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Difficulties Assessing Adherence to Gluten-free Diet in Celiac Patients

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Abstract To date the only efficient treatment of celiac disease is a lifelong gluten-free diet (GFD), which involves relevant lifestyle changes. Numerous methods measure adherence to GFD, but none is completely reliable. The aim of the study was to compare three frequently used methods to measure adherence to GFD and study factors that influence adherence to GFD. Eighty-one celiac patients 15 years or older, on GFD were evaluated by dietitian interview, a Celiac Dietary Adherence Test (CDAT) and blood antitransglutaminase antibodies (tTG). Factors influencing adherence were assessed by an ad-hoc questionnaire following WHO criteria. Adherent and non-adherent patients were classified in the same category in 44.4% of cases (n=36), (non-adherent=35.8% and adherent= 8.6%). In general, methods identified better non-adherent than adherent individuals. Among the 5 realms defined by WHO, when tTG (positive/negative) defined adherence, logistic regression identified ten significant variables (information about disease, income, education, cost of gluten-free products, eating in restaurants, time on GFD, symptoms at diagnosis, number of symptoms at time of diagnosis, other chronic diseases present, allergy/food intolerance plus a chronic disease and CD). Using the interview as reference, two variables were significant (self-perception of knowledge of the GFD, and presence of gastrointestinal symptoms when gluten is consumed). Results illustrate the difficulties of measuring both adherence to GFD and the factors that influences it. Further studies should explore new markers able to measure the amount of gluten necessary to activate autoantibodies production and the time they take to stop their production once the patient stops gluten ingestion.

Keywords: *celiac disease, adherence, CDAT, serum antitransglutaminase antibodies, interview*

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1. Introduction

Celiac disease (CD) is a systemic immune-mediated disorder triggered by gluten in genetically susceptible persons. Interaction of genetic (risk genes) and environmental (gluten) factors plus the immune effector system results in the appearance of the disease. The microbiota, epigenetic components and other factors (infections early in life and others) are likely to participate in the pathogenesis of the condition, but the mechanisms involved in the process remain unclear. CD is characterized by innate and acquired immune responses, production of autoantibodies, variable clinical presentations and variable degrees of small intestinal mucosa damage [1,2]. Until now, the only efficient treatment is a lifelong gluten-free diet (GFD), which is effective, but involves relevant lifestyle changes affecting the family, school/work and social life [3,4,5]. Adherence to GFD is important because it not only improves symptoms, but also avoids complications [4,6,7]. Adherence to GFD is difficult to maintain and varies widely depending on the countries and cultural dietary habits of the population, ranging from 24 to 96% [8,9]. The World Health Organization (WHO) has defined "adherence to long-term treatment" as "the extent to which a person's behavior-taking a medication, following a diet and implementing lifestyle changes- is in accordance with the recommendations agreed upon with a health care provider". They describe five realms influencing adherence: factors related with the health system or health team, to socioeconomic features, to treatment, issues related with the patient and elements related to the disease [10].

Measuring adherence to chronic treatments is difficult and continues being a matter of debate. There are numerous methods to measure adherence to GFD during follow up, from histological assessment of small intestinal biopsies or changes in blood autoantibodies to non-invasive techniques, like an interview by a trained dietitian or validated short questioners. None of them is 100% reliable and reproducible. In celiac adults on GFD, duodenal mucosa achieves full recovery approximately in one third of patients [11,12]. Evidence supports that detection of blood autoantibodies is highly sensitive and specific for diagnosis of CD, but the available evidence also strongly suggest that during follow up they do not correlate with

intestinal damage [12,13,14] nor with the frequency of eating gluten containing foods, as reported by patients' themselves. Short questionnaires is an alternative approach currently yielding promising results, but they are not fully standardized yet [15,16]. To date, the evaluation by a trained dietitian appears as an effective and not invasive method, because it allows detecting unintentional gluten consumption [17,18]. Most available data assessing adherence to GFD by non-biological methods originates in European countries, USA, Canada; their conclusions are diverse and sometimes contradictory [19-23]. Differences in personal, cultural and socioeconomic factors that influence adherence may explain the variability, making difficult to extrapolate results to Hispanic societies, among others. In Latin American countries, the available information is scarce. This led us to set as objective of this study to measure adherence to GFD in celiac patients diagnosed and followed in Santiago, Chile, by three different methods that are commonly used in many countries: determination of blood antitransglutaminase antibodies (IgA-tTG), an interview by a trained nutritionist and the Celiac Disease Adherence Test (CDAT) developed by Leffler et al. [15]. A second objective was to evaluate the factors that may influence adherence to GFD following WHO criteria [10].

2. Material and Methods

Celiac patients controlled at the Diagnostic Center in the Institute of Nutrition and Food Technology (Cedinta), University of Chile, were invited to participate. Inclusion criteria were being older than 15 years of age, on GFD for at least 6 month, diagnosed by means of at least one positive autoantibody and exhibiting a Marsh 2 to 4 lesion [24] in the duodenal biopsies. Institutionalized patients and those with conditions that require special diets and/or medication, have disturbed cognitive ability and psychiatric patients were excluded. The protocol was approved by the institutional IRB and participants signed an informed consent prior to incorporation to the study.

Adherence by Non-biological methods. i) CDAT was translated and validated to Spanish, checked for local language and tested in a group of patients that did not participate in the protocol. The final version used agrees with that of Fueyo-Díaz, which was published while conducting this study [25]. Scores to define "adherent" or "non-adherent" were those originally published by Leffler [15], considering "adherent" patients that scored 7 to 12 points and "non-adherents" those scoring ≥ 13 points. ii) A semi-structured interview by a trained dietitian collected data on the patient's knowledge about GFD, cross contamination, type of food consumed, and a 24 hours food recall. iii) Factors associated with adherence to GFD were assessed by an ad-hoc questionnaire including 36 closed questions, which assessed the five realms described by WHO [10]. Treatment and follow up data was obtained directly from charts and the health team in charge of the patient.

Adherence by IgA-tTG. tTG was measured 5 ml venous blood sample by an ELISA test (Aeskulisa tTG-A Neo epítope IgA) following manufacturer's instructions (normalcy defined by ≤12 U). For the purpose of this study, tTG values over 12 U defined "non-adherence".

Analysis of results. Univariate analysis applied chi2 test and Pearson correlation using STATA 12.0. Results were analyzed in two ways: defining the adherent and non-adherent groups by the interview and then by tTG measurement. Adherent and non-adherent groups were compared for each of the variables assessed. For multivariate analysis, variables included in each of the five realms assessed were grouped and logistic regression was used for analysis within each group, first using adherence assessed by tTG (positive/negative) and then by results of the interview (adherent/ non-adherent). P values < 0.05 were considered significant.

3. Results

Eighty one celiac patients participated in the study, 74 were women (91.4%), with mean age 39.4 years (range 18.3-72.4) and mean age at diagnosis 34.8 years (range 22.3-66.3); 16 were overweight (20%) and 4 obese (5%). Mean length of GFD was 4.7 years (range 0.5-32.9 years, median 3.3 years).

3.1. Comparisons of Three Methods to Measure Adherence to GFD.

General characteristics of adherent and non-adherent patients are shown in Table 1 and Table 2. Both tTG and the interview classified 30 patients (37%) as adherents; however, individuals forming these two groups were not the same. CDAT classified 28 patients (34.6%) to be adherent. The three methods used coincided classifying adherent and non-adherent patients in the same category in 44.4% of cases (n=36), 29 (35.8%) in the non-adherent group and 7 (8.6%) among adherent cases. Comparing interviews and CDATs, they coincided in classifying adherents and non-adherents in 21.4% (n=17) and 49.4% (n=40), respectively. In turn, interview and tTG coincided in 14.8% (n=12) and 40.7% (n= 33), respectively. Finally, CDAT and tTG coincided in 17.3% (n=14) and 45.7% (n=37) of cases. In all comparisons, methods showed better matching classifying non-adherent than adherent individuals.

Table 1. General characteristics of 81 adherent and non-adherent participants according to nutritionist interview results

	adherents	non-adherents	p
TOTAL N	30	51	
Age. Mean (range) Median	41.6 years (18.3 - 69.3) 38.4 years	38.1 years (20.4 - 72.4) 35.3 years	0.24
At diagnosis. Mean (range) Median	37 years (2.3 - 66.3) 35.4 years	33.4 years (3.4 - 65.6) 31.8 years	0.24
Sex women, n (%)	27 (90%)	47 (92.2%)	0.74
Weight. Mean (range) Median	60.9 Kg (44 - 80) 58.5 Kg	59.4 Kg (44 - 85) 57 Kg	0.52
Height. Mean (range)	159 cm (146 - 173)	160 cm (147 - 179)	0.62
BMI (Kg/m^2). Mean (range)	24 (18.7 - 31)	23.2 (19 - 32.9)	0.24
Time on GFD Mean (range) Median	4.5 years (0.6 - 24.7) 3.5 years	4.75 years (0.6 a 32.9) 3.75 years	0.85

Table 2. General characteristics of 81 adherent and non-adherent participants according to tTG results

	adherents	non-adherents	P
TOTAL N	30	51	
Age. Mean (range) Median	37.7 years (23.7 - 71.9) 34.9 years	40.4 years (18.3 - 72.4) 40 years	0.34
At diagnosis. Mean (range) Median	31.3 years (2.3 - 65.6) 28.5 years	36.8 years (11.4 - 66.3) 35.9 years	0.07
Sex women, n (%)	26 (87%)	48 (94%)	0.25
Weight. Mean (range) Median	61.4 Kg (44 - 80) 57.5 Kg	59.2 Kg (47 - 85) 57 Kg	0.32
Height. Mean (range)	161 cm (147 - 179)	158 cm (146 - 172)	0.07
BMI (Kg/m^2). Mean (range)	23.5 (19 - 33)	23.5 (18.7 - 31)	0.96
Time on GFD Mean (range) Median	6.35 years (0.6 - 32.9) 4.85 years	3.75 years (0.6 - 16.8) 2.95 years	0.02

When tTG was used as reference, sensitivity and specificity were 0.7 and 0.5 for CDAT and 0.6 and 0.4 for interview, respectively. When the interview was taken as reference, sensitivity and specificity was 0.8 and 0.6 for CDAT and 0.6 and 0.4 for tTG, respectively.

CDAT was associated with interviews results (chi2, p= 0.001), but not with tTG (chi2, P= 0.079) and there was no association between the interview and tTG (chi2, P= 0.672).

CDAT cut off to define adherent cases was originally described at ≤12 points [15]. In this study, ROC analysis to assess the CDAT cut off yielded best sensitivity and specificity when setting cutoff at 12 points, similar to the original description [15].

3.2. Factors Associated with Adherence to GFD

Defining adherence by interview findings, the univariate analysis showed significant associations with two variables and the same two variables were significant by logistic regression (Table 3). Using tTG results to define adherence, ten variables showed positive Pearson correlation, eight of which were also significant by logistic regression (Table 4).

Table 3. Factors associated with adherence when nutritional interview is used for defining adherence (Pearson correlation and logistic regression)

	chi^2			Logistic Regression		
Variables	**Pearson**	**P**	**OR**	**Standard Error**	**P**	**Confidence interval**
Factors related with the patient: Self-perception of knowledge of GFD	7.48	0.01	6.83	5.70	0.02	1.33 - 35.08
Factors related to disease: Presence of GIT symptoms when gluten is consumed (either accidentally or deliberately)	5.93	0.02	4.63	2.91	0.02	1.35 - 15.87

Table 4. Factors associated with adherence when positive tTG is used for defining adherence (Pearson correlation and logistic regression)

	chi^2		Logistic Regression			
Variables	**Pearson**	**P**	**OR**	**Standard Error**	**P**	**Confidence interval**
Factors related with the health system or health team:						
Information provided by the health team about disease and treatment	4.29	0.04	0.34	0.18	0.04	0.12 - 0.94
Socioeconomic factors:						
Monthly income	NS	NS	0.32	0.16	0.02	0.12 - 0.85
Educational level	NS	NS	7.08	5.82	0.02	1.41 - 35.49
Influence of the cost of GF products	7.59	0.01	5.01	3.29	0.01	1.38 - 18.15
Factors related with treatment:						
Difficulties following GFD when eating in a restaurant	5.96	0.02	3.06	1.57	0.03	1.12- 8.36
Time on GFD	7.16	0.01	3.43	1.74	0.02	1.27 - 9.26
Factors related to disease:						
Presence/absence of GIT symptoms at the time of the diagnosis	5.3	0.02	NS	-	-	-
Number of digestive symptoms at the time of diagnosis	9.39	0.01	0.35	-	-	-
Chronic diseases other than CD	8.1	0.004	4.93	0.16	0.01	0.14 - 0.84
Allergy/food intolerance plus a chronic disease and CD	4.98	0.03	NS	2.74	0.004	1.66 - 14.68

4. Discussion

Results show that the three commonly used methods to assess adherence to GFD coincided in classifying individuals as non-adherent and adherent only in 35.8% (n=29) and 8.6% (n=7) of cases, respectively, which shows that reliable techniques to measure adherence are still lacking. In general, all three methods showed better concordance classifying non-adherents. The frequency of adherent patients obtained is among the lowest values reported in the literature, which range between 36 and 96% [8], but are similar to results previously obtained in Chilean population [9]. One of the difficulties of measuring adherence is that results vary not only due to the technique applied, but also because of cultural and environmental factors unrelated to the methods used. A good example of this is the variability reported in studies conducted in France 42% [26], the USA 79% [21] and Argentina 60% [27], all them using the same method (nutritional interview).

When analyzing adherence, concordance of blood tTG and qualitative methods is relevant, because tTG measurement is one of the routine tests used to follow up CD in many countries. In this study, 22% of patients

classified as adherent by the nutritional interview were tTG positive and 22% of those non-adherents were tTG negative.

The same controversial results have been reported in other countries; using interviews by a trained professional in the USA, 30% of non-adherent subjects had negative tTG values [28] while in The Netherlands, a study reported that 40% of dietary transgressions would remain unnoticed if adherence was assessed by blood antibodies or by Biaggi short questionnaire [29]. The relationship between blood autoantibodies and duodenal mucosal damage is also controversial. A meta-analysis that analyzed serum IgA-tTG and IgA-EMA versus histological findings concluded that correlation between them was poor [30]. The long half-life of antibodies considered specific for CD and the fact that they reflect immune/autoimmune responses rather than small intestinal mucosal status may contribute to it [31]. IgA- and IgG- class antibodies measured in blood often take 6-24 months to decrease after the antigen source is eliminated from diet [31]. Another confusion factor is the unknown degree of contamination of the so-called "gluten-free products" [32,33,34].

In this study, although concordance between the two non-invasive methods used was better, they also showed limitations. Interviews are attractive because they potentially cover all aspects of GFD, including detailed practical issues [29], but they require a trained dietitian, which often is not available, especially in public health systems. CDAT is also an attractive alternative because is easily applied [15], but unfortunately, it has not been conclusively validated. Presence of symptoms influences results; in this study, patients not developing symptoms when consuming gluten had 3.6 times more risk of being non-adherent. It is interesting that self-perception of celiac patients of his/her knowledge of CD seems more relevant that knowledge itself. Risk of being non-adherent was 5.8 times higher in those that self-reported having "insufficient knowledge" about GFD, similar to findings in the USA, where a negative perception of the patients 'own knowledge of GFD was associated with non-adherence [23]. Providing on-line training to a group of celiac patients has been reported to improve adherence [35]; other studies report that poor adherence is also associated with awareness/unawareness of gluten intake, decreased knowledge about GFD and specific behaviors while eating out at restaurants [28]. In Finland, nutritional interviews found that only current age and the age at diagnosis were relevant factors that influenced adherence to GFD [36], but nutritional advice did not correlate with adherence, a finding similar to ours. In a different kind of approach, social isolation has also been significantly associated with poorer adherence to GFD [37]. In general, results show that although changing biological factors is not possible, improving tools to take control of one's own treatment may yield satisfactory results.

As for methodologies, when adherence is assessed by a biological method like measuring tTG in blood, the variables associated with non-adherence were related with socioeconomic status, with treatment and with the disease itself. Risk of having tTG positive was 4 times higher in patients that considered that cost of gluten-free products made difficult following the diet and 2.4 times higher when the patients had been on GFD for less than 3 years. This latter suggests that learning how to follow the restrictive diet helps adhering; however, other authors have reported that maintaining GFD for a prolonged period of time was associated with opposite results [13]. Regarding comorbidities, our results show an association between having other chronic diseases in addition to CD and having positive tTG, but this association disappeared when evaluating adherence by nutritional interview. Leffler et al. evaluated adherence by CDAT and reported that the presence of other autoimmune diseases did not influence adherence [21]. In contrast, the association in our study is important; out of 51 celiac patients who had a tTG positive, 62.8% had an additional chronic disease and 66% of these were autoimmune conditions. Since only 34.4% of them classified as adherent by interview, we may speculate that they might have inadvertent transgressions, but it is also possible that the autoimmune "environment" in these patients will promote the presence of blood autoantibodies in general. In this line of thought, assessment of 847 subjects with Diabetes Mellitus type 1 found that 11.6% were tTG positive, but only 15/20 who underwent intestinal biopsy exhibited histological damage compatible with CD [38]. In another study, comparing celiac patients with other autoimmune diseases and controls, tTG was positive in 97% of celiac cases and in 49% of those with autoimmune conditions. Unfortunately, authors in this latter paper conclude only on technical problems implied in measuring tTG and do not comment as to why tTG may be positive in autoimmune diseases [39].

5. Conclusions

In summary, results of this study illustrate the difficulties of measuring both adherence to GFD and the factors that influence it. This situation may be due to failure to measure actual gluten ingestion, identify autoimmune manifestations due to CD and not to other conditions and not correcting for biases introduced by technical issues.

Author's Statements

All authors of this paper have read and approved the final version submitted. The authors declare no conflict of interest. All authors contributed equally to this work.

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