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Estimation of some biochemical and inflammatory markers in pediatric ulcerative colitis

Fatima A. Mohammad[1], Nadia Ghassan AbdulKareem[2]*, Baraa H. Ali[3]
[1]*Department of Chemistry, College of Science, University of Mosul, Al-Mosul/ Nineveh, Iraq.*
[2]*Department of Chemistry and Biochemistry, College of Medicine, Al-Iraqia University, Baghdad, Iraq.*
[3] *Northern Technical University / Mosul Medical Technical Institute / Department of Anesthesia Techniques / Nineveh, Iraq.*

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Abstract

This study investigates the relationship between biochemical and inflammatory markers and the extent of ulcerative colitis (UC) in pediatric patients. A case-control study involving 200 participants, comprising 100 healthy controls and 100 with UC patients, all aged 7–16 years, was conducted. Blood samples were collected and analyzed for water- and fat-soluble vitamins (B12, C, β-carotene, D, A, and E), inflammatory markers (erythrocyte sedimentation rate [ESR], interferon gamma [INF-γ], C-reactive protein [CRP], tumor necrosis factor [TNF-α]), hemoglobin, and Coenzyme Q10 (CoQ10), using ELIZA-based analysis and manual methods. Participants also supplied data regarding their family history of UC, rural or urban residency, and disease duration. Statistical analysis was performed using SPSS software, employing t-test, one-way analysis of variance, Pearson's correlation among parameters in the patient group and ROC curve.

Results showed a highly significant reduction ($P < 0.01$) in CoQ10 [39.59 vs. 31.61 ng/ml], hemoglobin, and most vitamins, except B12. Statistically highly significant increase ($P < 0.01$) in inflammatory markers [INF-γ, CRP, TNF-α, and ESR] in UC patients compared to the control group [100.79 vs. 53.38 ng/ml; 20.12 vs. 4.64 mg/L; 20.95 vs. 8.10 pg/ml; 36.10 vs. 8.11 mm/l hr respectively]. Significant correlations were observed between age and disease severity, as well as between disease duration and clinical remission. These findings highlight the potential of inflammatory biomarkers as novel diagnostic tools and reveal deficiencies in water- and fat-soluble vitamins, excluding B12, in pediatric UC patients.

Keywords: Pediatric ulcerative colitis, TNF-α, INF-γ, water and fat-soluble vitamins, CoQ10.

تقدير بعض المؤشرات البيوكيميائية والالتهابية في التهاب القولون التقرحي عند الأطفال

فاطمة عبد الحميد محمد[1]، نادية غسان عبد الكريم[2]*، براء حازم علي[3]
[1]قسم الكيمياء، كلية العلوم، جامعة الموصل، نينوى، العراق
[2]فرع الكيمياء والكيمياء الحياتية، كلية الطب، الجامعة العراقية، بغداد، العراق
[3]قسم تقنيات التخدير، المعهد التقني الطبي الموصل، الجامعة التقنية الشمالية، نينوى، العراق

*Email: Nadya_AbdulKareem@aliraqia.edu.iq

الخلاصة

تبحث هذه الدراسة العلاقة بين المعلمات الكيميائية الحيوية والالتهابية ومدى التهاب القولون التقرحي لدى الأطفال المرضى. أجريت الدراسة على 200 مشارك (100 من الضوابط الأصحاء و100 مريض بالتهاب القولون التقرحي)، تتراوح أعمارهم بين 7 و16 عامًا. تم تحليل عينات الدم بحثًا عن الفيتامينات القابلة للذوبان في الماء والدهون (B12 وC وبيتا كاروتين وD وA و E) والمعلمات الالتهابية (معدل ترسيب كريات الدم الحمراء [ESR والإنترفيرون جاما INF−γ والبروتين التفاعلي−CRP وعامل نخر الورم TNF−α] والهيموجلوبين والإنزيم المساعد (CoQ10) باستخدام تقنية الاليزا والطرق التقليدية في التحاليل، كما قدم المشاركون معلومات عن التاريخ العائلي لالتهاب القولون التقرحي والإقامة الريفية أو الحضرية ومدة المرض. استُخدم برنامج SPSS للتحليل الإحصائي، والذي شمل اختبار t، وتحليل التباين أحادي الاتجاه، ومعامل ارتباط بيرسون بين معايير مجموعة المرضى، ومنحنى ROC .أظهرت النتائج انخفاضًا كبيرًا (P <0.01) في CoQ10 31.61 .vs 39.59] نانوغرام/مل]، والهيموغلوبين، ومعظم الفيتامينات، باستثناء فيتامين ب12. كما لوحظت زيادة كبيرة (P <0.01) في مؤشرات الالتهاب [INF−γ، وCRP، وTNF−α، و ESR]لدى مرضى التهاب القولون التقرحي مقارنةً بالمجموعة الضابطة [100.79 نانوغرام/مل مقابل 53.38 نانوغرام/مل؛ 20.12 ملغم/لتر مقابل 4.64 ملغم/لتر؛ 20.95 بيكوغرام/مل مقابل 8.10 بيكوغرام/مل؛ 36.10 ملغم/لتر ساعة مقابل 8.11 مليغرام/لتر ساعة على التوالي]. تم العثور على ارتباطات بين العمر وشدة المرض، وبين مدة المرض والحالة السريري. تسلط النتائج الضوء على إمكانات المؤشرات الحيوية الالتهابية كأدوات تشخيصية جديدة وتكشف عن نقص الفيتامينات القابلة للذوبان في الماء والدهون، باستثناء فيتامين ب12، في مرضى التهاب القولون التقرحي الأطفال.

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel disorders that fall under the broad classification of inflammatory bowel disease (IBD) [1]. UC is a chronic inflammatory bowel disease that presents significant diagnostic and therapeutic challenges, particularly in pediatric populations. It is linked to reduced lifespan and a heightened risk of colorectal cancer and complications requiring colonoscopy [2]. The underlying mechanisms for risk UC, particularly those that develop early due to genetic and immune system defects, are not well understood [3]. Despite extensive research in adult UC, there is a lack of studies addressing pediatric-specific biomarkers and their diagnostic potential.

Environmental factors play a key role in the development of UC, with the highest incidence observed in northern Europe and America. The increased disease activity has been linked to Tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine that is essential for the start and regulation of an inflammatory response [4], as increased synthesis and release of cytokines, including inflammatory and regulatory cytokines like TNF-α, ILs, and IFN-α, are caused by dysregulated innate and adaptive immune responses. These proinflammatory cytokines maintain the inflammatory response and contribute to uncontrolled intestinal inflammation [5]. While the human body is unable to create vitamins, the gut microbiota plays a crucial role in mediating vitamin absorption and can generate vitamins on its own to make up for inadequate food intake [6]. The potential for deficient levels of vitamins, especially as a result of insufficient intake, dietary restrictions, malabsorption, and substantial nutritional excretion [7]. Furthermore, vitamin C deficiency, due to poor dietary intake, malabsorption, or intestinal dysfunction, is common in UC patients. Several low-residue diet plans omit fresh fruit and vegetables, which are the primary dietary sources of vitamin C and may exacerbate vitamin C malabsorption [8].

Vitamin E deficiency is commonly associated with IBD, largely because individuals with this condition often have trouble eating. Furthermore, ulceration of the small intestine reduces the surface area available for fat absorption, resulting in impaired fat absorption. This may easily lead to a deficiency in fat-soluble vitamins, especially vitamin E [9]. Vitamin D is involved in several biological processes, including maintaining intestinal barrier integrity and regulating gut mucosal immunity, in addition to its effects on bone [5]. Consequently, vitamin D deficiency has been connected to the activity of immune-mediated diseases like IBD [10] [11]. Reduced iron absorption in UC patients as a result of blood loss, malnutrition, chronic gastrointestinal tract inflammation or intestinal resection [12]. Important biological functions of carotenoids include their anti-inflammatory and antioxidant properties [13]. Carotene is released from food during digestion and absorbed by intestinal cells in humans and enters mixed micelles, where intestinal cells absorb it as a precursor to vitamin A [14]. Pathogenic disorders of the gastrointestinal system are frequently linked to vitamin A deficiency (VAD), as it regulates gut immunity, reduces inflammation, and retains the integrity of the epithelial barrier. VAD may contribute to the development of UC [15]. Trace element deficiencies are frequent in people with malabsorptive illnesses such as UC and persistent diarrhea [16]. Anthropometry may be used to compute body composition and combine it with other recording techniques to obtain a clinical nutrition picture [17].

This study aims to evaluate the diagnostic potential of biochemical and inflammatory markers in assessing the severity and extent of the disease to improve diagnostic precision, prognosis and management strategies for pediatric UC.

2. Subjects and methods

2.1. *Subjects and sampling:*

The diagnosis of UC was established following the standard criteria by a specialist physician, at the Gastroenterology and Hepatology teaching hospital in Baghdad-Medical-City. The study included clinical symptoms, radiographic findings, laboratory tests, and endoscopic examinations.

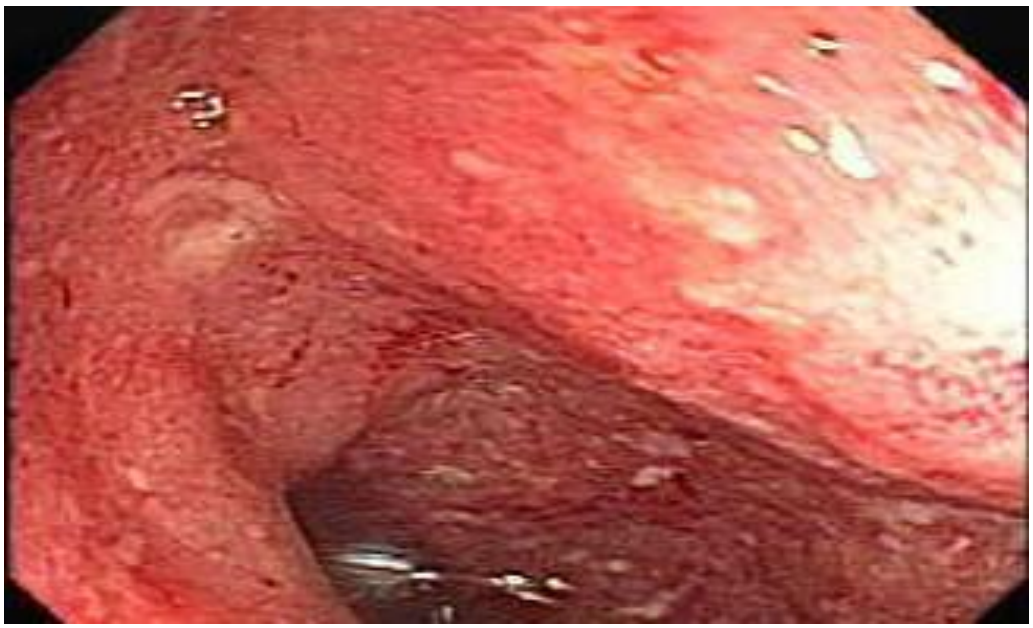


Image 1: Endoscopic findings in ulcerative colitis [18]

The study was conducted from December 2023 to March 2024, with informed consent obtained from each participant before its initiation. The study included 200 participants were randomly selected: 100 healthy individuals in the control group (Controls were selected from healthy children under the age of 18 who were present with their families in the same hospital in which the UC children were present and/or children accompanying relatives of the ill children), and 100 children with ulcerative colitis, the ages of the participants were from 7-16 years. A justification for the sample size is based on relevant literature and typical effect sizes observed in pediatric UC studies.

Exclusion criteria: presence of other gastrointestinal diseases, endocrine disorders, autoimmune diseases, or corticosteroid/ anti-autoimmune therapy use; participants older than 18 years.

When asking those accompanying the patients, it was explained that there was no precise planning and preparation of meals, but rather the meals were limited to sauces and spices, greasy or fried foods, high-fiber foods such as seeds and beans, milk products, and drinking sufficient amounts of water.

Blood samples were coagulated in gel tubes for 10-20 minutes, then centrifuged at 3000 RPM for 15 minutes at room temperature. The serum was carefully collected, aliquoted, and preserved at -20℃. An EDTA container was used for plasma collection after mixing for about 15-20 minutes, centrifuging at 3000 RPM for 15 minutes, and then carefully separating the plasma.

2.2 *Materials and methods:*

Use the following kits and procedures from the mentioned manufacturers and origins:

Kit names	Technique	Company	Origin
Human Vitamin B12(VB12)	Sandwich- ELISA Kit technology Cat.No：YHB3198Hu	SHANGHAI YEHUA Biological Technology	China
VD(Vitamin D)	Competitive-ELISA principle/ Catalog No: MBS2503525	MyBioSource.Com	USA
Human TNF alpha	Sandwich-ELISA Principle/ Catalog No: MBS824943	MyBioSource.Com	USA
Vitamin E	Manual technique [19]		
Vitamin C & A	Manual technique [20]		
ESR	Manual technique [21]		
Human Coenzyme Q10	Competitive- ELISA principle	HCUSABIO	China
INF-gamma	ELISA kit	BT-LAB	China
CRP	Latex test kit	Plasmatec	France
Human Beta Carotene	ELISA kit	MyBioSource.Com	USA

Use manual methods for the assay of Vitamins A, E, and C, ESR and hemoglobin; employing a spectrophotometer for measuring concentrations. Whereas for the analysis of rest markers (B-carotene, CoQ10, Vitamin D and B12, INF-gamma, and TNF-alpha) use ELISA kits by utilizing ELISA Human Reader and washer apparatus from Promega/ USA origin. CRP measured by (qualitative and semi-quantitative) latex test kit.

Laboratories typically validate their procedures following established guidelines. These recommendations offer a systematic approach to ensure that tests meet the required standards. Validating laboratory methods and blood analysis for accuracy and reliability is conducted throughout the use of standardised reference materials and calibration of instruments; accuracy is checked by bias assessment and trueness of the tests. Validation of reliability and

reproducibility of methods is done by replication, in addition to precision assessments, inter-laboratory testing (running internal quality control samples), and statistical analysis.

2.3 *Statistical evaluation:*

Data were analyzed using SPSS version 20, with statistical tools chosen based on the study design, data, and hypotheses. Descriptive statistics were expressed as mean ± standard deviation, and standard error was computed for ESR, CRP, TNF-α, INF-γ, all types of vitamins, hemoglobin, Coenzyme Q10, and age using independent sample t-test and one-way analysis of variance (ANOVA) to assess. For instance, to fit the hypothesis, a t-test is used to compare the two study groups (control vs. UC patients) to test whether an observed difference is statistically significant. ANOVA is typically used for more than two groups (e.g., disease severity levels). It helps us determine if any one of the groups varies substantially from the others by addressing hypotheses of multiple group comparisons.

Categorical variables, such as sex and family history, disease extent, and clinical remission, were analyzed using the Chi-square (χ^2) test.

A P-value < 0.01 was considered statistically highly significant, while P≤ 0.05 was considered statistically significant. Pearson's correlation was used to assess the relationships between parameters within each group. Additionally, post-hoc effect size analysis (Cohen's d) was performed to evaluate the magnitude of differences between groups, finding that the study's sample size (n = 100/ each group) was more than sufficient to identify significant group differences and highlight the markers' diagnostic value in pediatric UC.

ROC curves and measurements are used to determine sensitivity, specificity, and cut-off values for highly accurate indicators in the patient population. Additionally, we employed a ROC curve to assess the diagnostic accuracy of the novel biomarker, aiming to evaluate how well it differentiates between participants, an important factor in understanding its clinical utility.

Ethical permission number (4C/136 D.D 22/11/2023) was granted by the Council board of Sciences College/ University of Mosul. The data were digitally recorded and secured to ensure accuracy and confidentiality.

3. Results

To evaluate the clinical significance and strength of the observed differences between pediatric UC patients and healthy controls, post-hoc effect size calculations (Cohen's d) were carried out for important biochemical and inflammatory indicators. Extremely large effect sizes were found in the study for TNF-α (d = 4.63), INF-γ (d = 4.66), and CRP (d = 8.86), showing highly significant rises in the patient group. Vitamin D had a notably strong effect size (d = 7.02), which was markedly reduced in UC patients. Additionally, Coenzyme Q10 had a large effect size (d = 2.19), supporting its potential diagnostic value.

Table 1 presents a highly significant decrease (P<0.01) in CoQ10 and most vitamins, while vitamin B12 levels showed no significant difference (P=0.708). There were highly significant elevated levels (P< 0.001) of inflammatory markers in Patients compared to the control group.

Table 1: Demographic and Clinical Characteristics

Parameters	Study Groups	N	Mean ± Std. E	Mean difference	P-value	95% Confidence Interval of the Difference	
						Lower	Upper
Vitamin B12 (pmol/L)	Control	100	234.36 ± 6.68	-3.288	0.708	-20.59	14.01
	Patients	100	237.65 ± 5.68				
Vitamin D (pg/ml)	Control	100	47.71 ± 0.57	34.536	0.001	33.16	35.91
	Patients	100	13.17 ± 0.40				
Co Q10 (ng/ml)	Control	100	39.59 ± 0.27	7.979	0.001	6.96	9.00
	Patients	100	31.61 ± 0.44				
B carotene (mg/dl)	Control	100	0.21 ± 0.007	0.0463	0.001	0.025	0.68
	Patients	100	0.16 ± 0.007				
Vitamin A (mg/dl)	Control	100	0.05 ± 0.0016	0.020	0.001	0.015	0.025
	Patients	100	0.03 ± 0.0017				
Vitamin E (mg/dl)	Control	100	1.003 ± 0.03	0.321	0.001	0.24	0.41
	Patients	100	0.68 ± 0.03				
ESR (mm/1 hr)	Control	100	8.11 ± 0.26	-27.99	0.001	-29.90	-26.09
	Patients	100	36.10 ± 0.93				
Hemoglobin (Hb) (g/dl)	Control	100	11.93 ± 0.15	4.069	0.001	3.66	4.47
	Patients	100	7.86 ± 0.14				
INF-γ (ng/ml)	Control	100	53.38 ± 0.97	-47.417-	0.001	-50.20	-44.63
	Patients	100	100.79 ± 1.03				
CRP (mg/L)	Control	100	4.64 ± 0.13	-15.487-	0.001	-15.97	-14.99
	Patients	100	20.12 ± 0.21				
TNF-α (pg/ml)	Control	100	8.10 ± 0.157	-12.67-	0.001	-13.44	-11.89
	Patients	100	20.95 ± 0.36				
Vitamin C (mg/dl)	Control	100	1.81 ± 0.027	0.732	0.001	0.64	0.825
	Patients	100	1.078 ± 0.037				
Age (years)	Control	100	12.04 ± 0.22	0.020	0.950	-0.60	0.64
	Patients	100	12.02 ± 0.23				
Duration of the disease (months)	Patients	100	12.76 ± 0.75				
Highly significant difference at P-value < 0.01							

These findings imply that UC patients have a high impact of oxidative stress and pro-inflammatory inflammation. Food restriction and the extent of the condition may be exacerbated by vitamin deficiencies, especially in vitamins D and E, which have immunomodulatory functions. In pediatric UC, elevated levels of TNF-α and CRP support their functions as markers of systemic inflammation. Its potential as a new biomarker is further supported by the low CoQ10, which indicates oxidative stress and mitochondrial malfunction.

Table 2 presents the number and percentage of demographic and clinical criteria obtained from patient questionnaires, excluding blood analysis. It reveals no significant difference ($P>$ 0.05) in the gender distribution between males and females when comparing the control group compared to the Patient group, and in the geographical distribution of residence between rural and urban areas in the control group, even though there were 57% of patients lived in rural areas.

Whereas, the percentage of patients who have a family history of illness from mother or father was one third of the number ($P<$ 0.01); besides this, there was a highly significant

elevation ($P< 0.01$) in the no. of patients having left-sided colitis and about 71% with mild clinical remission.

Table 2: Characteristics of the study groups

Assessed factors	Study groups	Sub-groups	No.%	Asymptomatic Significance	Pearson Chi^2 value
Sex	Control	Male	53 %	0.157	2.003
		Female	47 %		
	Patients	Male	43 %		
		Female	57 %		
Home distribution	Control	Rural	50 %	0.321	0.985
		Urbane	50 %		
	Patients	Rural	57 %		
		Urbane	43 %		
Mother history	Patients	Yes	35 %	0.001	200.00
		No	65 %		
Father history	Patients	Yes	38 %	0.001	200.00
		No	62 %		
Disease extent	Patients	Proctitis	20 %	0.001	200.00
		Left sided colitis	49 %		
		Pancolitis	31 %		
Clinical remission	Patients	Mild UC	71 %	0.001	200.00
		Moderate UC	20 %		
		Sever	9 %		

The idea that pediatric UC affects a variety of groups is supported by the absence of residential or sex-based differences. Genetic susceptibility in pediatric UC is highlighted by a strong family history. Mild remission is more common in those patients, which may indicate early identification or a less severe disease profile.

Table 3 shows a significant difference ($P\leq 0.05$) in the mean levels of CoQ10 (P value=0.021), and age (P value= 0.033) among patients categorized by disease extent. Additionally, although there are no statistically significant differences in the duration of the disease, it seems clear that prolonging the duration leads to an increase in the extent of the disease.

Table 3: Mean comparison of analyzed parameters in patients sub-grouped according to the extent of the disease.

Disease extent	Statistics	B12	Vit D	CO Q-10	B-Carot	Vit A	Vit E	ESR	HB	INF-ɣ	CRP	TNF-α	Vit C	Age	Duration
E1 N=20	X± ST.D	217.719±46.65	13.67±4.52	32.127±3.09	0.178±0.08	.036±0.022	0.71±0.28	37.39±8.58	7.75±1.59	102.31±10.84	19.72±1.98	20.92±2.18	0.92±0.34	12.25±2.57	11.9±5.6
E2 N=49	X± ST.D	240.718±56.32	13.015±4.028	32.52±4.91	0.15±0.073	.034±0.0155	0.62±0.29	37.12±10.11	7.74±1.31	99.42±10.06	20.01±2.085	20.76±3.74	1.08±0.34	11.44±2.03	12.7±8.03
E3 N=31	X± ST.D	245.51±62.09	13.097±3.81	29.83±3.75	0.17±0.07	.03±00.015	0.75±0.29	33.66±8.018	8.12±1.4	101.98±10.21	20.56±2.155	20.67±4.12	1.17±0.4	12.77±2.3	13.38±7.7
	F	1.61	0.192	3.99	1.063	0.836	1.98	1.58	0.78	0.86	1.12	0.029	2.90	3.52	0.24
	P-value	0.21	0.83	**0.021***	0.35	0.44	0.14	0.21	0.46	0.42	0.33	0.97	0.06	**0.033***	0.78

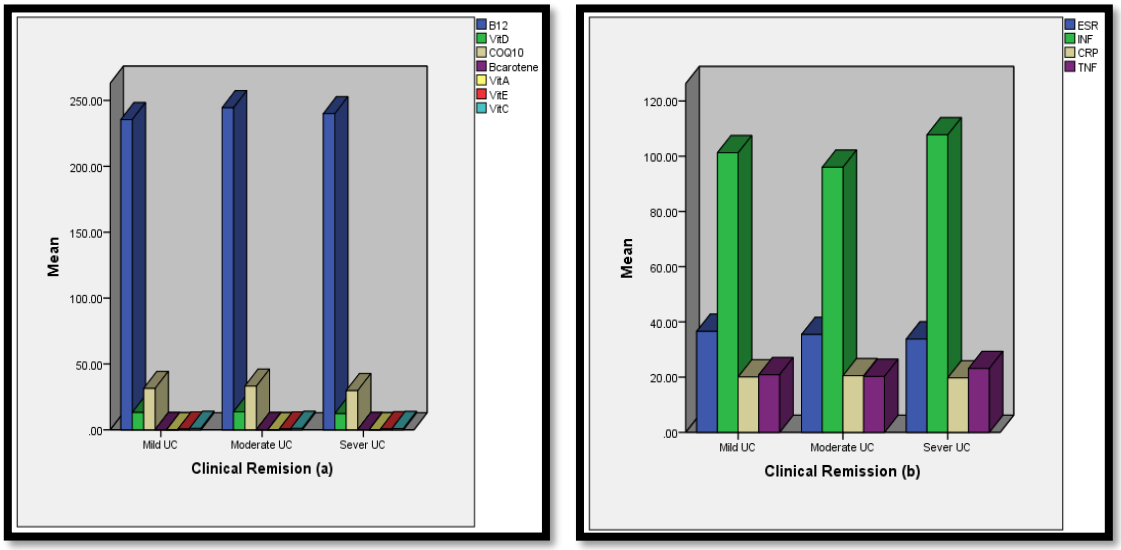
X: mean / ST.D: standard deviation / N: number of patients
E1:Proctitis / E2: Left sided colitis / E3: Pancolitis

F: degree of freedom
*: significance at P ≤ 0.05 level

As illustrated in Table 3, the disease extent was classified into three sub-groups: Proctitis, Left sided colitis and Pancolitis. Significant differences ($P \leq 0.05$) were observed in the mean levels of Co Q10 and the age of patients among the three sub-groups, were the largest mean age appearing in the Pancolitis group. Meanwhile, it was found no significant differences in the mean levels of vitamin D, ESR, CRP, and TNF- α when compared among the different groups.

Antioxidant protections (e.g., CoQ10) decrease with the severity of the disease, presumably as a result of increased oxidative stress and inflammatory process. Age distribution and illness severity are correlated; older children exhibited more widespread disease, suggesting a cumulative load of inflammation.

Figure 1 demonstrates significant differences in the mean levels of INF-γ (*P* value= 0.012) among the sub-groups of clinical remission, that divided into mild, moderate, and severe; the highest mean level appears in severe remission cases.



(a) **(b)**

Figure 1. Mean comparison of (a) Vitamins, (b) Inflammatory biomarkers according to the Clinical Remission.

Table 4 displays a weak but significant correlation ($P \leq 0.05$) among assessed parameters in the Patient group, in which inflammatory factors occupied the forefront, and significant correlations ($P \leq 0.05$) with the rest of the factors.

Table 4: Pearson Correlations among assessed parameters in the ulcerative colitis patients.

Correlated parameters	Pearson Correlations r- value	Significance *P*-value
*Co Q10 * INF-γ*	-0.196-	0.05
*Vitamin A * ESR*	0.228	0.022
*Hemoglobin * CRP*	0.216	0.013
*INF-γ * CRP*	0.232	0.02
*TNF * Duration of the disease*	-0.236-	0.018
*Vitamin C * Age*	0.236	0.018

Correlation is significant at the P≤ 0.05 level.

According to clinical interpretation of these correlations, the negative connection between CoQ10 and INF-γ indicates that CoQ10 has a protective, anti-inflammatory function. The complex character of UC pathophysiology or individual heterogeneity may be reflected in the poor relationships.

Our results indicate no significant differences in the parameter levels of parameters between male and female patients ($P > 0.05$), and no significant $P > 0.05$) were found in all measured parameters in patients having parents' history of UC disease.
Residency distribution of participants shown in Figure 2 were classified into rural and urban; the results of mean comparison of assessed parameters in the patients display significant differences ($P \leq 0.05$) in Co Q10, Vitamin A, and TNF-α (t-test: P value/ -2.18-:0.031; -2.005-:0.049; and 2.09:0.039) consecutively.

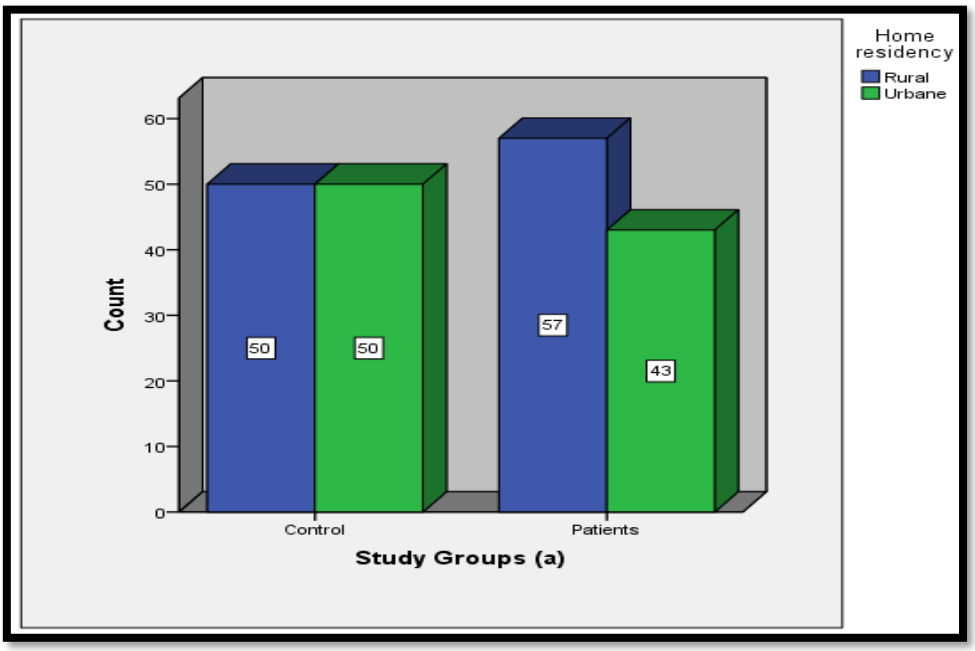


Figure 2: Residence distribution between the study groups.

Table 5 and Figure 3 clearly show the diagnostic ability of inflammatory factors to diagnose Pediatric UC with nearly 100% specificity and 100% sensitivity.

Table 5: ROC of distractors in pediatric ulcerative colitis patients.

Variable(s)	Area	Asymptotic Significance [b]	CUTOFF	Sensitivity	Specificity
ESR	1.000	0.001	17.5	1.00	1.00
INF-γ	1.000	0.001	76.41	1.00	1.00
CRP	1.000	0.001	11.69	1.00	1.00
TNF-α	1.000	0.001	13.365	1.00	1.00

[b]***Null hypothesis: true area = 0.5***

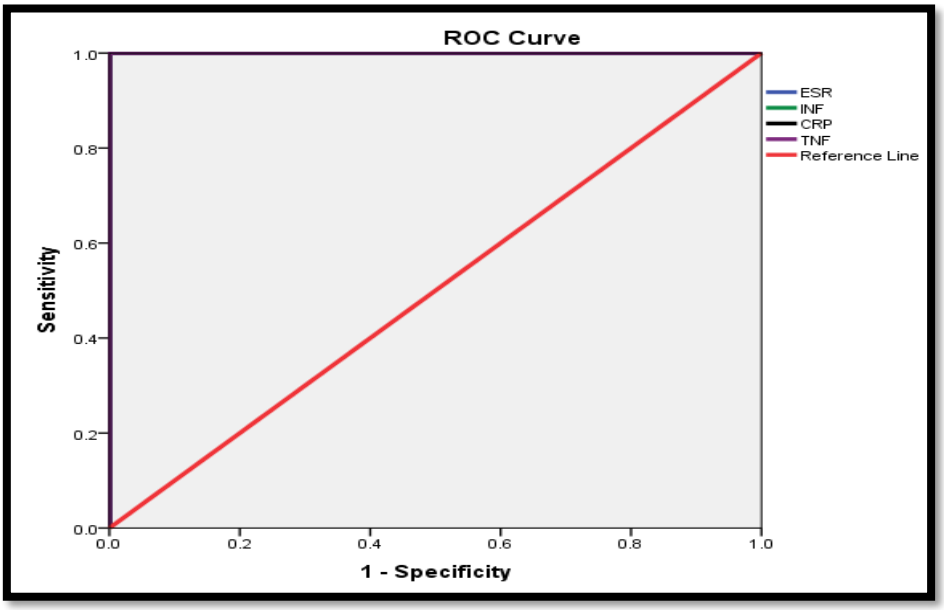


Figure 3: ROC Curve.

To detect pediatric UC, these inflammatory indicators show outstanding discriminatory ability. They are useful as non-invasive substitutes for or supplements to invasive diagnostic procedures like endoscopy because of their excellent sensitivity and specificity. Clinically, this validates their application for illness monitoring, therapy response assessment, and early identification.

4. Discussion

Millions of Americans suffer from inflammatory bowel disorders (IBDs), a group of clinically diverse intestinal conditions that harm the intestinal epithelium [22]. Chronic inflammation in UC patients may contribute to vitamin deficiency by increasing metabolic demands and impairing nutrient absorption. Low hemoglobin levels in UC patients are likely due to chronic gastrointestinal blood loss, leading to iron deficiency anemia [23].

Multiple factors may contribute to vitamin deficiencies in UC patients. Inadequate vitamin consumption, since patients may cut back on their food intake to feel better. Intestinal dysfunction or persistent diarrhea as a cause of malabsorption. Patients with ulcerative colitis (UC) may have chronic inflammation of the large intestine that impacts the gut flora, which is known to generate specific vitamins, including vitamin B. Vitamin absorption mainly takes place in the small intestine, while UC can disrupt gut microbiota, impairing the synthesis and absorption of vitamin B. Additionally, since the large intestine lacks vitamin transporters, this further affects the amount of vitamins that can be absorbed. Furthermore, the excretion of water-soluble vitamins in the urine needs to be taken into account. The elevated need for antioxidants brought on by intestinal inflammation may account for the low vitamin C levels in UC patients [23].

Two of the main risk factors for IBD are inflammation and oxidative stress damage [24]. Potential mechanisms through which vitamin E contributes to the prevention and management of IBD include immune system enhancement, intestinal barrier strengthening and preservation [25], oxidative damage repair, suppression of inflammatory cytokines, gut microbiota modulation, and other pertinent factors [24]. Accordingly, Vitamin E deficiency is often known to be associated with IBD [26].

The pathophysiology of UC has been linked to vitamin D, where active vitamin D (VD3) regulates inflammation in UC through the nucleotide-binding oligomerization domain (NOD)-like receptor protein (NLRP6), which is highly expressed in intestinal tissue and can interfere with the signaling pathway linked to the innate immune response. Since the NLRP6 inflammasome is thought to be crucial for preserving intestinal homeostasis, so, D has been implicated in the pathogenesis of UC. Nucleotide-binding oligomerization domain (NOD)-like receptor protein (NLRP6), which is abundantly expressed in intestinal tissue and can block the innate immune response-related signaling process, is the mechanism by which active Vitamin D (VD3) modulates inflammation in UC. The NLRP6 inflammasome is critical for intestinal homeostasis, and its dysregulation may contribute to UC pathogenesis. Vitamin D modulates this pathway by reducing NLRP6 activity, potentially aiding in UC treatment. VD3-VDReceptor inhibited NLRP6 transcription, which resulted in a reduction in NLRP6 inflammasome activity that made VD3 useful in the treatment of acute UC [27] [28].

Vitamin A and its metabolites, control intestinal inflammation by preserving the immunity and tolerability of the intestinal wall, restoring intestinal inflammation generated by lipopolysaccharides, restoring barrier dysfunction, and lowering the amounts of tight junction proteins. These strategies improved the gut barrier by up regulating the synthesis of short-chain fatty acids, IL-10 expression, and mucins [29].
Vitamin A deficiency causes intestinal inflammation, elevated redox stress and reactive oxygen species levels, unbalanced inflammatory and immune stimulating cytokines, impaired barrier integrity, and disruptions in the gut flora. Due to dietary restrictions limiting the intake of β-carotene-rich foods so its deficiency is more likely in ulcerative colitis, which is linked to health effects due to its activity as provitamin A and antioxidant precursor [30]. Table 4 demonstrates a weak correlation (r=0.228) between Vitamin A and ESR. Our insight into this relationship goes back to the cause (Vitamin A deficiency) and outcomes (elevated ESR) of the inflammatory process; while no direct studies have been conducted on this specific correlation.

In contrast to our results (57% of patients live in rural cities), another study found that the frequency of UC is higher in urban versus rural areas, [31]. This confirms the results reached in this study in terms of the existence of a correlation between CRP and IFN- γ (Table 4), as well as confirming that CRP is a discriminator as listed in Table 5.
CRP release from hepatocyte in response to circulating TNF-α. ESR is a quick and easy to measure changes in the acute phase response caused by plasma levels of protein and hemoglobin in IBD. Therefore, the size, shape, and quantity of erythrocytes, in addition to other confounder variables like age, sex, and anemia, have a significant impact on the ESR [32].
Further understanding of the molecular processes behind UC might be possible through research on the proteins implicated in the pathogenesis of IBD [33].
To manage mild to moderate symptoms or control more severe UC, patients with UC often turn to anti-inflammatory therapies, immunosuppressants, or anti-tumor necrosis factor (TNF) treatment. Alternatively, diminish the pathologic changes through minimizing the levels of pro-inflammatory cytokines (IFN-γ and TNF-α) in serum [34] [35], and this is agreed with our results concerning the significant increased levels of INF-γ and TNF-α, CRP, and ESR in UC patients in comparison to control, and specifically in Table 5 demonstrating the most important distractor factors in pediatric UC which are the inflammatory biomarkers; this could be joined with the expression of NF-κB in colonic tissues that responds to the UC severity and consequently influence TNF-α and induce and regulate the development of body immunity and inflammation [36]. Accordingly, TNF-α plays a crucial role in the

inflammatory events of UC and can impact the decision to use anti-TNF therapy; also, the amounts of IFN-γ, which controls inflammation and immune responses, can be utilized to direct the administration of immunosuppressive medications and predict the seriousness of a disease. ESR is a commonly utilized indicator of systemic inflammation that correlates with disease activity, used to monitor treatment response and to guide the escalation or de-escalation of medication.

The heart, liver, kidney, pancreas, and muscle mitochondria are the main producers of the fat-soluble substance coenzyme Q10 (CoQ10), which is used to make a lot of ATP [37], Table 1 shows the concentration of CoQ10 in patients is highly significant lower than control group ($P<0.001$), and in table 3 the CoQ10 level in Pancolitis has significantly the lowest mean value than other type of disease extent ($P=0.021$). These results suggest that Co-Q10 may have strong anti-oxidant and anti-inflammatory properties, hence protecting against UC [38], and this is clear in the negative correlation between CoQ10 and INF-γ in Table 4. In individuals with mild-to-moderate remission phase, CoQ10 appears to be an effective inflammatory reducer, confirmed in research by Faris F and his colleague [39]. CoQ10 prevents UC in a dose-dependent manner, inhibits inflammatory biomarkers' production, and restores oxidant/antioxidant hemostasis primarily through Nrf2/HO-1 and caspase-3 pathway regulation [40].

In Pancolitis, the more severe type of UC, the body tries to counteract the oxidative damage by releasing a rush of reactive oxygen species, which can reduce antioxidant savings, including CoQ10. By decreasing the efficiency of energy generation and escalating oxidative stress, UC can also affect mitochondrial activity. So, increased oxidative stress and defective mitochondria linked to Pancolitis are probably the causes of the decrease of CoQ10, and its levels might be a useful indicator for determining the severity of the illness, in addition to reducing the level of inflammatory mediators [41] [42].

The clinical importance of inflammatory parameters in Table 5 and Figure 3, and their ability to replace invasive diagnostic methods due to their availability, ease of working with them, giving highly sensitive and specific results in a short and rapid time and not requiring patient preparation before performing the analysis.

Our results in Table 2 and Figure 2 show an elevation in the percentage of patients living in rural residences more to urban living, but this increase was statistically not significant; in addition to 13% of UC patients had both fathers and mothers who were UC diseased.

The hygiene hypothesis has two different aspects:

The first one proposes that exposure of children to enteric pathogens combined with low sanitation in rural settings may increase the incidence of UC, in addition to the strong genetic factors from the father and mother in these areas, where consanguineous marriage is common. On the other hand, the study showed that a significant number of pediatric patients with UC live in urban areas. This may be due to improved sanitation in these areas, less exposure to intestinal pathogens, and increased use of antibiotics, which may lead to an increased susceptibility to developing an inappropriate immune response upon exposure to new antigens (such as gastrointestinal infections) later.

In 80 % of pediatric, UC affects the whole colon, but in some cases it is restricted to left-sided colitis or Proctitis [43]. Our results in Table 3 reveal significant differences ($P < 0.05$) of age among stages of the disease (LSD among left sided colitis [maximum number of children at ages 10-11 years old] and Pancolitis [maximum number of children at ages 12-13 years old]). This might be brought on by environmental risk factors including vitamin D

deficiency, refined foods, high sugars, fats, animal proteins, a low fiber-diet, and stress [44] [45].

Limitations of the research may be due to small sample size and selection bias could occur because all patients were selected from one center, and the study focus on a few inflammatory and biochemical indicators, which may not completely portray the disease's complexity, in addition, the biomarkers' long-term effect were not fully captured by short-term study, also the confounding factors such as food, seasonal fluctuations, and stress have an impact on biomarkers. Addressing these limitations is critical to yield more generalizable and reliable statistical results, which is achieved through:

1. Finding out the number of respondents to poll using a power analysis, and employing statistical methods capable of managing minor sample sizes or/and increasing sample size with follow-up patients over time.
2. Perform a meta-analysis to improve external validity and increase the robustness of the study, in addition to replicating the findings across multiple centers or geographical areas.
3. Lack of longitudinal data and its impact on causal inference: therefore, it is preferable to use cross-sectional data to discuss associations and include direct causality.

Conclusion

This study demonstrates that pediatric UC is linked with measurable abnormalities in biochemical and inflammatory markers, which show strong correlations with disease extent and severity, suggesting their potential value in clinical monitoring.

The clinical significance may arise from deficiency in water and fat-soluble vitamins (except Vitamin B12), which would affect particularly the prognostication, diagnosis, and management of anemia and other vitamin-related disorders.

Conflict of interest

No conflict of interest.

Recommendations

1. Routine assessment of inflammatory biomarkers such as CRP, TNF-α, and INF-γ is recommended for pediatric UC patients.
2. Clinical follow-up techniques should incorporate routine assessment of vitamins and Coenzyme Q10 levels.
3. Specific supplementation with micronutrients, particularly of water and fat soluble vitamins and CoQ10 to avoid hypovitaminosis.
4. Investigation of long-term effects of mitigating micronutrient deficiencies on illness progression, remission maintenance, and quality of life, help guide supplementation strategies.

This study's primary **strengths** were:

1) Thorough assessment of the individuals' fat- and water-soluble vitamins;
2) The unified and well-collected set of samples that were examined using precise laboratory measures;
3) New spectrum tests of various inflammatory factors used in pediatric UC.
4) The conclusive results of deficiency in vitamin levels and clinically significant elevation of inflammatory factors with degrees of sensitivity and specificity of nearly 100%, which qualifies them to be diagnostic biomarkers and as discriminators in different disease extent and clinical remission.

The study's weaknesses is that cause-and-effect linkages should be carefully considered when interpreting the data. In addition to certain confounding factors that linked to the initiation and pathophysiology of UC, among them the genetic vulnerability, environmental variables, intestinal epithelial barrier failure, and dysregulated immune response.

The study's gap is diagnosing UC and determining how inflammatory biomarkers and biochemical factors affect its severity and breadth. Some important aspects are the newly discovered inflammatory biomarkers and the impact of immune system indicators, such as INF-γ, CRP, ESR, and TNF-α, on the extent and severity of UC. Examining unconventional biochemical indicators (such as water-soluble, lipid-soluble vitamins and Coenzyme Q10) in connection to the severity of UC. and evaluating the efficacy of those variables (biochemical and inflammatory markers) for early detection of severe or widespread UC in order to facilitate prompt interventions, in addition to the combinatorial approaches in assessing the diagnostic potential of integrating different indicators to better stratify UC patients according to the severity of their disease in comparison to current standard clinical procedures, this lead to longitudinal monitoring of examining the relationships between changes in the biomarkers and the long-term course of UC, remission periods, and relapse detection in order to potentially develop more individualized treatments.

The clinical importance of the Gap is finding more accurate, reliable, and non-invasive biomarkers; developing more personalized treatment regimens; decreasing the frequency of invasive procedures (such as colonoscopies); and improving patient outcomes are all potential ways to close this knowledge gap and better assess disease activity and predict the progression of UC.
New therapeutic targets and a deeper knowledge of the molecular mechanisms of UC are both aided by scientific progress to lessen the likelihood of major complications and hospitalizations, enhance UC diagnostic methods, and contribute to reduced healthcare costs.

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