1130-0108/2015/107/4/196-201
Revista Española de Enfermedades Digestivas
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Rev Esp Enferm Dig (Madrid
Vol. 107, N.º 4, pp. 196-201, 2015

ORIGINAL PAPERS

Benefit on health-related quality of life of adherence to gluten-free diet in adult patients with celiac disease

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ABSTRACT

Introduction: Celiac disease (CD) affects health-related quality of life (HRQOL) of patients suffering it. The exclusion of gluten from the diet (GFD) improves HRQOL, but involves difficulties in following the diet that could adversely affect HRQOL.

Objective: To determine the effect of adherence to the diet on HRQOL of adult CD patients.

Methods: A prospective, cross-sectional, multicenter study of CD patients treated with a GFD for longer than 1 year. Adherence to the GFD was measured using the Morisky scale, and health status using the specific CD-QOL questionnaire and the generic EuroQol-5D questionnaire.

Results: 366 patients from 7 hospitals were included: 71.5% of patients reported a perfect treatment adherence, 23.5% unintentional poor adherence and 5% intentional poor adherence. Good adherence to a GFD was related to a higher mean score on the CD-QOL (75 *vs.* 68, respectively, $p < 0.05$) and EuroQol-5D (0.9 *vs.* 0.8, respectively, $p < 0.05$). Ease of adherence to a GFD was also related to a better HRQOL (total CD-QOL score of 82 *vs.* 67 in patients who consider the GFD difficult to follow, $p < 0.05$). Good symptom control was also related to a better HRQOL (total CD-QOL score of 78 *vs.* 67 in asymptomatic *vs.* symptomatic patients, $p < 0.01$). The worse scored dimension of CD-QOL was related to "inadequate treatment."

Conclusions: In CD, good adherence to a GFD and adequate symptom control result in improved HRQOL. Many patients consider that the lack of therapeutic alternatives to diet worsens their quality of life.

Key words: Celiac disease. Quality of life. Gluten-free diet. Adherence to treatment.

INTRODUCTION

Celiac disease (CD), due to its chronic nature, impact on health, psychological distress, social and family connotations, and need for permanent treatment, adversely affects quality of life (HRQOL) of patients. There is proven evidence that having CD affects the general perception of HRQOL and the feeling of well-being (1,2), which has been associated with factors such as the presence of symptoms, female gender, associated diseases, having fatigability, and not having received treatment (3,4). In addition, many studies have shown repeatedly that starting the treatment, with complete and permanent exclusion of gluten from the diet (GFD) achieves not only to relieve symptoms but also to improve HRQOL (5,6). The improvement in HRQOL induced by a GFD is substantial, though this good response is not apparent in patients with clinically silent CD or diagnosed by serology only (7). This is probably due to the fact that asymptomatic patients diagnosed only by serology have an unchanged quality of life (8-11).

However, following a GFD also generates difficulties and limitations in the life of patients with CD under treatment. A national survey of members of the Canadian Celiac Association revealed difficulties in following a GFD in 44% of patients, with limitations in daily life from avoiding restaurants, avoiding travel, etc. (12). A similar study, where a survey was sent to the members of the German Coeliac Society, showed that, though the GFD improved patients' symptoms and HRQOL, they continued to have poorer anxiety, fatigue and quality of life scores measured with the generic SF-36 questionnaire than the reference general population (13). Also an American study that conducted a survey of members of the Westchester Celiac Sprue Support Group found that following a GFD had a negative impact in some areas such as family in 67% of cases or work in 41% of cases (14). A more recent American study confirmed the negative impact of the GFD on the life of patients by applying the generic FS-12 questionnaire (15). Similarly, a survey directed to members of the Coeliac UK Charity showed that, although 96% of celiacs reported correct compliance with the GFD, impaired HRQOL persisted with regard to exclusion from social and leisure activities (16). It is not surprising, in view of the above, that celiac patients may continue to experience a substantial long-term burden by following the diet (17).

Received: 08-01-2015
Accepted: 04-02-2015

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Casellas F, Rodrigo L, Lucendo AJ, Fernández-Bañares F, Molina-Infante J, Vivas S, Rosinach M, Dueñas C, López-Vivancos J. Benefit on health-related quality of life of adherence to gluten-free diet in adult patients with celiac disease. Rev Esp Enferm Dig 2015;107:196-201.

Adequate treatment adherence, in this case to a GFD, is a determining factor in improving the health of celiac patients and for improving their HRQOL (18). Noncompliers or partial compliers of treatment are those with poorer scores on generic quality of life questionnaires such as the WHOQOL-BREF or SF-36, both the overall score and most their domains (19-21). In a prospective study of celiac patients who started a GFD, it was shown that HRQOL measured according to SF-36 improved during the first year of follow-up, but that HRQOL worsened significantly at 4 years of follow-up, which was explained by the authors by a lack of strict compliance to the GFD (22). The association of adequate compliance with a GFD and better HRQOL is not limited to adult celiac patients, but also has been reproduced in adolescents in whom a study showed that noncompliers with CD have poorer HRQOL, more physical and family problems and greater concern about their disease (23). However, there is some disagreement on health perception and adherence to the GFD since there are also other authors who, also using generic questionnaires, such as SF-36, have observed that the degree of compliance to the GFD is not associated with quality of life (24-26). In this regard, it has been observed that asymptomatic patients diagnosed by serology, in contrast to what occurs with symptomatic cases, may even experience deterioration in their health perception during following of a GFD (27). A randomized clinical trial analyzing the effect of an online interactive intervention to optimize adherence to the GFD showed that, although the intervention program effectively improve adherence to the GFD, measurements of HRQOL did not differ between patients who followed the interactive program and controls (28). This disagreement in the effect of adherence to the GFD on HRQOL of celiac patients could be related to the use of generic questionnaires instead of specific questionnaires for celiac disease, since they may be more sensitive to changes in HRQOL in the specific situation of celiac patients.

In order to improve the result of the generic questionnaires for measuring HRQOL in celiac disease, specific questionnaires for application in adult celiac patients have recently been designed, such as the Coeliac Quality of Life Questionnaire (CD-QOL) and Celiac Disease Questionnaire (CDQ) (29,30). The purpose of this project was therefore to examine the effect of adherence to the GFD on health perception of celiac patients measured using a specific questionnaire. A study was conducted in previously diagnosed celiac patients treated with a GFD in which adherence to the GFD was related to quality of life assessed with the specific questionnaire CD-QOL, because it is the only currently specific questionnaire translated and validated to Spanish available (31).

MATERIALS AND METHODS

A prospective, cross-sectional, multicenter, observational study was designed to establish the influence of following the GFD on HRQOL of celiac patients. The study was approved by the Ethics Committee of the Hospital Universitari Vall d'Hebron (Barcelona, Spain), with code PRAG254-2012.

The study included adult patients with celiac disease previously diagnosed according to the commonly accepted criteria (positive serum-IgA-tissue-transglutaminase antibodies with compatible endoscopic biopsy of duodenum) (32,33).

In order to participate in the study, patients had to be between 16 and 75 years of age, and have a duration of celiac disease since diagnosis greater than one year. All patients received treatment with a GFD. Patients with celiac disease who could not read or understand questionnaires, with other relevant concomitant chronic diseases, or who refused to sign informed consent were excluded from the study.

Procedure

Patients who met the criteria for participation in the study were explained the protocol and signed an informed consent form. The quality of life and treatment adherence questionnaires were then administered, and clinical and epidemiological data were collected. The variables measured in this study phase were:

Quality of life

For determination of quality of life, the Spanish version of the specific questionnaire for patients with celiac disease CD-QOL (31), and the generic EuroQol-5D questionnaire were administered. The latter questionnaire is a generic questionnaire validated in Spanish consisting of two parts. The first part assesses health state through five dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions includes three items related to three severity levels. As the result, 243 different health states may be obtained. In the second part, patients score their health state on a visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

As a specific measurement of HRQOL, the CD-QOL was chosen because it is a specific questionnaire and it has been previously translated and validated in Spanish (31). The CD-QOL is a self-administered questionnaire consisting of 20 items, to be answered using a Likert scale, distributed into 4 dimensions: Dysphoria, limitations, health concerns, and inadequate treatment –that should be answered on a Likert scale. Administration of the questionnaire yields an overall score expressed on a scale of 0 (worst quality of life) to 100 (best quality of life), and four domains, each expressed on the same 0-100 scale, where 100 corresponds to the best quality of life. The instructions given in the original publication were followed to calculate the score on the questionnaire.

Monitoring of adherence to the GFD

Compliance with the GFD was assessed using the adaptation of the self-administered questionnaire by Morisky et al. (36). Since this questionnaire was originally described for medication adherence, it was adapted to be applied to adherence to the GFD, and a fifth response was added: "I never forget to follow the diet". This adaptation has previously been used in other studies of adherence to a

GFD in celiac disease (37). This questionnaire consists of four items referring to treatment compliance, which are answered using a binary scale (yes/no). The first two questions relate to unintentional non-adherence (I sometimes forget to follow the diet/I sometimes am not very careful in following the diet), while the last two questions relate to intentional non-adherence (when I feel better, I sometimes stop the diet/if I do not feel well, I sometimes stop the diet). If the answer to either of the questions 3 or 4 is yes, the patient is considered to have voluntarily discontinued the diet. If answer to either of the questions 1 or 2 is yes, the patient is considered to have unintentional non-compliance with due to carelessness or forgetfulness. If no question is answered yes, diet adherence is considered to be good or perfect.

Statistical analysis

In accordance with the established objective, for statistical analysis, patients were stratified into three groups according to the degree of adherence to the GFD: Good compliance, unintentional noncompliance, and intentional noncompliance. Normality of variables was analyzed using a Kolmogorov test. Since some variables did not follow a normal distribution, descriptive statistics was performed using the median and 25-75 percentiles, and comparative statistics between groups using the respective nonparametric tests (Spearman correlation to correlate the CD-QOL with the EuroQol-5D and EIDF, and the Mann-Whitney or Kruskal-Wallis tests as necessary, to determine the existence of statistical differences between quantitative variables). A value of $p < 0.05$ was considered statistically significant. For statistical calculation, the GraphPad Prism version 5.00 for Windows program was used.

RESULTS

The study was conducted in seven Spanish hospitals, where the questionnaires were administered to a total of 366 adult celiac patients receiving a GFD for a median of 4 years. Table I summarizes the main characteristics of the patients included. As regards following their diet, most patients (71.5%) stated they never forget to follow the diet, which was considered a perfect adherence to treatment. Of the remaining patients, 23.5% had unintentional noncompliance and 5.0% had intentional noncompliance of the diet (Table II). Fifteen patients did not answer Morisky test or did so incorrectly, and were not included in the statistical analysis of the study.

Effect of following the gluten-free diet on HRQOL

The overall score on the CD-QOL questionnaire by degree of adherence to the GFD according to the results of the Morisky scale are shown in figure 1. It can be seen that the score obtained by the 251 celiac patients who reported perfect adherence to the GFD is significantly higher than that obtained by 83 celiac patients who reported unintended noncompliance and the 17 celiac patients who reported intentional noncompliance. This reflects that correct adherence to the GFD is associated with better quality of life assessed by the specific questionnaire.

Table I. Epidemiological characteristics of patients included in the study

Variables	
Total number	366
Age	40.0 [28.0-49.2]
Sex (% women)	70.0%
Smoking (% smokers)	16.1%
Time since onset (months)	48.0 [24.0-113.5]
Classic symptoms (%)	24.8%
Associated diseases (%)	22.9%
Education (none / primary / secondary / university)	5 / 68 / 157 / 131
Civil status (single / married / other)	151 / 183 / 322
PLACE OF RESIDENCE ($< 1 \bullet 10^5$ / $1 \bullet 10^5$ to $5 \bullet 10^5$ / $> 5 \bullet 10^5$ inhabitants	174 / 156 / 36

Results are given in absolute numbers, percentage, or medians with [25th-75th percentile].

The differences in quality of life according to adherence to the GFD established according to the generic EuroQol-5D questionnaire were similar. Comparisons were made of the median index and median visual analogue scale of the EuroQol-5D between the groups with different degrees of adherence to the GFD (Fig. 2). The differences obtained in the EuroQol-5D score were statistically significant between the group with perfect adherence to the GFD and the groups with unintentional or intentional noncompliance, for both index ($p = 0.01$) and the visual analogue scale of the EuroQol-5D ($p < 0.05$). This indicates that good adherence to the GFD is associated with a better quality of life.

Table II. Degree of adherence to diet according to results of Morisky scale

I never forget to follow the GFD	251 (71.5%)	Good compliance
I sometimes forget to follow the GFD	49 (13.9%)	Noncompliance
I am sometimes not very careful	34 (9.6%)	Unintentional
When I feel well I sometimes stop the diet	13 (3.8%)	Noncompliance
If I don't feel well I sometimes stop the diet	4 (1.2%)	Intentional

Results expressed in absolute terms values and percentage (in parentheses) of patients included in the statistical analysis. Fifteen patients who did not answer the Morisky test or did so incorrectly were excluded from the analysis.

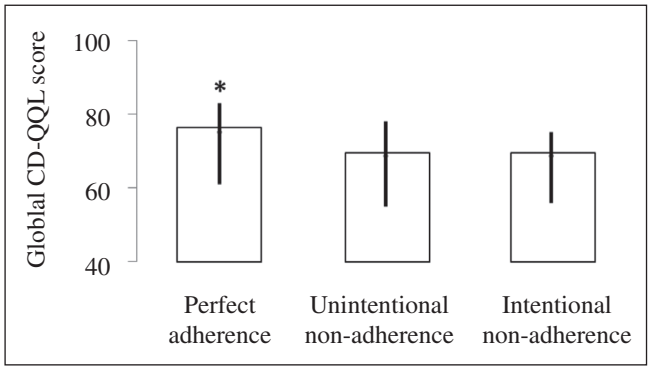

Fig. 1. Median and percentiles [25-75] of overall score on CD-QOL questionnaire by degree of adherence to the GFD. Celiac patients with perfect adherence to the GFD (n = 251) achieved a significantly higher score (* = p < 0.05) than patients reporting an unintentional (n = 83) or intentional (n = 17) nonadherence.

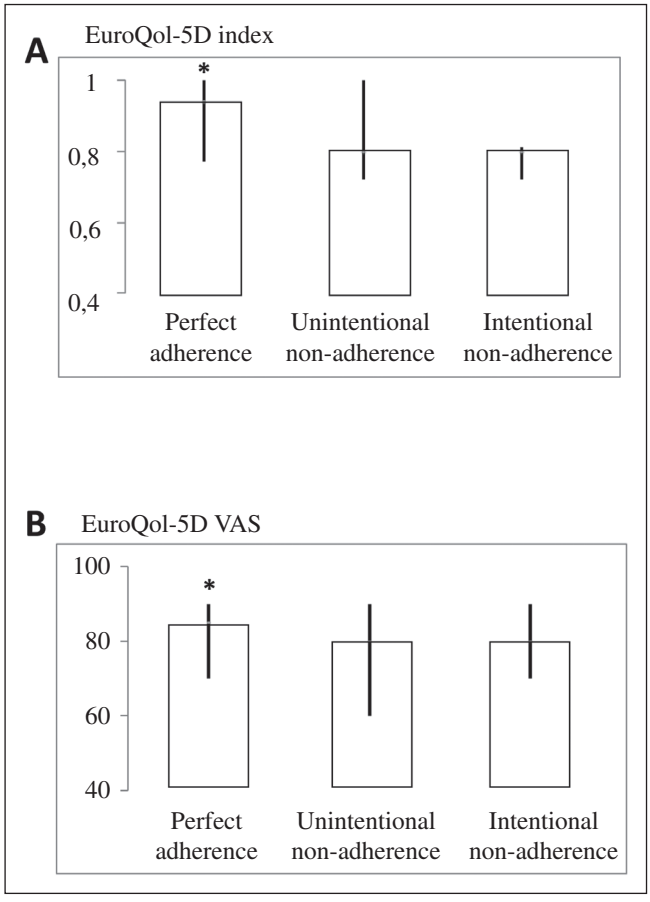

Fig. 2. Median and percentiles [25-75] of EuroQol-5D index (A) and visual analogue scale (B) according to the degree of adherence to the GFD. Celiac patients who have perfect adherence to the GFD obtained a significantly higher EuroQol-5D index (*p = 0.01) and score on the visual analogue scale (* = p < 0.05) than patients reporting unintentional or intentional nonadherence.

The results obtained in the four domains of the CD-QOL according to the degree of adherence to the GFD are shown in table III. Analysis of the results of the CD-QOL dimensions suggests that in all groups following the GFD the worst scored dimension was that related to "inadequate treatment." Individual results of each domain for each of the three degrees of adherence to the GFD show that the "dysphoria" and "health concerns" dimensions are significantly better scored in the group with complete adherence than in the groups with nonadherence (Kruskal-Wallis test, $p < 0.05$ for both). From these results it can be deduced that the fact of suffering a celiac disease and having to follow a dietary treatment negatively impacts perceived quality of life by patients, but if they correctly follow the diet they report the perception of having fewer health concerns and better dysphoria.

To analyze the importance of achieving a good HRQOL measured according to the CDQOL specific questionnaire, the results for adherence, symptom improvement (patients were asked if symptoms had disappeared, had improved or remained the same or worse) and presence of symptoms related to the disease (patients were asked if they had any symptoms or remained asymptomatic) were stratified based on whether the overall CD-QOL score was above 60 percentile (good quality of life, n = 274) or below the 40 percentile (poor quality of life, n = 28). According to this distribution, the degree of adherence was independent of whether quality of life was good or bad (complete adherence to the GFD in 67% and 70% respectively, p = ns). However, having a good quality of life was significantly related to symptom improvement and the absence of symptoms at study entry (Fig. 3).

DISCUSSION

Celiac disease is of great importance because of its increasing incidence, occurrence at any age with a broad range of clinical manifestations, sometimes with a considerable delay in diagnosis and requiring lifelong treatment (38). The purpose of this study was to examine the relationship between adherence to the GFD and health perception of celiac patients, measured using a specific questionnaire validated in the study population, the CD-QOL. A prospective, crossover multicenter study was conducted in 351 celiac patients previously diagnosed and treated with GFD, in which adherence to the GFD measured according to the Morisky test was related to HRQOL. The results of the present study show that patients correctly following the GFD have better HRQOL. The analysis by quality of life dimensions suggests that better HRQOL is associated with less dysphoria and fewer health concerns. The poorer scored dimension in all groups of adherence to the GFD was "inadequate treatment." This result can be interpreted in the sense that celiac patients on treatment perceive that not having other alternatives to the gluten-free diet for controlling the disease limits their quality of life. It was not an objective of the study to determine the reasons for failure

Table III. Median score and percentiles [25-75] obtained in each domain of the CD-QOL in the groups distributed according to degree of adherence to the gluten-free diet

	Perfect adherence (n = 251)	*Unintentional noncompliance (n = 83)*	*Intentional noncompliance (n = 17)*
Overall	75.0 [61.2-83.7] #	68.7 [55.0-78.7]	68.7 [56.2-75.6]
Dysphoria	94.0 [81.0-100.0]#	88.0 [75.0-100.0]	94.0 [69.0-97.0]
Limitations	75.0 [58.0-89.0]	75.0 [58.0-89.0]	67.0 [54.5-79.5]
Health concerns	75.0 [55.0-90.0]#	70.0 [45.0-90.0]	60.0 [47.5-70.0]
Inadequate treatment	50.0 [25.0-63.0]	50.0 [25.0-63.0]	50.0 [25.0-50.0]

Results are given on a 0-100 scale, where 100 correspond to the best quality of life. The worst scored dimension in all degree of treatment adherence groups was "inadequate treatment", $p < 0.05$. (# = $p < 0.05$ in the same domain *versus* other degrees of adherence to the GFD).

of treatment adherence or potential factors involved in this, and therefore psychological profiles of patients were not established that might have influenced this (39).

Achieving a good HRQOL in celiac patients with the GFD is important because those who obtain a good score on the CD-QOL questionnaire are those who have obtained a good response to diet and remain free of disease symptoms. This finding confirms the need for taking all necessary measures to achieve good compliance with the GFD.

The rate of correct adherence to the GFD in patients included in the study was 71.5%. This value is consistent with the expected rate, because other series have published a rate of good adherence of up to 75% in adolescents (40) or from 70-81% in adults (41,42). Most publications have analysed adherence to the GFD and their results have shown that correct adherence to treatment achieves a good symptomatic response. However, there is much less information on how the degree of adherence is related to changes in health perception of celiac patients. The present study shows that patients with partial or no adherence have a poorer HRQOL than those defined as good compliers of the GFD. The results of this study agree with those previously published, which had suggested the presence of a relationship between HRQOL and adherence to the GFD, so that using the SF-36 generic instrument it was shown that, with regard to the HRQOL before starting GFD, patients who have better HRQOL after 4 years of follow-up are those who have strict compliance with the diet (43). Adherence has thus been advocated as an independent factor involved in HRQOL of celiac patients (44). One limitation of the study, due to its design, is the lack of a measurement of quality of life before starting treatment. This would allow determining the degree of gain in perception of health measured with specific instruments for celiac disease according to the degree of adherence to the diet, a very interesting aspect, but which remains open for future prospective studies designed for this purpose.

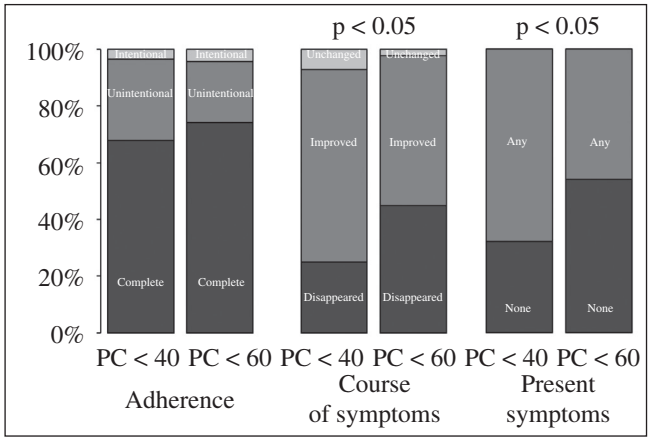

Fig. 3. Effect to having good or poor quality of life according to the overall CD-QOL score was above the 60th percentile or below the 40th percentile, respectively, in adherence to the GFD and symptoms. Having a good quality of life (PC > 60) was significantly related to improvement in symptoms and the absence of symptoms at the time of inclusion.

From the results of this study, it can be established that the better the quality of life of celiac patients the better is their clinical response and the fewer the symptoms they have. This is another reason to promote perfect adherence to the GFD. However, treatment of celiac disease also induces negative subjective appraisals, so that it has been suggested that celiac patients report high concern about treatment, even worse than in other gastrointestinal chronic gastrointestinal diseases such as gastroesophageal reflux disease (45). The factors that have been related to concern about treatment in celiac disease include the high cost of food, having to eat out, problems with meals at school, limitations in the time to prepare food and poor treatment adherence. In the same study, this low adherence to the GFD was s found to be associated with a greater severity of symptoms and a worse perception of the importance of treatment, therefore justifying another reason to enhance adherence to the GFD in celiac patients. Other studies have shown that maintaining the GFD has a negative impact on the life of celiac patients, who report difficulties in eating out, travelling or family life (14). Taking together all these data, it can be concluded that complete adherence to the GFD results in significant benefits for the health and quality of life of celiac patients, but this is also at the expense of creating a concern and a limitation for certain activities of daily life. It could also be suggested alternative explanations for the findings of the study, as being celiac patients with worse quality of life those with lower adherence to the gluten-free diet.

In conclusion, the results of this study suggest that most celiac patients consider they correctly follow the GFD. Adequate compliance with the GFD is related to better quality of life measured with a specific instrument for celiac patients and this is associated with good control of symptoms. On the other hand, according to the results of the "inadequate treatment" dimension of the CD-QOL, celiac patients on diet treatment perceive that not having other alternatives to the gluten-free diet for controlling the disease limits their quality of life.

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