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ORIGINAL ARTICLE

Quality of life in celiac disease and the effect of gluten-free diet

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Abstract

Background and Aim: Patients with celiac disease (CD) have a poor health-related quality of life (HR-QOL). We assessed the QOL in patients with CD using both generic (SF-12) and specific (CD-QOL) questionnaires, and the effect of gluten-free diet (GFD) on HR-QOL.
Methods: We conducted a prospective follow-up study based on consecutive patients of suspected CD between June 2014 and November 2015. After taking a detailed history, all patients were subjected to laboratory investigations (including complete blood count, biochemistry, and the IgA tTG antibody), followed by endoscopy and duodenal biopsies for histopathology. The HR-QOL was assessed using SF-12 and CD-QOL questionnaires. Patients who were strictly adherent to GFD were re-assessed at the end of 6 months for laboratory parameters and QOL.
Results: Sixty adult patients of CD, with mean age of 28.85 ± 12.43 years, and a M:F ratio of 1.3:1, were enrolled in the study. The mean PCS (physical health composite scale score) and MCS (mental health composite scale score) at baseline were 37.20 ± 11.09 and 41.88 ± 8.39, which showed a statistically significant improvement after GFD to 50.30 ± 9.88 and 50.22 ± 9.04, respectively. Though there was no significant difference in the total CD-QOL score after GFD, there was a significant improvement in the dysphoria and health-concern subscales. We also found a negative correlation of the pre-GFD symptom score (based on number of positive symptoms) with PCS and MCS and a positive correlation with the CD-QOL score.
Conclusion: This study has shown a reduced HR-QOL in adult CD patients, which improves significantly on GFD, and is associated with a higher symptom number.

Introduction

Health-related quality of life (HR-QOL) is the product of psychological, physical, and social well-being, and the perception of one's position in life compared to others.[1] Monitoring HR-QOL enables a more comprehensive evaluation of the disease and benefits of treatment. The stigma of a chronic disorder and the need for major dietary restrictions increase the self-perceived burden of illness and may adversely affect patient's QOL. In patients with celiac disease (CD), poor adherence to gluten-free diet (GFD), social and economic issues associated with lifelong GFD, associated medical comorbidities, and several intestinal as well as extraintestinal symptoms in CD are also associated with a poor HR-QOL.[2] Both generic (general) and individual (specific) tools can be used to measure the HR-QOL in CD.[3,4] The majority of the previous studies were limited by the use of generic tools (SF-36 or SF-12). However, the specific and validated celiac disease quality of life (CD-QOL) survey has been found to have high internal consistency and reliability.[4]

Studies on HR-QOL in CD have shown conflicting results, with some studies showing QOL in CD to be comparable to general population, whereas others showing poorer QOL.[5–9] Different scoring systems used in these studies limit their comparability. In a national survey conducted by Green *et al.*,[7] 63% of the patients claimed to have modest or poor QOL at baseline. Casellas *et al.*[10] have shown an impaired HR-QOL in untreated CD patients, assessed by Gastrointestinal QOL and EuroQol-5D questionnaires, in all five domains, that is, symptoms, physical, social, emotional dysfunction, and treatment effects, with significantly higher scores in CD patients on GFD, similar to those of general population.

Patients with psychiatric, neurologic, or gastrointestinal comorbidities are also more likely to have reduced QOL.[11]

As the prevalence of CD has been shown to be increasing in South East Asia, and there being no data on QOL from this part of the world, the present study was planned to assess QOL in north Indian patients of CD using SF-12 and CD-QOL questionnaires, and the effect of GFD on QOL.

Methods

This study was a single center prospective follow-up study, based on the consecutive patients of suspected CD attending the gastroenterology clinic of a tertiary-care referral hospital at the Postgraduate Institute of Medical Education and Research, Chandigarh, India between June 2014 and November 2015. This study was approved by the Ethical Committee of the institute and was conducted in compliance with the guidelines of good clinical practice of World Medical Assembly Declaration of Helsinki.[12] Informed written consent was taken from all the patients before participation in the study. Patients (age > 12 years) having history suggestive of malabsorption (chronic diarrhea, anemia, and short stature) with a positive IgA tissue transglutaminase antibody (IgA antitTG) were enrolled in the study. CD was diagnosed according to the standard ESPGHAN guidelines.[13] Patients with chronic illnesses (chronic kidney disease, cirrhosis, and congestive cardiac failure), pregnant/lactating females, and those unwilling to go for endoscopy were excluded from the study. Detailed history and physical examination of all patients were recorded, and baseline complete blood counts and biochemical investigations were done. The serum IgA tTG antibody was repeated at our center for all enrolled patients by a commercially available ELISA kit (Biocompare) using recombinant human tTG, with a 10 EliA U/mL cut-off for the positive test (range 0.1 to >128). After obtaining informed consent, esophagogastroduodenoscopy was carried out using an Olympus GIF 180 H endoscope with a CV 180 processor, under conscious sedation with intravenous midazolam, and all procedures were performed by a single endoscopist who was aware of the clinical details of the patients. Duodenal biopsies were taken for histopathological examination and the presence and severity of villous atrophy were reported according to the modified Marsh criteria.[14]

Evaluation of QOL. Patients fulfilling the inclusion criteria with consistent histopathology were evaluated initially for QOL before starting GFD. The general health was evaluated using the SF-12 questionnaire, which comprises composite scores in eight domains: general health, physical functioning, social functioning, physical and emotional role functioning, vitality, bodily pain and mental health, and yields a physical health composite score (PCS) and a mental health composite score (MCS). The scale scores were calculated by summing the responses and then transformed into a 0–100 scale, with a higher score indicating better health.[3]

The disease-related QOL of adult patients was assessed using celiac-specific questionnaire, that is, CD-QOL.[4] CD-QOL is a self-administered questionnaire, which has 20 items across four clinically relevant subscales that are to be answered using a Likert scale. These include the health-concern subscale, which assesses increased concern about other health problems and cancer risk, the inadequate treatment subscale, which assesses the concerns regarding the treatment of CD such as feelings of inadequate treatment or that the disease is incurable, the dysphoria subscale, which assesses the psychological impacts specifically due to disease such as feelings of depression, and the limitations subscale, which assesses limitations due to CD such as difficulty in social interactions, social stigmatization, difficulty in traveling, etc. The overall score is expressed on a scale of 0–100, with a higher score indicating poorer health.

The questionnaires were made in Hindi (local language) for ease of understanding of the patients. An initial interview of the patients was done by the physician, and the patients were asked to fill the questionnaire, after which they were counseled by a dietician and started on GFD and nutritional supplements. They were followed up initially monthly for 3 months and after 6 months of GFD, and strict adherence to GFD (defined as fully adherent in the last 28 days with no history of dietary transgressions) was reinforced at each visit by an expert dietician.[15] At the end of 6 months, patients who were fully adherent with GFD were evaluated for symptoms, laboratory investigations (hemoglobin, biochemistry, and the IgAtTG antibody), and QOL.

Statistical analysis

All data were acquired prospectively in an enclosed proforma and analyzed using SPSS version 17 software. Symptoms, laboratory parameters, and the QOL data obtained at baseline and during follow-up were compared. QOL was presented as median and interquartile range and this was compared using the WilCoxon Signed Rank test. Laboratory parameters were checked for normality using the Kolmogorov Smirnov test of normality. If data were normally distributed, then the time-related difference was calculated using the paired *t* test, otherwise, the WilCoxon Signed Rank test was applied. Statistical dependence between two variables was assessed with the Spearman's Rank correlation test.

Results

Sixty suspected adult patients with CD (after applying exclusion criteria) were enrolled in the study. Out of the 60, one patient was excluded as his endoscopic and histopathological features were not consistent with CD. The mean age of the patients was 28.85 ± 12.43 year, with 46.2% belonging to the age group

Table 1 Sociodemographic characters at baseline

Demographic profile	*n* (%)
Age (mean±SD) in years	28.85 ± 12.43
Age categories	
12–25 years	24 (46.2)
25–50 years	23 (44.2)
>50 years	5 (9.6)
Male:female	1.3:1 (56:44)
Diabetes mellitus	4 (7.7%)
Hypothyroidism	1 (1.9%)
Liver disease	3 (5.8%)
Previous bone fracture	1 (1.9%)
Family history of celiac disease	4 (7.7%)

Table 2 Clinical characteristics before and after treatment

Clinical features	Pre-GFD *n* (%)	Post-GFD at 6 months *n* (%)	*P* value
Generalized weakness	45 (86.5)	18 (34.6)	<0.001
Generalized fatigue	44 (84.6)	18 (34.6)	<0.001
Abdominal pain	33 (63.5)	11 (21.2)	<0.001
Dyspepsia	33 (63.5)	9 (17.3)	<0.001
Weight loss	27 (51.9)	6 (11.5)	<0.001
Flatulence	26 (50.0)	9 (17.3)	<0.001
Mood swing	25 (48.1)	14 (26.9)	0.007
Diarrhea	24 (46.2)	3 (5.80)	<0.001
Depression	23 (44.2)	10 (19.2)	<0.001
Headache	18 (34.6)	5 (9.60)	0.001
Constipation	17 (32.7)	5 (9.60)	0.004
Menstrual irregularity[†]	6 (26.08)	2 (8.69)	0.125
Bony pain	10 (19.2)	2 (3.80)	0.008
Body ache	10 (19.2)	6 (11.5)	0.388
Oral ulcers	9 (17.3)	1 (1.90)	0.021
Muscle incoordination	9 (17.3)	4 (7.70)	0.063
Perioral numbness	6 (11.5)	2 (3.80)	0.125
Skin rash	5 (9.60)	3 (5.80)	0.687
Bleeding episodes	5 (9.60)	2 (3.80)	0.250
Seizures	3 (5.80)	0 (0)	0.250
Visual abnormality	1 (1.90)	1 (1.90)	1.000
Loss of dark adaptation	1 (1.90)	0 (0)	1.000

[†]Out of total number of females.

12–25 years, and a male:female ratio of 1.3:1. The baseline demographic profile is shown in Table 1. During follow-up, three patients were not compliant with GFD and four patients were lost to follow-up, hence data of 52 patients were available at the end of 6 months. Table 2 shows the clinical features of patients at presentation and after 6 months of GFD. On follow-up after 6 months, there was a significant reduction in most of the clinical symptoms. Mean BMI of patients at baseline was 20.14 kg/m^2, which increased to 21.7 kg/m^2 after 6 months of GFD.

The hemoglobin levels significantly increased after 6 months of GFD, from 11.8 g/dL at baseline to 13.05 g/dL (*P* value: <0.001). 34 (57.7%) patients had anemia during enrollment in the study, with 10 (19.25%) having mild anemia, 12 (23.1%) with moderate anemia, and 8 (15.4%) with severe anemia. Post-GFD, there was a decrease in the numbers in each class, with 6 (11.5%) having mild anemia, 7 (13.5%) with moderate anemia, only 1 (1.9%) with severe anemia, and no anemia in 38 (73.1%) patients. IgA tTG antibody levels also decreased from 128 units to 10.05 units (*P* value: <0.001). There was no significant change in other parameters like blood urea and liver enzymes. 31 patients (59.6%) had scalloping while grooving was seen in 29 (55.8%). On histology, 4 patients (7.7%) had mild villous atrophy (Marsh 3a), while 42 (80.9%) had subtotal (Marsh 3b), and 1 (1.9%) had total villous atrophy (Marsh 3c).

Quality of life

General health evaluation. The general health of the patients was evaluated using the SF-12 questionnaire. The mean PCS before and after GFD were 37.20 ± 11.09 and 50.30 ± 9.88, while the mean MCS before and after GFD were 41.88 ± 8.39 and 50.22 ± 9.04, respectively, with a statistically significant increase in both scores post-GFD (Table 3). Patients with clinical symptoms of diarrhea ($P = 0.005$), mouth ulcer ($P = 0.008$), generalized weakness ($P = 0.009$), and fatigue ($P = 0.002$) were found to have a lower PCS than patients with other symptoms. Similarly, patients with dyspepsia ($P = 0.049$), mood swings ($P = 0.007$), and depression ($P = 0.012$) were found to have a lower MCS than patients with other symptoms.

Table 3 General health scores before and after treatment

	Pre-GFD	Post-GFD at 6 months	*P* value[†]
PCS(mean),SD	37.20,(11.09)	50.30,(9.88)	<0.001
MCS(mean),SD	41.88,(8.39)	50.22,(9.04)	<0.001

[†]Wilcoxon signed rank test.
GFD, gluten-free diet; MCS, mental health composite scale score; PCS, physical health composite scale score.

CD-QOL questionnaire. The median score showed a significant reduction from 10 to 8 for the dysphoria subscale and 13 to 9 for the health-concern subscale after 6 months of GFD. However, scores pertinent to inadequate treatment showed a significant rise from 3 to 6. Similarly, the limitation subscale score was 27 at baseline and remained the same after GFD. The median total CD-QOL score before GFD was 54.5, which reduced to 48 after the introduction of GFD; however, this was not found to be significant (Table 4).

Symptom score. A symptom score was evolved, which was initially not planned in the study, by assigning one point to all positive symptoms while a score of 0 was assigned when a particular symptom was absent. The median score at baseline was 7 (range 1–13), which significantly decreased to 2 (range 0–9) after 6 months of GFD ($P < 0.001$).

We did not find any gender differences in PCS, MCS, CDQOL, and symptom scores.

Correlation between scores. Correlation of the pre-GFD symptom score with various pre-GFD scores was evaluated (Table 5) and it was found that there is a negative correlation of the pre-GFD symptom score with the PCS and MCS and a positive correlation with the CD-QOL score. The correlation was statistically significant in the case of PCS while the negative correlation with MCS was not statistically significant. There was a significant negative correlation of the CD-QOL score with the PCS (Spearman rho −0.416, $P = 0.002$) and the MCS (Spearman rho −0.437, $P = 0.001$), which implies a worse disease-related QOL if the subject is having a low PCS (low general health score) or is more psychosocially and emotionally impaired (a low MCS).

Discussion

We evaluated HR-QOL in patients of CD using the generic SF-12 questionnaire and the specific CD-QOL score, and assessed the effect of GFD on HR-QOL. This study has shown a low PCS and MCS in patients of CD, thereby implicating a poor general health of these patients in both physical and mental health domains. Previous studies have shown similar results with reduced SF-36 scores in CD patients. While Hallert *et al.*[5]

Table 4 Celiac disease quality of life scores

	Pre-GFD	Post-GFD at 6 months	*P* value†
CD-QOL score, median(range)	54.5(26–73)	48(24–84)	0.689
Limitation subscale, median(range)	27(10–40)	27(10–45)	0.451
Dysphoria subscale, median(range)	10(4–18)	8(4–15)	0.001
Health-concern subscale, median(range)	13(5–19)	9(5–21)	<0.001
Inadequate treatment subscale, median(range)	3(2–10)	6(2–9)	<0.001

†Wilcoxon signed rank test.
CD-QOL, celiac disease quality of life questionnaire; GFD, gluten-free diet.

Table 5 Correlation of the pre GFD symptom score with pre GFD scores

Scoring system	Spearman rho	*P* value
PCS	−0.429	0.002
MCS	−0.341	0.013
Total CD-QOL score	0.635	<0.001
Limitation subscale score	0.553	<0.001
Dysphoria subscale score	0.525	<0.001
Health subscale score	0.441	0.001

CD-QOL score, celiac disease specific quality of life score; MCS, mental health composite scale score; PCS, physical health composite scale score.

showed a SF-36 score of 62.8, Barratt *et al.*[15] showed a much lower SF-36 score of 43 with a still lower score in nonadherent patients. We have also shown a significant increase in both scores with 6 months of GFD, signifying that GFD improves the general health of patients.

When we assessed the general health of our patients using the multi-item generic SF-12 questionnaire, the mean PCS before GFD was 37.30, which increased to 50.30 with GFD, and the mean MCS before and after GFD were 41.88 and 50.22, respectively. Patients with symptoms of diarrhea, mouth ulcers, generalized weakness, and fatigue had significantly lower PCS scores, possibly due to greater limitation in the domains of physical functioning (daily activities), physical role (work-related activities), bodily pain, and general health, experienced by these patients. Patients with dyspepsia, mood swings, and depression had a lower MCS compared to other patients as they scored low on mental health, emotional role, and vitality. A study by Zarkadas *et al.*,[6] using the SF-12 questionnaire in patients of CD, showed a lower QOL score for women and in the first year after diagnosis, suggesting a greater burden for women and newly diagnosed CD patients. In a study by Tontini *et al.*[16] on 43 adult CD patients, both typical and atypical CD patients had a significantly lower PCS and MCS compared to healthy controls, with women having a worse HR-QOL. They also showed that patients with typical symptoms have the quickest improvement on GFD with both scores becoming comparable to controls within 1 month of GFD, compared to atypical patients where the scores became comparable only after 12 months of GFD. No gender difference was, however, observed in our study. In a recent meta-analysis[17] based on 18 studies of HR-QOL in CD, one-year treatment with GFD significantly improved the PCS and MCS; however, the QOL remained lower as compared to nonceliac controls. The QOL was still lower in symptom-detected and non-strict GFD adherent patients. Sainsbury *et al.*[18] have shown that reduced QOL in CD is more strongly related to the presence of psychological symptoms, particularly depression, maladaptive coping, and poorer GFD adherence compared to gastrointestinal symptom severity.

Previous studies on CD QOL were limited by their use of generic rather than CD-specific assessment instruments. Therefore, Dorn *et al.*[4] developed and validated the CD-QOL questionnaire for the assessment of QOL specifically in CD patients, with higher CD-QOL implying a poorer QOL. In our study, the median CD-QOL score before the introduction of GFD was 54.5, and it fell to 48 after 6 months of GFD. Even though there was no statistically significant difference in total CD-QOL, there was a significant difference in scores pertaining to dysphoria, health, and inadequate treatment. A possible explanation for this may be that even though patients show improvement in general health after GFD, more psychosocial impairment in daily life is brought by GFD in the form of expenses, lack of taste, cultural habits, lack of availability, etc. In a study by Rodríguez *et al.*[19] on a Spanish cohort of adult CD patients, the HR-QOL level as assessed by CD-QOL was moderate, with a mean CD-QOL index of 56.3 points. The maximum points were scored on the dysphoria subscale, followed by limitations and health problems. The median limitation subscale in our study remained the same despite GFD. This signifies that despite a symptomatic improvement, patients are still limited in specific areas such as feelings of social stigma, availability of foods, difficulty in socializing and long travel, fear of contamination of food with gluten, etc.

Some previous studies have shown that the HR-QOL in CD is worse in patients with more number of symptoms or increasing severity of symptoms.[20,21] Usai *et al.*[21] showed that HR-QOL is worse in patients with more number of symptoms (lowest QOL score in patients with more than six symptoms) and comorbidities. We thus calculated a symptom score based on the number of positive symptoms, and have shown an improvement in this score (from 7 to 2) with 6 months of GFD, thereby showing an improvement in QOL with alleviation of symptoms. We have also correlated the symptom score with other established HR-QOL scores, and found a negative correlation with PCS and MCS, indicating poor general health in patients with more symptoms. There was a positive correlation between the symptom score and the total CD-QOL score, limitation score, dysphoria score, and health score, thus implying that the more symptomatic patients have greater psychological symptoms (such as anxiety and depression), which are associated with lower QOL. These patients also feel more limited in their daily activities and socially restricted, and have greater concern regarding their health like concern for cancer and long-term outcomes. As expected, we saw a negative correlation of the CD-QOL score with PCS and MCS.

While earlier CD was often seen to present with gastrointestinal symptoms like diarrhea, recent studies have shown a higher number of patients presenting with atypical manifestations like

anemia, bone disease, or psychiatric symptoms.[22,23] Among other symptoms, CD patients have also been shown to have experienced more stressful events than general population.[24] A wide range of psychiatric symptoms have been shown to be associated with CD with improvement in symptoms after GFD.[25] In our study, 44.2% patients had depression and 48.1% had mood swings. Nearly 60% of our patients had anemia at the time of enrollment in study. The median hemoglobin of our cohort was 11.8 g/dL, which improved to 13.05 g/dL after 6 months of GFD. IgA tTG antibody levels also decreased from a mean of 128 units to 10.05 units (*P* value: <0.001), and 57 (96.6%) patients had normalized their IgA tTG antibody levels within 6 months of GFD, highlighting strict GFD adherence. The normalized IgA tTG antibody levels have been used as a marker of on-going strict GFD adherence as well as improvement in duodenal histology.[26]

Our study is the first study from India to assess the QOL in CD using formal questionnaires, as well as to assess the effect of GFD on QOL. However, this study has some limitations. We do not have a control group with which the QOL parameters of CD patients could be compared. The questionnaires were also filled by patients themselves, and not by an interviewer. We have not correlated the QOL parameters with the disease duration, the socio-economic, and the educational status of patients. We have also assessed the effect of GFD only until 6 months. We also realize that in our country, we do not have a support group for CD patients consisting of a multidisciplinary team to safeguard the QOL of CD patients in the long term.

In conclusion, our study has shown a reduced HR-QOL in adult CD patients using formal questionnaires, which improves significantly on GFD. We have also shown poor QOL to be associated with a higher symptom number. This study makes a strong case for the need of a nation-wide support group for patients of CD.

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