Perception of following gluten-free diet and adherence to treatment in pediatric patients with celiac disease

Percepción de estar haciendo bien la dieta sin gluten y adherencia al tratamiento en pacientes pediátricos con enfermedad celíaca

Karin W. Schilling[a], Karla Yohannessen[a], Magdalena Araya[b]

[a]Hospital Roberto del Río, Santiago, Chile
[b]INTA, University of Chile, Santiago, Chile

Abstract

Introduction: Celiac disease (CD) is a chronic immune-mediated enteropathy present in ~1% of population. Gluten-free diet (GFD) is the only treatment for this condition and the main limitation of its efficacy is the lack of adherence. **Objective:** To assess factors influencing adherence to GFD in pediatric patients and measure the concordance between serological results and a nutritional adherence questionnaire. **Patients and Methods:** celiac patients younger than 18 years of age, diagnosed CD following ESPGHAN criteria, on GFD for at least 6 months and consulting at Hospital Roberto del Río, Santiago, in 2008-2016, were assessed. Clinical presentation, nutritional evaluation and factors related to adherence to treatment (diet) were registered. A subsample answered Biaggi´s nutritional questionnaire. **Results:** Of 65 evaluated patients, 44% and 30,1% adhered to GFD according to blood autoantibodies (TTG and EMA) and the adherence questionnaire, respectively. "Age at debut" (p = 0.049), "perception of following GFD correctly" (p = 0.002) and "behavior in social events" (p = 0.005) were significantly associated with adherence to GFD. There was concordance between serological test and Biagi's questionnaire (p = 0.0001). **Discussion:** Adherence to GFD was lower than reported in literature. Intervention of some of the identified variables associated with adherence may help improving follow-up of celiac patients, especially those that due to diverse situations cannot measure their antibodies periodically.

Correspondence:
Prof. Magdalena Araya
maraya@inta.uchile.cl

EDITORIAL iku

Introduction

Celiac disease (CD) is an immune-mediated chronic enteropathy, produced by the interaction of certain haplotypes (genes) of the host that provide the genetic susceptibility[1] and the environment, which contributes the prolamins of gluten in the diet[2]. Other factors, such as epigenetics and host microbiota, would participate in the pathogenesis of CD through less-known mechanisms[3]. It is currently recognized as a high-frequency autoimmune condition, which appears at any age[4], reaching a global prevalence of 1-3% of the population[5]. It is diagnosed by serology (measurement of antibodies against tissue transglutaminase 2(TTG), anti-endomysial (EMA) antibodies or deamidated gliadin peptides (DGP) and histological confirmation in duodenal biopsies, which show various degrees of lymphocytic infiltration, crypt hyperplasia, and villous flattening[4,6]. By now, the only effective treatment for CD is the gluten-free diet (GFD), strict, permanent and lifelong[4]. This diet eliminates wheat, rye, and barley from the diet, included in both natural and processed foods[7]. Oats are also usually eliminated because it has a high probability of being contaminated[8]. The main limitation of this treatment is the lack of adherence of patients to GFD.

The treatment of CD includes patients follow-up, periodic and long-term, to evaluate the clinical course and adherence to GFD. This evaluation is difficult because there is no reliable and reproducible method to measure the actual gluten intake. The current strategy is based on the consensus of specialists[4]. They recommend periodic check-ups that estimate the adherence based on what the patient reports and the measurement of antibodies that reflect autoimmunity. The most used are TTG[9,10]. It is expected that, by not eating gluten, patients will show blood clearance and progressive reduction of the intestinal mucosa damage and autoimmunity phenomena. However, the usefulness of these antibodies for follow-up has currently under discussion[11-13], exposing again the problem of how to ensure that the information provided by the patient is accurate and reliable. Foreign data show that adherence to GFD in children is 80-95% and in adolescents and adults 36-52%[14,15]. Assessing adherence through interviews by specialized professionals and validated questionnaires is giving promising results, but not yet definitive ones[12,16]. In Chile, studies indicate that pediatric patients who adhere to GFD vary between 24-34%[17-19], without significant variations over time. The World Health Organization (WHO) has described five types of factors that influence the adherence to a chronic treatment: related to the disease, the patient, the treatment, the health system or health team, and the socioeconomic characteristics. The information about how these factors affect the celiac patient and the GFD is insufficient. Considering that the available data in our country are scarce, show low degrees of adherence and that in the national public health system the follow-up is by serology (TTG and occasionally EMA), the objective of this study was to evaluate the factors that influence in adherence to GFD. Additionally, the concordance between the measured antibodies (TTG and EMA) and the nutritional adherence questionnaire was evaluated.

Patients and Methods

Study group

Cross-sectional, analytical study that assessed the universe of patients diagnosed with CD treated at the Gastroenterology Service of the Roberto del Río Hospital (HRR), Santiago, 2008-2016. Patients under 18 years of age, diagnosed by serology and intestinal biopsy[4] and following GFD for at least six months before the study were included. The protocol was accepted by the Ethics Committee of the Institute of Nutrition and Food Technology (INTA), University of Chile, by the HRR Management, and the Ethics Committee of the North Metropolitan Health Service (SSMN). The records of consultations during the period were reviewed (code K90.0, diagnosis of CE in the international statistical classification of diseases and related health problems ICD10, WHO 2005). Out of 101 patients detected, 86 met inclusion criteria and were contacted by telephone to invite them to participate. However, 15 were not available and six did not show up for the interview (despite four telephone attempts). Although this represents a selection bias in the study group, the information on the clinical records showed that demographic and biological characteristics of these 15 and six mentioned patients did not show significant differences from patients included in the analysis. After explaining the protocol and obtaining informed consent, 65 patients entered the study. The participants (patients and/or parents or guardians) answered an ad hoc questionnaire that addressed the five groups of factors indicated by the WHO[20].

The following were recorded: *General data*: sociodemographic characteristics and socioeconomic level (according to Esomar survey, Adimark, October 2000). *History*: weight, height, and physical examination. The clinical characteristics were registered at the time of diagnosis and during the last three months, including date and age of diagnosis, gastrointestinal symptoms (diarrhea, abdominal distension, anorexia, constipation, steatorrhea, malnutrition, abdominal pain, vomiting, celiac crisis), extra gastrointestinal symptoms (anemia, short stature, pubertal delay, dental enamel

hypoplasia); and the presence of associated autoimmune diseases (diabetes mellitus type I, autoimmune thyroiditis, autoimmune hepatitis, dermatitis herpetiformis). Patients were classified as typical, atypical or silent. The anthropometry followed the current Chilean criteria (Ministry of Health of Chile)[21], corrected by Tanner[22] as needed. *Disease Management*: During the last three months, the diet was recorded, including the perception (of parents/guardians and the patient if adolescent) of following GFD correctly; knowledge of the allowed foods and the availability of those in the country, knowledge of the gluten-free symbols and if the patient does or does not read the food ingredients list before buying it. A knowledge score was made, giving a point to each correct answer (minimum 0 and maximum 4). In addition, we asked: i) if they knew support groups for celiac patients and if they attended their meetings or visited their websites; ii) if the school was aware of the patient's condition, whether or not the patient had received support from the school and if the school allowed the patient to bring his/her own food or if he/she had to consume the food provided by the school; iii) if the patient does or does not break the regime when eating out of home, the behavior in birthdays or social events out of home, if in thi¿ese occasion the patient chooses only gluten-free foods, consumes anything, brings food from home or does not participate in this kind of events; iv) patient's behavior in case of need for treatments with oral medications, and for the intake of food (wine, wafer, bread, matzo) in religious ceremonies; v) access to an evaluation and/or check-up with nutritionist, psychologist and/or social worker. A subgroup (patients entered to the study after 2009) also answered the adherence questionnaire to the gluten-free diet described by Biagi[16].

Procedures

EMA and TTG were measured within two weeks after the interview. The measurement of serum IgA ruled out IgA deficiency in all participants. It was not possible to measure TTG in four patients and EMA in nine. In both cases, patients did not attend sample collection. The anthropometric evaluation (weight and height) was performed with a Seca digital scale. The Biagi questionnaire was applied following author's instructions. It is based on four questions that inform about if the patient eats gluten voluntarily, the behavior they have when eating outside, reading the labeling of packaged foods looking for if they contain gluten and if only eats foods guaranteed by some Association of celiac patients[16].

Analysis of results

Descriptive statistics were applied; the analysis was carried out in two ways: a) accepting that adherence

is represented by the negative results of the serological markers (TTG antibodies and negative EMA) and b) by the data obtained by the nutritional questionnaire (Biagi). The concordance between the TTG and the nutritional adherence questionnaire was analyzed with Kappa index; the association between the evaluated factors and the results of EMA and TTG (both negative), with chi-square test; Odd Ratio was used as a measure of association (95% confidence interval). Logistic regression was applied to the factors associated with the results of EMA and TTG (positive-negative). "Good adherence to GFD" was defined when EMA and TTG were both negative.

Results

The universe of patients (2008-2016) with diagnosis of CD was 101, which represents 0.04% of the new consultations made at the HRR during the period[23]. 86/101 patients met the inclusion criteria and 65 (75.6%) agreed to enter the study. 61.5% were girls, a percentage higher than in the general population in that age group[24]. 69.2% of patients were eutrophic, 10.8% at risk or malnourished, and 20% were overweight or obese. In the assessed age group, the percentage of eutrophic/at nutritional risk was higher and the percentage of obesity was lower than in the general population[25]. 86% of the patients lived in the Metropolitan Region, 93.8% was using Fonasa (public health system) as health system and 86% was in middle socioeconomic level (SEL), according to Esomar 2000 classification. 50.8% of the patients were preschool children or had completed 4th grade or less. 66.1% of mothers and 55.4% of fathers had completed secondary education or higher. Table 1 shows the variables related to the patient and his/her disease and table 2 the knowledge, disease management, and lifestyle. 52.3% of the interviewed patients (or guardians) stated that the GFD was handled correctly. There was 100% of concordance between the responses of adolescents and their parents or guardians. 43.1% (28 patients) received at least one medication permanently, mainly levothyroxine, insulin, zinc sulfate, polyvitamins, ferrous sulfate, folic acid, and valproic acid. 6.2% reported receiving food in religious ceremonies, 10.8% did not commune due to fear of getting sick, and 43% had doubts about their first communion.

Graph 1 shows the frequency of adherence/transgression to the GFD measured by the presence of antibodies EMA +/-, TTG +/-, EMA and TTG +/-, and EMA or TTG +/-. According to the adherence questionnaire to the GFD (scores 3 and 4 of Biagi), 30.8% adhered strictly to the GFD. There was concordance between the questionnaire and both tests performed

and their combinations, being all P significant with moderate concordance force (table 3). In the analysis of adherence defined by serology (chi-square), only three variables were significant: "age of disease onset" (p = 0.049), "perception of doing well the GFD" (p = 0.002) and "behavior of the patient in front of food in social events"(p = 0.005). Assessed by serology at the time of the interview, those diagnosed before two years of age, between 2-10 years and after 10 years old, 60.7%, 28% and 33.3% were adherent to the GFD, respectively. At the time of the interview, 63.3% of those who "think that they are correctly following GFD" had negative

both antibodies. Among patients whose guardian thinks that they are making mistakes in the GFD, 75.9% had some positive serology, but 24.1% of the patients, although they stated to transgress the regimen, maintained both blood antibodies negative. The third significant variable was the "habits that patients have at birthdays and/or social events" (p = 0.005). Those who choose only gluten-free foods or those who take food from their homes had a significantly higher frequency of negative TTG and EMA (adherence) than those who do not follow the diet on social occasions. 63.2% of those who choose "only gluten-free" and 57.1% of those who take food from home, had negative serology. 8/9 (88.9%) patients who "eat everything" had some positive test (EMA or TTG). Meanwhile, 90% of patients who do not attend birthdays had positive serology (EMA or TTG). In relation to EMA, there were two significant variables: "read

Table 1. Variables related to the child and his/her illness

	n	%
Type of illness		
Classical	47	72.3
Atypical	14	21.5
Silent	4	6.2
Birth weight		
Adequate for gestational age	51	80.9
Breast feeding (exclusive)		
No breast feeding	6	9.2
< 6 mo	32	49.2
≥ 6 mo	27	41.6
Age at first symptoms		
<2 years	32	49.2
2-10 years	26	40.0
>10 years	7	10.8
Initial symptoms/signs		
Only gastrointestinal	31	47.7
Only extra gastrointestinal	9	13.8
Gastrointestinal & extra gastrointestinal	21	32.3
Asymptomatic	4	6.2
Age at study		
< 6 years	8	12.3
6-12 years	27	41.5
> 12 years	30	46.2
Present symptoms/signs		
Only gastrointestinal	22	33.9
Only extra gastrointestinal	6	9.2
Gastrointestinal & extra gastrointestinal	10	15.4
Asymptomatic	27	41.5
Symptoms/signs at study		
Diarrhea	29	44.6
Abdominal distension	32	49.2
Anemia	9	13.9
Short stature	15	23.1
Pubertal delay	3	4.6
Dental enamel hypoplasia	7	10.8
Autoimmunity	14	21.5
Diabetes Mellitus I	5	7.7
Thyroiditis	5	7.7
Dermatitis herpetiformis	6	9.2

Table 2. Variables related to knowledge on celiac disease and life style

	n	%
Person guiding diet		
Mother	55	84.6
Patient	7	10.8
Other	3	4.6
Believes diet is correctly followed	34	52.3
Knows gluten-free foods	58	89.2
Looks for ingredients	50	76.9
Knows gluten-free symbols	59	90.8
Knows lists of gluten-free foods	56	86.2
Knows support groups	37	56.9
Feels helped by support groups	27	41.5
Has informed school	63	96.9
Feels supported at school	41	63.1
Routinely eats out of home	33	50.8
In birthday parties		
Chooses only gluten-free foods	21	32.3
Does not choose	10	15.4
Takes own foods from home	22	33.8
Does not go to social events or birthdays	12	18.5
Lives with other celiac persons	4	6.2
Takes medicines	28	43.1
Religious ceremonies		
Receives traditional host	1	1.5
Receives bread, wine, matzo, others	3	4.6
Does not receive foods during ceremonies	61	93.9
Receives health care by		
Gastroenterologist	65	100
Nutritionist	55	84.6
Psychologist	10	15.4
Social worker	4	6.2

Graph 1. Percentage of patients adhering or not adhering gluten free-diet (GFD), defined by negative serology (TTG* and EMA**). *antitransglutaminase 2 antibodies. **anti endomysial antibodies.
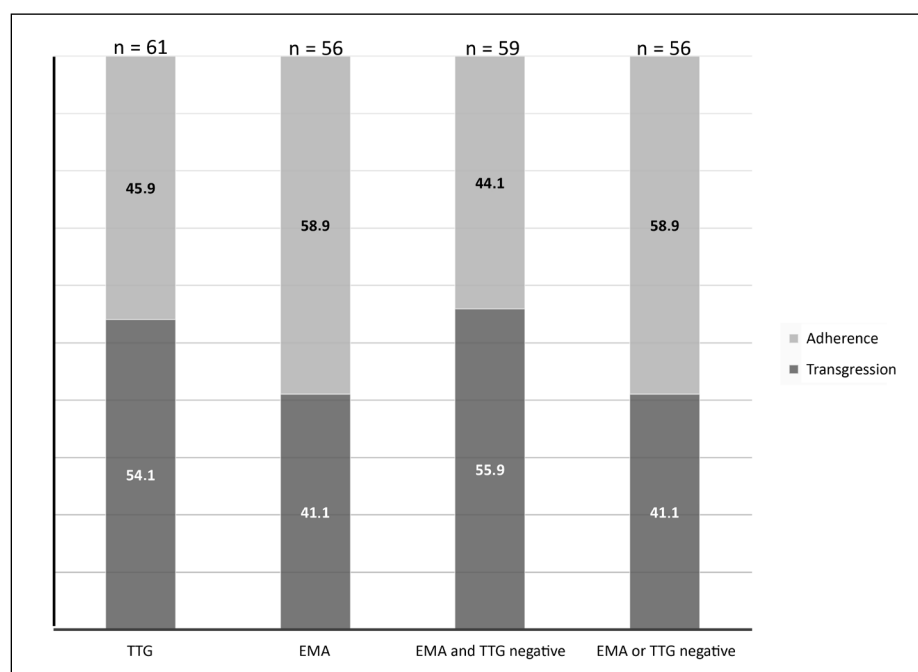
Table 3. Concordance serology/autoimmune antibodies EMA and TTG and Biagi's adherence questionnaire*

Encuesta	TTG	EMA	EMA and TTG negative	EMA or TTG negative
Concordance	74.3%	73.3%	78.8%	73.3%
Kappa	0.5039	0.5000	0.5808	0.5000
Pr	0.0003	0.0008	0.0001	0.0008

*= Biaggi 2009.

Table 4. Logistic Regression with EMA-TTG, OR, adjusted

	OR	IC 95%	p
Perception	4.4	1.0 - 18.4	0.043
Birthday parties			
Takes food from home	1.7	0.4 - 7.5	0.464
Eats anything	5.1	0.4 - 56.8	0.189
Dos not go	16.7	1.5 - 189.2	0.023
Age at debut CD < 2y	1.6	0.6 - 4.4	0.321
Knowledge 3	1.5	0.4 - 5.6	0.512

ingredients in the nutrition labeling" (p = 0.041) and "feel welcomed by the foundations supporting the celiac patient" (p = 0.045), but these variables were not significant for the combination EMA-TTG. The self-perception analysis of the GFD and the Biagi questionnaire showed 72% of concordance. 10/11 patients in whom there was no concordance thought they were doing well with the diet and the Biagi questionnaire classified them as transgressors.

The logistic regression provided a predictive model that included three variables: "perception of following well the GFD" (p = 0.003), "patient's behavior in front of foods in social events" (p = 0.003) and "age of disease onset" (p = 0.049). In the logistic regression model only two out of the three variables reached statistical significance (table 4).

The GFD Knowledge Score did not show significant differences for adherence by serology. When dividing patients into those with a score of ≤ 3 and those with a score of 4 in the Biagi questionnaire, half of the patients were grouped in each group. Patients with Score ≤ 3 had 1.5 times more risk of transgressing the diet. Although this variable was not significant in the chi-square analysis, due to the importance of patient education, it was included in the multivariable logistic regression analysis.

Discussion

The adherence to GFD in this study is lower than the one published in the international literature for this age group[14,19], but similar to the ones described in our country in previous studies[17-19], both by measurement of TTG and EMA antibodies and the questionnaire developed by Biagi. This indicates that the adherence to GFD among our pediatric patients is not only low but

has not changed significantly in the last two decades. It is interesting that both methodologies showed concordance since other studies have not shown it[11].

The variable "perception" of following the GFD correctly, was the one that showed the best association with negative markers, being always statistically significant. The patient who believes that he/she is not doing a correct diet has 3.4 times higher risk of not adhering than the patient that believes that he/she follows GFD correctly The second t variable best associated with adherence was age of diagnosis. Patients diagnosed before two years of age showed significantly higher adherence to GFD than those diagnosed at later ages. One can think that the earlier CD is diagnosed, the easier it is to incorporate and accept the limitations imposed by GFD[8]. The "attitude in birthdays" was significant when making a univariate analysis, but it lost significance in the logistic regression of association, except in the group that "does not attend birthdays", which showed a greater risk of "transgressing the GFD". This implies that not taking celiac children to birthday parties does not protect them from transgressions to diet. That 90% of patients who did not attend a birthday presented positive serology (EMA or TTG) is against the expected; it could be interpreted as a behavioral option to avoid the opportunity to transgress[26].

The guardian and/or the patient's "perception" of "being doing GFD properly" shows that two out of three patients who believe that they are following the diet, are really achieving it. This contrasts with the variables referring to knowledge itself about diet and gluten-free foods, which did not achieve statistical significance in any of the analyses. On the other hand, in patients whose guardian thinks that they make mistakes in GFD, 75.9% have some positive serology. It is interesting that 24.1% of patients (seven children), despite thinking that they are doing poorly, either because they eat gluten in an obvious way or because they do not have clear their indications of feeding, maintained negative both antibodies. This supports the idea that serology is not a good indicator for follow-up[11,27-29]; it also opens the possibility that some patients have certain tolerance to small amounts of gluten without arising a detectable autoimmune response[30]. Another possibility is that the time elapsed between the transgression of the diet and the measurement of markers was insufficient to produce a detectable change. Undoubtedly, it is necessary to improve the capacities to measure gluten intake in celiac patients along time. Measurements of gluten in stools and/or urine seem an interesting option, but the currently available results are not sufficient to propose them as marker of follow-up in t CD[31-35].

In this respect, it is relevant to remind that if there are doubts about whether a patient has elevated antibodies because he/she does not adhere to GFD or because he/she does not respond to treatment, a new duodenal biopsy is useful, as well as a genetic study if it shows absence of risk haplotypes. Unfortunately, genetic studies are not usually practiced in our country. It is interesting that the patient or guardian that reads the nutritional labeling of packaged foods showed significant association with negative EMA. This relation with adherence could reflect a behavior of greater commitment to leading a good management of the disease.

Results show that for health professionals to provide effective counseling to celiac patients, in addition to know the biological aspects of the disease, it is necessary they manage the emotional and social aspects imposed by chronic diseases. It must be considered that treatments that involve restrictions in daily life are difficult to maintain in the long-term and can affect quality of life[26,36,37]. This is important to highlight since we must recognize the enormous benefit that most patients who follow GFD have; they manage to stay asymptomatic and avoid the risks of long-term complications. In this sense, the chronic or sporadic consumption of medications and the intake of foods related to religious ceremonies gain interest. In the first case, it is important to choose gluten-free medicines and in case of not having safe alternatives, put in the balance the risk/benefit of each treatment. In the case of foods consumed in religious ceremonies, alternatives suitable for celiacs must be offered to maintain adherence to GFD, such as communion wafer for celiacs, as is the case in our country, where wafers are certified by the Archbishopric of Santiago. These aspects favor the integral recovery of the patient (physical, emotional and spiritual).

Due to the importance of patient education in the treatment of CD[38,39], the multivariable logistic regression analysis was adjusted by the knowledge score, although this was not significant in the univariate analysis. The fact that the "perception" of being doing correctly the GFD maintain its significance, seems to us a very relevant finding since it can be used to modify/reinforce behaviors and improve the follow-up and adherence to the treatment of celiac patients[4].

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have

followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Acknwoledgements

References

1. Fasano A, Catassi C. Clinical practice. Celiac disease. The New England journal of medicine. 2012;367(25):2419-26. PubMed PMID: 23252527.
2. Kagnoff MF. Overview and pathogenesis of celiac disease. Gastroenterology. 2005;128(4 Suppl 1):S10-8. PubMed PMID: 15825116.
3. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell. 2007;128(4):635-8. PubMed PMID: 17320500.
4. Husby S, Koletzko S, Korponay-Szabo IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. Journal of pediatric gastroenterology and nutrition. 2012;54(1):136-60. PubMed PMID: 22197856.
5. Kang JY, Kang AH, Green A, Gwee KA, Ho KY. Systematic review: worldwide variation in the frequency of coeliac disease and changes over time. Alimentary pharmacology & therapeutics. 2013;38(3):226-45. PubMed PMID: 23782240.
6. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology. 1992;102(1):330-54. PubMed PMID: 1727768.
7. Kupper C. Dietary guidelines and implementation for celiac disease. Gastroenterology. 2005;128(4 Suppl 1):S121-7. PubMed PMID: 15825119.
8. Nasr I, Leffler DA, Ciclitira PJ. Management of celiac disease. Gastrointestinal endoscopy clinics of North America. 2012;22(4):695-704. PubMed PMID: 23083987.
9. Rostom A, Dube C, Cranney A, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. Gastroenterology. 2005;128(4 Suppl 1):S38-46. PubMed PMID: 15825125.
10. Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? Gastroenterology. 2005;128(4 Suppl 1):S25-32. PubMed PMID: 15825123.
11. Vahedi K, Mascart F, Mary JY, et al. Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. The American journal of gastroenterology. 2003;98(5):1079-87. PubMed PMID: 12809831.
12. Leffler DA, Dennis M, Edwards George JB, et al. A simple validated gluten-free diet adherence survey for adults with celiac disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2009;7(5):530-6, 6 e1-2. PubMed PMID: 19268725.
13. Mohaidle A, Mella JM, Pereyra L, et al. [Role of antibodies in celiac disease after one year of treatment to predict the adherence to gluten-free diet]. Acta gastroenterologica Latinoamericana. 2011;41(1):23-8. PubMed PMID: 21539065. Rol de los anticuerpos en la enfermedad celiaca luego de un ano de tratamiento para predecir la adherencia a la dieta libre de gluten.
14. Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Journal of pediatric gastroenterology and nutrition. 2005;40(1):1-19. PubMed PMID: 15625418.
15. Fasano A, Araya M, Bhatnagar S, et al. Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition consensus report on celiac disease. Journal of pediatric gastroenterology and nutrition. 2008;47(2):214-9. PubMed PMID: 18664878.
16. Biagi F, Andrealli A, Bianchi PI, Marchese A, Klersy C, Corazza GR. A gluten-free diet score to evaluate dietary compliance in patients with coeliac disease. The British journal of nutrition. 2009;102(6):882-7. PubMed PMID: 19331704.
17. Mondragon A AM, Roessler Jl, Rios G, Bergenfried C, Alarcon T. . La dieta sin gluten del celíaco ¿afecta la dieta familiar? (Does a gluten free diet affects the celiac patient's family diet?) Rev Chil Nutr. 1999;26(1):53-61.
18. Canales P PAM, Alliende F, Hunter B, Alarcón T, Chávez E. . Estado actual del diagnóstico y presentaciones clínicas de enfermedad celíaca. Estudio multicéntrico (Diagnosis and clinical presentations of celiac disease. A multicenter study). Rev Med Chile. 2008;136:296-303.
19. Bravo F MM. Bravo F, Muñoz MP. Adherencia e impacto de la dieta sin gluten en niños con enfermedad celíaca. Rev Chil Pediatr. 2011;82(3):191-7.
20. Organization Wh. Adherence to long term therapies. 2003.
21. Chile MdSd. http://wwwminsalcl/. 2008.
22. Tanner JM. Growth regulation and the genetics of growth. Progress in clinical and biological research. 1985;200:19-32. PubMed PMID: 4080738.
23. Norte SdSM. http/wwwssmncl/infoestadistica/indexphp/consultas-de-especialidad/. 2016.
24. Estadística INd. Población Chile 2015. http/wwwpopulationpyramidnet/es/chile/20165/. 2015.
25. Chile JMdEd. Informe mapa nutricional 2015. http/wwwjunaebcl>uploads>2017/03. 2016.
26. Bacigalupe GP, Aleksandra, . Celiac is

a social disease: Family challenges and strategies. Families, Systems, & Health. 2015;33(1):46-54.

27. Leffler DA, Edwards George JB, Dennis M, Cook EF, Schuppan D, Kelly CP. A prospective comparative study of five measures of gluten-free diet adherence in adults with coeliac disease. Alimentary pharmacology & therapeutics. 2007;26(9):1227-35. PubMed PMID: 17944737.

28. Newnham ED, Shepherd SJ, Strauss BJ, Hosking P, Gibson PR. Adherence to the gluten-free diet can achieve the therapeutic goals in almost all patients with coeliac disease: A 5-year longitudinal study from diagnosis. Journal of gastroenterology and hepatology. 2016;31(2):342-9. PubMed PMID: 26212198.

29. Viljamaa M, Collin P, Huhtala H, Sievanen H, Maki M, Kaukinen K. Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. Alimentary pharmacology & therapeutics. 2005;22(4):317-24. PubMed PMID: 16097998.

30. Ciclitira PJ, Ellis HJ, Lundin KE. Gluten-free diet--what is toxic? Best practice & research Clinical gastroenterology.

2005;19(3):359-71. PubMed PMID: 15925842.

31. Comino I, Real A, Vivas S, et al. Monitoring of gluten-free diet compliance in celiac patients by assessment of gliadin 33-mer equivalent epitopes in feces. The American journal of clinical nutrition. 2012;95(3):670-7. PubMed PMID: 22258271. Pubmed Central PMCID: 3278243.

32. Comino I, Fernández-Banares F, Esteve M, et al. Fecal Gluten Peptides Reveal Limitations of Serological Tests and Food Questionnaires for Monitoring Gluten-Free Diet in Celiac Disease Patients. The American journal of gastroenterology. 2016;111(10):1456-65..

33. Lind MV, Madsen ML, Rumessen JJ, et al. Plasma Alkylresorcinols Reflect Gluten Intake and Distinguish between Gluten-Rich and Gluten-Poor Diets in a Population at Risk of Metabolic Syndrome. The Journal of nutrition. 2016;146(10):1991-8. PubMed PMID: 27629576.

34. Moreno ML, Cebolla A, Muñoz-Suano A, et al. Detection of gluten immunogenic peptides in the urine of patients with celiac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing. Gut. 2017;66(2):250-

7. PubMed PMID: 26608460. Pubmed Central PMCID: 5284479.

35. Moreno ML, Rodriguez-Herrera A, Sousa C, Comino I. Biomarkers to Monitor Gluten-Free Diet Compliance in Celiac Patients. Nutrients. 2017;9(1). PubMed PMID: 28067823. Pubmed Central PMCID: 5295090.

36. Lee A, Newman JM. Celiac diet: its impact on quality of life. Journal of the American Dietetic Association. 2003;103(11):1533-5. PubMed PMID: 14576723.

37. Cranney A, Zarkadas M, Graham ID, Switzer C. The Canadian celiac health survey--the Ottawa chapter pilot. BMC gastroenterology. 2003;3:8. PubMed PMID: 12740024. Pubmed Central PMCID: 161796.

38. Ciacci C, Cirillo M, Cavallaro R, Mazzacca G. Long-term follow-up of celiac adults on gluten-free diet: prevalence and correlates of intestinal damage. Digestion. 2002;66(3):178-85. PubMed PMID: 12481164.

39. Butterworth JR, Banfield LM, Iqbal TH, Cooper BT. Factors relating to compliance with a gluten-free diet in patients with coeliac disease: comparison of white Caucasian and South Asian patients. Clinical nutrition. 2004;23(5):1127-34. PubMed PMID: 15380905.