



The Association of Psychological Disorders with Extraintestinal Symptoms in Patients with Irritable Bowel Syndrome

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Quantitative Study

Abstract

Background: Extraintestinal symptoms are common in patients with irritable bowel syndrome (IBS). In the present study, we determined the relationship between psychological disorders and extraintestinal symptoms in patients with IBS.

Methods: Adult patients with IBS referred to 4 gastroenterology clinics in Isfahan, Iran, completed the irritable bowel severity scoring system (IBSSS), extraintestinal symptoms scale, Hospital Anxiety and Depression Scale, and Irritable Bowel Syndrome Quality of Life (IBS-QOL) Questionnaire. Univariate and multivariate analyses were conducted.

Results: The patients included 113 females and 45 males with mean age of 34.8 ± 11.1 years. Cumulative frequency of extraintestinal symptoms was 3.3 ± 2.4 (0 to 10). Anxiety and depression were present in 79.7% and 54.4% of the patients, respectively. Frequency of extraintestinal symptoms was correlated with anxiety and depression ($r = 0.289$ to 0.531), IBS severity ($r = 0.373$ to 0.505), and quality of life ($r = -0.317$ to -0.398). Severity of IBS was independently associated with extraintestinal digestive symptoms' frequency ($\beta = 0.248$). Female gender, education level, and anxiety were independently associated with extraintestinal non-digestive symptoms' frequency ($\beta = -0.225$ to 0.260). Severity of IBS and frequency of non-digestive symptoms were independent predictors of quality of life ($\beta = -0.494$ and -0.218). After controlling for psychological factors, IBS severity and depression were independent predictors of quality of life ($\beta = -0.435$ and -0.318).

Conclusion: Extraintestinal symptoms and psychological disorders are common in patients with IBS and impact their quality of life. Psychological disorders are associated with extraintestinal symptoms, especially non-digestive symptoms. These results highlight the need for an integrated biopsychosocial approach to the management of IBS patients with physical and mental comorbidities.

Keywords: Irritable bowel syndrome, Anxiety, Depression, Psychological, Comorbidity, Quality of life

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Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders (FGIDs) characterized by abdominal pain or discomfort accompanied with disturbed bowel habit (Longstreth, Thompson, Chey, Houghton, Mearin & Spiller, 2006). The prevalence of IBS in the general population is between 3% and 15%, and it is one of the most prevalent diagnoses in outpatient gastroenterology clinics (Chang, 2004). With IBS being a chronic disease and most patients aged between 30 to 50 years, the financial and health burden associated with IBS is considerable (Agarwal & Spiegel, 2011).

Patients with IBS consult physicians for a variety of complaints other than intestinal symptoms, i.e. extraintestinal symptoms. Excess health care costs in IBS have been attributed mostly to such comorbid disorders (Whitehead, Palsson, & Jones, 2002). Extraintestinal symptoms such as symptoms related to the upper digestive system, urinary symptoms, and chronic somatic pains, as well as non-specific symptoms such as fatigue and sleep disturbances are frequently seen in IBS patients (Whitehead Palsson, & Jones. 2002; Whitehead Palsson, Levy. 2007). Such accompanying symptoms and disorders increase the burden associated with IBS and significantly impair the patient's quality of life which can be even more than that of IBS symptoms (Lee, Lee, Kim, Sung, Park, Jin, et al., 2010; Lackner, Keefer, Brenner, Gudleski, Satchidanand, et al., 2013).

The etiology of extraintestinal symptoms in patients with IBS is not well understood. There may be shared pathophysiological mechanisms and risk factors (Whitehead et al., 2002). Widespread visceral (Bouin, Lupien, Riberdy, Boivin, Plourde, & Poitras, 2004) and somatic hypersensitivity (Stabell, Stubhaug, Flaegstad, & Nielsen, 2013), central sensitization (Chang, 2005), and psychosocial factors (Whitehead et al., 2002) are implicated in this regard. Psychological disorders, mostly anxiety, depression, and somatoform disorders, are frequently observed in patients with IBS and

have an important role in the disease course and treatment outcomes (Palsson & Drossman, 2005). Therefore, psychological disorders may explain, albeit not all of, the excess comorbidities seen in patients with IBS.

Due to the impact of extraintestinal symptoms on the quality of life of patients with IBS, therapeutic plans should also consider the controlling of these symptoms. Therefore, the investigation of extraintestinal symptoms and recognition of the etiology of and associated factors to these symptoms are important. Considering limited number of studies performed in this field, the present study was conducted to determine the relationship between psychological disorders and extraintestinal symptoms in patients with IBS. The secondary aim of the study was to evaluate the independent impact of these factors on patients' quality of life.

Methods

This cross-sectional multicenter study was conducted on patients with IBS who referred consecutively to 4 private gastroenterology clinics in Isfahan city (Iran) between the years of 2013 and 2014. Inclusion criteria consisted of an age between 18 and 65 years, diagnosis of IBS based on the Rome III criteria (Longstreth et al., 2006), and the ability to complete the study questionnaires either through self-administration or interview. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences, Isfahan, and verbal consent was obtained from patients.

After being diagnosed by the gastroenterologist based on the Rome III criteria and necessary work-ups, patients were referred to trained interviewers and filled out the self-administered questionnaires and provided demographic data including age, gender, and education level (year).

The irritable bowel severity scoring system (IBSSS) was used to measure the severity of IBS symptoms. It is one of the most commonly applied outcome measures for IBS with appropriate psychometric properties. The scale

contains 5 items including severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, satisfaction with bowel habit, and the overall impact of symptoms on daily life. Each item is scored from 0 to 100 using a 10 cm visual analogue scale (except for pain frequency). The total score of the scale ranges from 0 to 500 with higher scores indicating greater severity. The scores can also be categorized into mild (< 175), moderate (175 to 300), and severe (> 300) cases (Francis, Morris, & Whorwell, 1997).

Based on similar studies evaluating extraintestinal comorbidities in patients with IBS, we generated a list of common symptoms to evaluate the frequency of these symptoms. The items include digestive symptoms (nausea/vomiting, early satiety, postprandial fullness, excessive belching, and heartburn) and non-digestive symptoms (urgency for urination, headache, backache, thigh pain, muscles or joints pain, and fatigue). The items are rated by 5-point Likert responses; never, rarely, sometimes, often, and always. Symptoms are considered present when experienced by the patient often or always. In a pilot study, this scale was found to have acceptable reliability (Cronbach's alpha = 0.7) and validity in comparison to IBS severity and quality of life scales (Gholamrezaei, Nemati, Minakari, Daghighzadeh, Tavakkoli & Emami, 2010).

The Irritable Bowel Syndrome-Quality of Life (IBS-QOL), which is one of the most commonly applied and well validated questionnaires for the assessment of quality of life in patients with IBS, was used in this study. The IBS-QOL comprises 34 items with 5-point response scales (scored 0 to 4) and covers 8 dimensions of quality of life including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual concerns, and relationships. Higher values indicate better quality of life after converting the raw score into 0 to 100 points (Drossman, Patrick, Whitehead, Toner, Diamant, Hu, et al., 2000).

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate psychological

disorders. It contains 14 items in 2 dimensions of anxiety and depression. Each item is rated on a 4-point Likert scale (scored 0 to 3), giving a maximum score of 21 for each of the subscales. At the cut-off score of 8, the HADS has a sensitivity and specificity of above 80% in diagnosing clinically important anxiety and depression disorders (Bjelland, Dahl, Haug, & Neckelmann, 2002).

For all the above mentioned questionnaires, linguistically validated and reliable Persian versions were used in this study (Montazeri, Vahdaninia, Ebrahimi, & Jarvandi, 2003; Gholamrezaei, Zolfaghari, Farajzadegan, Nemati, Daghighzadeh, Tavakkoli, et al., 2011; Gholamrezaei et al., 2010). An interviewer was available if the patient required explanation for completing the questionnaires.

Sample size was calculated as 160 cases using the G*Power software (version 3.1.7, Franz Faul, Kiel University, Germany). Type I error probability and power were considered as 0.05 and 0.95, respectively. A medium effect size (f^2) of 0.15 and 8 predictors for quality of life were considered for the multiple linear regression tests.

Data were analyzed using the SPSS software (version 16.0, SPSS Inc., Chicago IL, USA). Data are presented as mean \pm standard deviation (SD), mean [standard of error], and number (%). Normal distribution of quantitative data was checked using the Kolmogorov-Smirnov test. Comparisons were made using Fisher's exact test and independent sample t-test (or Mann-Whitney test) for qualitative and quantitative data, respectively. The Spearman's rho was applied to test the correlation between the study variables. Linear regression analyses were performed to find factors associated with cumulative frequency of extraintestinal symptoms as well as independent predictors of quality of life. A P value of less than 0.05 was considered significant in all analyses.

Results

Demographic data and disease characteristics

During the study period, 193 patients with IBS were invited to participate, among which

14 patients were not willing to attend the study and 21 patients filled out the questionnaire incompletely. Finally, 158 patients with complete data were included in the study (mean age = 34.8 ± 11.1 , 71.5% female). Demographic data and disease characteristics are presented in table 1. No statistically significant difference was observed between female and male patients regarding demographic data or IBS characteristics (all $P > 0.05$).

Table 1: Demographic data and disease characteristics (n = 158)

Variable	
Age (year) (mean \pm SD)	34.8 \pm 11.1
Gender [Number (%)]	
Female	113 (71.5)
Male	45 (28.4)
Education level (year) (mean \pm SD)	11.7 \pm 3.9
IBS symptoms duration (year) (mean [SE])	5.8 [0.5]
IBS subtypes [Number (%)]	
IBS-C	45 (28.5)
IBS-D	26 (16.5)
IBS-M	82 (51.9)
IBS-U	5 (3.2)
IBS severity [Number (%)]	
Mild	24 (15.2)
Moderate	82 (51.9)
Severe	52 (32.9)

SD: Standard deviation; SE: Standard of error

Frequency of extraintestinal digestive and non-digestive symptoms (presented often/always) is reported in table 2. Frequency of postprandial fullness, headache, thigh pain, and fatigue was significantly higher in female than male patients (all $P < 0.05$). Moreover, the cumulative frequency of extraintestinal symptoms was higher in females than males (3.7 ± 2.4 vs. 2.3 ± 1.9 ; $P = 0.002$).

Anxiety and depression were present in 77.8 and 55.6% of males and 80.5 and 54.0% of females with no significant difference between genders (both $P > 0.05$). Correlations between demographic data, extraintestinal symptoms'

frequency, disease severity, anxiety, depression, and quality of life are presented in table 3. In summary, the frequency of extraintestinal symptoms (total, digestive, and non-digestive) was correlated with anxiety and depression severity ($r = 0.289$ to 0.531), IBS severity ($r = 0.373$ to 0.505), and quality of life score ($r = -0.317$ to -0.398). Age and education level were correlated with the frequency of non-digestive symptoms ($r = 0.208$ and -0.289). Anxiety and depression severity were positively correlated with IBS severity ($r = 0.314$ to 0.451) and negatively correlated with quality of life score ($r = -0.425$ to -0.502).

Linear regression analyses were conducted to find independent predictors of extraintestinal symptoms' frequency and quality of life. Female gender, education level, IBS severity, and severity of anxiety and depression were all independently associated with total extraintestinal symptoms' frequency ($\beta = -0.186$ to 0.233 , Table 4). After separating digestive and non-digestive symptoms, IBS severity was associated with extraintestinal digestive symptoms' frequency and female gender, education level, and anxiety severity were associated with extraintestinal non-digestive symptoms' frequency ($\beta = -0.225$ to 0.260). Furthermore, there was a non-statistically significant association between depression severity and frequency of extraintestinal digestive and non-digestive symptoms ($\beta = 0.182$ and $\beta = 0.203$, $P = 0.073$ and $P = 0.061$, respectively; Table 4).

With regard to the quality of life, linear regression models were used with and without including psychological factors. In the first model, severity of IBS and frequency of non-digestive extraintestinal symptoms were independently associated with IBS-QOL score ($\beta = -0.494$, $\beta = -0.218$). The association between extraintestinal symptoms and quality of life disappeared after including psychological factors in the analysis (Model 2). IBS severity and depression were independent predictors of quality of life in the second model ($\beta = -0.435$, $\beta = -0.318$; Table 5).

Table 2: Frequency^a of extraintestinal symptoms in female and male patients

	Female (n = 113)	Male (n = 45)	P*
Digestive symptoms			
Nausea/vomiting	13 (11.5)	2 (4.4)	0.235
Early satiety	33 (29.2)	10 (22.2)	0.432
Postprandial fullness	59 (52.2)	11 (24.4)	0.002
Excessive belching	33 (29.2)	12 (26.6)	0.846
Heartburn	28 (24.7)	11 (24.4)	> 0.999
Non-digestive symptoms			
Urgency for urination	39 (34.5)	12 (26.6)	0.451
Headache	28 (24.7)	2 (4.4)	0.002
Backache	34 (30.0)	8 (17.7)	0.161
Thigh pain	26 (23.0)	4 (8.8)	0.044
Muscles or joints pain	40 (35.3)	10 (22.2)	0.130
Fatigue	67 (59.2)	18 (40.0)	0.034

Data are presented as number (valid percent).

^aSymptom was considered present if experienced often/always; *Fisher's exact test

Table 3: Correlations between demographic data, extraintestinal symptoms' frequency, disease severity, anxiety, depression, and quality of life

	EIS frequency			IBSSS	IBS-QOL
	Total	Digestive	Non-digestive		
Age	0.134	-0.026	0.208*	0.093	0.004
Education level	-0.206*	-0.035	-0.289*	-0.166*	0.161*
Anxiety	0.531**	0.342**	0.526**	0.451**	-0.425**
Depression	0.447**	0.289**	0.440**	0.314**	-0.502**
EIS frequency					
Total				0.505**	-0.398**
Digestive				0.373**	-0.317**
Non-digestive				0.473**	-0.361**
IBSSS					-0.494**

Data are presented as Spearman's correlation coefficients. EIS: Extraintestinal symptoms, IBSSS: Irritable bowel severity scoring system, IBS-QOL: Irritable bowel syndrome-quality of life

*P < 0.05, **P < 0.01

Table 4. Multiple linear regression models of possible predictors of extraintestinal symptoms' frequency

	Extraintestinal symptoms' frequency		
	Total	Digestive	Non-digestive
Age	0.001	-0.063	0.047
Gender (Female vs. Male)	0.193**	0.109	0.193**
Education level	-0.186*	-0.051	-0.225**
IBSSS	0.219**	0.248**	0.130
Anxiety	0.218**	0.066	0.260**
Depression	0.233**	0.203	0.182
R ² (adjusted)	0.452 (0.425)	0.206 (0.166)	0.420 (0.391)

Data are presented as standardized coefficients (Beta). IBSSS: Irritable bowel severity scoring system

*P < 0.05, **P < 0.01

Table 5: Multiple linear regression models of possible predictors of quality of life

	Model 1	Model 2
Age	0.116	0.132
Gender (Female vs. Male)	0.025	-0.035
Education level	0.056	0.066
IBSSS	-0.494**	-0.435**
EIS frequency		
Digestive	-0.066	-0.003
Non-digestive	-0.218*	-0.081
Anxiety	-	-0.039
Depression	-	-0.318**
R ² (adjusted)	0.419 (0.390)	0.501 (0.466)

Data are presented as standardized coefficients (Beta). IBSSS: Irritable Bowel Severity Scoring System, EIS: Extraintestinal symptoms, *P < 0.05, **P < 0.01

Discussion

We evaluated the relationship between psychological disorders and extraintestinal symptoms in patients with IBS. In our study, clinically important levels of anxiety and depression were found in about 80 and 55% of the patients, respectively. Previous studies have shown high frequency of psychological disorders, notably anxiety and depression (20% to 50%), in patients with IBS (Fond et al., 2014). The higher frequency of anxiety and depression in our study may be attributed to the tertiary care setting of the study. We also found various digestive and non-digestive extraintestinal symptoms in up to half of the participants. Associations were found between psychological disorders and extraintestinal symptoms which were more evident for non-digestive symptoms and independent from IBS severity and patients' demographic factors. It should be noted that the causality between psychological disorders and extraintestinal complaints cannot be concluded from our study results. The existence of a reciprocal relation between psychological dysfunction and extraintestinal symptoms in a way that each causes development and/or progression of the other is plausible.

Comorbidities in patients with IBS can be divided into 2 general groups of digestive and non-digestive complaints. With regards to digestive disorders, up to 50% of patients with IBS have concomitant symptoms of

gastroesophageal reflux disease (GERD), and there is considerable overlap between IBS and functional dyspepsia (FD) (Whitehead et al., 2002). Similar to our study, previous studies have found postprandial fullness, epigastric pain, nausea/vomiting, early satiety, and bloating in about half of the patients with IBS (Whitehead et al., 2002). It is hypothesized that IBS, FD, and GERD share some common pathophysiological mechanisms which can explain the considerable overlap among these gastrointestinal disorders (Whitehead et al., 2002). In our study, IBS severity was independently associated with digestive symptoms, but it was not independently associated with anxiety. In addition, the association of depression with digestive symptoms was not statistically significant. Accordingly, high frequency of extraintestinal digestive symptoms in patients with IBS seems to be due to a shared pathophysiology (Whitehead et al., 2002), but may not be attributed to the high frequency of psychological disorders in these patients.

On the other hand, we found that anxiety and depression had correlation with non-digestive symptoms which was stronger than that with digestive symptoms. Moreover, there was no independent association between IBS severity and non-digestive symptoms. Nevertheless, female gender, lower education level, and higher anxiety were independent predictors for the presence of non-digestive symptoms. In the

study by Lembo, Zaman, Krueger, Tomenson, and Creed, 2009, on 3048 individuals, of which 12.2% had IBS, psychological disorders and IBS were independently correlated with the number of extraintestinal symptoms. Furthermore, there was a direct relationship between psychological disorders and extraintestinal symptoms (Lembo et al., 2009). These findings are in favor of possible common risk factors for some of the observed comorbidities in IBS as well as highlighting the role of psychological dysfunction in non-digestive comorbidities associated with IBS. However, some investigators believe that comorbidities in patients with IBS are due to biased symptom perception and a general tendency to exaggerated symptom reporting rather than a shared pathophysiology (Whitehead et al., 2007). If this was true, we would expect to see an association between psychological factors and both digestive and non-digestive symptoms; however, only an association with non-digestive complaints was evident in our study. It must be noted that we evaluated a limited number of non-digestive complaints mostly related to pain conditions and fatigue. In addition, we did not evaluate other psychological factors such as somatization and catastrophizing which are common in patients with IBS and can affect symptom reporting (van Oudenhove, Vandenberghe, Vos, Holvoet, & Tack, 2011; Lackner, Jaccard, Baum, Smith, Krasner, Katz, et al. 2011; van Tilburg, Palsson, & Whitehead, 2013). Hence, our study results can not be generalized to other physical comorbidities and a more comprehensive psychiatric evaluation of patients is required in future studies.

Previous studies have shown an association between IBS and a number of chronic somatic pain conditions such as fibromyalgia (Whitehead et al., 2002), headaches (Lau, Lin, Chen, Wang, & Kao, 2014), and back pain (Lackner, Ma, Keefer, Brenner, DGudleski, Satchidanand, et al., 2013). Lackner et al. (2013) reported an average of 5 comorbidities

(1 mental, 4 physical) in patients with IBS. They found that, compared with other comorbidities, generalized anxiety, depression, back pain, agoraphobia, tension headache, and insomnia are associated with greater illness and symptom burdens. Similar to our results, they found that mental comorbidity had greater impact on quality of life than physical comorbidity (Lackner et al., 2013). When we controlled for anxiety and depression, the association of extraintestinal symptoms and quality of life disappeared in the regression analysis. It seems that IBS physical comorbidities can affect quality of life, but when they are psychologically distressing for the patient. Indeed, some of the extraintestinal complaints in patients with IBS can be attributed to drug intolerance (Poitras, Gougeon, Binn, & Bouin, 2008). These complaints are not, however, associated with psychological comorbidity and rather are of a somatic origin (Poitras et al., 2008).

The results of our study have important clinical implications. Due to unclear pathophysiology, and therefore, limited available pharmacological treatments, managing IBS is challenging. There is no reliable biomarker to be considered as the goal of treatment. Accordingly, treatments are aimed to enhance the quality of life and psychological well-being of the patients. However, current medical treatments such as laxatives, antispasmodics, and bulking agents can provide IBS specific symptomatic relief (Ford, Quigley, Lacy, Lembo, Saito, Schiller, et al, 2014a), but are not expected to have efficacy for extraintestinal symptoms, especially non-digestive symptoms. We showed that these symptoms significantly impact the patients' quality of life and may also affect their psychological well-being. Antidepressants are widely prescribed by gastroenterologist and are shown to be effective for treatment of IBS. These drugs have central analgesic effects. Therefore, they may be efficacious for patients with IBS and somatic pain comorbidities (Dekel, Drossman, & Sperber, 2013). Furthermore, considering the

high frequency of psychological disorders in patients with IBS, antidepressants can be beneficial for patients with these mental comorbidities (Dekel et al., 2013). However, there is no direct evidence on the efficacy of antidepressants on physical comorbidities in patients with IBS and studies on mental comorbidities are scarce (Ford, Moayyedi, Lacy, Lembo, Saito, Schiller, et al., 2014b). Hence, more clinical trials are warranted in this regard.

Increasing number of studies have evaluated and shown the efficacy of various psychological therapies in patients with IBS (Ford et al., 2014b). These treatments can improve IBS symptoms as well as psychological well-being (Henrich, Knittle, De Gucht, Warren, Dombrowski & Maes, 2015). We previously showed that training on coping strategies can improve digestive symptoms, anxiety, and depression in patients with IBS. We also found more improvement in extraintestinal symptoms through this psychological treatment than standard care (Kheir-Abadi, Bagherian, Nemati, Daghighzadeh, Maracy & Gholamrezaei, 2010). An interesting finding was a correlation between improvement in psychological symptoms and extraintestinal symptoms which was independent from improvement of IBS symptoms (Kheir-Abadi et al., 2010). Along with the results of the present study, these findings indicate the need for an integrated pharmacological and psycho-behavioral approach for the management of patients with IBS and physical and mental comorbidities.

The present study had a number of limitations. This study was performed only in private tertiary care clinics and the results are not generalizable to other care settings. Determination of the cause and effect relationship between psychological symptoms and extraintestinal symptoms was not possible by this cross-sectional study. Moreover, we did not evaluate a comprehensive list of digestive and non-digestive symptoms, did not evaluate the severity of symptoms, and only assessed anxiety and depression as psychological factors.

Since other symptoms and psychological disorders are frequently observed in patients with IBS, a more comprehensive evaluation is required in future studies.

Conclusion

Digestive and non-digestive extraintestinal symptoms and psychological disorders are frequently observed in patients with IBS and have a great impact on patients' quality of life. Psychological disorders are associated with extraintestinal symptoms, especially non-digestive symptoms. These results highlight the need for an integrated pharmacological and psycho-behavioral approach to the management of patients with IBS and physical and mental comorbidities. Further studies with more comprehensive evaluation of extraintestinal symptoms as well as clinical trials on the efficacy of integrative therapies for patients with IBS and comorbidities are required.

Conflict of Interests

Authors have no conflict of interests.

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