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Health-related quality of life in patients with inflammatory bowel disease: a single-center experience

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Abstract

Background Inflammatory bowel disease (IBD) has a negative impact on health-related quality of life (HRQoL). The aim of the study was to assess HRQoL of IBD patients in South-Western Greece.

Methods 89 IBD patients [38 (42.7%) Crohn's disease (CD), 51 (57.3%) ulcerative colitis (UC)] were included. HRQoL was assessed using IBD questionnaire (IBDQ), which tests four health domains: bowel symptoms (BS), systemic symptoms (SS), emotional function (EF) and social function (SF). Total score (TS) ranges from 32 to 224. Disease activity was measured using Crohn's Disease Activity Index (CDAI) (CD), and Truelove and Witts classification (UC). The impact of epidemiological and disease-specific characteristics on IBDQ was studied.

Results No statistically significant difference was found in all IBDQ scores between UC and CD patients. No correlation was found regarding age, sex, smoking, anemia, disease duration and use of corticosteroids, 5-aminosalicylates or immunosuppressives with HRQoL. The factors found to have a major negative impact on all IBDQ scores was disease severity both in CD and UC, and education on bowel symptoms in CD. On multivariate analysis, only high disease activity had significant effects on total and dimensional scores of IBDQ in UC (TS, P=0.005; BS, P<0.001; SS, P=0.004; EF, P=0.05; SF, P=0.001), whereas in CD, only CDAI (TS, P=0.001; BS, P=0.004; SS, P=0.001; EF, P=0.003; SF, P=0.003) and education (TS, P=0.047; BS, P=0.004; SS, P=0.03) had significant effects.

Conclusions IBD patients in remission experience better HRQoL than patients with active disease. Induction of remission should become the mainstay of care regarding improvement in HRQoL.

Keywords Inflammatory bowel diseases, quality of life, Crohn's disease, ulcerative colitis

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Introduction

Patients with inflammatory bowel disease (IBD) have a normal life expectancy [1]; however, the relapsing course of the disease and its early onset have significant social, psychological and financial repercussions [2,3]. Health-related quality of life (HRQoL) is a quantitative measurement of subjective perception of health state, including emotional and social function and has a recognized importance to evaluate, manage and follow up patients [4]. Many studies have investigated the HRQoL in IBD, which appears to be impaired [5].

Patients with active disease have significantly impaired HRQoL compared to patients in remission [6-8]. In addition, concomitant anxiety and depression seem to affect HRQoL [9]. There are reports [10,11] suggesting lower HRQoL scores in patients with short disease duration compared to patients with longer course of the disease; however, this is not supported by others [8,12].

There is also conflicting data on the effect of type of IBD treatment on HRQoL. Immunosuppressives have been reported to have a negative effect [13,14], although other studies were unable to support such a correlation [7]. Use of corticosteroids seems to lower IBDQ scores [7,11,14], especially in CD. Regarding tumor necrosis factor (TNF)-α inhibitors, most data report a positive impact on HRQoL [15]. According to a recent review [15], TNF-α inhibitors improved HRQoL compared to placebo to a level of patients in remission.

Aim of the current study was to investigate the role of

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Conflict of Interest: None

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demographic, disease-specific characteristics and different treatment regimens on HRQoL of patients with IBD, either Crohn's disease (CD) or ulcerative colitis (UC) in a reference center for patients with IBD in South-Western Greece.

Patients and methods

Eighty nine consecutive patients with confirmed diagnosis of IBD [CD, 38 (42.7%) and UC, 51 (57.3%)] from March 2008 to September 2012, were recruited in an observational, cross-sectional study. Median disease duration was 52 months (1-372). The participants were either hospitalized (n=10) or outpatients (n=79). Outpatients had the questionnaires administered to them using diary cards at their follow-up visit and hospitalized patients within two days from their hospital admission. Diagnosis of IBD was based on clinical, endoscopic, radiologic and histological criteria. Exclusion criteria were: current alcohol and/or drug abuse and psychotic disease. Demographic data and data about disease activity, duration and treatment were also collected.

Patients were classified according to disease duration: a) short disease duration, <24 months; b) medium disease duration, 24-60 months; and c) long disease duration, >60 months. This classification was based on previous studies [16-18]. Anemia was defined as hemoglobin levels <13 g/dL in males, and <12 g/dL in females. Patients were classified into three categories according to educational level: a) primary or less; b) secondary; c) tertiary or above, and in four classes according to employment status: a) unemployed; b) retired; c) employed part-time; and d) employed full-time.

Assessment of HRQoL

We used the IBD Questionnaire (IBDQ) to assess HRQoL. This disease-specific questionnaire comprises 32 questions divided into four health subscales: bowel symptoms (10 questions); systemic symptoms, including sleep disorders and fatigue (5 questions); emotional function such as depression, aggression and irritation (12 questions); and social function, meaning the ability to participate in social activities and to work (5 questions). The participant was invited to choose one of seven graded responses. Consequently, the total score ranges from 32 to 224 points, with lower scores reflecting worse HRQoL. The IBDQ has been translated and validated in Greece [19] and has been shown to be a reliable and sensitive tool to measure HRQoL [20].

Evaluation of disease activity

Disease activity in CD was measured using the Crohn's Disease Activity Index (CDAI). Regarding the assessment of disease activity in UC, 'Truelove and Witts' classification was used [21] which stratifies patients in three grades of disease severity: mild, moderate and severe.

Statistical analysis

Data analyses were performed using IBM SPSS Statistics 19 for Windows. P values lower than 0.05 were considered statistically significant. Results are reported as percentages, median and range. Statistical comparisons between the two groups were made using Pearson chi-square or Student's t-test. Kruskal-Wallis analysis was used to make comparisons between IBDQ scores and descriptive variables. The independent influence of demographic and disease-related factors on HRQoL (total and dimensional scores) was assessed by multiple linear regression analysis.

Results

The demographic characteristics of the study population are shown in Table 1. The total and subscale scores of IBDQ are presented in Table 2**.** No statistically significant difference was found in total and dimensional IBDQ scores between patients with CD and UC. There was a predominance of females in the CD group (P=0.015). There was also no significant difference on HRQoL regarding sex (total score, P=0.26; bowel symptoms, P=0.99; systemic symptoms, P=0.22; emotional function, P=0.07 and social function, P=0.49) and this result was consistent in both CD and UC group. Similarly, age was not significantly associated with HRQoL (total score, P=0.66; bowel symptoms, P=0.28; systemic symptoms, P=0.56; emotional function, P=0.91; social function, P=0.63).

51.7% of CD and 22.5% of UC patients were smokers, and this difference was significant (P=0.012). Smoking did not correlate with any IBDQ scores neither on total study population (total score, P=0.27; bowel symptoms, P=0.15; systemic symptoms, P=0.9; emotional function, P=0.47; social function, P=0.13) nor in CD and UC patients. Similarly, no significant association was observed regarding the presence of anemia or hemoglobin levels. No significant difference was found between educational level and total score (P=0.2), systemic symptoms (P=0.7), emotional function (P=0.6) and social function (P=0.7). However, a significant correlation was found for bowel symptoms (P=0.008), with those of higher education scoring lower. Similarly, subgroup analysis regarding type of disease (CD or UC) showed no significant association apart for bowel symptoms which were found to be associated with education in CD (P=0.015). The correlation between employment status and HRQoL was not significant [total score (P=0.38), bowel symptoms (P=0.37), systemic symptoms (P=0.6), emotional function (P=0.52), social function (P=0.8)]. No significant associations were demonstrated either for CD or UC.

Treatment

Only biologic agents (infliximab, adalimumab) were found to have a negative impact on HRQoL of all IBD patients regarding systemic symptoms (P=0.04), and social function

Table 1 Demographic and disease characteristics of the study population

		Total (n=89)	CD (n=38)	UC (n=51)	P value
Sex (M/F) N (%)		48/41 (53.9/46.1)	14/24 (37.8/62.2)	34/17 (66.7/33.3)	0.015
Age, years median (range)		43 (16-77)	35 (20-75)	46 (16-77)	0.135
Age >50 years N (%)		35 (39.3)	10 (26.3)	25 (49%)	0.195
Smoking (%)		34.8	51.7	22.5	0.012
Education (%)	Primary or less	35	23	45.5	
	Secondary	30	42.4	19.4	0.107
	Tertiary or above	35	34.6	35.2	
Employment status (%)	Unemployed	31	23.5	35.7	
	Retired	22	5.9	32	0.05
	Employed full-time	11	11.8	10.7	
	Employed part-time	36	58.8	21.5	
Hospitalized (%)		10 (11.2)	5 (13.1)	5 (9.8)	0.809
Disease duration (months) Median (range)		52 (1-372)	40 (1-199)	84 (1-372)	0.003
Disease duration N (%): <24 months		17 (19.8)	26.5	15.2	0.164
24-60 months		26 (32.1)	38.2	26.1	
>60 months		43 (48.1)	35.3	58.7	
Disease activity		-	62.3 (4-162)	Mild: 40 (83) Moderate: 7 (10.6) Severe: 4 (6.4)	-
Immunosuppressive treatment (%)		30.8	25	35.6	0.49
Immunosuppressive treatment + corticosteroids (%)		42.3	25	44	0.652
Treatment with corticosteroids (%)		17.9	15.6	20	0.793
Treatment with biologic agents (%)		32.9	24.2	37.8	0.162
Hb (g/dL, median, range)		13.45 (9.5-16)	13.25 (10.3-16)	13.5 (9.5-15.8)	0.233
Ht (%, median, range)		40 (28-50.2)	39 (30.9-47.1)	41.3 (28-50.2)	0.027
Anemia (%)		21.4	31	15.4	0.297
Surgery (%)		11.1	14.3	8.7	0.428

CD, Crohn's disease; UC, Ulcerative colitis;, Hb, hemoglobin; Ht, hematocrit; NS, not significant; M, male; F, female

(P=0.037); there was a trend for statistical significance regarding total score (P=0.076) and emotional domain (0.085). This significant correlation was observed in UC (systemic symptoms, P=0.01; social function, P=0.05) but not in CD patients. The UC patients receiving biologic agents had undergone disease-related surgical operation in a higher proportion (17.6% versus 0%, P=0.026) and had shorter disease duration (median: 31 months versus 102 months, P=0.039), compared to UC patients non-users of anti-TNF-α agents. Lastly, surgical treatment was found to be significantly correlated with system function domain in UC (P=0.03).

Disease activity

Regarding disease activity in CD, CDAI was significantly associated with all IBDQ scores (total score, P<0.001; bowel

Table 2 Total and subscale IBDQ scores

	Total Median (range)	CD Median (range)	UC Median (range)	P value
Total score	186 (76-220)	174 (94-220)	190 (76-220)	0.735
Bowel symptoms	60 (28-70)	55 (28-70)	60 (37-70)	0.862
Systemic symptoms	30 (5-35)	30 (11-35)	30 (5-35)	0.839
Emotional function	67 (21-83)	67 (33-83)	68 (21-83)	0.675
Social function	34 (6-35)	33 (13-35)	34 (6-35)	0.598

CD, Crohn's disease; UC, ulcerative colitis; NS, not significant; IBDQ, inflammatory bowel disease questionnaire

symptoms, P=0.002; systemic symptoms, P=0.001; emotional function, P<0.001; social function, P<0.001). Similarly in UC, IBDQ, total and dimensional, was found to have a significant negative correlation with disease activity (total score, P=0.004; bowel symptoms, P=0.009; systemic symptoms, P=0.017; emotional function, P=0.019; social function, P=0.005).

Hospitalized patients had greater disease activity in both UC (P<0.001) and CD (P=0.001). A significant correlation was found between hospitalization and all IBDQ scores (total score, P<0.001; bowel symptoms, P=0.007; systemic symptoms, P=0.001; emotional function, P=0.001; social function, P<0.001). Similar significant associations were observed in both CD (total score, P=0.011; bowel symptoms, P=0.4; systemic symptoms, P=0.016; emotional function, P=0.005; social function, P=0.01) and UC (total score, P=0.014; bowel symptoms, P=0.036; systemic symptoms, P=0.032; emotional function, P=0.041; social function, P=0.01).

Disease duration

There was a significant difference regarding median disease duration between patients with CD and UC (40 versus 84 months respectively, P=0.003). No significant correlation was found between disease duration group and type of disease (CD or UC) (P=0.164). No correlation was demonstrated between disease duration group and IBDQ scores in the study population (total score, P=0.3; bowel symptoms, P=0.06; systemic symptoms, P=0.32; emotional function, P=0.64; social function, P=0.39); similar findings were observed in CD (total score, P=0.68; bowel symptoms, P=0.16; systemic symptoms, P=0.73; emotional function, P=0.92; social function, P=0.6) and in UC (total score, P=0.41; bowel symptoms, P=0.37; systemic symptoms, P=0.12; emotional function, P=0.65; social function, P=0.89).

Multivariate analysis

CD: Multiple linear regression analysis was used to develop a model for predicting total and dimensional scores of IBDQ including sex, age, smoking, CDAI, education, and disease duration. Only CDAI (total score: beta= -0.726, P=0.001; bowel symptoms: beta=-0.632, P=0.004; systemic symptoms: beta= -0.762, P=0.001; emotional function: beta=-0.639, P=0.003; social function: beta=-0.707, P=0.003) and education (total score: beta=-0.417, P=0.047; bowel symptoms: beta=-0.65, P=0.004; systemic symptoms: beta=-0.44, P=0.033) had significant partial effects in the full model. UC: Similarly, a model was developed including sex, age, smoking, grade of disease activity, disease duration, use of biologic agents, and history of surgery. Only severe grade had significant partial effects in the full model regarding total and dimensional scores (total score: beta=-77.838, P=0.005; bowel symptoms: beta=-26.804, P<0.001; systemic symptoms: beta=-11.808, P=0.004; emotional function: beta=-20.902, P=0.05; social function: beta=-18.323, P=0.001).

Discussion

This study demonstrates that IBD patients with disease in remission experience better HRQoL than patients with active disease. There were no differences in HRQoL between patients with CD and UC. In addition, sex, age, smoking, anemia and disease duration were not found to contribute to lower scores of IBDQ in all subscales.

Pallis AG *et al* [12] demonstrated results consistent with ours, reporting disease activity as the major variable affecting QoL, whereas age, smoking, type of disease (CD or UC) and disease duration had no impact. In addition, their IBDQ scores reflected a relatively good QoL in their sample population, similarly to our observations (mean total IBDQ score, 178 and 186 respectively). Another recent Greek study [22] aimed to identify personality and psychological distress variables associated with HRQoL in 185 IBD patients. Somatization, low education level, and reaction-formation defense mechanism were independently associated with HRQoL.

Similarly to other studies [6,10,12], we found no significant difference regarding HRQoL between CD and UC patients. However, some authors suggest that CD patients have more severe psychosocial dysfunction, reduced well-being, anxiety and depression as well as more profound effects on HRQoL than patients with UC [7,8,23]. High disease activity is the most important factor of reduced HRQoL, in both CD and UC. This finding is in accordance with many other studies [6-8,12,24,25]. It seems that disease activity is related to the level of fatigue and sleep difficulties and that these factors are independently associated with an impaired IBDQ [5,7]. Gray *et al* [26] suggested that behavioral dysfunction is the mechanism through which disease severity partially impairs HRQoL. In a recent trial [27] of 504 IBD patients (403 CD and 101 UC), vitamin D deficiency was present in 49.8% (10.9% severe). Vitamin D deficiency was associated with lower HRQoL (assessed with short IBDQ) in CD (regression coefficient -2.21, 95% CI, -4.1 to -0.33) but not in UC (regression coefficient 0.41, 95% CI, -2.91 to 3.73), as well as with increased disease activity in CD (regression coefficient 1.07, 95% CI, 0.43-1.71). However, this study fails to show if there is a pathogenetic role of vitamin D deficiency on impaired QoL or if both are consequences of increased disease activity.

HRQoL has been shown to be more impaired in female compared to male patients with IBD [28-30]; however, similarly to our study, this is not supported by others [31,32]. Females have greater disease-related concerns [33], evaluate their symptoms as being more severe [34] and generally are more affected by psychosocial factors [32]. On the other hand, even in the general population, females score lower than males in self-rated QoL assessments [35].

Jaghult *et al* [9] reported that patients with longer disease duration have better HRQoL than patients with short duration and also that this correlation may be due to the fact that the disease tends to be more active at first appearance [16-18] or that the patient may have not as yet been treated adequately. However, we have found no correlation of HRQoL with disease duration in our study population. This might be reflecting a

type 2 statistical error, although similar results are presented in studies with large study populations, regarding assessment of HRQoL in both UC [36,37] and CD [38]. According to Kuriyama *et al* [37], HRQoL did not differ among UC patients with different disease durations. However, the factors that affected HRQoL varied according to disease duration with disease activity, being "on sick leave or hospitalized" and complications due to corticosteroids, being the predominant factors impairing HRQoL in patients with disease duration of less than 5 years; 5-9 years; and 10 years or more, respectively. In our study, similarly to other reports, [5,9,11] age was not found as a predisposing factor of impaired QoL, either in CD or UC, although there are reports supporting that IBD runs a more aggressive course in older patients [39,40]. There is little data on the impact of education on QoL in IBD patients [41]. We found that a higher educational level is independently associated with lower scores for bowel symptoms in CD. This might reflect a better perception of disease-related symptoms in patients with a higher educational level and better IBD knowledge.

The data regarding the impact of different treatments on HRQoL is conflicting [7,11,14]. In our study, a non-significant difference was found among users and non-users of 5-ASA, corticosteroids and immunosuppressives. However, this may reflect the small number of patients included. An interesting finding of our study was that patients with UC using anti-TNF-α agents had a worse QoL compared to non-users. Following analysis of the disease characteristics of this subgroup of patients, we observed shorter disease duration and a higher rate of past surgical intervention. Thus, this association probably depicts the higher disease severity in this cohort, and thus, the impairment of QoL and not a direct impact of biologics.

Considering that disease activity is the major predisposing factor of impaired QoL, use of effective treatment regimens aiming to maintain patients in remission is of great importance. The benefit of psychological interventions in IBD is controversial [42]. In a recent review [43], no efficacy of psychological therapy was found in adult IBD patients in disease activity, HRQoL, emotional state and coping, whereas it appears to be more beneficial in adolescents. In addition, stress management psychotherapy does not improve disease activity or reduce relapse but it might improve HRQoL, especially in UC patients [44]. Therefore, future research will evaluate the efficacy of such interventions on IBD, as well as to determine subgroup of patients who will benefit more from them.

Our study is limited by various factors. Firstly, the cross-sectional design and the small population size, secondly, most patients received combined medication and thus, there is a risk of bias on the impact of different treatment regimens on HRQoL, and lastly, the vast majority of our patients had disease in remission. However, our main conclusion on the association between disease severity and HRQoL is robust, considering the statistical significance in a rather small sample size and the similarity of our results with studies with larger population [6-8,12,24].

In conclusion, we demonstrated a strong impact of disease activity on HRQoL in IBD patients, independently of type of disease. Patients in remission have a greater perception of life, lower emotional and social dysfunction compared to patients with active disease. Disease duration, age and gender do not affect QoL in IBD. It is still questionable if psychological support should be included in the general management of these patients or if it should be oriented to certain patients, whereas effective treatment of patients' disease seems to play the greater role on improvement of QoL. Future research is needed to conclude on the impact of other factors, apart from disease activity, on HRQoL for which there are discrepancies among studies, in order to define the subgroup of patients who are more likely to have impaired HRQoL.

Summary Box

What is already known:

- Health-related quality of life (HRQoL) is a quantitative measurement of subjective perception of health state
- Patients with active inflammatory bowel disease (IBD) have significantly impaired HRQoL compared to patients in remission
- There are conflicting data on the role of demographic, disease-specific characteristics and treatment on HRQoL in IBD

What the new findings are:

- There is no difference regarding IBD Questionnaire (IBDQ) scores between ulcerative colitis and Crohn's disease patients in South-Western Greece
- IBD patients in remission experience better HRQoL than patients with active disease in this population
- Other parameters such as sex, age, smoking, anemia, disease duration and treatment were not found to contribute to lower scores of IBDQ in all subscales

References

1. Ekbom A, Helmick C, Zack M, Holmberg L, Adami HO. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology* 1992;**103**:954-960.
2. Ross SC, Strachan J, Russell RK, Wilson SL. Psychosocial functioning and health-related quality of life in paediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011;**53**:480-488.
3. Pallis AG, Mouzas IA. Quality of health care in inflammatory bowel disease and its assessment. *Ann Gastroenterol* 2002;**15**:143-147.
4. Mouzas IA, Pallis AG. Assessing quality of life in medical trials on patients with inflammatory bowel disease. *Ann Gastroenterol* 2000;**13**:261-263.
5. Graff LA, Walker JR, Lix L, et al. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. *Clin Gastroenterol Hepatol* 2006;**4**:1491-1501.

6. Zhou Y, Ren W, Irvine EJ, Yang D. Assessing health-related quality of life in patients with inflammatory bowel disease in Zhejiang, China. *J Clin Nurs* 2010;**19**:79-88.
7. Romberg-Camps MJL, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg Cohort. *Inflamm Bowel Dis* 2010;**16**:2137-2147.
8. Mnif L, Mzid A, Amouri A, Chtourou L, Tahri N. Health-related quality of life in patients with inflammatory bowel disease: a Tunisian study. *Tunis Med* 2010;**88**:933-936.
9. Moser G. Depression and anxiety in inflammatory bowel disease. *Gastroenterol Hepatol* 2009;**32**(Suppl 2):9-12.
10. Jaghult S, Saboonchi F, Johansson UB, Wredling R, Kapraali M. Identifying predictors of low health-related quality of life among patients with inflammatory bowel disease: comparison between Crohn's disease and ulcerative colitis with disease duration. *J Clin Nurs* 2011;**20**:1578-1587.
11. Haapamaki J, Turunen U, Roine RP, Farkkila MA, Arkkila PET. Impact of demographic factors, medication and symptoms on disease-specific quality of life in inflammatory bowel disease. *Qual Life Res* 2009;**18**:961-969.
12. Pallis AG, Vlachonikolis IG, Mouzas IA. Assessing health-related quality of life in patients with inflammatory bowel disease in Crete, Greece. *BMC Gastroenterol* 2002;**2**:1.
13. Hoivik ML, Moum B, Solberg IC, et al.; IBSEN Study Group. Health-related quality of life in patients with ulcerative colitis after a 10-year disease course: results from the IBSEN study. *Inflamm Bowel Dis* 2012;**18**:1540-1549.
14. Bernklev T, Jahnsen J, Schulz T, et al. Course of disease, drug treatment and health-related quality of life in patients with inflammatory bowel disease 5 years after initial diagnosis. *Eur J Gastroenterol Hepatol* 2005;**17**:1037-1045.
15. Vogelaar L, Spijker AV, van der Woude CJ. The impact of biologics on health-related quality of life in patients with inflammatory bowel disease. *Clin Exp Gastroenterol* 2009;**2**:101-109.
16. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995;**30**:699-706.
17. Henriksen M, Jahnsen J, Lygren I, et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). *Inflamm Bowel Dis* 2006;**12**:543-550.
18. Wolters FL, Russel MG, Sijbrandij J, et al. Disease outcome of inflammatory bowel disease patients: general outline of a Europe-wide population-based 10-year clinical follow-up study. *Scand J Gastroenterol Suppl* 2006;**243**:46-54.
19. Pallis AG, Vlachonikolis IG, Mouzas IA. Quality of life of Greek patients with inflammatory bowel disease. Validation of the Greek translation of the inflammatory bowel disease questionnaire. *Digestion* 2001;**63**:240-246.
20. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality of life instrument for adult patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1999;**28**:23-27.
21. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955;**ii**:1041-1048.
22. Hyphantis TN, Tomenson B, Bai M, Tsianos E, Mavreas V, Creed F. Psychological distress, somatization, and defense mechanisms associated with quality of life in inflammatory bowel disease patients. *Dig Dis Sci* 2010;**55**:724-732.
23. Simren M, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Bjornsson ES. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;**97**:389-396.
24. Casellas F, Lopez-Vinancos J, Badia X, Vilaseca J, Malagelada JR. Influence of inflammatory bowel disease on different dimensions of quality of life. *Eur J Gastroenterol Hepatol* 2001;**13**:567-572.
25. Casellas F, Arenas JI, Baudet JS, et al. Impairement of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. *Inflamm Bowel Dis* 2005;**11**:488-496.
26. Gray WN, Denson LA, Baldassano RN, Hommel KA. Disease activity, behavioral dysfunction, and health-related quality of life in adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**:1581-1586.
27. Ulitsky A, Ananathakrishnan AN, Naik A, et al. Vitamin D deficiency in patients with inflammatory bowel diseases: association with disease activity and quality of life. *J Parent Enter Nutr* 2011;**35**:308-316.
28. Irvine EJ. Quality of life in inflammatory bowel disease: biases and other factors affecting scores. *Scand J Gastroenterol Suppl* 1995;**208**:136-140.
29. Casellas F, Lopez-Vinancos J, Casado A, Malagelada JR. Factors affecting health related quality of life of patients with inflammatory bowel disease. *Qual Life Res* 2002;**11**:775-781.
30. Rubin GP, Hungin APS, Chinn DJ, Dwarakanath D. Quality of life in patients with established inflammatory bowel disease: a UK general practice survey. *Aliment Pharmacol Ther* 2004;**19**:529-535.
31. Kim WH, Cho YS, Yoo HM, Park IS, Park EC, Lim JG. Quality of life in Korean patients with inflammatory bowel diseases: ulcerative colitis, Crohn's disease and intestinal Behcet's disease. *Int J Col Dis* 1999;**14**:52-57.
32. Drossman DA, Patrick DL, Mitchell CM, Zagami EA, Appelbaum MI. Health-related quality of life in inflammatory bowel disease. Functional status and patient worries and concerns. *Dig Dis Sci* 1989;**34**:1379-1386.
33. Maunder A, Toner B, De Rooy E, Moskovitz D. Influence of sex and disease on illness-related concerns in inflammatory bowel disease. *Can J Gastroenterol* 1999;**13**:728-732.
34. De Rooy EC, Toner BB, Maunder RG, et al. Concerns of patients with inflammatory bowel disease: results from a clinical population. *Am J Gastroenterol* 2001;**96**:1816-1821.
35. Dimenas E, Carlsson G, Glise H, Israelsson B, Wiklund I. Reference of norm values as part of documentation of quality of life instruments for use in upper gastrointestinal disease. *Scand J Gastroenterol Suppl* 1996;**221**:8-13.
36. Hjortswang H, Jarnerot G, Curman B, et al. The influence of demographic and disease-related factors on health-related quality of life in patients with ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003;**15**:1011-1020.
37. Kuriyama M, Kato J, Kuwaki K, et al. Clinical factors that impair health-related quality pf life in ulcerative colitis patients vary with the disease duration. *Eur J Gastroenterol Hepatol* 2008;**20**:634-641.
38. Gibson PR, Weston AR, Shann A, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. *J Gastroenterol Hepatol* 2007;**22**:1306-1312.
39. Akerkar GA, Peppercorn MA. Inflammtory bowel disease in the elderly. Practical treatment guidelines. *Age Ageing* 1997;**10**:199-208.
40. Gupta S, Saverymuttu SH, Keshavarzian A, Hodgson HJ. Is the pattern of inflammatory bowel disease different in the elderly? *Age Ageing* 1985;**14**:366-370.
41. Sainsbury A, Heatley RV. Review article: psychosocial factors in the quality of life of patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2005;**21**:499-508.
42. Von Wietersheim J, Kessler H. Psychotherapy with chronic inflammatory bowel disease patients: a review. *Inflamm Bowel Dis* 2006;**12**:1175-1184.
43. Timmer A, Preiss JC, Motschall E, Rucker G, Jantschek G, Moser G. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev* 2011;**16**:CD006913.
44. Boye B, Lundin KE, Jantschek G, et al. INSPIRE study: Does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflamm Bowel Dis* 2011;**17**:1863-1873.