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Chitinase 3-Like-1 [CPa9-HNE] and Vit-D levels in Crohn's Disease

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Abstract: Background: Inflammatory Bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract, leading to various symptoms and complications, which includes conditions like Crohn's disease (CD)and ulcerative colitis (UC). These conditions are characterized by periods of active inflammation and remission, leading to a range of symptoms such as abdominal pain, diarrhea, weight loss, and fatigue. A defect in immune response, a product of environmental and genetic factors, are considered central cause to pathogenesis and etiology of IBD[1]

GP39 is a cartilage-specific protein associated with immune responses, predominantly expressed by activated T cells. Its involvement in the pathogenesis of IBD has been demonstrated through studies showing elevated levels of GP39 in the serum of IBD patients compared to healthy controls. Recently established that IBD associated with Vit-D deficiency.

Objectives: The study aimed to address the potential advantages of (HCgp39 and Vit-D) as biomarkers for IBD and its medical treatment.

Methods: The total number of samples collected was 120 samples from all subjects, where 60 samples were collected from patients (D=30 and UC=30)) The study also included collecting 60 samples from healthy subjects as a control group. A (5 mL) blood sample was obtained from every patient as part of the study's protocol. Serum

was separated from by centrifugation for HCgp39 and Vitamin D3 analysis by ELISA.

Results: The results show a decrease in Vit-D3 was indicated in CD and UC patient groups ($P \leq 0.05$), while HCgp38 levels were non-changed significantly in patient groups compared to control subjects, ($P > 0.05$).

Conclusions: In conclusion, the results suggests that serum decreased Vit- D correlated well with disease activity in both CD and UC. Targeting Vit-D3 could present a novel approach to regulate metabolic pathways and modulate immune responses, potentially providing new avenues for drug development and personalized treatment strategies for individuals with IBD

Key words: (Inflammatory Bowel disease), (Crohn's disease), (Ulcerative colitis), Vitamin D, HCgp39.

1. Introduction

Inflammatory Bowel disease is characterized by chronic inflammation of the gastrointestinal tract, leading to various symptoms and complications, which includes conditions like Crohn's disease (CD)and ulcerative colitis (UC). These conditions are characterized by periods of active inflammation and remission, resulting in symptoms such as stomach pain, diarrhea, and weight loss, and fatigue. A defect in immune response, a product of environmental and genetic factors, are considered central cause to pathogenesis and etiology of IBD.[2]

Altered metabolism and energy production are known to occur in inflamed tissues, including the intestines of individuals with IBD. Pyruvate kinase M2 (PKM2) is a key glycolytic enzyme that is complicated in several cellular functions including apoptosis. PKM2 expression is up-regulated in patients with CD, representing its potential part in the pathophysiology of the disease.[3]

Calprotectin is a protein that embraces about 45% of neutrophil cytosolic proteins. It is elaborate in the employment of leukocytes and has antimicrobial activity aganist pathogens. Augmented serum calprotectin levels are a known biochemical pointer of intestinal provocation and it is presently the most commonly used biomarker of provocation in (IBD). GP39 is a cartilage-specific protein associated with immune responses, predominantly expressed by activated T cells. Its involvement in the pathogenesis of IBD has been demonstrated through studies showing elevated levels of GP39 in the serum of IBD patients compared to healthy controls. Recently established that IBD associated with Vit-D deficiency.[4]

Serum PMK2 and CALP levels with decreased Vit- D correlated well with disease activity in both CD and UC. PMK2 and CALP high levels are indicative of active inflammation, therefore Understanding the PKM2 and CALP -IBD correlation offers promising opportunities for therapeutic interventions. Targeting of these biomarkers with Vit-D3 could present a novel approach to regulate

metabolic pathways and modulate immune responses, potentially providing new avenues for drug development and personalized treatment strategies for individuals with IBD

Chitinase-3-like protein 1 or human cartilage Glycoprotein 39 (HC gp-39) is a protein that is mainly produced by chondrocytes and synoviocytes. It is a associated with inflammatory bowel disease (IBD) and may be served as useful disease marker in IBD.[5]

Several studies have indicated that patients with IBD have lower levels of vitamin D, especially during periods of increased disease activity, suggesting a potential influence of vitamin D on IBD. However, it is crucial to take into account the idea of reverse causality, as intestinal inflammation has been observed to decrease Vitamin D levels. As a result, these studies have not conclusively determined when (Vitamin D) Insufficiency is a reason or a consequence of (IBD) in Individuals, and the interpretation of these findings is somewhat constrained. Inflammatory bowel disease continues to be a significant global health concern with increasing prevalence and incidence rates.[6], [7]

The study aimed to identify biochemical markers for IBD diagnosis and prediction, these advancements will play a pivotal role in the development of more effective prevention and treatment strategies.

2. Materials and Methods

2.1 Subjects

The total number of samples collected was 120 samples from all subjects, where 60 samples were collected from patients (CD=30 and UC=30) whose ages ranged from 25 to 55 years, their mean age was (31.27 +13.4) The study also included collecting 60 samples from healthy subjects as a control group, their ages ranged from 25 to 55 years, their mean age was (34.625 +14.32yr). Participants were recruited for this study during the period from December 2022 to Aprile2023 at the hospital in Baghdad province, Iraq. Moreover, knowledgeable agreement was gotten from all study contributors prior to sample gathering. General data were recorded from the patients, including age, gender, family history as. All laboratory investigations were achieved in the laboratory Hospital and clinical biochemistry laboratory research at The College of Medicine, University of Al-Qadisiyah Iraq

The Study comprising blood sample collection and experimental procedures was permitted by The ethical committee of the Gastroenterology and Hepatology Teaching – Hospital of medical city – Baghdad and the College of Medicine, university of Al-Qadisiyah, Iraq,Informed consent was obtained from all participants before sample collection.

2.2 Methods

Blood samples (5 mL) were collected from all research groups. 2 mL of blood was deposited in EDTA Vacationer tubes. The neutrophils/lymphocytes and hemoglobin ratio were determined using the CBC hematology analyzer. Serum was extracted from the remaining 3 mL of blood clot for 30 min by centrifugation at (4000 Rpm) for 15- 20 Minutes at (4°C). Enzyme-linked immunosorbent assay (ELISA) measurements were used for, PCK2, CALP, GP38 and Vitamin D.

2.3 Statistical analysis

The information was provided as means ± standard deviation of the mean (SD). SPSS version 23, a statistical software package typically used in the social sciences, was used for the statistical study. The Chi-square test was used to analyse differences between groups, and quantitative measurements were reported as numbers and percentages. The Andersen-Darling test was used to determine the data's

normality. To see if there were any significant differences between the control and experimental groups, the Student's t-test was achieved. To compare important variances among several subjects, a one-way analysis of variance (ANOVA) was performed, followed by a post hoc analysis using Tukey's test. A level of $P \leq 0.05$ was considered statistically significant for all analyses.

3. Results

3.1 General description of the studied groups

120 recruitments classified as three groups, the first group: patients **with Crohn's disease** about (40 patients) they were n=21 males mean ± SD (28±11.47yr) and n=19 female (34±14.74yr), The second group: patients with **ulcerative colitis** (40 patients) they were(n= 21 males with (28±11.47yr) and(n= 19 females with age 34±14.74 yr), the third group include 40 **healthy subjects** they were (n=19 males with age 37±14.69yr) and (n=21 females with age 32±13.99yr) (Table .1 and.2).

{A Chi2 test} was performed between Status and Sex. All predictable cell frequencies were greater than 5, thus the conventions for(the Chi2 test) were met. There was no statistically noteworthy relationship concerning Status and Sex, $\chi^2(2) = 0.27$, p = .875, (Cramer's V) = 0.05.

Non-significant changes were observed in mean age of all patient groups compared to control

3.2 Neutrophils%, lymphocytes%, NLR and Hb in CD, UC and controls

The %Neutrophils in patients with CD show high value (M = 69.29, SD = 7.68), while in patients with UC the Neutrophils (M = 62.38, SD = 6.26), and the lowest represented in healthy group (M = 51.29, SD=2.63). for the Lymphocytes as a marker there is no big difference between the means of the studied group, where patients with CD, UC (M = 2.43, SD = 0.36), (M = 2.23, SD = 0.27) and for the healthy group (M = 2.23, SD = 0.24). Patients with CD the Hb has (M = 13.27, SD = 1.33), and for UC patients (M=11.54, SD = 1.95), at last the healthy group has Hb mean (M = 12.26, SD = 2.03).

ANOVA shows a significant difference between the categorical variable Groups (CD – UC – Con) and the metric variable %**Neutrophils,** (*P* = <0.001), while no significant change was observed in %**Lymphocytes, (***P* = 0.369), and and Hb(*P*= 0.321)Table (4)

3.3 Serum HCgp39 and Vitamin D levels in CD, UC and Control groups

In CD patients GP39 levels shoed intermediate concentrations (Mean = 2.14, SD = 0.19), while in healthy groups show low value with (Mean = 2.08, SD = 0.3). in UC patients GP39 show highest concentrations (Mean = 2.14, SD = 0.19). Vit-D3 levels were significantly decreased in CD and UC compared to control (Table 5).

4. Discussion

4.1 Demographic characteristic of patients with IBD

IBD is a group of Chronic provocative conditions of the Digestive tract, primarily comprising (CD) and (UC).[8] The result showed non-significant change in mean age between patient groups and control (P >0.05) IBD can develop at any age, but it often starts in young adulthood. Both CD and UC tend to be Identified in people amongst the ages of(15 and 35), although they can happen at Any age, including childhood and later adulthood.

IBD affects both sexes, but there are some differences. Historically, UC has been found to affect men and women equally, while CD has shown a slight predominance in women. However, the gender distribution may vary in different populations. In agreement with this, the present data showed non-significant changes in sex associated with CD and UC pathogenesis (P>0.05).[9], [10]

4.2 Demographic characteristic of patients with IBD

IBD is a group of chronic provocative conditions of the digestive tract, primarily comprising CD and UC.[11] The result showed non-significant change in mean age between patient groups and control (P >0.05) IBD can develop at any age, but it often starts in young adulthood. Both CD and UC tend to be identified in people amongst the ages of 15 and 35, although they can happen at any age, including childhood and later adulthood.

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4.3 The neutrophil, lymphocytes counts and NLR in IBD

The correlation between neutrophils and IBD, including CD and UC, is a subject of interest in medical research. Neutrophils are a kind of WBCs that plays a crucial role in the body's immune reaction to infections and provocation. In IBD, neutrophils are involved in the inflammatory process within the gastrointestinal tract. A significant difference between the categorical variable Groups (CD – UC – Cont) and the metric variable %Neutrophils, (P <0.001).

For the %Neutrophils patients with CD disease have a higher %Neutrophils (and patients with UC tends to be the same compared to the healthy subjects.

By ROC test the area under curve of which is about 86.9%, indicate that's the Neutrophils% test is a good indicator to determine an inflammation status in patients with IBD, p value <0.05 and cutoff value 67 at which IBD disease is diagnosed, the highest Sensitivity about 0.7 and specificity 0.87, the CI 95% (0.802 – 0.936).

These results relay by other studies, [12]–[13] that act as the same opinion about the role of %neutrophils in disease status. Here are some key points regarding the correlation between neutrophils and CD and UC:

Neutrophil Infiltration In both CD and UC, mean there is an penetration of neutrophils into the reddened gastrointestinal mucosa. The presence of neutrophils is an indicator of active inflammation.[14]

Neutrophil Activated neutrophils release various inflammatory mediators and enzymes that contribute to tissue damage and inflammation in the gut.

And for the histological Evaluation Neutrophil infiltration is a prominent feature seen on histological examination of biopsy samples taken from inflamed areas of the gut in both CD and UC.[15], [16],

The degree of neutrophil infiltration and activation correlates with the severity of inflammation and disease activity in both conditions.[17]

It's important to note that while neutrophils are associated with inflammation in IBD, they are not specific to CD or UC.[18] The two conditions have distinct patterns of inflammation and may involve different regions of the gastrointestinal tract. Therefore, other clinical and diagnostic parameters are essential for differentiating between CD and UC.

Neutrophils are just one aspect of the complex immune response seen in Crohn's disease and Ulcerative Colitis. The pathogenesis of IBD involves a combination of genetic, environmental, and immune-related factors.18], [19]

The correlation between lymphocytes and inflammatory bowel diseases (IBD), including CD and UC, is a subject of interest in medical research. Lymphocytes are a type of white blood cell that plays a crucial role in the body's immune response. In IBD, lymphocytes are involved in the immune-mediated inflammation of the gastrointestinal tract.[20]

ANOVA shows a significant difference between the categorical variable Groups (CD – UC – Con) and the metric variable %**Lymphocytes, (***P* = 0.003). with %Lymphocytes, where patients with CD and UC show higher levels of Lymphocytes, compared with healthy.

In both CD and UC, there is an infiltration of lymphocytes into the inflamed gastrointestinal mucosa. The presence of lymphocytes is an indicator of ongoing inflammation. Lymphocytes, especially T-cells, play a significant role in orchestrating the immune response in IBD. Dysregulation of the immune system, particularly an imbalance between pro-inflammatory and anti-inflammatory lymphocytes, is thought to contribute to the development and perpetuation of IBD.[21]

Lymphocyte infiltration is a characteristic histological feature seen on biopsy samples taken from inflamed areas of the gut in both CD and UC. Lymphocytes secrete various cytokines and chemokines that contribute to the inflammatory process in IBD.[22]

It's important to note that while lymphocytes are associated with inflammation in IBD, they are not specific to CD or UC. Both conditions involve immune-mediated inflammation of the gastrointestinal tract, and the specific pattern and distribution of lymphocyte involvement may differ between CD and UC.[23]

4.4 Chitinase-3-like protein 1 (CHI3L1), HC Gp39 levels in IBD

YKL-40 is a 40-kDa heparin-and-chitin binding-glycoprotein and also known as [Chitinase-3-like protein 1] (CHI3L1) a(38-kDa heparin-binding glycoprotein or human tendon glycoprotein 39 (HC gp-39) A link between and HCgp38 and of IBD severity on the can be contributed to fibrosis and provocation throughout the normal course of IBD.24] The outcomes presented none important changes in HCgp39 levels in individuals with CD and UC compare to control (*P*>0.05). these results are consistent with Zhao T. study, who found a similar outcome, showing HCgp39 levels was only augmented in IBD individuals with arthritis, IBD individuals without arthritis presented no variance from control subject. [25]Amongst the peptides resulting from YKL-40, the human cartilage glycoprotein-39 level was raised in IBD. [26] Studies described rised levels of YKL-40 related to the activity of the illness.[27], [28] In cooperation CD and UC, the YKL-40 levels were significantly associated with C-reactive protein level and illness action.[29] In CD, YKL-40levels was revealed advanced in individuals with intestinal attacks than in those without abdominal attacks.[30] Volkers et al. found that YKL-40 levels are rised in 40-50% of UC and CD individuals when disease in active form, and the level was also rised in 30% of individuals with CD which is clinically inactive.[31]

4.5 Vitamin D levels in IBD

Before going studies have found low[vitamin D] levels to be associated with increased IBD severity Vitamin D deficiency has since been shown to influence Pathogenesis of Autoimmune disorders.[32], [33] A studies and epidemiologic data suggest that the same relationship exists in IBD, However, unlike other non-gastrointestinal autoimmune disorders, IBD can itself reduce vitamin D levels due to malabsorption.[34]–[35] currently research showed significant decrease in the Vit-D3 levels in CD and UC compared to control (P <0.05). the presence of CD may have contributed to lower vitamin D levels. IBD – Particularly active illness can result in vitamin D malabsorption and, as a result, low vitamin D levels. VDR-knockout IBD mouse models developed more severe colitis than wild-type mice, although exogenous treatment of vitamin D or an equivalent VDR agonist alleviated symptoms..[36] In humans, a large retrospective study of 403 CD and 101 UC patients found that vitamin D deficiency was associated with increased disease activity and decreased quality of life in (CD), but not (UC).[37] A study of UC patients found that vitamin D-deficient patients were significantly more likely than vitamin D-sufficient patients to have active disease and be on corticosteroid therapy.[38] Another study involving CD patients and age - sex matched controls similarly found lower vitamin D levels among CD patients and these levels were inversely correlated with disease activity, The largest randomized trial of vitamin D as a treatment for CD involved 94 participants and found no significant difference in clinical relapse rates, although there was a trend toward statistical significance (P = 0.06). Alternatively, vitamin D may not lie along the causal pathway of CD pathogenesis, but exists as a confounder influenced by inflammation.[39]

5. Acknowledgements

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6. Tables

TABLE 1:EFFECT OF STATUS ON THE STUDIED GROUPS

Groups	Sex		Chi^2	P – value
	m	f		
CD	21	19	0.27	0.875
Con.	19	21		
UC	21	19		

TABLE 2:MEAN AGE OF THE STUDIED GROUPS

Parameter		sex	Frequency	Mean	SD	Minimum	Maximum
Age	CD	m	21	28	11.47	14	55
		f	19	34	14.74	17	65
	Con	m	19	37	14.69	12	74
		f	21	32.48	13.99	17	73

	UC	m	21	28	11.47	14	55
		f	19	34	14.74	17	65

Table 3:The % neutrophils, %lymphocytes and Hb in patient with CD, UC and control groups the data are presented as mean ± SD

Parameter	Groups	CD	Con	UC
	Frequency	40	40	40
ESR	Mean	41.18	29	35.83
	Std. Deviation	22.18	20.58	17.73
	Minimum	15	3	10
	Maximum	121	82	84
CRP	Mean	57.68	0.6	49.03
	Std. Deviation	8.53	0.45	12.3
	Minimum	41	0.1	28
	Maximum	72	2.1	66
%Neutrophils	Mean	69.29	51.29	62.38
	Std. Deviation	7.68	2.63	6.26
	Minimum	52	46.8	50
	Maximum	78	56.3	76
%Lymphocytes	Mean	2.43	2.23	2.23
	Std. Deviation	0.36	0.24	0.27
	Minimum	1.82	1.7	1.78
	Maximum	2.9	2.6	2.8
NLR	Mean	29.14	23.29	28.16
	Std. Deviation	5.23	2.8	4.4
	Minimum	17.92	19.71	21.15
	Maximum	40.50	28.17	39.03
Hb	Mean	13.27	12.26	11.54
	Std. Deviation	1.33	2.03	1.95
	Minimum	9.7	8.1	8.2
	Maximum	15.2	15.3	15.1

TABLE 4:ONE WAY ANOVA COMPARING MEANS OF % NEUTROPHILS AND %LYMPHOCYTES BETWEEN THE CATEGORICAL VARIABLE GROUPS (CD – UC – CON)

	Mean ± SD			
Parameter	**UC (N = 40)**	**Ctrl (N = 40)**	**Cons (N = 40)**	***P* - value**
%Neutrophils	62.38 ± 6.26***	51.29 ± 2.63	69.29 ± 7.68***	<0.001
%Lymphocytes	2.25 ± 0.27	2.23 ± 0.24	2.43 ± 0.36	0.369 NS
Hb	11.54±1.95	12.26± 2.03	13.27± 1.33	0.321 NS

*P<0.05, **P<0.01, ***P<0.001, NS non-significant

TABLE 5:THE (MEAN ± SD) OF HCGP39 AND VITD, IN THE CATEGORICAL VARIABLE GROUPS (CD – UC – CON)

		Status		
		CD	**Con**	**UC**
HCgp39 (pg/ml)	Mean	2.14	2.08	2.14
	Std. Deviation	0.19	0.3	0.19
	Minimum	1.44	1.01	1.44
	Maximum	2.5	2.6	2.5
	Maximum	6.4	1.28	7.5
Vit-D3 (ng/ml)	Mean	20.34	38.16	11.67
	Std. Deviation	3.5	4.23	2.13
	Minimum	7.23	34.78	10.2
	Maximum	40.31	66.87	35.4

References

1. M. Friedrich *et al.*, "IL-1-driven stromal–neutrophil interactions define a subset of patients with inflammatory bowel disease that does not respond to therapies," *Nat Med*, vol. 27, no. 11, pp. 1970–1981, 2021.
2. C. He et al., "View from the Biological Property: Insight into the Functional Diversity and Complexity of the Gut Mucus," Int J Mol Sci, vol. 24, no. 4, p. 4227, 2023.
3. A. A. Almousa, M. Morris, S. Fowler, J. Jones, and J. Alcorn, "Elevation of serum pyruvate kinase M2 (PKM2) in IBD and its relationship to IBD indices," Clin Biochem, vol. 53, pp. 19–24, 2018.

4. M. Henriksen et al., “C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study,” Gut, vol. 57, no. 11, pp. 1518–1523, 2008.
5. S. S. C. Ho, J. I. Keenan, and A. S. Day, “Urinary chitinase 3-like 1 and intestinal fatty-acid binding proteins are not elevated in children with inflammatory bowel disease,” Intest Res, vol. 20, no. 4, pp. 509–513, 2022.
6. J. Fletcher, S. C. Cooper, S. Ghosh, and M. Hewison, “The role of vitamin D in inflammatory bowel disease: mechanism to management,” Nutrients, vol. 11, no. 5, p. 1019, 2019.
7. J. Gubatan and A. C. Moss, “Vitamin D in inflammatory bowel disease: more than just a supplement,” Curr Opin Gastroenterol, vol. 34, no. 4, pp. 217–225, 2018.
8. S. Flynn and S. Eisenstein, “Inflammatory bowel disease presentation and diagnosis,” Surgical Clinics, vol. 99, no. 6, pp. 1051–1062, 2019.
9. G. G. Kaplan and J. W. Windsor, “The four epidemiological stages in the global evolution of inflammatory bowel disease,” Nat Rev Gastroenterol Hepatol, vol. 18, no. 1, pp. 56–66, 2021.
10. A. N. Ananthakrishnan, T. Donaldson, K. Lasch, and V. Yajnik, “Management of inflammatory bowel disease in the elderly patient: challenges and opportunities,” Inflamm Bowel Dis, vol. 23, no. 6, pp. 882–893, 2017.
11. S. Flynn and S. Eisenstein, “Inflammatory bowel disease presentation and diagnosis,” Surgical Clinics, vol. 99, no. 6, pp. 1051–1062, 2019.
12. E. Benvenuti, A. Pierini, E. Gori, C. Lucarelli, G. Lubas, and V. Marchetti, “Neutrophil-to-lymphocyte ratio (NLR) in canine inflammatory bowel disease (IBD),” Vet Sci, vol. 7, no. 3, p. 141, 2020.
13. B. O. Langley, S. E. Guedry, J. Z. Goldenberg, D. A. Hanes, J. A. Beardsley, and J. J. Ryan, “Inflammatory Bowel Disease and Neutrophil–Lymphocyte Ratio: A Systematic Scoping Review,” J Clin Med, vol. 10, no. 18, p. 4219, 2021.
14. S. Saraiva et al., “Evaluation of fatigue in inflammatory bowel disease-a useful tool in daily practice,” Scand J Gastroenterol, vol. 54, no. 4, pp. 465–470, 2019.
15. B. O. Langley, S. E. Guedry, J. Z. Goldenberg, D. A. Hanes, J. A. Beardsley, and J. J. Ryan, “Inflammatory Bowel Disease and Neutrophil–Lymphocyte Ratio: A Systematic Scoping Review,” J Clin Med, vol. 10, no. 18, p. 4219, 2021.
16. B. O. Langley, S. E. Guedry, J. Z. Goldenberg, D. A. Hanes, J. A. Beardsley, and J. J. Ryan, “Inflammatory Bowel Disease and Neutrophil–Lymphocyte Ratio: A Systematic Scoping Review,” J Clin Med, vol. 10, no. 18, p. 4219, 2021.
17. H. Chen, X. Wu, C. Xu, J. Lin, and Z. Liu, “Dichotomous roles of neutrophils in modulating pathogenic and repair processes of inflammatory bowel diseases,” Precis Clin Med, vol. 4, no. 4, pp. 246–257, 2021.
18. G. Wang et al., “Human umbilical cord mesenchymal stem cells alleviate inflammatory bowel disease by inhibiting ERK phosphorylation in neutrophils,” Inflammopharmacology, vol. 28, pp. 603–616, 2020.
19. M. Friedrich et al., “IL-1-driven stromal–neutrophil interactions define a subset of patients with inflammatory bowel disease that does not respond to therapies,” Nat Med, vol. 27, no. 11, pp. 1970–1981, 2021.

20. P. Giuffrida, G. R. Corazza, and A. Di Sabatino, “Old and new lymphocyte players in inflammatory bowel disease,” Dig Dis Sci, vol. 63, pp. 277–288, 2018.
21. A. Kaur and P. Goggolidou, “Ulcerative colitis: understanding its cellular pathology could provide insights into novel therapies,” J Inflamm, vol. 17, pp. 1–8, 2020.
22. X. Zhang et al., “Blockade of IDO-kynurenine-AhR axis ameliorated colitis-associated colon cancer via inhibiting immune tolerance,” Cell Mol Gastroenterol Hepatol, vol. 12, no. 4, pp. 1179–1199, 2021.
23. A. Maoz, M. Dennis, and J. K. Greenson, “The Crohn’s-like lymphoid reaction to colorectal cancer-tertiary lymphoid structures with immunologic and potentially therapeutic relevance in colorectal cancer,” Front Immunol, vol. 10, p. 1884, 2019.
24. U. Roesler et al., “Identification of Chitinase-3-Like Protein 1 as a Novel Neutrophil Antigenic Target in Crohn’s,” J Crohns Colitis, vol. 894, p. 904, 2019.
25. T. Zhao, Z. Su, Y. Li, X. Zhang, and Q. You, “Chitinase-3 like-protein-1 function and its role in diseases,” Signal Transduct Target Ther, vol. 5, no. 1, p. 201, 2020.
26. C. Deutschmann et al., “Identification of chitinase-3-like protein 1 as a novel neutrophil antigenic target in Crohn’s disease,” J Crohns Colitis, vol. 13, no. 7, pp. 894–904, 2019.
27. P. Chen et al., “Serum biomarkers for inflammatory bowel disease,” Front Med (Lausanne), vol. 7, p. 123, 2020.
28. A. Jankowska-Konsur, Ł. Magdalena, K. Rubas, D. Nowicka-Suszko, M. A. J. Joanna, and J. C. Szepietowski, “Chitinase-3-like protein 1 (YKL-40): a new biomarker of inflammation in pyoderma gangrenosum,” Acta Derm Venereol, vol. 102, 2022.
29. S. S. C. Ho, J. I. Keenan, and A. S. Day, “Urinary chitinase 3-like 1 and intestinal fatty-acid binding proteins are not elevated in children with inflammatory bowel disease,” Intest Res, vol. 20, no. 4, pp. 509–513, 2022.
30. C. Douadi et al., “Anti-TNF agents restrict Adherent-invasive Escherichia coli replication within macrophages through modulation of Chitinase 3-like 1 in patients with Crohn’s disease,” J Crohns Colitis, vol. 16, no. 7, pp. 1140–1150, 2022.
31. A. G. Volkers et al., “Fecal Calprotectin, Chitinase 3-Like-1, S100A12 and Osteoprotegerin as Markers of Disease Activity in Children with Crohn’s Disease,” Gastrointestinal Disorders, vol. 4, no. 3, pp. 180–189, 2022.
32. J. Gubatan and A. C. Moss, “Vitamin D in inflammatory bowel disease: more than just a supplement,” Curr Opin Gastroenterol, vol. 34, no. 4, pp. 217–225, 2018.
33. J. Gubatan, N. D. Chou, O. H. Nielsen, and A. C. Moss, “Systematic review with meta-analysis: association of vitamin D status with clinical outcomes in adult patients with inflammatory bowel disease,” Aliment Pharmacol Ther, vol. 50, no. 11–12, pp. 1146–1158, 2019.
34. J. H. White, “Vitamin D deficiency and the pathogenesis of Crohn’s disease,” J Steroid Biochem Mol Biol, vol. 175, pp. 23–28, 2018.
35. J. Lund-Nielsen, S. Vedel-Krogh, C. J. Kobylecki, J. Brynskov, S. Afzal, and B. G. Nordestgaard, “Vitamin D and inflammatory bowel disease: Mendelian randomization analyses in the Copenhagen studies and UK Biobank,” J Clin Endocrinol Metab, vol. 103, no. 9, pp. 3267–3277, 2018.

36. S.-A. Tabatabaeizadeh, N. Tafazoli, G. A. Ferns, A. Avan, and M. Ghayour-Mobarhan, “Vitamin D, the gut microbiome and inflammatory bowel disease,” J Res Med Sci, vol. 23, 2018.
37. S. O. Frigstad et al., “Vitamin D deficiency in inflammatory bowel disease: prevalence and predictors in a Norwegian outpatient population,” Scand J Gastroenterol, vol. 52, no. 1, pp. 100–106, 2017.
38. D. Caviezel, S. Maissen, J. H. Niess, C. Kiss, and P. Hruz, “High prevalence of vitamin D deficiency among patients with inflammatory bowel disease,” Inflamm Intest Dis, vol. 2, no. 4, pp. 200–210, 2018.
39. P. López-Muñoz, B. Beltrán, E. Sáez-González, A. Alba, P. Nos, and M. Iborra, “Influence of vitamin D deficiency on inflammatory markers and clinical disease activity in IBD patients,” Nutrients, vol. 11, no. 5, p. 1059, 2019.