Factors associated with adherence to treatment in Iranian patients with inflammatory bowel disease

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Background: In this study, we investigated several socioeconomic, clinical, and psychological factors associated with medication adherence in a sample of Iranian patients with inflammatory bowel disease (IBD). **Materials and Methods:** This study was conducted on 110 IBD patients from 2013 to 2014 in Isfahan, Iran. The patients were invited to complete three anonymous questionnaires including the Hospital and Anxiety Depression Scale (HADS) for assessing the levels of anxiety and depression; IBD Questionnaire-Short Form (IBDQ-9) for the quality of life; and a visual analog scale assessing the medication adherence. A self-assessment adherence rate of more than 80% was considered "appropriate adherence." **Results:** Overall, 99 patients completed the questionnaires. Among them, 77.8% reportedly adhered to their medications. There was no statistical difference between adherence and nonadherence rates in terms of gender, educational status, disease type, disease severity, and family history of IBD. Conversely, single patients (100% vs. 74.1%; $P = 0.03$), nonsmokers (79.4% vs. 0.0%; $P = 0.04$), patients receiving immunosuppressive drugs (100% vs. 71.9%; $P = 0.01$), and corticosteroids (95.1% vs. 65.5%; $P = 0.01$) were more likely to be adhered than their counterparts. No differences emerged in terms of the mean HADS scores in either of the sexes. The mean IBDQ-9 score was significantly higher in adhered patients only in females (31.08 ± 11.6 vs. 24.7 ± 9.1; $P = 0.04$) but not in males. **Conclusion:** The adherence rate in our study is almost similar to developed countries. Single marital status, not smoking, receiving corticosteroids and immunosuppressive drugs, and higher IBDQ-9 score in females are associated with higher adherence rate.

Key words: Adherence, inflammatory bowel disease, nonadherence, treatment

INTRODUCTION

Inflammatory bowel disease (IBD) is a unifying concept of several diseases which is characterized by recurrent episodes of remission and the exacerbation of various gastrointestinal symptoms including abdominal pain and/or diarrhea. IBD is generally divided into Crohn's disease (CD) and ulcerative colitis (UC).[1] IBD is typically diagnosed in young adults before the age of 30 years. The peak age of onset is between 15 and 30 years; however, it can occur at any age.[2] The pathogenesis of IBD is not fully understood but is suggested to be multifactorial with both genetic and environmental components.[2,3]

IBD is a chronic and lifelong disease with severely disabling symptoms which affect the health-related quality of life.[4,5] The effective management of IBD requires a long-term use of medications to maintain disease remission. However, long and ongoing treatments might be costly, difficult to maintain, and have unpleasant side effects for many patients. Nonadherence to prescribed medication is relatively common in patients with IBD, and it is reported in 7%–75% of the patients in different studies.[5-9] It is well established that medication nonadherence is associated

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with increased risk of disease relapse, greater risk of colon cancer, and reduced quality of life.[10] Therefore, in recent years, many studies have investigated the factors associated with treatment nonadherence in these patients. Although some consistencies exist in the predictors of nonadherence between studies, it is more common that different studies report conflicting results.[5-8]

Despite the relatively high prevalence of IBD in Iran,[11] to date, no study has investigated the medication adherence rate in these patients. In this study, as the first report from Iran, we evaluated the treatment adherence rate in a sample of Iranian patients with IBD and investigated the association of several factors that were collated into four categories (i.e., socioeconomic, clinical, treatment, and psychological) with medication nonadherence in this population.

MATERIALS AND METHODS

Study population and setting
In the time period of January 2013 to February 2014, we prospectively enrolled 110 consecutive patients with confirmed diagnosis of IBD who had referred to outpatient clinics of Pour-Sinaye-Hakim, Isfahan, Iran. Pour-Sinaye-Hakim is one of the main tertiary care centers for gastroenterology diseases in Isfahan province. The inclusion criteria were (1) confirmed diagnosis of IBD according to conventional endoscopic, radiological, and histological criteria; (2) disease duration of at least 6 months; and (3) being over than 18 years of age. We excluded patients with comorbid conditions that could act as confounders in data gathering and interpretation, new patients, and persons unable to fill up tests and questionnaires. The protocols of the study were completely explained, and a written informed consent was obtained from the patients. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences (research project number: 291081).

The following demographic and clinical data were collected from each patient: age, gender, age at onset of disease, disease duration, level of education (illiterate, less than high school, high school graduate, and academic education), occupational status (unemployed, employed, retired, student, and housewife), marital status (single and married), smoking status (yes and no), disease type (UC and CD), current medications, previous surgery (yes and no), and family history of IBD (yes and no). The patients who attended this survey were invited to fill out three questionnaires which included: the Hospital and Anxiety Depression Scale (HADS)[12] for assessing the levels of anxiety and depression, IBD Questionnaire-Short Form (IBDQ-9)[13] for assessing the quality of life, and the a self-reporting visual analogue scale (VAS) questionnaire assessing the treatment

adherence. Participation in the survey was voluntary, and all respondents were assured that the questionnaires would remain anonymous and confidential. The questionnaires were filled out under the supervision of trained researchers. For patients who were illiterate, the questionnaires were filled out in face-to-face interviews by researcher. Upon completion of the questionnaires, the patients were invited to join educational programs and received the appropriate disease education.

Study questionnaires
Hospital and Anxiety Depression Scale
The anxiety and depression of the patients were measured using the HADS questionnaire.[12] The HADS is a validated and widely used self-administered instrument which contains 14 items dividing into two subscales of HADS-anxiety (HADS-A) and HADS-depression (HADS-D). Each subscale has seven items that are scored on a 4-point Likert scale (ranging from 0 to 3). The total score for each subscale is measured by simple summation of the individual items, and the higher scores reflect greater levels of anxiety and depression. Scores in each subscale (anxiety and depression) range from 0 to 21. A cutoff value of 11 and more is generally accepted as significant psychological morbidity. The Persian version of HADS was used in this study which has been shown to have satisfactory reliability and validity (Cronbach's alpha: HADS-A = 0.82 and HADS-D: 0.76).[14]

Inflammatory Bowel Disease Questionnaire-Short Form
The IBDQ is a widely used disease-specific instrument for assessing the quality of life in patients with IBD. The original IBDQ (IBDQ36) contains 36 items on nausea, gases, bowel movement frequency, abdominal cramps, need to delay appointments or commitments, fatigue, happiness, and perceived energy. A short form of IBDQ36 (IBDQ-9) includes 9 items which are the most representative dimensions of the IBDQ36 and has been demonstrated to be valid and reproducible. We used a Persian version of this questionnaire which has been translated and validated recently.[15]

Assessment of treatment adherence
To assess the treatment adherence, all studied participants were provided with a self-reporting VAS (rating from 0 to 10; with 0 = least adherence and 10 = most adherence) and were asked to assess their adherence to treatment during the previous 4 weeks. A self-assessment adherence rate of more than 8/10 was considered "appropriate treatment adherence" as suggested by several similar previous studies.[5,16]

Statistical analysis
Statistical analysis was performed with SPSS statistical software (version 20; SPSS, Chicago, IL, USA). Comparisons

of continuous variables among patients with treatment adherence and those with treatment nonadherence were made by two-sided *t*-test, and the comparison of categorical data was performed by Chi-square test. A stepwise logistic regression analysis was recruited to identify factors associated with adherence. $P < 0.05$ was considered statistically significant.

RESULTS

Respondents' characteristics
Of the total 110 volunteers who participated in this survey, 99 respondents completed the questionnaires appropriately (90.0% cooperation rate). Eleven patients were excluded (five patients were unable to fill up questionnaires, four patients due to incomplete information, and two were newly diagnosed). The respondents were consisted of 67 (67.6%) females and 32 males (32.4%). The mean age of the respondents was 40.6 ± 12.1 years (range: 18–68 years). The mean of age at onset of disease was 33.3 ± 13.5 years and the mean duration of disease was 7 ± 4.6 years. Among the 99 enrolled patients, a total of 77 (77.8%) patient reported a VAS score of 8/10 or above for treatment adherence.

Treatment adherence and socioeconomic status
Table 1 summarizes the treatment adherence according to the socioeconomic status of the patients. There was no statistical difference between adherence and nonadherence in terms of gender ($P = 0.56$), educational status ($P = 0.12$), and occupational status ($P = 0.51$). On the other hand, single patients (100% vs. 74.1%; $P = 0.03$) and nonsmokers (79.4% vs. 0.0%; $P = 0.04$) were statistically more adherent than their married or smoker counterparts. Similarly, in the logistic regression model, we found no significant association between adherence and socioeconomic status.

Treatment adherence and disease characteristics
Table 2 presents the treatment adherence rates according to the disease characteristics of the patients. Among the patients, 56 (56.5%) patients had UC and the remaining 43 (43.5%) had CD. The statistical analysis revealed no significant difference between adherence and nonadherence with respect to any of the studied disease characteristics including disease type ($P = 0.16$), disease severity ($P = 0.22$), previous surgery for IBD ($P = 0.25$), and positive family history of IBD ($P = 0.23$). Moreover, there was no significant association between disease characteristic and adherence to treatment based on logistic regression.

Treatment adherence and inflammatory bowel disease medications
Table 3 summarizes the treatment adherence according to the medication types of the patients. No statistical

Table 1: The treatment adherence according to the socioeconomic status of the patients (*n*=99)

	n	Adherent (%)	Nonadherent (%)	*P**
Gender				
Females	67	76.1	23.9	0.56
Males	32	81.2	18.8	
Marital status				
Single	14	100	0	0.03
Married	85	74.1	25.9	
Educational status				
literate	8	50.0	50.0	0.12
Less than high school	25	80.0	20.0	
High school diploma	37	81.1	18.9	
Academic education	29	79.3	20.7	
Occupational status				
Unemployed	25	68.0	32.0	0.51
Self-employed	46	78.8	22.2	
Retired	10	78.8	22.2	
Student	12	83.3	16.7	
Housewife	6	100	0	
Current smoker				
Yes	2	0	100	0.04
No	97	79.4	20.6	

*Chi-square test

Table 2: The treatment adherence according to the disease characteristics of the patients (*n*=99)

	n	Adherent (%)	Nonadherent (%)	*P**
Disease type				
UC	56	78.6	21.4	0.16
CD	43	76.7	23.3	
Disease severity				
Mild	65	75.4	25.6	0.22
Moderate	25	72.0	28	
Severe	9	100	0	
Previous surgery				
Yes	50	84.0	16.0	0.25
No	49	71.4	28.6	
Family history of IBD				
Yes	20	90	10	0.23
No	79	72.1	27.9	

*Chi-square test. UC = Ulcerative colitis; CD = Crohn's disease; IBD = Inflammatory bowel disease

difference between adherence and nonadherence was observed regarding patients taking 5-aminosalicylic acid (5-ASA) ($P = 0.34$), thiopurine ($P = 0.07$), and anti-tumor necrosis factor alpha (anti-TNFα) ($P = 0.31$). Conversely, patients who were treated with immunosuppressive drugs (100% vs. 71.9%; $P = 0.01$) and corticosteroids (95.1% vs. 65.5%; $P = 0.01$) were significantly more adhered than patients who did not take these drugs. Logistic regression showed that taking steroid was significantly associated with increased chance of adherence to treatment by 15 (confidence interval: 2.069–21 $P = 0.008$).

Treatment adherence and Hospital and Anxiety Depression Scale and Inflammatory Bowel Disease Questionnaires-Short Form

There was no statistically significant association between adherence and nonadherence in terms of mean HADS-A and HADS-D scores in either of the sexes. The mean IBDQ-9 score was significantly higher in adhered patients than nonadhered cases in females (31.08 ± 11.6 vs. 24.7 ± 9.1; $P = 0.04$), but the difference in mean of IBDQ-9 in males was not significant (28.2 ± 5.1 vs. 23.8 ± 7.3; $P = 0.14$). The details of treatment adherence according to the mean scores of the questionnaires are presented in Table 4.

DISCUSSION

Medication nonadherence is associated with both adverse clinical outcomes and economic burden including increased hospital admissions, inadequate use of health-care professionals' time, and increased sickness-related work absence.[5-9] In this study, we evaluated the association of several socioeconomic, clinical, treatment, and psychological factors with treatment adherence and nonadherence in a sample of Iranian patients with IBD. The findings of this

Table 3: The treatment adherence according to the medication types of the patients (*n*=99)

	n	Adherent (%)	Nonadherent (%)	*P**
5-ASA				
Yes	90	78.9	21.1	0.34
No	9	66.6	33.3	
Corticosteroids				
Yes	41	95.1	4.9	0.01
No	58	65.5	34.5	
Thiopurine				
Yes	43	86.0	14.0	0.07
No	56	71.4	28.6	
Immunosuppressive				
Yes	17	100	0	0.01
No	82	71.9	28.1	
Anti-TNFα				
Yes	79	77.2	22.8	0.31
No	20	70.0	30.0	

*Chi-square test. 5-ASA = 5-aminosalicylic acid; TNF-α = Tumor necrosis factor-alpha

Table 4: The treatment adherence according to the mean scores of the questionnaires

Sex	Questionnaire	Adherent		Nonadherent		*P**
		n	Mean score	*n*	Mean score	
Males	HADS-A	26	8.3±3.6	6	11.1±2.9	0.06
	HADS-D	27	5.7±3.8	5	7.4±1.3	0.27
	IBDQ-9	25	23.8±7.3	7	28.2±5.1	0.14
Females	HADS-A	50	10.42±4.05	17	9.6±4.5	0.51
	HADS-D	49	7.5±5.2	18	6.0±6.4	0.34
	IBDQ-9	52	31.08±11.6	15	24.7±9.1	0.04

*Two-sided *t*-test. HADS-A = Hospital and Anxiety Depression Scale-Anxiety; HADS-D = Hospital and Anxiety Depression Scale-Depression; IBDQ-9 = Inflammatory Bowel Disease Questionnaire-Short Form

study carry significant implications for gastrointestinal specialists in recognizing the barriers of medication nonadherence and developing effective management strategies that will promote the treatment adherence.

In our survey, the overall frequency of medication adherence was about 77.8% which is relatively high and is similar to the results obtained from Western and developed countries. As for comparison, similar surveys in other countries revealed that in Canada 73%,[17] in United Kingdom 71%,[18] in France 89.6%,[16] and in Australia 71.3%[19] of the adult patients with IBD were adhered to their medications. The results of two systematic literature reviews of studies on adult patients with IBD demonstrated that treatment nonadherence rates range from 7% to 75% in different populations.[5,20] Such considerable variation in adherence rates between the studies reflects the inconsistencies in study design and methods, makes it difficult to compare the results, and limits the generalizability of the findings. As, an example, the questionnaires used for the assessment of medication adherence are different among the studies. Several studies,[5,16] including our study, used the VAS for the assessment of medication adherence among the patients. However, a number of studies[5,20] have used the eight-item Morisky Medication Adherence Scale[21] for assessment of adherence. Besides, differences in the demographic and epidemiological features of the studied samples may also contribute in discordance regarding the adherence rates between the studies. As to mention, the lower ranges of the medication adherence rate generally pertain to surveys obtained from developing countries where IBD medications are not easily accessible or the costs of medications are high.[5,20] However, in Iran, like the most developed countries, IBD medications are easily accessible with relatively low costs as the health-care insurance system covers almost 70% of the drug expenditure. This may explain the observation of the relatively high rate of treatment adherence our study as the accessibility and the costs of medication are not significant contributors of nonadherence in Iran.

With respect to the socioeconomic and demographic variables, we observed that single patients and nonsmokers were more likely to be adhered to their medications. We did not observe any significant relationship between other demographic variables including sex, level of education, and occupational status. Although the association of sociodemographic variables and treatment adherence has been largely investigated in previous similar works, none of the demographic variables have been found to be consistently associated with adherence in IBD patients.[20] Both systematic reviews of the field have indicated that the majority of the studies have found no significant relationship between age, sex, marital status, education,

and occupation and treatment adherence.[5,20] In our survey, we found a significant association between smoking and higher nonadherence rate which was in line with the results obtained by Nahon *et al.*[16] and Horváth *et al.*[22] studies. It is to be mentioned that in our survey, only two patients were smokers with both reporting nonadherence, resulting in a nonadherence rate of 100% for the smokers. Therefore, it should be acknowledged that the relatively small number of smokers in our survey might have influenced our results.

We found no significant association between nonadherence and variables related to IBD characteristics including disease type, disease severity, and positive family history of IBD. In our survey, all patients (100%) with severe disease reported to be adhered to their medications, whereas 75.4% of the patients with mild and 72.7% of the patients with moderate disease were adhered. Nevertheless, these differences did not reach the significant threshold [Table 2]. The association between treatment adherence and disease characteristics is a matter of debate, and conflicting results exist in the literature. In a number of studies, the authors reported a significant association between disease severity, disease duration, and disease activity and treatment adherence,[22,23] whereas other studies found no significant relationship.[16,17] Vangeli *et al.*[20] in their systematic review of factors associated with treatment nonadherence indicated that only a minority of published studies have found a positive association between disease duration (21% of the published studies) or disease activity (25% of the published studies) and treatment adherence; in contrary, the majority of the authors have not confirmed these associations. Thus, although controversial results exist in the literature regarding the association of disease characteristics and treatment adherence, our findings are in agreement with the bulk of literature.

In our study, patients who were under treatment with corticosteroids, immunosuppressive drugs, and thiopurine were more likely to be adhered to their medications. In contrast, we observed no significant difference between adherence and nonadherence rate in patients who were under 5-ASA or anti-TNFα medications. It is notable that 100% of the patients who received immunosuppressive medications reported to be adhered in our study [Table 3]. In the literature, greater rates of medication adherence were generally found to be associated with treatment with corticosteroids[24] and immunosuppressive[15,19] drugs. Despite heterogeneity in the medication types assessed in different studies, it is consistently demonstrated that less frequent dosing of medications is associated with a greater likelihood of adherence.[20,25,26]

Psychological distresses such as anxiety and depression have been reported to be associated with treatment nonadherence,[5,16] disease activity, and poor quality of life[27] in patients with IBD. In our study, we used the validated scale of HADS questionnaire for the measurement of anxiety and depression. We observed no significant difference in the means of HADS-A and HADS-D questionnaires between the adherence and nonadherence groups. In contrast with our findings, Goodhand *et al.*[7] in a similar work using HADS questionnaire found that the higher HADS-D scores were statistically associated with higher nonadherence rates. Furthermore, despite heterogeneity in methods of depression measurement across studies, depression was consistently associated with treatment nonadherence.[19] Finally, in our study, the mean IBDQ-9 score was significantly higher in adhered patients than the nonadhered cases in females, but the corresponding figure was not significant for males. This observation was almost similar to the study of López San Román *et al.*[28] who observed that adherence was more likely in patients with higher IBDQ-32 scores.

Study limitations
The findings of this study must be interpreted in view of its limitations. The relatively small sample size is the main limitation of our study that may affect the generalizability of our results. Furthermore, several other sociodemographic factors including monthly income, socioeconomic status, number of family members, history of divorce, and previous smoking might be associated with medication adherence in this population that were not investigated in our study. Therefore, with respect to the vast cultural and socioeconomic diversity in Iran, future studies with larger sample size are warranted to shed more light on this issue.

CONCLUSION

In this study, as the first report from Iran, we presented the treatment adherence rate and investigated the association of several socioeconomic, clinical, treatment, and psychological factors with treatment adherence. The adherence rate in our study was relatively high and was almost similar to the reports from developed countries. Single marital status, no smoking, receiving corticosteroids and immunosuppressive drugs, and higher IBDQ-9 score are associated with higher adherence rate in our study. Studies with larger sample sizes are warranted to shed more light on this issue.

Conflicts of interest

There are no conflicts of interest.

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