Annals of Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iann20

Inflammatory biomarkers and psychological variables to assess quality of life in patients with inflammatory bowel disease: a cross-sectional study

Rafael González-Moret, Ausias Cebolla-Martí, Isabel Almodóvar-Fernández, Jaime Navarrete, Ángeles García-Esparza, José M. Soria & Juan F. Lisón

To cite this article: Rafael González-Moret, Ausias Cebolla-Martí, Isabel Almodóvar-Fernández, Jaime Navarrete, Ángeles García-Esparza, José M. Soria & Juan F. Lisón (2024) Inflammatory biomarkers and psychological variables to assess quality of life in patients with inflammatory bowel disease: a cross-sectional study, Annals of Medicine, 56:1, 2357738, DOI: 10.1080/07853890.2024.2357738

To link to this article: https://doi.org/10.1080/07853890.2024.2357738

Published online: 31 May 2024.

ANNALS OF MEDICINE
2024, VOL. 56, NO. 1, 2357738
https://doi.org/10.1080/07853890.2024.2357738

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Inflammatory biomarkers and psychological variables to assess quality of life in patients with inflammatory bowel disease: a cross-sectional study

Rafael González-Moret[a], Ausias Cebolla-Martí[b,c], Isabel Almodóvar-Fernández[d], Jaime Navarrete[e,f], Ángeles García-Esparza[g], José M. Soria[h,i] and Juan F. Lisón[c,h,i]

[a]Department of Nursing and Physiotherapy, Faculty of Health Sciences, University CEU-Cardenal Herrera, CEU Universities, Valencia, Spain; [b]Department of Psychology, Universidad de Valencia, Valencia, Spain; [c]Centre of Physiopathology of Obesity and Nutrition (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain; [d]Nursing Pre-departmental Unit, Universitat Jaume I, Castellón, Spain; [e]Teaching, Research & Innovation Unit, Parc Sanitari Sant Joan de Déu, Barcelona, Spain; [f]CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain; [g]Department of Pharmacy, Faculty of Health Sciences, University CEU-Cardenal Herrera, CEU Universities, Valencia, Spain; [h]Departament of Biomedical Science, Faculty of Health Sciences, University CEU-Cardenal Herrera, CEU Universities, Valencia, Spain; [i]Institute of Biomedical Sciences, University CEU-Cardenal Herrera, CEU Universities, Valencia, Spain

ABSTRACT

Background: Inflammatory bowel disease (IBD) is a chronic gastrointestinal condition. While inflammatory biomarkers are valuable for diagnosing and monitoring the disease, their correlation with patients' quality of life (QoL) is not well-established.

Purpose: This study aims to investigate the correlations between inflammatory biomarkers and the quality of life (QoL) variables of individuals diagnosed with IBD in clinical remission.

Methods: The sample of this cross-sectional study included 74 patients (80% women; 45 ± 11 years old) diagnosed with IBD. Outcome variables included faecal calprotectin (FC), C-reactive protein (CRP), cortisol levels from hair samples, and anxiety and depression assessed using the Hospital Anxiety and Depression Scale (HADS-A and HADS-D, respectively), alongside QoL evaluated with the Inflammatory Bowel Disease Questionnaire 32 (IBDQ-32). Bivariate correlations were calculated using the Pearson correlation coefficient, and stepwise linear regression analyses were conducted to identify independent factors contributing to IBDQ-32 scores.

Results: The IBDQ-32 did not significantly correlate with any biomarkers. However, it exhibited a large and statistically significant negative correlation with HADS-A ($r = -0.651$) and HADS-D ($r = -0.611$) scores ($p < 0.001$). Stepwise linear regression analyses indicated that HADS-A was a significant and independent predictor for IBDQ-32 scores (Adjusted $R^2 = 0.41$, $\beta = -0.65$, $p < 0.001$).

Conclusions: Inflammatory markers such as CRP, FC, or cortisol in hair do not play a decisive role in assessing the QoL of IBD patients. These findings emphasize the significance of considering psychological factors in evaluating and managing QoL in IBD patients in order to identify severity, suggesting that instruments like HADS should be integral to comprehensive patient assessments.

ARTICLE HISTORY
Received 23 February 2024
Revised 29 April 2024
Accepted 30 April 2024

KEYWORDS
Inflammatory bowel disease; quality of life; biomarkers; anxiety; depression

Introduction

Inflammatory bowel disease (IBD) is a chronic disease of unknown aetiology comprising ulcerative colitis (UC) and Crohn's disease (CD). People affected by IBD usually have disease flare ups in which digestive ulcers and damage to the intestinal mucosa occur. Thus, it has been widely described those patients with IBD present periods of activation of symptoms and periods of remission. This may be because of the sum of predisposing genetic and environmental factors such as diet, tobacco use, or stress at any given time [1,2]. Biomarkers such as C-reactive protein (CRP), faecal calprotectin (FC), or cortisol have been used to monitor inflammatory processes [3] and have proven very useful for diagnosing and monitoring IBD [4,5].

However, while these biomarkers offer insight into inflammatory activity, their direct correlation with patient-reported outcomes, particularly quality of life (QoL), remains nuanced [6,7]. Remarkably, no study to date has comprehensively explored the relationship between these biomarkers and QoL in the context of IBD.

CONTACT José Miguel Soria López jose.soria@uchceu.es Department of Biomedical Sciences, Universidad CEU Cardenal Herrera – Campus Elche, Plaza Reyes católicos, 19, 03204, Elche, Alicante, Spain.

Beyond the physiological manifestations of digestive ulcers, mounting evidence underscores the profound impact of IBD on mental health, with a substantial proportion of patients experiencing comorbid conditions such as anxiety and depression [8–11]. Notably, poor mental health has been consistently linked to disease severity among IBD patients [12–16].

For instance, recent research highlights the mediating role of psychological distress in exacerbating Crohn's disease activity in response to stressful life events [11]. In this context, one plausible psychological construct influencing symptom severity is somatization, defined as distress stemming from somatic symptoms [17].

Given this context, our study aims to uncover connections between the QoL of individuals with IBD and biomarker profiles, including CRP, FC, and cortisol, as well as psychological variables like anxiety and depression. In addition, the innovative use of hair cortisol analysis here seeks to offer valuable insights into the feasibility of this measure and the intricate interplay of biological and psychosocial factors in IBD.

Methods

Design

This cross-sectional study obtained approval (Identification code: MINDFULNESS-EII2016) from the Human Ethics Committee of Sagunto Hospital, in compliance with the ethical principles delineated in the Declaration of Helsinki. The data were collected as part of a previous randomized controlled trial [2] and were used for secondary analysis.

Participants

Eligible participants in this study were individuals aged between 18 and 55 years, diagnosed with either Crohn's disease (CD) or ulcerative colitis (UC) in accordance with the diagnostic criteria established by the European Crohn's and Colitis Organization (ECCO). Additionally, these participants were required to be in clinical remission for a period of three months prior to enrolment, as previously documented [1,2,18]. Furthermore, the following inclusion criteria were applied: participants were expected to be free from cognitive impairment, UC patients were required to have a partial Mayo Score of 2 points or less with no individual item scores exceeding 1 point, while CD patients were expected to exhibit a Harvey-Bradshaw score of less than 5 points. Moreover, participants must have remained free from disease flare-ups for the preceding 12 months and should not have undergone alterations in their medication regimen or modifications to their standard treatment within the previous 3 months. Exclusions from the study comprised individuals who lacked proficiency in the Spanish language, those with diagnosed psychiatric disorders, individuals who had recently experienced significant emotional distress, or individuals who were pregnant at the time of recruitment. It's important to note that all study participants gave written informed consent, signifying their willingness to participate in the research before its start.

Data collection (outcome measures)

The concentration of faecal calprotectin (FC) was determined through fluorescent enzyme immunoassay analysis, with a measurement range spanning from 0 to 100 mg/g of dry weight. This analysis was conducted using a UniCap 100 analyser. Simultaneously, levels of plasma C-reactive protein (CRP) and cortisol were assessed using hair samples collected during the patients' most recent hospital consultations. For CRP quantification, an immunoturbidimetric assay was performed utilizing a Cobas 8000 analyser (module c701). This method relies on the formation of insoluble immune complexes proportional to the CRP concentration, with changes in turbidity quantified spectrophotometrically in milligrams per millilitre. Cortisol levels were determined following the manufacturer's instructions (DRG Instruments GmbH, Germany) using a high-sensitivity cortisol enzyme-linked immunosorbent assay kit designed for saliva and hair samples (ELISA, Salivary Cortisol ELISA DRG, DRG Instruments GmbH; Ref.: SLV 2930. Lot.: 63K047). This assay exhibited a sensitivity of 0.024 ng/ml and a detection range spanning from 0 to 30 ng/ml.

To mitigate potential biases arising from different kit lots, all sample analyses were conducted simultaneously at the study's conclusion [19]. Hair samples were obtained from the posterior vertex area of each patient, meticulously cleaned with 2.5 ml of isopropanol through agitation (1,800 rpm for 2.5 min) to eliminate contaminants and external steroids without affecting internal steroid levels. After drying for 36 h at room temperature, the samples were cut into fragments measuring less than 2 mm with scissors. Subsequently, 120–150 mg of each sample was placed into microtubes, and 1.5 ml of methanol was added, followed by an 18-h incubation at 30 °C with stirring (100 rpm, Mixer block®). After centrifugation of the vials at 7,000 g for 2 min, 750 µl of the liquid phase was recovered and incubated in fresh microtubes at 38 °C

until complete desiccation. The obtained residue was then reconstituted in 0.2 ml of 0.05 M phosphate-buffered saline.

To measure the patient QoL we used the Inflammatory Bowel Disease Questionnaire 32 (IBDQ-32); which contains 32 items distributed into 4 dimensions (bowel and systemic symptoms, emotional condition and social function). The responses to each item are expressed on a 7-point scale, where 7 corresponds to the best perception of health-related QoL and 1 to the worst. In this study, the global score was used for all 32 items. The IBDQ-32 has also been validated in Spanish and showed adequate psychometric properties [20]. In addition, the levels of anxiety and depression in the patients were evaluated using the Hospital Anxiety and Depression Scale (HADS), a tool encompassing a total of 14 questions. Within this questionnaire, 7 questions pertain to the assessment of anxiety symptoms (referred to as HADS-A), while the remaining 7 questions gauge symptoms of depression (referred to as HADS-D). Each individual item in the scale is assigned a score within the range of 0 to 3, resulting in a possible score range of 0 to 21 points for each subscale.

Moreover, this scale has also been validated in Spanish for which it showed adequate psychometric properties [21]. In addition, it had an internal consistency (Cronbach alpha) of 0.90 for the full scale, with the depression subscale and anxiety subscale reaching 0.84 and 0.85, respectively. Completion of theIBDQ-32 and HADS assessments was managed by a nurse who delivered the questionnaires to the patients to be immediately filled in.

All data are available in Zenodo.

Data analysis

No studies have investigated the correlation between hair cortisol levels and quality of life in patients with Inflammatory Bowel Disease (IBD). The following assumption was made to test the hypothesis that hair cortisol levels are related to quality of life: higher levels of cortisol in hair are associated with worse quality of life. We conducted an exploratory power analysis using the G*Power (v3.1.9.2, Heinrich-Heine-Universität Düsseldorf, Germany) software and determined that 67 participants would yield 80% statistical power at a 5% significance level for a small to moderate effect size ($r = 0.3$). Compliance with the assumption of normality was checked for each dependent variable using Shapiro–Wilks tests. To establish the independent association between IBDQ-32 and the other outcome measures (FC, CRP, hair cortisol, HADS-A, and HADS-D), we computed bivariate correlations for all study participants using the Pearson correlation coefficient. To avoid increasing type I error by repeating the statistical tests for each of the dependent variables, a Bonferroni adjustment was applied to the significance level. Thus, the alpha level for the 5 comparisons was 0.05/5, that is, $p = 0.01$. The strength of the Pearson correlation was interpreted in accordance with recommendations by Hopkins et al. where correlations in the range of 0.0–0.1 were considered trivial, 0.1–0.3 denoted small, 0.3–0.5 signified moderate, 0.5–0.7 represented large, 0.7–0.9 indicated very large, and 0.9–1 approximated an almost perfect correlation [22]. Furthermore, stepwise linear regression analyses were executed to develop a model aimed at identifying independent factors contributing to IBDQ-32 scores. Prior to variable selection, we scrutinized the correlation coefficients between the independent variables and QoL, selecting only those with statistically significant correlations for further analysis. All statistical analyses were carried out using SPSS software (version 27.0 for Windows, SPSS Inc., Chicago, IL).

Results

A comprehensive screening process involved a total of 93 patients for this study. Of these, 19 individuals were excluded; four patients declined participation, and 15 did not meet the specified inclusion criteria. An overview of the demographic and clinical characteristics of the study population is presented in Table 1. The mean age of the included participants was 45 years (SD = 11), with a predominance of female participants (80%). Regarding the distribution of IBD subtypes among the participants, it was evenly distributed, with each subtype comprising 50% of the cohort. The mean duration of disease was 10.8 years (SD = 8.4), indicating a substantial period of illness management among the participants. Notably, all participants were in clinical

Table 1. Characteristics of the study population with ulcerative colitis or Crohn's disease.

Age (y)	45.0 (11.0)
Sex (men/women)	15/59
CD/UC (%)	50/50
Disease duration (y)	10.8 (8.4)
Faecal calprotectin (µg/g)	212 (342)
Cortisol in hair (µg/mL)	1.9 (3.0)
C-reactive protein (mg/dL)	2.0 (2.7)
IBDQ-32	10.5 (4.6)
HADS Anxiety	10.6 (4.6)
HADS Depression	6.2 (4.3)

Abbreviations: CD = Crohn's disease; UC = ulcerative colitis; IBDQ = Inflammatory Bowel Disease Questionnaire; HADS = Hospital Anxiety and Depression Scale. Data are presented as means with SD.

remission at the time of enrollment, ensuring a homogeneous baseline for the study.

Interestingly, the IBDQ-32 did not significantly correlate with any of the biomarkers (fecal calprotectin [FC], C-reactive protein [CRP], or hair cortisol), as shown in Table 2. However, the IBDQ-32 demonstrated a large and statistically significant negative correlation with the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and Hospital Anxiety and Depression Scale-Depression (HADS-D) scores. The associations between IBDQ-32 and the independent variables are systematically summarized in Table 2. Furthermore, stepwise linear regression analyses were conducted to explore the predictors of IBDQ-32 scores, as detailed in Table 3. Notably, our analysis revealed that HADS-A was a significant and independent predictor for the IBDQ-32 outcome (Adjusted R^2 = 0.41, β = −0.65, $p < 0.001$). Model 1, which included HADS-A as the sole predictor, explained 41.3% of the variation in the IBDQ-32 scores. Subsequently, Model 2 was constructed by adding HADS-D alongside HADS-A, resulting in an increased explanatory power, with 45.6% of the variation in IBDQ-32 scores being accounted for.

Discussion

This study endeavors to elucidate the intricate interplay between C-reactive protein (CRP), fecal calprotectin (FC), hair cortisol levels, and psychological variables such as anxiety and depression in relation to the quality of life (QoL) among patients diagnosed with inflammatory bowel disease (IBD). To our knowledge, this investigation represents the inaugural effort to establish correlations between concentrations of inflammation biomarkers and QoL in this context.

Contrary to our initial hypotheses, the correlations between concentrations of inflammation biomarkers and QoL were found to be weak and non-significant. However, as anticipated, levels of anxiety and depression exhibited a robust and significant negative correlation with QoL. Previous studies have underscored the utility of biological markers in tracking disease progression. Indeed, several investigations have demonstrated strong correlations between gastrointestinal disease remission and reduced levels of specific biomarkers [23,24]. Furthermore, associations between certain gastrointestinal assessments and QoL parameters linked to disease severity have been documented. Notably, faecal calprotectin, a biomarker previously associated with intestinal inflammation and dysbiosis, has shown correlations with increased digestive symptoms and diminished QoL scores [25]. Nevertheless, consistent with our findings, the relationship between fluctuations in biomarker concentrations during the course of gastrointestinal disease and the QoL index may sometimes be insignificant [26,27]. This could be attributed, in part, to the comprehensive nature of the QoL index, which is influenced by various parameters, with certain factors such as the perception of anxiety disorders or depression carrying significant weight [28]. In this regard, alongside physical symptoms, IBD presents substantial psychosocial challenges, with rates of depression as high as 25.3% and anxiety as high as 32.1%, escalating to 38.9% and 57.6%, respectively, during active disease states [29]. Moreover, recent meta-analyses have indicated that depression and anxiety predict poorer clinical outcomes in IBD, including disease flares, hospitalization, therapy escalation, and surgery [30]. Therefore, addressing mental health concerns should be prioritized in IBD treatment and taken into account in order to stablish the severity of the disorder [31].

Consistent with these findings, our study revealed that scores on the Hospital Anxiety and Depression Scale (HADS-D and HADS-A) accounted for 45.6% of the variance in IBDQ-32 scores. Thus, parameters such as HADS-A or HADS-D are pivotal in assessing QoL and, consequently, integral to QoL index scores [32–35]. Indeed, therapies aimed at ameliorating anxiety or depression processes in these patients, evaluated using HADS-A and HADS-D, improved QoL perceptions and mean QoL index scores [36]. Moreover, a meta-analysis

Table 2. Correlation coefficients for the *Inflammatory Bowel Disease Questionnaire-32* and independent variables.

Variables	FC	CRP	Cortisol in hair	HADS-A	HADS-D
IBDQ-32	0.219	−0.103	0.102	−0.651*	−0.611*
FC		0.073	0.032	−0.278	−0.108
CRP			−0.010	0.014	0.120
Cortisol in hair				−0.229	−0.194
HADS-A					0.684*

Abbreviations: CRP = C-reactive protein; FC = faecal calprotectin ; HADS = *Hospital Anxiety and Depression Scale* and IBDQ = *Inflammatory Bowel Disease Questionnaire*, *$p < 0.01$.

Table 3. Multiple stepwise linear regression analyses with the *Inflammatory Bowel Disease Questionnaire-32* as the dependent variable.

	IBDQ-32				
Independent variables	R^2	Adjusted R^2	R^2 change	Standardised Beta coefficient	Beta significance
Model 1	0.42	0.41	0.42		
HADS-A				−0.65	< 0.001
Model 2	0.47	0.45	0.05		
HADS-A				−0.43	0.002
HADS-D				−0.31	0.025

Abbreviations: HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression and IBDQ-32 = Inflammatory Bowel Disease Questionnaire-32.

across various medical conditions demonstrated that psychosocial interventions reduced inflammation and proinflammatory cytokine levels by 18–48% compared to controls [37]. The precise mechanisms underlying this phenomenon remain incompletely understood, but interventions targeting negative psychological factors appear to influence immune system function and inflammation, partly through activation of the parasympathetic nervous system [38,39]. This could be particularly relevant for IBD, as psychological and behavioral factors are believed to influence intestinal inflammation and disease activity *via* the gut-brain axis [40].

Another possible explanation for the absence of correlation between inflammation biomarkers and QoL in IBD may be that all patients included in this study were in clinical remission, thus excluding those with active disease, wherein inflammatory marker levels significantly elevate [4,5]. Finally, as proposed by Knisely and colleagues, the lack of correlation between biomarkers and patients could also be associated with cytokine gene polymorphisms. Therefore, genetic studies of these polymorphisms could serve as valuable predictive and monitoring tools for IBD [6].

The results of our study demonstrated a small negative correlation between anxiety levels and fecal calprotectin levels ($r = -0.278$, $p = 0.038$). This finding aligns with results obtained by Narula et al. who conducted a prospective longitudinal follow-up study with 414 IBD patients and found that IBD patients with abnormal anxiety sub-scores had poorer IBD-related outcomes compared to those without elevated anxiety sub-scores [41]. Additionally, a recent meta-analysis involving 28 RCTs and 1789 participants with IBD concluded that treatments addressing mood outcomes, such as anxiety, have beneficial effects on both generic inflammation and disease-specific biomarkers, such as fecal calprotectin [42]. Moreover, psychological interventions demonstrated larger treatment effects on mood compared to exercise or antidepressants.

Regarding depression, our results did not exhibit significant correlations with any of the studied biomarkers. Cross-sectional studies have shown significant variability in this regard, with some indicating modest to moderate correlations between CRP and fecal calprotectin levels and depressive symptoms [43,44], while others report no significant findings [45,46]. Consistent with our findings, no differences in IBD-related outcomes were observed in individuals with abnormal depression sub-scores compared to those without elevated depression scores [41]. Longitudinal data on IBD are more limited and, also in line with our results, indicate non-significant associations between inflammation and depression [47].

Strengths and limitations

One strength of this study is the use of objective measures of inflammation, minimizing potential bias associated with self-reported data. Another strength is the novel use of hair cortisol levels in IBD patients, providing insight into cortisol levels over an extended period. However, the cross-sectional design of this study precludes solid conclusions regarding causality. Additionally, the HADS questionnaire does not differentiate between trait anxiety and state anxiety, despite being a useful tool for determining levels of anxiety and depression. Furthermore, the small sample size prevented independent analysis of patients with ulcerative colitis and Crohn's disease. Finally, as our participants were in clinical remission, our results may not be generalizable to other disease statuses, such as active disease. Further investigation into the timing of inflammation and disease activity in a larger sample, allowing for independent analysis of patients with ulcerative colitis and Crohn's disease, is warranted.

Conclusion

In summary, the findings of this study suggest that inflammation biomarkers such as CRP, FC, and cortisol are valuable for the follow-up and monitoring of IBD but do not determine patient QoL. Conversely, variables such as anxiety and depression, measured using instruments like the HADS, appear to correlate more strongly with QoL in these patients. Therefore, these instruments should be considered in the comprehensive assessment of patients to enhance their QoL.

Acknowledgments

We are grateful to the CIBER of Epidemiology and Public Health (CIBERESP CB22/02/00052) and to the CIBER of Physiopathology of Obesity and Nutrition (CIBERobn, CB06/03/0052) for its support. CIBER is an initiative of the Instituto de Salud Carlos III (ISCIII). The CIBER and ISCIII did not play any role in the analysis and interpretation of data, in the writing of the manuscript, or in the decision to submit the paper for publication.

Authors contributions

All authors contributed to the conception and design of the study, analysis and interpretation of data, critical review, and final approval of the manuscript for publication. Data acquisition was conducted by RGM, JMS, IAF, JFL, JN, ACM, and AGE. Drafting of the manuscript was primarily led by RGM, JMS, and JFL. Each author affirms their dedication to maintaining the accuracy and integrity of all aspects of the study.

Authorship statement

All listed authors meet the authorship criteria and all authors are in agreement with the content of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethics statement

This study was approved by the Human Ethics Committee at the Hospital Universitario de Sagunto (Spain).

Funding

Part of the project was financed by the Cardenal Herrera CEU University Elche Funder: CEU-UCH 2023-2024, INDI23/62 Funder: CEU-UCH 2023-2024, GIR2313 and INDI23/20.

ORCID

Rafael González-Moret http://orcid.org/0000-0003-2926-6649
Ausias Cebolla-Martí http://orcid.org/0000-0002-3456-9743
Isabel Almodóvar-Fernández http://orcid.org/0000-0002-0580-664X
Jaime Navarrete http://orcid.org/0000-0002-9482-4822
Ángeles García-Esparza http://orcid.org/0000-0001-6510-0879
José M. Soria http://orcid.org/0000-0001-9144-5096
Juan F. Lisón http://orcid.org/0000-0002-4983-4052

Data availability statement

The data that support the findings of this study are available from the corresponding author, [S JM], upon reasonable request.

References

[1] Cebolla A, Navarrete J, González-Moret R, et al. Effectiveness of a blended internet-based mindfulness intervention in inflammatory bowel disease patients: a mixed-methods non-randomized controlled trial. Mindfulness. 2021;12(11):1–8. doi: 10.1007/s12671-021-01741-2.
[2] González-Moret R, Cebolla A, Cortés X, et al. The effect of a mindfulness-based therapy on different biomarkers among patients with inflammatory bowel disease: a randomised controlled trial. Sci Rep. 2020;10(1):6071. doi: 10.1038/s41598-020-63168-4.
[3] Sands BE. Biomarkers of inflammation in inflammatory bowel disease. Gastroenterology. 2015;149(5):1275–1285.e2. doi: 10.1053/J.GASTRO.2015.07.003.
[4] Dai C, Jiang M, Sun MJ. Fecal markers in the management of inflammatory bowel disease. Postgrad Med. 2018;130(7):597–606. doi: 10.1080/00325481.2018.1503919.
[5] Lężyk-Ciemniak E, Tworkiewicz M, Wilczyńska D, et al. Usefulness of testing for fecal calprotectin in pediatric gastroenterology clinical practice. Med Princ Pract. 2021;30(4):311–319. doi: 10.1159/000512631.
[6] Knisely MR, Conley YP, Szigethy E. Cytokine genetic variants and health-related quality of life in crohn's disease: an exploratory study. Biol Res Nurs. 2019;21(5):544–551. doi: 10.1177/1099800419860906.
[7] Weaver KR, Melkus GD, Fletcher J, et al. Perceived stress, its physiological correlates, and quality of life in patients with irritable bowel syndrome. Biol Res Nurs. 2018;20(3):312–320. doi: 10.1177/1099800418756733.
[8] Addolorato G, Capristo E, Stefanini GF, et al. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. Scand J Gastroenterol. 1997;32(10):1013–1021. doi: 10.3109/00365529709011218.
[9] Knowles SR, Graff LA, Wilding H, et al. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses-Part I. Inflamm Bowel Dis. 2018;24(4):742–751. doi: 10.1093/ibd/izx100.
[10] Wong JJ, Sceats L, Dehghan M, et al. Depression and health care use in patients with inflammatory bowel disease. J Crohns Colitis. 2019;13(1):19–26. doi: 10.1093/ecco-jcc/jjy145.
[11] Sarid O, Slonim-Nevo V, Schwartz D, et al. Differing relationship of psycho-social variables with active ulcerative colitis or crohn's disease. Int J Behav Med. 2018;25(3):341–350. doi: 10.1007/s12529-018-9712-5.
[12] Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of anxiety and depression in patients with inflammatory bowel disease. Can J Gastroenterol Hepatol. 2017;2017. doi: 10.1155/2017/6496727.
[13] Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease:a review of comorbidity and management. Inflamm Bowel Dis. 2009;15(7):1105–1118. doi: 10.1002/ibd.20873.
[14] Neuendorf R, Harding A, Stello N, et al. Depression and anxiety in patients with inflammatory bowel disease: a systematic review. J Psychosom Res. 2016;87:70–80. doi: 10.1016/j.jpsychores.2016.06.001.
[15] Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and crohn's disease. J Health Psychol. 2012;18(7):972–983. doi: 10.1177/1359105312459094.
[16] Trindade IA, Ferreira C, Pinto-Gouveia J. Inflammatory bowel disease: the harmful mechanism of experiential avoidance for patients' quality of life. J Health Psychol. 2015;21(12):2882–2892. doi: 10.1177/1359105315587142.
[17] Regev S, Odes S, Slonim-Nevo V, et al. Differential relationships of somatization, depression, and anxiety to severity of crohn's disease. J Health Psychol. 2020;26(13):2390–2401. doi: 10.1177/1359105320909879.
[18] Navarrete J, González-Moret R, Cortés X, et al. Dispositional mindfulness and inflammatory bowel disease: mindful awareness mediates the relation between severity and quality of life, stress, and fatigue. Mindfulness. 2021;12(6):1524–1533. doi: 10.1007/s12671-021-01620-w.
[19] Albar WF, Russell EW, Koren G, et al. Human hair cortisol analysis: comparison of the internationally-reported ELISA methods. Clin Invest Med. 2013;36(6):E312–6. doi: 10.25011/cim.v36i6.20629.
[20] Masachs M, Casellas F, Malagelada JR. [Spanish translation, adaptation, and validation of the 32-item questionnaire on quality of life for inflammatory bowel disease(IBDQ-32)]. Rev Esp Enferm Dig. 2007;99(9):511–519. doi: 10.4321/S1130-01082007000900006.

[21] Herrero MJ, Blanch J, Peri JM, et al. A validation study of the hospital anxiety and depression scale (HADS) in a spanish population. Gen Hosp Psychiatry. 2003; 25(4):277–283. doi: 10.1016/S0163-8343(03)00043-4.
[22] Hopkins AG, Marshall SW, Batterham AM, et al. Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc. 2009;41(1):3–13. doi: 10.1249/MSS.0b013e31818cb278.
[23] Tibble JA, Sigthorsson G, Bridger S, et al. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. Gastroenterology. 2000;119(1):15–22. doi: 10.1053/gast.2000.8523.
[24] Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55(3):426–431. doi: 10.1136/gut.2005.069476.
[25] Beaufils F, Mas E, Mittaine M, et al. Increased fecal calprotectin is associated with worse gastrointestinal symptoms and quality of life scores in children with cystic fibrosis. J Clin Med. 2020;9(12):4080. doi: 10.3390/JCM9124080.
[26] Mavroudis G, Simren M, Jonefjäll B, et al. Symptoms compatible with functional bowel disorders are common in patients with quiescent ulcerative colitis and influence the quality of life but not the course of the disease. Therap Adv Gastroenterol. 2019;12: 1756284819827689. doi: 10.1177/1756284819827689.
[27] Naftali TI, Bar-Lev Schleider L, Scklerovsky Benjaminov F, et al. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: a randomized controlled trial. PLoS One. 2021;16(2):e0246871. doi: 10.1371/journal.pone.0246871.
[28] Kantidakis JD, Moulding R, Knowles SR. Psychological mediators of psychological distress and quality of life in inflammatory bowel disease. J Psychosom Res. 2021;149:110596. doi: 10.1016/J.JPSYCHORES.2021.110596.
[29] Barberio B, Zamani M, Black CJ, et al. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021; 6(5):359–370. doi: 10.1016/S2468-1253(21)00014-5.
[30] Fairbrass KM, Lovatt J, Barberio B, et al. Bidirectional brain – gut axis effects influence mood and prognosis in IBD: a systematic review and meta-analysis. Gut. 2022;71(9):1773–1780. doi: 10.1136/gutjnl-2021-325985.
[31] Fairbrass KM, Gracie DJ, Ford AC. Relative contribution of disease activity and psychological health to prognosis of inflammatory bowel disease during 6.5 years of longitudinal follow-Up. Gastroenterology. 2022; 163(1):190–203.e5. doi: 10.1053/j.gastro.2022.03.014.
[32] Chan W, Shim HH, Lim MS, et al. Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. Dig Liver Dis. 2017; 49(12):1314–1319. doi: 10.1016/J.DLD.2017.08.020.
[33] Renna ME, O'Toole MS, Spaeth PE, et al. The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: a systematic review and meta-analysis. Depress Anxiety. 2018;35(11):1081–1094. doi: 10.1002/da.22790.
[34] Miehsler W, Weichselberger M, Offerlbauer-Ernst A, et al. Which patients with IBD need psychological interventions? A controlled study. Inflamm Bowel Dis. 2008;14(9):1273–1280. doi: 10.1002/ibd.20462.
[35] Moser G. Depresión y ansiedad en la enfermedad inflamatoria intestinal. Gastroenterol Hepatol. 2009;32(2): 9–12. doi: 10.1016/S0210-5705(09)72599-3.
[36] Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: a multicenter randomized controlled trial. J Consult Clin Psychol. 2017;85(9):918–925. doi: 10.1037/CCP0000227.
[37] Ballesio A, Zagaria A, Vacca M, et al. Comparative efficacy of psychological interventions on immune biomarkers: a systematic review and network meta-analysis (NMA). Brain Behav Immun. 2023;111:424–435. doi: 10.1016/j.bbi.2023.05.006.
[38] O'Connor DB, Thayer JF, Vedhara K. Stress and health: a review of psychobiological processes. Annu Rev Psychol. 2021;72(1):663–688. doi: 10.1146/annurev-psych-062520-122331.
[39] Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014;140(3):774–815. doi: 10.1037/a0035302.
[40] Günther C, Rothhammer V, Karow M, et al. The gut-brain axis in inflammatory bowel disease – current and future perspectives. Int J Mol Sci. 2021;22(16):8870. doi: 10.3390/ijms22168870.
[41] Narula N, Pinto-Sanchez MI, Calo NC, et al. Anxiety but not depression predicts poor outcomes in inflammatory bowel disease. Inflamm Bowel Dis. 2019;25(7):1255–1261. doi: 10.1093/ibd/izy385.
[42] Seaton N, Hudson J, Harding S, et al. Do interventions for mood improve inflammatory biomarkers in inflammatory bowel disease? a systematic review and meta-analysis. eBioMedicine. 2024;100:104910. doi: 10.1016/j.ebiom.2023.104910.
[43] Geiss T, Schaefert RM, Berens S, et al. Risk of depression in patients with inflammatory bowel disease. J Dig Dis. 2018;19(8):456–467. doi: 10.1111/1751-2980.12644.
[44] Iordache MM, Tocia C, Aschie M, et al. Intestinal permeability and depression in patients with inflammatory bowel disease. J Clin Med. 2022;11(17):5121. doi: 10.3390/jcm11175121.
[45] Goodhand JR, Wahed M, Mawdsley JE, et al. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. Inflamm Bowel Dis. 2012;18(12):2301–2309. doi: 10.1002/ibd.22916.
[46] Mules TC, Swaminathan A, Hirschfeld E, et al. The impact of disease activity on psychological symptoms and quality of life in patients with inflammatory bowel disease – results from the stress, anxiety and depression with disease activity (SADD) study. Aliment Pharmacol Ther. 2022;55(2):201–211. doi: 10.1111/apt.16616.
[47] Gracie DJ, Ford AC. Defining the relationship between depression and disease activity in IBD using clinical disease activity indices: merit or misnomer? Am J Gastroenterol. 2018;113(5):773–774. doi: 10.1038/s41395-018-0014-y.