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Impact of Synbiotic Therapy on the Quality of Life in Patients with Mild-to-Moderately Active Ulcerative Colitis

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ABSTRACT

Background & Aim: Ulcerative colitis is a chronic inflammatory disease that negatively affects patients' quality of life, workforce participation, and nutrition during active disease periods. This study aimed to explore how synbiotic treatment affected the quality of life in patients with mild-to-moderate ulcerative colitis.
Methods: Forty ulcerative colitis patients with mild-to-moderate disease activity were enrolled in the study and divided in two randomized groups; 20 patients received synbiotic therapy and 20 patients receive placebo for 8 weeks. Quality of life scores of both groups were compared at the start and the end of therapy. Quality of life was determined using a short form-36 (SF-36) questionnaire.
Results: Increases in mean SF-36 scores were found in both groups at the end of the study. Although the increase was higher in patients who received synbiotic therapy, the difference was not statistically significant (p=0.268 for mental indicators and p=0.182 for physical indicators). At the end of the treatment, a significant increase was observed in the social functioning and mental health sub-dimension scores from mental indicators and in the general health status sub-dimension score from physical indicators, in the synbiotic group (p=0.008, p=0.005, p=0.036 respectively.). The social functioning sub-dimension score from mental indicators and bodily pain and general health sub-dimension scores from physical indicators were found to be significantly higher in the group that went into remission after synbiotic treatment compared to patients with mild disease activity (p=0.034, p=0.017, 0.031, respectively). SF-36 scores were higher in patients with mild activity or those in remission in both groups.
Conclusions: Synbiotic use provides an increase in the SF-36 score; however, this increase is not statistically significant.

Key words: ulcerative colitis – quality of life – synbiotic – probiotic – prebiotic.

Abbreviations: BP: bodily pain; GH: general health status; HRQoL: health-related quality of life; IBD: inflammatory bowel disease; IBDQ: IBD questionnaire; PF: physical functioning; QoL: quality of life; RE: role limitations-emotional; RP: role limitations-physical; SF: social functioning; SF-36: Short Form-36 Health Survey; UC: ulcerative colitis; VT: vitality.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease that negatively affects patients' quality of life (QoL), workforce participation, and nutrition during active disease periods, characterized by abdominal pain and bloody diarrhea [1, 2]. Quality of life in individuals with UC is significantly lower than in the general population. Factors that negatively affect QoL include long duration of disease, recurrence periods and symptoms such as fever, fatigue, frequent defecation, treatment-associated problems and psychosocial and socioeconomic factors [3, 4]. Treatment targets include induction and maintenance of clinical remission and mucosal healing, prevention of recurrence and complications, and improvement of QoL [2, 5].

Health-related QoL (HRQoL) is an individual's social and emotional well-being, physical functioning, ability to work and the absence of disease symptoms. It combines the social, emotional and physical aspects of the general health perception and evaluates the effects of the disease thoroughly [2, 6]. Quality of life, another important indicator of treatment success, has not been clearly evaluated in patients with UC [2]. The QoL of patients with inflammatory bowel disease (IBD) is mostly assessed with specifically designed scales for the disease

or with scales of general health condition [4]. In recent studies, the Short Form-36 Health Survey (SF-36) and European HRQoL Index have been applied to evaluate general health status in IBD. The IBD Questionnaire (IBDQ) scale, which is specifically designed for IBD, has also been used [7-12].

Studies to assess the QoL in IBD showed that patients in remission and active disease have significantly different questionnaire scores [4]. Recent studies show that probiotics have positive effects on reducing symptoms, entering remission, and the prolongation of the remission period in patients with UC [13, 14]. However, there are few studies that investigate the role of synbiotic usage on patients' QoL.

This study is a randomized placebo-controlled study to evaluate the effects of synbiotics on QoL in patients with mild-to-moderately active UC.

METHODS

Study Population

Patients with mild-to-moderately active UC, who were previously or newly diagnosed by clinical, endoscopic and histopathological findings were included in the study.

The main hypothesis of the study was to determine if synbiotic supplementation caused an increase in the QoL as measured by SF-36 form in patients with mild-to-moderately active UC. Sample size estimation was based on normative data for the SF-36 form in a Turkish urban population [15], and the effect size calculations were based on previously established threshold values for minimal clinically important differences [16]. A 10-points increase in either mental or physical indicators of SF-36 form was used as the basis for sample size calculation. The sample size was estimated at 40 participants (20 for each group) with 80% power and 0.05 alpha error probability.

Patients under 18 years of age, patients with severe disease activity, patients who were receiving corticosteroid or biological therapy, patients who used synbiotic or probiotic preparation and antibiotics within two weeks before the study, and patients who had concurrent enteric infection were excluded. Forty-six patients were assessed for eligibility, six were excluded because either they did not meet the inclusion criteria (4 patients) or declined to participate in the study (2 patients). The demographic characteristics of patients, type and duration of UC and medications used in treatment were determined. Clinical activities were evaluated according to Truelove-Witts severity index at the beginning and end of the study.

Study Design

This study was conducted as randomized placebo-controlled, single-blind study. "Random Allocation Software" program was used for randomization, and forty patients were randomized to the synbiotic and control groups. For 8 weeks, a synbiotic preparation composed of 6 probiotic strains ($3x10^9$) CFU; "Lactobacillus acidophilus, Lactobacillus plantarum, Enterococcus faecium, Bifidobacterium longum, Bifidobacterium lactis, and Streptococcus thermophilus," and fructooligosaccharides (225 mg/tablet), which is a prebiotic fiber, for the synbiotic group, or placebo, which had the same taste and appearance as the original product, for the control group were initiated with one tablet to be used after breakfast and dinner.

Patients were given medical nutrition therapy according to the UC during the study.

Data Collection Instruments

Short Form-36 Health Survey QoL Scale was used to evaluate the effects of the disease, disease activity and treatment on QoL. Short Form-36 Health Survey was created by Ware and Sherbourne to evaluate the QoL of individuals based on mental and physical health [12]. The studies on the validity and reliability of this scale in Turkey were done by Kocyigit et al. [17]. Short Form-36 Health Survey is a self-report scale that evaluates the QoL of individuals within the previous 4 weeks without considering disease, age, and treatment group within the overall health concept [18]. This scale consists of 2 main dimensions, physical and mental (includes 36 statements), and 8 sub-dimensions, general health status (GH), vitality (VT), role limitations-physical (RP), physical functioning (PF), mental health (MH), role limitations-emotional (RE), bodily pain (BP), and social functioning (SF) [12, 19]. The physical indicator score was measured by taking the average of PF, GH status, RP, and pain scores. The mental indicator score was measured by taking the average of RE, VT, MH, and SF. The two main dimension and each sub-dimension scores are between 0 and 100, with 0 representing poor health condition and 100 representing good health condition. The higher scores on this scale represent better QoL [18, 19].

Statistical Analysis

The results of the study were evaluated using the "SPSS 22.0 for Windows" package program. The per-protocol analysis was adopted in the analysis of all data in the study. The Shapiro-Wilk test was used to determine whether continuous data showed normal distribution. The paired sample t-test was used for the comparison of normally distributed and repetitive quantitative data of both groups. Student's t-test was performed for the comparison of normally distributed and non-repetitive data, and the Mann-Whitney U test was used to compare non-normally distributed and non-repetitive data. Chi-square (χ^2) analysis was applied to determine the relationship between categorical variables. The Wilcoxon paired two-sample tests were performed for the comparison of quantitative data of the control and study groups within themselves (before and after). In the study, p-values less than 0.05 were considered statistically significant.

Ethical Approval

The Medical Faculty Clinical Research Ethics Committee approved this study (Approval no:175). The study was conducted according to the World Medical Association Declaration of Helsinki. After potential participants were informed about the purpose of the study, and how it would be conducted, those willing to participate provided their written consent.

RESULTS

Patients' Characteristics

In the synbiotic group, one patient voluntarily left the study because of an increase in gas complaints, and another patient voluntarily left the study because he did not want to

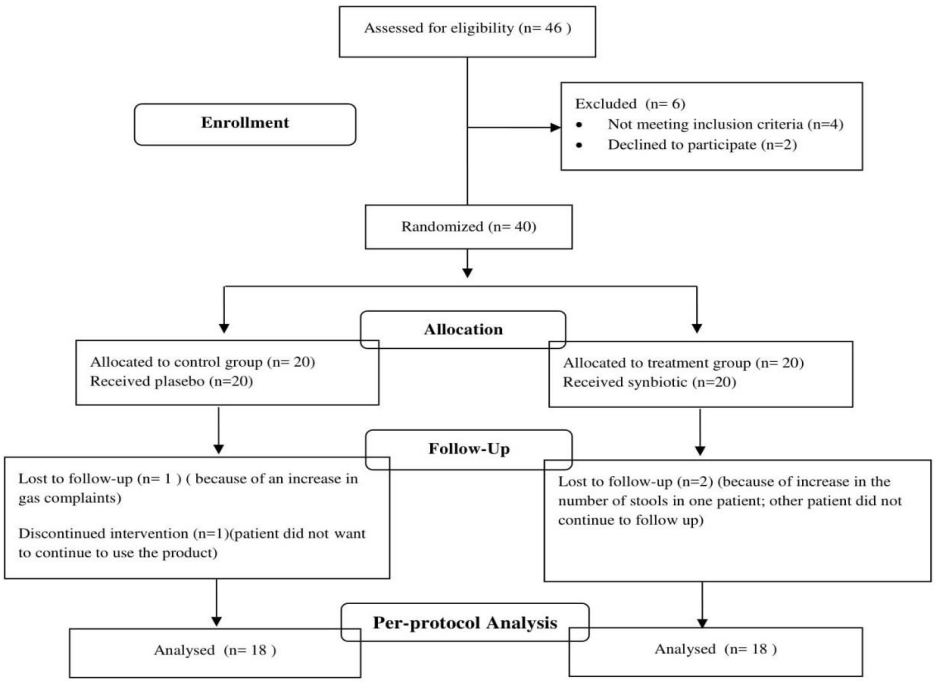

Fig. 1. Flow diagram of the randomized-controlled trial.

continue to use the product. In the control group, one of the patients voluntarily left the study on the grounds that there was an increase in the number of stools, and one patient was excluded from the study because he did not come to the final examinations. As a result, the study was evaluated over the findings of 18 patients in each group. The flowchart of the study protocol is shown in Fig. 1.

There were 10 male and 8 female patients in the control group and 9 male and 9 female patients in the synbiotic group. The mean age was 40±12.67 years in the control group and 44.94±14.14 years in the synbiotic group. The mean years since the diagnosis of ulcerative colitis was 4.58±4.39 years in the control group and 4.67±6.23 years in the synbiotic group. 55.6% of the patients in the control group had extensive colitis, and 44.4% of the patients in the synbiotic group had distal colitis. The vast majority of patients were treated with mesalazine alone in both groups (control group 61.1% and synbiotic group 88.9%). The results are shown in Table I.

Table I. General characteristics of control and synbiotic groups

General Characteristics	Control Group (n=18)		Synbiotic Group (n=18)		
	n	%	n	%	p[x]
Gender					
Female	8	44.4	9	50.0	0.999
Male	10	55.6	9	50.0	
Duration of UC (year, median, min-max)	3.75 (0-15)		3.00 (0-25)		0.524[y]
Age (year) (X±SD)	40.00±12.67		44.94±14.14		0.277[z]
Type of UC					
Extensive colitis	10	55.6	5	27.8	
Proctitis	3	16.6	8	44.4	0.139
Left-sided colitis	5	27.8	5	27.8	
Medical treatments for UC					
Mesalazine	11	61.1	16	88.9	0.121
Mesalazine and Azathioprine	7	38.9	2	11.1	
Truelove -Witts Clinic Activity İndex					
Mild	15	83.3	6	33.3	0.006
Moderate	3	16.7	12	66.7	

[1]UC: Ulcerative colitis; [x] Pearson ki-square (χ^2) and Fisher's Exact test was used for comparison ($p < 0.05$);. [y] Mann Whitney U test was used for comparison of duration of UC ($p < 0.05$);. [z] Student *t* test was used for comparison of age ($p < 0.05$).

Quality of Life Assessment

According to the Truelove-Witts Severity Index, 83.3% of the patients in the control group had mild activity at the beginning of the study, and 61.1% of them had mild activity at the end of the study. 33.3% of the patients were in clinical remission, and this change in the disease activity was statistically significant (p=0.005). In the synbiotic group, 66.7% of the patients had moderate activity at baseline and the remission rate was 55.6% at the end of the study. 33.3% of them remained in the mild activity category, and these changes were significant (p=0.001) (Table II).

Patients with mild activity or remission in the control group were observed to have higher SF-36 scores both in the beginning and at the end of the study. Within the patients in the control group, only RE dimensions of the SF-36 scores were significantly different between the beginning and the end of the study. Other parameters were not significantly different. At the beginning of the study, the RE score was 57.78±19.79 in patients with mild activity, whereas it was 33.33±0 in patients with moderate activity. Similarly, the RE score was significantly higher in patients in remission than in patients with mild-to-moderate activity at the end of the study (83.33±18.26 and 63.89±17.16) (Table III).

In the synbiotic group, the total score of VT, MH and physical indicators, as well as the average score of PF and RP scores of patients with moderate disease activity were statistically significantly lower than the patients with mild disease activity at the beginning of the study. However, the reduced scores due to disease activity on the total score of mental indicators, SF, RE, BP and GH were not significant (Table III). At the end of the study, SF-36 scores increased in the synbiotic group due to the absence of patients with moderate disease activity, and the increase in the number of patients in remission. SF, BP and GH of patients were also improved compared to baseline at the end of the study. SF (97.5±7.91 and 84.4±20.9), BP (93.5±11.76 and 74.38±17.51), and GH (73.5±14.54 and 49.38±21.95) scores were significantly higher among the patients in remission (Table III).

Quality of Life after Treatment

The average SF-36 scores of the patients in both the control and the synbiotic groups were lower at the beginning of the study and increased at the end of the study. VT (56.39±32.30 and 69.17±26.58) and RE (53.70±20.26 and 70.37±19.43) were significantly increased in the control group. The mental indicators main dimension score (60.81±26.90 and 72.61±19.71) was also increased. The average scores of physical indicators main dimension (62.26±27.35 and 75.87±23.13), RP (54.94±46.02 and 79.17±40.5), and BP (63.47±31.24 and 78.19±25.55) were also significantly increased. Differences in SF, PF, MH and GH scores were not significantly different (Table IV).

In the synbiotic group, mental indicators (53.2±22.7 and 74.4±15.9) and physical indicators (57.2±21.8 and 78.5±15.1) main dimensions and SF (66.7±34.8 and 91.7±16), RE (42.6±33.9 and 68.5±29.1), MH (51.8±23.7 and 70.4±19.1), RP (38.9±42.2 and 84.7±32.2), BP (63.3±28.9 and 85.0±17.2), and GH (51.4±20.3 and 62.8±21.5) sub-dimensions were significantly different. However, increases in VT and PF scores were not significant (Table IV).

Despite the fact that the increase in the SF-36 scores was higher in the synbiotic group, this difference was not statistically significant [the increase in the SF-36 scores for mental indicators were 11.8±16.9 in the control group and 22.1±22.9 in the synbiotic group (p=0.268) and for physical indicators were 13.6±16.1 in the control group and 21.4±19.0 in the synbiotic group (p=0.261)] .

DISCUSSION

Although there is much evidence suggesting that UC negatively affects the QoL of patients, in studies evaluating the effectiveness of medical treatments, the QoL, an important indicator of treatment success, has generally been underestimated. Although many papers reported the effects of probiotic and prebiotic usage on QoL in UC patients, the number of studies investigating the efficacy of synbiotics is quite limited. In the literature, scales such as IBD questionnaires and HRQoL were generally used to evaluate the QoL in UC patients [7-12, 20, 21]. In the current study, SF-36 scale was used to evaluate patients' QoL, because the IBDQ scale, which was developed specifically for patients with IBD, has not been adapted to the Turkish population.

It has been shown that the medications used for the treatment of UC can affect the QoL of patients. It was determined that 5-aminosalicylic acid treatment increased the QoL of the patients with active UC, according to both IBDQ and SF-36 scales cumulative and sub-dimensional scores, both in the control and the study groups [22]. Patients treated with vedolizumab were shown to have higher IBDQ scores, and the patients with mild disease activity were observed to have higher reducing rates of QoL scores [23]. Similarly, vedolizumab was shown to provide improvement in the mean IBDQ score and mean SF-36 in the study group compared to placebo [24].

Table II. Truelove-Witts scores in the control and synbiotic groups at the beginning and end of the study

Truelove-Witts Clinic Activity İndex	Control Group (n=18)					Synbiotic Group (n=18)				
	Baseline		Week 8			Baseline		Week 8		
	n	%	n	%	p^x	n	%	n	%	p^y
Remission	-	-	6	33.3	0.005	-	-	10	55.6	< 0.001
Mild	15	83.3	11	61.1		6	33.3	6	33.3	
Moderate	3	16.7	1	5.6		12	66.7	2	11.1	

[1] Wilcoxon Test was used for comparison (p<0.05). p^x: the difference between before and after in the control group; p^y: the difference between before and after in the synbiotic group.

Table III. Quality of life at the beginning and end of the study in the control and synbiotic groups

Dimensions of Quality of Life Scale	Control Group (n=18)						Synbiotic Group (n=18)					
	Before			After			Before			After		
	Mild (n=15)	Moderate (n=3)		Remission (n=6)	Mild-to-Moderately (n=12)		Mild (n=6)	Moderate (n=12)		Remission (n=10)	Mild (n=8)	
	X±SD	X±SD	p	X±SD	X±SD	p	X±SD	X±SD	p	X±SD	X±SD	p
Mental indicators	66.4±25.9	32.8±5.5	0.051	83.8±10.3	67.0±21.2	0.075	67.2±25.0	46.2±18.7	0.075	78.9±13.4	68.7±18.1	0.131
Vitality	63.3±30.6	21.7±19.1	0.057	77.5±16.4	65.0±30.2	0.300	76.7±31.4	39.2±25.9	0.024	68.0±20.6	65.6±23.1	0.929
Social functioning	74.2±33.9	33.3±19.1	0.067	93.8±10.5	69.8±29.4	0.085	77.1±30.0	61.5±37.1	0.362	97.5±7.91	84.4±20.9	0.034
Role limitations-emotional	57.8±19.8	33.3±0.0	0.046	83.3±18.3	63.9±17.2	0.043	44.4±40.4	41.7±32.2	0.882	76.7±27.4	58.3±29.6	0.183
Mental health	70.4±27.5	42.7±22.0	0.137	80.7±17.4	69.3±27.4	0.423	70.7±16.9	42.3±21.2	0.009	73.6±16.7	66.5±22.2	0.531
Physical indicators	68.3±25.9	32.1±2.6	0.050	88.0±8.2	69.8±25.9	0.206	76.4±24.2	47.6±12.9	0.035	85.6±7.6	69.7±17.7	0.007
Physical functioning	76.3±31.8	51.7±10.5	0.143	88.3±22.1	80.4±24.1	0.266	91.7±9.3	66.7±25.3	0.033	80.5±10.1	83.1±17.7	0.420
Role limitations-physical	66.67±43.9	8.33±14.4	0.066	100.0±0.0	68.75±46.6	0.121	75.0±41.83	20.83±29.84	0.021	95.0±10.5	71.88±45.2	0.310
Bodily pain	70.17±29.2	30.0±18.0	0.063	92.92±13.1	70.83±27.5	0.060	74.58±33.3	57.71±26.03	0.342	93.50±11.8	74.38±17.5	0.017
General health status	60.0±26.1	38.33±32.2	0.171	70.83±21.8	59.17±26.2	0.346	64.17±21.3	45.0±17.19	0.060	73.50±14.5	49.38±21.9	0.031

[1] Mann Whitney U Test was used for comparison ($p<0.05$).

Table IV. Evaluation of changes in quality of life of patients in the control and synbiotic groups after treatment

Dimensions of Quality of Life Scale	Control Group (n=18)				Synbiotic Group (n=18)				
	Before	After	Changes		Before	After	Changes		
	X±SD	X±SD	X±SD	p^x	X±SD	X±SD	X±SD	p^y	p^z
Mental indicators	60.8±26.9	72.6±19.7	11.8±16.9	0.018	53.2±22.7	74.4±15.9	21.2±22.9	0.004	0.268
Vitality	56.4±32.3	69.2±26.6	12.8±20.2	0.024	51.7±32.5	66.9±21.1	15.3±31.8	0.058	0.912
Social functioning	67.4±35.1	77.8±26.9	10.4±24.4	0.087	66.7±34.8	91.7±16.0	25.0±34.0	0.008	0.358
Role limitations-emotional	53.7±20.3	70.4±19.4	16.7±23.6	0.013	42.6±33.9	68.5±29.1	25.9±33.4	0.008	0.455
Mental health	65.8±28.2	73.1±24.6	7.3±23.0	0.184	51.8±23.7	70.4±19.1	18.7±22.3	0.005	0.182
Physical indicators	62.3±27.4	75.9±23.1	13.6±16.1	0.002	57.2±21.8	78.5±15.1	21.4±19.0	0.002	0.261
Physical functioning	72.2±30.6	83.1±23.1	10.8±22.3	0.074	75.0±24.2	81.7±13.6	6.7±20.8	0.257	0.748
Role limitations-physical	54.9±46.0	79.2±40.5	22.2±42.8	0.048	38.9±42.2	84.7±32.2	45.8±43.9	0.003	0.172
Bodily pain	63.5±31.2	78.2±25.6	14.7±20.4	0.010	63.3±28.9	85.0±17.2	21.7±27.6	0.009	0.860
General health status	56.4±27.4	63.1±24.8	6.7±19.1	0.202	51.4±20.3	62.8±21.5	11.4±21.2	0.036^x	0.622

[x,y] Wilcoxon test was used for non-normally distributed parameters, [x]Paired Samples test was used for normally distributed parameters ($p<0.05$). [x]The difference between pre-test and post-test in control group, [y] The difference between pre-test and post-test in synbiotic group; [z] The difference between the two groups' pre-test and post-test. [z]Mann Whitney U Test was used for comparison ($p<0.05$).

Studies investigating the effect of disease activity on QoL of UC patients have shown that HRQoL scores of UC patients are lower, and intestinal symptoms, systemic symptoms, emotional functions, and social functions are more severely affected in patients with severe UC than in patients with mild UC [25].

Total scores of IBDQ were higher in patients in remission compared to patients with mild-to-moderately active UC [9, 26, 27]. Similarly, IBDQ total scores were significantly lower in patients with mild-to-moderately active disease than in patients with mild disease activity; it was observed that the total IBDQ score was negatively correlated with the Mayo index score [4].

Our study showed that patients with moderately active UC had lower SF-36 scores in main and sub-dimensional parameters in both control and synbiotic groups at the beginning of the study. We also found that scale scores were higher in patients in remission at the end of the follow-up period. SF, GH, and BP scores were significantly higher in patients in remission in the synbiotic group.

Four weeks of probiotic usage provided an insignificant increase in total IBDQ scores in patients with UC. However, in patients with ileal pouch-anal anastomosis, IBDQ scores were significantly higher in the study group with long-term usage. Moreover, it was determined that the IBDQ scores of patients in remission were higher than in the placebo group [28, 29]. In another study, the effect of mesalazine versus probiotics on the QoL in patients in remission was examined, and the QoL scale scores were found to be similar both in the beginning and at the end of the study [30].

Supplementary prebiotic lactulose usage for four months duration increased the IBDQ scores of patients in the study group by 48±14 points, (from 123±20 to 171±18, p=0.026), whereas there was not a significant increase in this score in the control group. The improvement in QoL was higher in the study group [31]. Inulin supplement in addition to mesalazine treatment was shown to improve the QoL, and the scores increased both in the placebo and the inulin group, but the results were not statistically significant [32].

We found two studies in the literature investigating the relationship between the use of synbiotics and QoL. In a study by Haskey et al., children in a remission period of UC were divided into two groups. Synbiotic therapy (B.longum and inulin) was given to one group and placebo (non-resistant maltodextrin + ascorbic acid) was given to other group for 10 months in phase I. In phase II (at 10 months), the study was unblinded and synbiotic therapy was administered to each group. In the first phase of the study, severe symptoms were observed in the 60% of the control group and no symptoms were observed in the synbiotic group, and thus QoL scores were found to be much higher in the synbiotic group compared to the placebo group. Phase II QoL scores were also reported to be significantly better with synbiotic therapy [33]. In another study, the effects of synbiotics, probiotics, and prebiotics on the QoL of active UC patients were compared. At the end of the study, the total IBDQ scores increased in all groups; however, only the increase in the synbiotic group was significant (from 162 to 169 in probiotic group; from 174 to 182 in prebiotic group; and from 168 to 176 in synbiotic group, p=0.03). In addition, in the sub-dimensional parameters, significant improvement was observed in the emotional function score in the probiotic group, bowel function score in the prebiotic group, and systemic and social function scores in the synbiotic group [28]. In these studies, patients with UC in remission were included. In our study, we evaluated the effects of synbiotic addition on the QoL in UC patients with mild-to-moderate activity. Patients who were in remission and had severe disease requiring steroid therapy and biologic therapy were not included. Considering that disease activity is also an important condition affecting the QoL, it cannot be ignored that the remission that can be achieved with the main treatment will also positively affect the QoL scales independently of the synbiotic treatment. The placebo effect should also be considered.

In our study, we observed that, in both the control and the synbiotic groups, the mean scores of SF-36 components were lower at the beginning of the study and increased at the end. There were significant changes in the mental and physical indicators main dimension scores and mean VT, RE, RP and BP sub-dimensional scores of the control group. In the synbiotic group, mental and physical indicators main dimension scores and GH, SF, RE, MH, RP and BP sub-dimensional scores showed significant increases. These increases in SF-36 components scores showed that the patients QoL was positively affected at the end of the treatment.

CONCLUSION

Our study showed that the disease activity adversely affected the QoL of the patients and the QoL scores increased after treatment. At the end of the treatment, a significant increase was observed in the SF and MH sub-dimensional scores from mental indicators and in GH status sub-dimensional score from physical indicators, in the synbiotic group. The SF sub-dimensional score from mental indicators and BP and GH sub-dimensional scores from physical indicators were found to be significantly higher in the group that went into remission after synbiotic treatment compared to patients with mild disease activity. QoL scores were higher in the synbiotic group compared to the placebo group at the end of 8 weeks, but the difference was not statistically significant.

Conflicts of interest: None to declare.

Authors' contribution: H.K.A., E.A.Y. and M.A. conceived and designed the study. H.K.A. and M.A. collected the data. H.K.A., E.A.Y. and M.A. analyzed the data and interpreted the results. H.K.A. and M.A. drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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