Quality of life in inflammatory bowel disease patients: A cross-sectional study

Farzaneh Habibi[1,2], **Mohammad Emadoddin Habibi**[1,2], **Ali Gharavinia**[1,2], **Sadegh Baradaran Mahdavi**[1,2], **Mohammad Javad Akbarpour**[1], **Abdolmehdi Baghaei**[1,2], **Mohammad Hassan Emami**[1,3]

[1]Gastrointestinal Diseases Research Center, Poursina Hakim Research Center, Isfahan University of Medical Sciences, [2]Student Research Committee, School of Medicine, Isfahan University of Medical Sciences, [3]Department of Internal Medicine, Division of Gastroenterology, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Inflammatory bowel disease (IBD) has a significant impact on health-related quality of life (HRQOL). This study aims to investigate the variables which can be attributed to HRQOL in IBD patients. **Materials and Methods:** Seventy-one patients filled in IBD questionnaire (IBDQ-32), Pittsburgh sleep quality index questionnaire, and sociodemographic questionnaire. Disease activity was assessed by Crohn's disease activity index (CDAI) and ulcerative colitis activity index (UCAI). The correlations of sleep quality, sociodemographic variables, and disease characteristics with IBDQ were investigated. **Results:** IBDQ-32 mean score was lower in patients who had hospitalization ($P = 0.01$), poor sleep quality ($P < 0.001$), anemia ($P = 0.03$), more severe disease ($P = 0.01$), and those who had not consumed folic acid ($P = 0.01$) relative to their counterparts. A multivariate regression analysis identified the predictors of decreased HRQOL as not consuming folic acid ($P = 0.008$), poor sleep quality ($P = 0.014$), and disease severity ($P = 0.043$). **Conclusion:** Impaired HRQOL was significantly associated with poor sleep quality, lack of folic acid consumption, and disease severity in IBD patients. Therefore, evaluation of folic acid level and efficacy of its supplementation in prospective studies is recommended. Treatment of sleep disturbance with pharmacological agents and nonpharmacological methods should be kept in mind as well.

Key words: Anemia, folic acid, health-related quality of life, inflammatory bowel disease, sleep quality

INTRODUCTION

Inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing diseases of unknown etiology. The incidence of UC and CD has increased in Europe from 6 per 100,000 person years in UC and 1 per 100,000 person years in CD in 1962 to 9.8 in UC and 6.3 in CD in 2010. The prevalence of UC and CD ranges from 37 to 246/100,000 persons and 26 - 199/100,000 persons, respectively.[1]

Health-related quality of life (HRQOL) is defined as "the state of well-being that is a composite of 2 components, the ability to perform everyday activities that reflect physical, psychological and social well-being and patient satisfaction with levels of functioning and control of the disease." Although life expectancy of IBD patients is near to the mean of healthy population, IBD basically damages HRQOL. Chronic nature of disease, frequent recurrence of symptoms, extraintestinal manifestations, the effect of medical and surgical treatments and their side effects, stress of developing cancer, and needing surgery have impacts on daily lives of patients and cause significant reduction in quality of life (QOL). It seems that the most important factor which affects HRQOL in IBD patients is presence or absence of inflammatory activity although the impact of other sociodemographic factors should be considered. Nevertheless, physical symptoms of IBD do not explain decrements in HRQOL completely.[2] Moreover, some investigators have shown that disease characteristics including endoscopic activity index and disease activity index are associated with HRQOL, but

Address for correspondence: Dr. Sadegh Baradaran Mahdavi, School of Medicine, Isfahan University of Medical Sciences, Hezar Jarib Avenue, Isfahan, Iran. E-mail: sadegh.b.mahdavi@gmail.com

disease distribution, disease duration, hospitalization, and demographic variables such as education, economic status, and marital status do not have significant effect on IBD questionnaire (IBDQ) total score.[3,4] However, a recent study introduced female gender, older age, lower education, and socioeconomic level as factors associated to worse QOL in IBD patients.[2] Some available studies support the impact of female gender and older age on worse HRQOL[5,6] while the others have not reported any associations.[3,4]

Normal sleep is necessary for being healthy and having high QOL. A healthy sleep-wake cycle is critical for regulation of immune and neuroendocrine system. Fatigue and poor sleep quality are common in patients with active IBD and also inactive IBD. Strong relationship was observed between poor sleep quality and disease activity. Patients in clinical remission with abnormal sleep have a high likelihood of having histologically active disease (subclinical disease activity).[7] Association between sleep disturbance and disease activity was also observed in immune-mediated diseases such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis.[8] Moreover, sleep disturbance has relations with fatigue during day, mood, depression, and more physical symptoms.[9] In the general population, persistent insomnia has been associated with higher risk of developing clinical anxiety or depression.[10]

The precise incidence and prevalence of IBD have not been established in Iran. According to unofficial reports, these diseases are not rare in Iran.[11] Furthermore, there is a lack of data about QOL and associated factors in Iranian IBD patients. The current study aimed to describe the QOL and its predictors in these patients. The prevalence of poor sleep quality in IBD patients and relationship with QOL is also investigated in this research.

MATERIALS AND METHODS

Patients and setting
We conducted an analytical cross-sectional study. IBD patients presenting to Poursina Hakim Gastroenterology Clinic in Isfahan were invited in waiting rooms before their regular physician appointments and were given verbal information to participate the study before completing questionnaires including sociodemographic, medical treatments, sleep quality, and QOL. The patients were interviewed by a physician to complete disease activity indexes. Samples were obtained to assess complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), stool examination, and fecal calprotectin. Inclusion criteria were confirmed diagnosis of IBD based on British guideline practice,[12] no unrelated comorbidities including congestive heart failure, cirrhosis, peptic ulcer, diabetes or cancer, interest and voluntary participation in the study, and

capability of filling out the questionnaires either by writing or answering the questions read by research assistant. The patients who had hospitalization, surgery during 3 last months, or confirmed psychological disease were excluded from the study. To determine the sample size for estimating the correlation coefficient in IBD patients, we utilized the following formula considering $\alpha = 0.05$ as type one error regard to 95% of confidence interval and $\beta = 0.2$ as type two error and $R = 0.33$ as correlation coefficient between QOL and sleep quality based on previous researches. The number of sample population was measured about 70 according to this formula. We focused on 80 as final sample size due to possible losses of patients for every reason. The patients were selected through the convenience sampling method.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2}{\left(\frac{1}{2} ln \frac{1+r}{1-r} \right)^2} + 3 \approx 70$$

Study measurements
Demographic and medical information
Demographic information, including current age, marital status, education, occupation status, and smoking, were asked from the patients. Height and weight were measured to calculate body mass index. Medical information including IBD type, date of diagnosis, type of treatment (5-ASA, corticosteroids, or immune modulators), anatomical distribution, and related surgeries were gathered through reviewing the patients' documents.

Quality of sleep
We used the Pittsburgh sleep quality index (PSQI) questionnaire developed by Buysee *et al.* for subjective assessment of sleep quality. It assesses sleep quality over the last month, containing 19 items with 7 components, including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Every component scored from 0 to 3. The global score ranged from 0 to 21. Higher scores showed the poorer sleep quality. The global score more than 5 was distinguished as bad sleep quality. The reliability and validity of Persian version of PSQI has been demonstrated by Farrahi Moghaddam *et al.*[13]

Quality of life
IBDQ was used to assess QOL. IBDQ as a disease-specific questionnaire included 32 questions. The questions consisted of 4 domains as follows: Bowel symptoms (10 questions), systemic symptoms (5 questions), emotional functioning (12 questions), and social functioning (5 questions). Every question score ranged from 1 to 7 which 7 corresponded to the highest level of

functioning. Total score ranged from 32 to 224. Higher score showed higher HRQOL. Persian version of IBDQ was validated by Maleki *et al*.[14]

Severity of disease

UC activity index (UCAI) was used to measure severity of disease in UC patients. UCAI was calculated by Seo *et al*. formula as following: "UCAI = (60 × number of bloody stools per day) + (13 × number of bowel movements per day) + (0.5 × ESR [mm/h]) − (4 × hemoglobin [g/dl]) − (15 × serum albumin [g/dl]) +200." UCAI <150 shows mild, between 150 and 220 shows moderate, and more than 220 shows severe UC disease.

Crohn's disease activity index (CDAI) was used to measure disease activity in CD patients. This index had 8 questions which were filled out by physician. CDAI ranges from 0 to 600 and the higher score corresponds to more severe disease.[15]

Statistical analysis

The SPSS statistical software (version 23.0, IBM Corp.) was used for data analysis. Frequency and mean ± standard deviation (SD) were used for descriptive statistics. The univariate analyses explored the link between HRQOL scores and sociodemographic, clinical, and sleep quality variables using Student's *t*-test and ANOVA. Variables which were statistically significant in the univariate analysis were included in a multivariate regression model, the IBDQ total scores were used as dependent variables, and age, gender, marital status, disease duration, current medical therapy, folic acid consumption, hospitalization, education level, CDAI, and UCAI were used as independent or explanatory variables. Selection of explanatory variables was based on literature reviews[2-7,16-19] and clinical experience. Assumptions for using regression analyses such as normality of dependent variable, independence of observations (residuals), linear relationship between the dependent variable and each of independent variables, data homoscedasticity, and presence of outliers were all investigated. $P < 0.05$ was considered statistically significant for interpreting analyses.

Ethical considerations

Ethical protocols of the current study were reviewed and approved by Isfahan University of Medical Sciences' Ethics Committee (research project number: 395047). All patients were explained about aims of study and the ways of gathering information. Written consent was obtained from all the patients before recruitment to the study.

RESULTS

The demographic and disease characteristics of all 46 UC and 25 CD patients are listed in Table 1. Forty-six percent of CD group and 65.2% of UC group were females. Means of age ± SDs were 37.6 ± 11.85 and 39.2 ± 12.14 in CD and UC groups, respectively. The patients who were smokers or categorized as severe disease by UCAI or CDAI index and those who were operated due to IBD complications were omitted due to inconsiderable number. None of our sample patients consumed biologic agents or enteral products. Our patients did not have complications such as anal fissure, fistula, or abscess.

Descriptive statistics of inflammatory bowel disease questionnaire-32

The mean score of IBDQ-32 was 156.92 ± 42.86 ranging from 32 to 213. Significant difference was not seen between mean of IBDQ-32 score in CD and UC groups (156.92 ± 49.48 for CD and 156.91 ± 39.40 for UC, $P = 0.99$). Therefore, those were considered together in following analyses. Table 2 summarizes the descriptive values for the 4 domains and overall score of IBDQ-32.

Descriptive statistics of Pittsburgh sleep quality index

The mean of PSQI total score was 5.9 ± 4.04. Forty-four percent of patients had poor sleep quality based on PSQI questionnaire scoring.

Determinants of quality of life

Univariate analysis of all the psychosocial, clinical, demographic, and sleep quality variables revealed significant associations. The mean value of the IBDQ-32 was significantly lower among patients who had hospitalization (142.30 vs. 169.69, $P = 0.01$), patients with anemia (140.38 vs. 163.86, $P = 0.03$), and the ones who did not consume folic acid (138.08 vs. 166.52, $P = 0.02$). Patients who had poor sleep quality (133.77 vs. 179.61, $P < 0.001$) and more severe disease (133.73 vs. 164.18, $P = 0.01$) also presented with significantly lower IBDQ-32 scores [Table 3].

Statistically significant variables in the univariate analysis were included in a multivariate regression model [Table 4]. Folic acid consumption was associated with higher HRQOL ($P = 0.008$).

DISCUSSION

IBD is a multifactorial disease that possibly is caused by the interaction of environmental, immunogenetics, and lifestyle. The impact of IBD on patients' QOL is influenced by early age of onset, fluctuating disease course, and lack of definite cure. The current study showed that individuals who had suffered from more severe disease, those with poor sleep quality, and those who had not consumed folic acid, presented with lower HRQOL scores. Interestingly, of these QOL predictors, folic acid consumption was found to be strongest.

Table 1: Clinical and demographic characteristics of inflammatory bowel disease patients

	CD	UC
Number of patients (*n*)	25	46
Gender, *n* (%)		
Female	16 (46)	30 (65.2)
Age, mean±SD (minimum–maximum)	37.6±11.85 (22–73)	39.2±12.14 (21–60)
Marital status, *n* (%)		
Married	16 (64)	36 (81.8)
Employed, *n* (%)	13 (52)	18 (39.1)
Duration of IBD (years), mean±SD (minimum–maximum)	8.24±6.23 (1–30)	8.15±5.06 (1–18)
Current medical therapy, *n* (%)		
5-ASA	3 (12.5)	11 (25)
5-ASA + corticosteroid	1 (4.2)	3 (6.8)
5-ASA + immunomodulator	13 (54.2)	21 (47.7)
5-ASA + corticosteroid+immunomodulator	7 (29.2)	9 (20.5)
Folic acid consumption, *n* (%)	16 (64)	31 (67.4)
Post-IBD-related hospital admission, mean±SD (minimum–maximum)	1.61±3.21 (0–12)	2.09±4.13 (0–15)
Education level, *n* (%)		
Illiterate	1 (4)	2 (4.4)
Elementary	4 (16)	2 (4.4)
Junior high school	4 (16)	6 (13.3)
Diploma	6 (24)	18 (40)
University	10 (40)	17 (37.8)
CDAI, mean±SD (minimum–maximum)	65.76±42.17 (14–192)	-
UCAI, mean±SD (minimum–maximum)	-	126.25±33.82 (75.1-203.3)
PSQI, mean±SD (minimum–maximum)	5.88±4.16 (0-17)	6.04±4.03 (0-16)
Good sleepers, *n* (%)	13 (54.2)	25 (56.8)
BMI, mean±SD (minimum–maximum)	24.49±4.92 (16.27–33.23)	25.99±5.85 (16.2–39.96)

5-ASA = 5-aminosalicylic acid; SD = Standard deviation; CDAI = Crohn's disease activity index; UCAI = Ulcerative colitis activity index; IBD = Inflammatory bowel disease; PSQI = Pittsburgh sleep quality index; BMI = Body mass index; CD = Crohn's disease; UC = Ulcerative colitis

Table 2: Descriptive statistics for the 4 domains and overall score of the inflammatory bowel disease questionnaire-32

	IBD type[a]	IBDQ-32 scores		
		Mean±SD	Minimum (reference value[b])	Maximum (reference value[b])
Bowel-related symptoms	UC	51.33±13.70	23 (10)	70 (70)
	CD	50.04±17.45	10 (10)	70 (70)
Systemic function	UC	23.856±6.52	9 (5)	35 (35)
	CD	23.64±8.04	8 (5)	34 (35)
Social function	UC	26.72±8.77	6 (5)	35 (35)
	CD	25.64±9.16	6 (5)	35 (35)
Emotional function	UC	55.02±14.72	26 (12)	80 (84)
	CD	57.84±17.21	12 (12)	76 (84)
Global function	UC	156.91±39.40	86 (32)	210 (224)
	CD	156.92±49.48	32 (32)	213 (224)

[a]UC = Ulcerative colitis; CD = Crohn's disease; [b]Reference value = Possible max or min score of related domain of the questionnaire; IBD = Inflammatory bowel disease; IBDQ = Inflammatory bowel disease questionnaire; SD = Standard deviation

Our data showed that 44% of patients had poor sleep quality. Poorer sleep quality in IBD patients comparing to healthy controls was also reported by other researchers. Poor sleep quality is highly prevalent in active disease (77% of patients) and even in inactive disease (49% of patients).[20] Poor sleep quality may cause daytime sleepiness, fatigue, and daytime dysfunction which decreases HRQOL. This was also reported by Keefer *et al.* that sleep parameters greatly influence QOL.[21]

One study among healthy young adults found that sleep restriction was significantly associated with increased levels of interleukin (IL) 17, CRP, and markers of systemic inflammation. Therefore, long-term sleep restriction may lead to persistent changes in the immune system.[17] Sleep disturbances have been associated with exacerbation of symptoms such as pain and fatigue in multiple chronic inflammatory conditions as well as worsening disease course.[22]

Table 3: The relationship between clinical and demographic characteristics of inflammatory bowel disease patients and inflammatory bowel disease questionnaire-32 total score

	IBDQ-32 mean score	*P*
Type of disease[a]		
CD	156.92	0.99
UC	156.91	
Gender		
Female	155.61	0.73
Male	159.32	
Age (years)		
≤30	155.09	0.8
>30	157.79	
Disease duration (years)		
≤5	150.70	0.386
>5	160.73	
Educational level[b]		
Illiterate	149.67	0.14
Elementary	123.83	
Junior high school	139.10	
Diploma	169.46	
University	162.19	
Working status		
Unemployed	157.8	0.84
Employed	155.7	
Hospitalization		
Yes	142.3	0.01
No	169.69	
Drugs		
5-ASA	168.29	0.2
5-ASA + corticosteroid	128.25	
5-ASA + immunomodulator	162.06	
5-ASA + corticosteroid + immunomodulator	144.38	
Anemia		
Non-anemic	163.86	0.034
Anemic	140.38	
Sleep quality		
Good	179.61	<0.001
Bad	133.77	
Folic acid		
Yes	166.65	0.01
No	139	
Disease severity		
In remission to mild	164.18	0.01
Moderate	133.73	
BMI		
Underweight	157.57	0.66
Normal	162.45	
Overweight	160.32	
Obese	144.5	

[a,b]The association between qualitative variables and IBDQ-32 scores was determined using independent *t*-test (for 2 groups) and ANOVA (for >2 groups), 5-ASA = 5-aminosalicylic acid; BMI = Body mass index; IBDQ = Inflammatory bowel disease questionnaire; CD = Crohn's disease; UC = Ulcerative colitis

Folic acid consumption was also related with a higher HRQOL in a univariate analysis and with the highest

Table 4: Multiple linear regression analysis between predictor variables and inflammatory bowel disease questionnaire-32 scores

Variable	*b*	Standardized error (β)	*B*	*t*	*P*
Hospitalization	−1.539	1.215	−0.136	−1.267	0.210
Folic acid consumption	26.712	9.780	0.294	2.731	0.008
Sleep quality	−3.045	1.206	−0.287	−2.524	0.014
Disease severity	−23.291	11.455	−0.228	−2.033	0.047
Anemia	13.637	10.290	0.144	1.325	0.190

statistical significance in a multivariate regression model. Due to chronic inflammation as well as side effects of long-term use of medications, IBD patients are at risk of folic acid deficiency. Folic acid deficiency was reported between 4.3% and as high as 54% of IBD patients.[18] The patients suffering from CD present folate deficiency more than the UC patients. Up to 80% of Crohn's patients have low levels of serum folate. The risk of folic acid deficiency increases in patients consuming sulfasalazine. Patients treated by high dose of sulfasalazine require 1 mg/d folic acid supplementation to preserve normal cell division. This is of great importance for patients who receive additionally methotrexate (MTX), azathioprine, 6–mercaptopurine, and mycophenolate, considering that MTX is a folic acid inhibitor and the other mentioned drugs are antimetabolites which can interfere with cell growth.[23] None of our patients consumed sulfasalazine or MTX, but 73.2% of cases used azathioprine. Deficiencies may also be attributed to malabsorption and dietary insufficiency issues as well as bacterial microflora changes.[22] Better QOL was reported in hepatitis C patients who received folic acid supplementation with pegylated interferon α-2a and ribavirin in comparing to patients who received their regular antihepatitis drugs.[24] We could not find any published research in which the effect of folic acid supplementation on IBD patients' QOL is studied.

Disease severity was related with lower QOL in our study which was consistent with other studies.[18,25] In the presence of more severe IBD, the patients may experience more gastrointestinal or extraintestinal symptoms, invasive treatments, and more complications that might increase anxiety and depression. These negative emotions have potential to impair daily functioning. It seems that disease severity is related to higher levels of fatigue and poor sleep quality, and these factors are independently correlated with lower QOL.[19] Gray *et al*. suggested that behavioral dysfunction is a mechanism which mediates disease severity to decrease overall perception of HRQOL. Increased internalizing symptoms such as depression and anxiety reduce HRQOL. Externalizing symptoms such as aggression, disruptive, and delinquent behaviors reduce HRQOL in adolescent IBD patients as well.[18]

Anemia and hospitalization were also related to a lower HRQOL in a univariate analysis, however, without statistical significance in a multivariate regression model. In our sample, 29.6% of patients were anemic. Chronic fatigue, a frequent IBD symptom itself, is commonly caused by anemia. Furthermore, one-third of IBD patients suffer from recurrent anemia which disturbs HRQOL. Treatment of IBD-associated anemia with iron led to improvement in patients' QOL. In patients with chronic renal failure, the treatment of anemia with iron ± erythropoietin improves QOL.[26]

In our sample, the patients who had hospitalization suffered from lower QOL (*P* = 0.001). Some previous studies reported the same findings as well.[16,22] Disease flare-ups need hospital admissions which may lead to adverse stress, anxiety, and work disability that decrease career fulfillment.[17]

We found no significant difference regarding HRQOL between CD and UC groups, similar to other studies.[16] Although some studies reported that CD patients have more severe psychosocial dysfunction, reduced well-being, anxiety, and depression as well as more profound effects on HRQOL in comparison to UC patients,[27,28] it may be contributed to the severity of CD which is variable in different areas of the world.

Some available studies support the impact of gender on HRQOL,[3] while the others do not confirm such results, similar to our study,[16] although psychosocial factors influence women more than men in general. Females have greater disease-related concerns as well and evaluate their symptoms more severe and have lower scores of QOL in general population.[29]

Strengths and limitations
Our prospective research examined various dimensions which may affect HRQOL in IBD patients: sociodemographic variables, disease characteristics, disease history, anemia, medical treatments, supplements (folic acid consumption), and sleeping status. However, our study is limited by some factors as well. Cross-sectional design of this study does not guarantee a cause and effect conclusion. Subjective assessment of sleep quality is not as precise as objective measures and possibly does not distinguish the patients in primary stages of sleep disturbance. Folic acid level was not tested among the patients as well.

CONCLUSIONS

We found that sleep disturbance is associated with IBD activity, one of the main concerns of IBD patients which should be managed appropriately. Pharmacological and nonpharmacological treatment of disease activity and sleep disturbance is recommended. Anemia induces somatic and also psychosocial adverse effects which should be paid attention more by physicians. Hospital admissions decrease QOL and might be an indicator of suboptimal treatment and need attention. Folic acid supplement had the strongest relationship with better QOL; therefore, evaluation of folic acid level and efficacy of its supplementation is recommended in further prospective researches. Other micronutrient deficiencies are important and may have a role in QOL in some cases but were not focused in this study.

Conflicts of interest
There are no conflicts of interest.

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