medical College both gave their approval. All participants as well as the parents or legal guardians of young people gave their consent, with individuals under the age of eighteen being accepted.

Declaration conflict of interest

We declare that there are no conflicts of interest in this work.

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