Preprints.org

Gluten-Free Diet Adherence Evaluation in Adults with Long-Standing Celiac Disease

Marek Kowalski , Danuta Domżał-Magrowska , Piotr Szcześniak , Magdalena Bulska ,
Daria Orszulak-Michalak , Ewa Małecka-Wojciesko [*]

Article

Gluten-Free Diet Adherence Evaluation in Adults with Long-Standing Celiac Disease

Marek K. Kowalski [1], **Danuta Domżał-Magrowska** [1], **Piotr Szcześniak** [2], **Magdalena Bulska** [2],
Daria Orszulak-Michalak [2] and **Ewa Małecka-Wojciesko** [1,*]

[1] Department of Digestive Tract Diseases, Medical University of Lodz, Lodz, Poland
[2] Department of Biopharmacy, Medical University of Lodz, Lodz, Poland
[*] Correspondence: ewa.malecka-panas@umed.lodz.pl

Abstract: Background: Celiac disease is an autoimmune disease that results from the interaction of genetic, immune and environmental factors. According to 2020 ESPGHAN guidelines, an elimination diet (i.e. excluding products that may contain gluten) is the basic method of treating celiac disease. Following a gluten-free diet is extremely problematic and patients often make unconscious deviations from the diet. Objective: The aim of the study was to asses the frequency of conscious diet mistakes and unconscious deviations from the gluten-free diet in a group of patients with long-standing celiac disease and their impact on the frequency of typical and atypical symptoms. Methods: The study included 38 patients, 30 women and 8 men with a verified diagnosis of celiac disease. The effectiveness of the gluten-free diet was assessed in all participants. Blood was collected to determine IgA anti tissue transglutaminase II antibodies and IgG antibodies against deamidated gliadin peptides by ELISA. All survey participants provided data concerning current gastrointestinal and systemic symptoms, bowel habits, comorbidities, dietary habits, physical activity and socioeconomic conditions. Results: 25 patients (65.78%) declared strict adherence to the gluten-free diet. However, in this group, 7 (18.4%) patients had significantly increased levels of anti-tTG antibodies (mean 82.3 RU/ml ±78.9 SD at N<20 RU/ml). Among the patients who consciously made diet mistakes, 6 (46.2%) demonstrated increased levels of anti-tTG antibodies. The analysis did not reveal any difference between the frequency of intestinal and extraintestinal symptoms in patients making diet mistakes and following the gluten-free diet. Conclusions: More than half of celiac patients unconsciously or consciously make diet mistakes, which indicates an urgent need to increase their education about the diet. Regardless of whether the gluten-free diet is followed, both typical and atypical symptoms of the disease have been observed among celiac patients.

Keywords: celiac disease; gluten free diet gluten-free diet adherence

1. Introduction

Celiac disease is an autoimmune disease that results from the interaction of genetic, immune and environmental factors. It is caused by an immune reaction induced by gluten and prolamin derivatives in genetically predisposed individuals with specific histocompatibility antigens (HLA-DQ2 or HLA-DQ8). After consuming products made from cereals rich in gluten, they are gradually digested in the stomach, duodenum and small intestine. Contact of gluten degradation products with the small intestinal mucosa leads to a complex immune response and, at a later stage, to the production in the submucosa of characteristic antibodies against gliadin, deamidated gliadin peptides, endomysium and tissue transglutaminase, which damage enterocytes and their stroma. This reaction leads to further morphological changes in the duodenal mucosa. Initially, there comes to crypt hyperplasia followed by gradual villous atrophy.

Characteristic intestinal symptoms of celiac disease are diarrhea (13-96%), abdominal pain (8-90%), vomiting (26-33%), flatulence (5-10%) and fatty foul-smelling stools [1–4]. Extraintestinal symptoms may be related to gastrointestinal distress, mainly due to malabsorption leading to numerous disorders affecting most systems. The most common are weight loss (44-60%), growth retardation in children (19-31%), anemia (3-30%), including anemia due to iron (40%), folic acid (20%) and vitamin B_{12} deficiency (17%). Deficiency of fat-soluble vitamins A, D, E and K is more common

in celiac individuals than in the general population. As a result, osteopenia (54%) and osteoporosis (12%) are observed, mainly in the course of vitamin D deficiency (34%), as well as hypocalcemia leading to tetany [5–9]. In the severe stage of the disease, which is currently extremely rare, features of malnutrition, sarcopenia, IgA deficiency, total protein deficiency, hypoalbuminemia, peripheral edema and ascites are observed [1,2,9–12]. In this group of patients, oral cavity pathologies were more frequently confirmed, primarily dental enamel defects, caries and recurrent aphthous lesions [13–18]. Celiac women have a higher incidence of menstrual cycle disorders (absent, late or irregular menstruation), infertility, multiple miscarriages, intrauterine growth restriction and low birth weight children than the general population [19–21]. These patients, especially those untreated, develop numerous neurological disorders such as gluten ataxia, progressive cerebellar ataxia, spinocerebellar degeneration, epilepsy, restless legs syndrome, myopathy and peripheral neuropathy associated with vitamin B1 and B12 deficiency as well as dementia [22–25].

Treatment of Celiac Disease

According to 2012 and 2020 ESPGHAN guidelines, an elimination diet (i.e. excluding products that may contain gluten) is the basic method of treating celiac disease [26,27]. Consuming 10 mg of gluten daily in patients with celiac disease should not cause disease exacerbation, although the daily dose in some cases may be many times higher [28–31]. The certification standards allow for gluten content of 20 ppm (20 mg/kg of product) in gluten-free products and 100 ppm in low-gluten products [32]. However, in most cases, constant adherence to a gluten-free diet, especially among young patients, leads to full recovery of the villi and resolution of the inflammatory infiltrate, despite the presence of trace amounts of gluten contamination in food [33]. In adults, especially over the age of 60, histopathological changes may not undergo complete remission despite strict adherence to a gluten-free diet [34,35].

Due to numerous difficulties that celiac patients encounter on a daily basis, it is necessary to take into account not only fully conscious and intentional deviations from the gluten-free diet, but also errors resulting from product contamination as well as simple dishonesty of manufacturers who do not provide the full composition of food products, hiding behind trade secrets.

2. Purpose of the Study

Celiac disease is one of the most common autoimmune diseases of the gastrointestinal tract. According to the pathophysiology of celiac disease, enterocytes are damaged during its course, leading to a gradual villous atrophy and crypt hyperplasia. In patients diagnosed with celiac disease, adherence to a gluten-free diet leads to regeneration of intestinal villi and to normalization of the level of characteristic antibodies. Over the years, public awareness of the gluten-free diet and the availability of products have improved significantly. Therefore, it is necessary to evaluate the current effectiveness of the diet. To exclude regular, unconscious dietary errors, a detailed interview should be conducted and the concentration of anti-transglutaminase antibodies should be assessed. Following a gluten-free diet is extremely problematic and patients often make unconscious deviations from the diet. Demonstration of common diet mistakes may be an important argument in the discussion on the need to deepen research into new methods of reducing the immunogenic gliadin concentration.

3. Aim

1. Assessment of the frequency of conscious diet mistakes in a group of patients with long-standing celiac disease.
2. Assessment of the frequency of unconscious deviations from the gluten-free diet in patients with celiac disease.
3. Assessment of the impact of deviations from the gluten-free diet on the frequency of typical and atypical symptoms

4. Material and Methods

Study and Control Groups

The study included 38 patients, 30 women and 8 men with a verified diagnosis of celiac disease. The mean age of patients in the study group was 35.87 ± 10.74 years. At the time of diagnosis, all of them had symptoms that could indicate celiac disease, histology of duodenal mucosa samples revealed Marsh grade 3 and confirmed the presence of HLA-DQ2 or DQ8 genes.

Antibody Concentration Among Patients Diagnosed with Celiac Disease

The effectiveness of the gluten-free diet was assessed in all participants. Blood was collected to determine IgA anti tissue transglutaminase II antibodies and IgG antibodies against deamidated gliadin peptides by ELISA (IBL International GMBH, Hamburg, Germany).

Survey Study

All survey participants provided data concerning current gastrointestinal and systemic symptoms, bowel habits, comorbidities, dietary habits, physical activity and socioeconomic conditions. Furthermore, the duration of the gluten-free diet, its adherence and the frequency of deviations (conscious diet mistakes) were assessed.

Statistical Analysis

In the analyzed study, independent groups were compared. Nominal variables are presented as percentages. To compare two nominal variables, the Chi^2 test with Yates' correction or the exact two-tailed Fisher test was used, depending on the size of the study groups. Continuous variables were tested for normality of distribution using the Shapiro-Wilk test. In the case of a normal distribution, variables are presented as means and standard deviations. Student's t-test was used to compare continuous variables in two groups of normal distribution. In the case of non-normal distribution, continuous variables were reported as medians and interquartile ranges (IQR). Mann-Whitney U test was used to compare two groups with non-normally distributed continuous variables. The level of statistical significance was $p < 0.05$.

Statistical analyses were performed using the Statistica 10 (Statsoft, Tulsa, USA).

5. Results

Evaluation of the Effectiveness of the Gluten-Free Diet Adherence

In the analyzed group of patients with celiac disease, 25 patients (65.78%) declared strict adherence to the gluten-free diet. However, in this group, 7 (18.4%) patients had significantly increased levels of anti-tTG antibodies (mean 82.3 RU/ml ±78.9 SD at N<20 RU/ml). After taking into account the group of patients who unconsciously made diet mistakes, strict adherence to the gluten-free diet was confirmed in 47.4% of the study group (n=18). Of the 13 patients declaring dietary deviations, two did not follow the gluten-free diet at all (Figure 1).
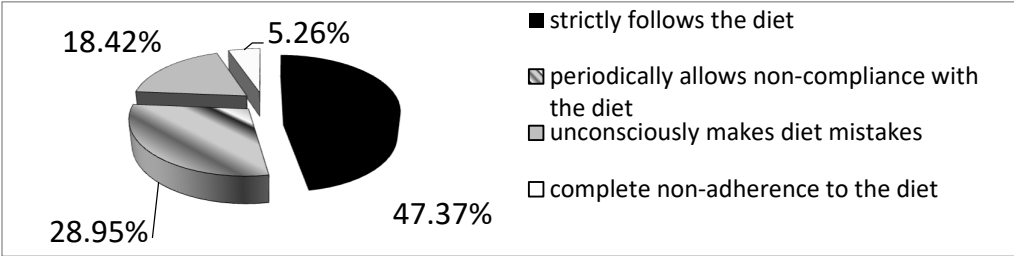

**Figure 1.** Declared adherence to the gluten-free diet in Group.

Analysis of Anti-Tissue Transglutaminase Antibody Levels and Their Impact on Reported Symptoms

Among the patients who consciously made diet mistakes, 6 (46.2%) demonstrated increased levels of anti-tTG antibodies (Figure 2). The mean duration of gluten-free diet adherence, measured in months, was shorter in the group of patients who periodically deviated from the diet than in the group following the recommendations (49.8 months ± 55.6 SD vs. 73.5 months ± 99.1 SD).
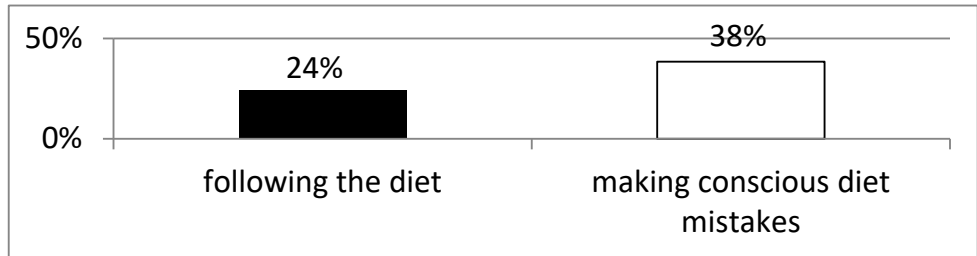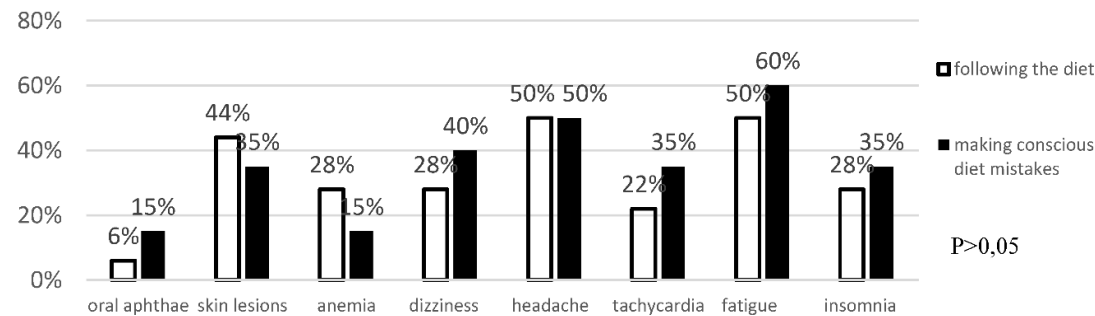

Figure 2. Evaluation of the frequency of elevated levels of anti-tissue transglutaminase antibodies (>20 UI/ml).

The analysis did not reveal any difference between the frequency of intestinal and extraintestinal symptoms in patients making diet mistakes and following the gluten-free diet (Figure 3 and 4).
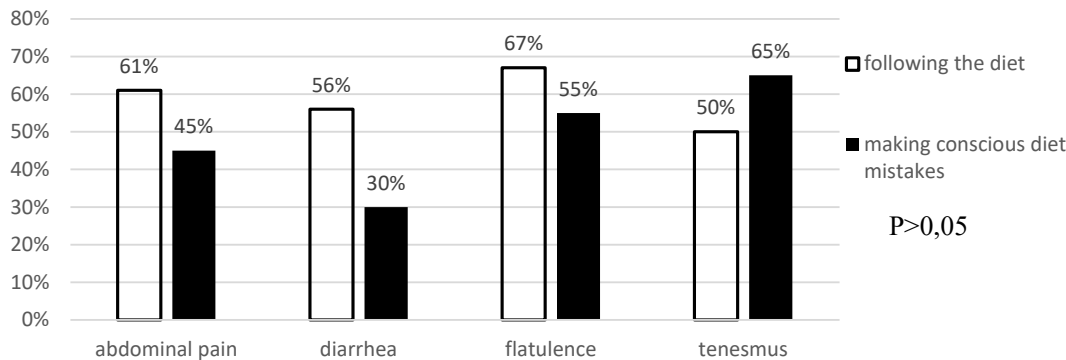
Figure 3. Evaluation of the frequency of intestinal symptoms in patients with celiac disease (Group 1) depending on the gluten-free diet adherence.

Figure 4. Evaluation of the frequency of extraintestinal symptoms in celiac patients (Group 1) depending on the gluten-free diet adherence.

6. Discussion

In the study group, only 65.78% of patients declared strict adherence to a gluten-free diet, 31.6% declared occasional deviations from the diet, whereas 5.26% did not follow the diet at all, mainly due to doubts regarding the diagnosis as well as the inconvenience of having to avoid certain foods.

Moreover, among patients declaring a strict gluten-free diet, 28% were suspected of making diet mistakes due to the detected elevated level of anti-tTG antibodies. Unconscious mistakes can be explained by numerous product contaminations and incorrect or incomplete descriptions on food labels. According to recent research, even in naturally gluten-free products, trace amounts of gluten are detected due to contamination resulting from production processes. This problem concerns both domestic [36–38] and foreign [39–42] products. Even in products with the crossed grain symbol, the safe gluten concentration is often exceeded [36,43–45]. Manufacturers of naturally gluten-free products omit information on the packaging about the possibility of gluten contamination during production [46]. Patients often make unconscious diet mistakes and make minor deviations from the diet, mainly during social gatherings and when eating meals in restaurants [47–49]. Improper education and insufficient celiac patients knowledge about the disease and the gluten-free diet play the main role in unconscious diet mistakes. In a survey conducted among 82 patients who had been following the diet for at least 6 years, no one identified correctly the gluten content of all 17 foods and only 30% identified at least 14 foods correctly [50]. Research points to insufficient knowledge as one of the leading factors responsible for poor adherence to the gluten-free diet. This problem concerns both patients and medical staff [51–53]. Moreover, a survey conducted on a group of 584 patients with celiac disease showed that less than 30% of the respondents consciously make diet mistakes [54]. In numerous studies, the frequency of conscious dietary errors ranges from 5 to 42%, depending on the country and the age of the study group [48,55–58]. One method of reducing errors was to provide gluten-free products on prescription but no increase in the frequency of mistakes was observed after their withdrawal [59]. In the analyzed Group 1, the mean time of gluten-free diet adherence was shorter in the group making dietary errors than in the group following the recommendations (49.8 months ± 55.6 SD vs. 73.5 months ± 99.1 SD). Meanwhile, Kurpp et al., and Webb et al., showed that patients diagnosed with celiac disease in adolescence or adulthood were more likely to follow dietary recommendations than those diagnosed with celiac disease in their youth [60,61].

In the conducted study, the level of IgA anti-tTG antibodies was determined to assess the compliance to gluten-free diet. In the study group, elevated levels of the above-mentioned antibodies were found in 34.2% of patients, including 28% of patients following the diet and 46.2% of patients deviating from it. In the study by Ferreira et al., 29% of patients who had been following a gluten-free diet for years also had high levels of anti-tissue transglutaminase antibodies [62]. In turn, Gładyś et al., demonstrated elevated levels of IgA anti-tTG despite normal duodenal biopsy results in 27.3% of the study participants. They confirmed the correlation between increased antibody levels and dietary errors in two tests [63]. In studies conducted in celiac patients after gluten challenge, a gradual, slow increase in antibodies was observed over many months or even years. This increase concerned both the level of anti-tTG and anti-EMA antibodies but occurred mainly in patients consuming significant amounts of gluten for a long time [64–67]. In some patients, no increase in antibody levels was observed despite withdrawal from the gluten-free diet [68]. Also in the analyzed Group 1, some of the patients declaring deviations from the diet did not develop anti-tTG or anti-DGP antibodies again, which may be related either to short periods of deviations or, contrary to the declarations, too low doses of gluten intake.

In the study by Bufler et al., high IgA anti-tTG titer correlated with the occurrence of dietary deviations [69]. Bannister et al., also demonstrated a direct correlation between low antibody titers and good adherence to the gluten-free diet [70]. Galli et al., observed a correlation between significant changes in the intestinal mucosa and high antibody levels. Moreover, reintroduction of the gluten-free diet was not only associated with their reduction, but in the group of patients in whom no histopathological improvement was observed, persistent antibody positivity was confirmed [71]. Qureshi [72] also reached similar conclusions in his meta-analysis. On the other hand, the consumption of foods containing small amounts of gluten, according to Selby et al., does not affect the risk of long-term villous atrophy [73]. To sum up, some studies confirm the great importance of antibodies in monitoring the gluten-free diet [74], but there is considerable controversy in this respect [75]. A number of studies indicate the lack of full intestinal villous recovery and making dietary errors while at the same time normalizing the level of anti-tissue transglutaminase antibodies [76–78]. This

may be due to IgA deficiency [79], as well as to reactivity against other biomarkers such as deamidated gliadin peptides or specific tissue transglutaminase epitopes [80]. For this reason, new biomarkers are sought for effective monitoring of adherence to the gluten-free diet [81–83]. High frequency of dietary errors in the study group, including unconscious mistakes, may result from significantly more difficult contact with dietitians in Poland and the short duration of doctor appointments. This may explain the patients' uncertain and inadequate knowledge about their diet. Furthermore, the presence of gluten in food declared as gluten-free cannot be ruled out with 100% certainty due to the lack of actual legal consequences in the case of contaminated products.

Nowadays, when we encounter highly processed food on a daily basis, the gluten-free diet has become an extremely demanding form of treatment. Patients must have knowledge of how to properly read food labels and follow current product testing for gluten content at the same time, taking into account the proper balance of the diet in terms of vitamins, minerals, and fiber [84]. This reduces their quality of life [85]. Moreover, gluten-free products, compared to those containing gluten, have a lower protein and fiber content as well as nutritional value than their gluten-containing counterparts. Due to the consumption of large amounts of meat, the gluten-free diet is also rich in saturated fats [86–89]. As the result, a poorly balanced gluten-free diet may lead to amino acid and protein deficiency, vitamin deficiency (especially vitamin A, B1, B6, B12 and D), electrolyte deficiency (especially iron, zinc, calcium and magnesium) and folic acid deficiency [90–93]. Moreover, gluten-free products are many times more expensive than their gluten-containing counterparts and some patients will be forced to limit their food intake or choose products of lower quality, which in many cases may be an additional factor intensifying deficiencies [94–96].

In the analyzed Group 1, no correlation was found between the reported complaints and proper adherence to the gluten-free diet. The lack of correlation between improper diet and the presented symptoms may result from the need for some patients to consume large doses of gluten over a long period of time. It should also be noted that the lack of a typical exacerbation of symptoms immediately after gluten consumption makes it much more difficult to identify products that may have been gluten-contaminated. In the study by Leffler et al., patients with confirmed celiac disease received 7.5 grams of gluten for 28 days. Only 10% of the study participants developed symptoms [97]. In the study by Pedoto et al., also only 3.6% of the study participants reported symptoms, whereas 40.6% made diet mistakes [98]. However, in the study by Silvester et al., as many as 72% of respondents declared discomfort after gluten consumption, mainly in the form of abdominal pain (80%). This study did not correlate the relationship between the declared symptoms and the objective increase in antibody titer [47]. However, regardless of the reported symptoms, the latest reports indicate a significant reduction in the quality of life of patients with celiac disease who do not follow the gluten-free diet [99]. The above studies may indirectly indicate a questionable correlation between deviations from the gluten-free diet, especially when these deviations are short-lasting and the presented symptoms but it undoubtedly affects the patients' quality of life.

7. Summary

Celiac disease is a common autoimmune disease of the digestive tract. Currently, the only available treatment method is a strict diet that completely excludes gluten. Due to difficulties in adherence to the diet, appropriate education is necessary among patients to improve the effectiveness of compliance with dietary recommendations. Further research and development of new treatment techniques should also be considered.

8. Conclusions

1. More than half of celiac patients unconsciously or consciously make diet mistakes, which indicates an urgent need to increase their education about the diet.
2. Regardless of whether the gluten-free diet is followed, both typical and atypical symptoms of the disease have been observed among celiac patients.

References

1. Garampazzi, A., et al., *Clinical pattern of celiac disease is still changing.* J Pediatr Gastroenterol Nutr, 2007. **45**(5): p. 611-4.
2. Dinler, G., E. Atalay, and A.G. Kalayci, *Celiac disease in 87 children with typical and atypical symptoms in Black Sea region of Turkey.* World J Pediatr, 2009. **5**(4): p. 282-6.
3. Bottaro, G., et al., *Changes in coeliac disease behaviour over the years.* Acta Paediatr, 1993. **82**(6-7): p. 566-8.
4. Faulkner-Hogg, K.B., W.S. Selby, and R.H. Loblay, *Dietary analysis in symptomatic patients with coeliac disease on a gluten-free diet: the role of trace amounts of gluten and non-gluten food intolerances.* Scand J Gastroenterol, 1999. **34**(8): p. 784-9.
5. Kalayci, A.G., et al., *Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood.* Pediatrics, 2001. **108**(5): p. E89.
6. Mautalen, C., et al., *Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients.* Am J Gastroenterol, 1997. **92**(2): p. 313-8.
7. Bai, J.C., et al., *Long-term effect of gluten restriction on bone mineral density of patients with coeliac disease.* Aliment Pharmacol Ther, 1997. **11**(1): p. 157-64.
8. Ciacci, C., et al., *Effects of dietary treatment on bone mineral density in adults with celiac disease: factors predicting response.* Am J Gastroenterol, 1997. **92**(6): p. 992-6.
9. Zanchetta, M.B., et al., *Impaired Bone Microarchitecture Improves After One Year On Gluten-Free Diet: A Prospective Longitudinal HRpQCT Study in Women with Celiac Disease.* J Bone Miner Res, 2016.
10. Catal, F., et al., *The hematologic manifestations of pediatric celiac disease at the time of diagnosis and efficiency of gluten-free diet.* Turk J Med Sci, 2015. **45**(3): p. 663-7.
11. Repo, M., et al., *Anemia and Iron Deficiency in Children with Potential Celiac Disease.* J Pediatr Gastroenterol Nutr, 2016.
12. Schosler, L., L.A. Christensen, and C.L. Hvas, *Symptoms and findings in adult-onset celiac disease in a historical Danish patient cohort.* Scand J Gastroenterol, 2016. **51**(3): p. 288-94.
13. Chang, M.S., et al., *Double-blind randomized controlled trial of rifaximin for persistent symptoms in patients with celiac disease.* Dig Dis Sci, 2011. **56**(10): p. 2939-46.
14. Bucci, P., et al., *Oral aphthous ulcers and dental enamel defects in children with coeliac disease.* Acta Paediatr, 2006. **95**(2): p. 203-7.
15. Costacurta, M., et al., *Oral manifestations of coeliac disease.: A clinical-statistic study.* Oral Implantol (Rome), 2010. **3**(1): p. 12-9.
16. Avsar, A. and A.G. Kalayci, *The presence and distribution of dental enamel defects and caries in children with celiac disease.* Turk J Pediatr, 2008. **50**(1): p. 45-50.
17. Cantekin, K., D. Arslan, and E. Delikan, *Presence and distribution of dental enamel defects, recurrent aphthous lesions and dental caries in children with celiac disease.* Pak J Med Sci, 2015. **31**(3): p. 606-9.
18. Acar, S., et al., *Oral findings and salivary parameters in children with celiac disease: a preliminary study.* Med Princ Pract, 2012. **21**(2): p. 129-33.
19. Martinelli, D., et al., *Reproductive life disorders in Italian celiac women. A case-control study.* BMC Gastroenterol, 2010. **10**: p. 89.
20. Singh, P., et al., *Celiac Disease in Women With Infertility: A Meta-Analysis.* J Clin Gastroenterol, 2016. **50**(1): p. 33-9.
21. Lasa, J.S., I. Zubiaurre, and L.O. Soifer, *Risk of infertility in patients with celiac disease: a meta-analysis of observational studies.* Arq Gastroenterol, 2014. **51**(2): p. 144-50.
22. Weinstock, L.B., et al., *Celiac disease is associated with restless legs syndrome.* Dig Dis Sci, 2010. **55**(6): p. 1667-73.
23. Manchanda, S., C.R. Davies, and D. Picchietti, *Celiac disease as a possible cause for low serum ferritin in patients with restless legs syndrome.* Sleep Med, 2009. **10**(7): p. 763-5.
24. Rodrigo, L., et al., *Gluten ataxia is better classified as non-celiac gluten sensitivity than as celiac disease: a comparative clinical study.* Immunol Res, 2016. **64**(2): p. 558-64.
25. Isikay, S., et al., *INCREASED TISSUE TRANSGLUTAMINASE LEVELS ARE ASSOCIATED WITH INCREASED EPILEPTIFORM ACTIVITY IN ELECTROENCEPHALOGRAPHY AMONG PATIENTS WITH CELIAC DISEASE.* Arq Gastroenterol, 2015. **52**(4): p. 272-7.
26. Husby, S., et al., *European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease*, in *J Pediatr Gastroenterol Nutr*. 2012: United States. p. 136-60.
27. Husby, S., et al., *European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020.* J Pediatr Gastroenterol Nutr, 2020. **70**(1): p. 141-156.
28. Lahdeaho, M.L., et al., *Small- bowel mucosal changes and antibody responses after low- and moderate-dose gluten challenge in celiac disease.* BMC Gastroenterol, 2011. **11**: p. 129.
29. Catassi, C., et al., *A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease.* Am J Clin Nutr, 2007. **85**(1): p. 160-6.

30. Bruins, M.J., *The clinical response to gluten challenge: a review of the literature.* Nutrients, 2013. **5**(11): p. 4614-41.

31. Akobeng, A.K. and A.G. Thomas, *Systematic review: tolerable amount of gluten for people with coeliac disease.* Aliment Pharmacol Ther, 2008. **27**(11): p. 1044-52.

32. Gibert, A., et al., *Consumption of gluten-free products: should the threshold value for trace amounts of gluten be at 20, 100 or 200 p.p.m.?* Eur J Gastroenterol Hepatol, 2006. **18**(11): p. 1187-95.

33. Zanini, B., et al., *Persistent Intraepithelial Lymphocytosis in Celiac Patients Adhering to Gluten-Free Diet Is Not Abolished Despite a Gluten Contamination Elimination Diet.* Nutrients, 2016. **8**(9).

34. Lanzini, A., et al., *Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet.* Aliment Pharmacol Ther, 2009. **29**(12): p. 1299-308.

35. Tursi, A., et al., *Endoscopic and histological findings in the duodenum of adults with celiac disease before and after changing to a gluten-free diet: a 2-year prospective study.* Endoscopy, 2006. **38**(7): p. 702-7.

36. Daniewski, W., A. Wojtasik, and H. Kunachowicz, *[Gluten content in special dietary use gluten-free products and other food products].* Rocz Panstw Zakl Hig, 2010. **61**(1): p. 51-5.

37. **BA, C.,** *Problemy z rozróżnianiem żywności bezglutenowej.* 2009, Pediatria Współczesna. Gastroenterologia, Hepatologia i Żywienie Dziecka. p. **117-122**.

38. A. Wojtasik, W.D., H. Kunachowicz, *Zawartość glutenu (gliadyny) w wybranych produktach spożywczych.* Bromat. Chem. Toksykol., 2010. **XLIII**(3): p. 362-371.

39. Koerner, T.B., et al., *Gluten contamination of naturally gluten-free flours and starches used by Canadians with celiac disease.* Food Addit Contam Part A Chem Anal Control Expo Risk Assess, 2013. **30**(12): p. 2017-21.

40. Thompson, T., A.R. Lee, and T. Grace, *Gluten contamination of grains, seeds, and flours in the United States: a pilot study.* J Am Diet Assoc, 2010. **110**(6): p. 937-40.

41. Miller, K., N. McGough, and H. Urwin, *Catering Gluten-Free When Simultaneously Using Wheat Flour.* J Food Prot, 2016. **79**(2): p. 282-7.

42. Colgrave, M.L., et al., *Proteomic profiling of 16 cereal grains and the application of targeted proteomics to detect wheat contamination.* J Proteome Res, 2015. **14**(6): p. 2659-68.

43. Gibert, A., et al., *Might gluten traces in wheat substitutes pose a risk in patients with celiac disease? A population-based probabilistic approach to risk estimation.* Am J Clin Nutr, 2013. **97**(1): p. 109-16.

44. La Vieille, S., et al., *Estimated levels of gluten incidentally present in a Canadian gluten-free diet.* Nutrients, 2014. **6**(2): p. 881-96.

45. Lee, H.J., Z. Anderson, and D. Ryu, *Gluten contamination in foods labeled as "gluten free" in the United States.* J Food Prot, 2014. **77**(10): p. 1830-3.

46. Sharma, G.M., M. Pereira, and K.M. Williams, *Gluten detection in foods available in the United States - a market survey.* Food Chem, 2015. **169**: p. 120-6.

47. Silvester, J.A., et al., *Symptomatic suspected gluten exposure is common among patients with coeliac disease on a gluten-free diet.* Aliment Pharmacol Ther, 2016.

48. Roma, E., et al., *Dietary compliance and life style of children with coeliac disease.* J Hum Nutr Diet, 2010. **23**(2): p. 176-82.

49. Black, J.L. and C. Orfila, *Impact of coeliac disease on dietary habits and quality of life.* J Hum Nutr Diet, 2011. **24**(6): p. 582-7.

50. Silvester, J.A., et al., *Is it gluten-free? Relationship between self-reported gluten-free diet adherence and knowledge of gluten content of foods.* Nutrition, 2016. **32**(7-8): p. 777-83.

51. Villafuerte-Galvez, J., et al., *Factors governing long-term adherence to a gluten-free diet in adult patients with coeliac disease.* Aliment Pharmacol Ther, 2015. **42**(6): p. 753-60.

52. Zarkadas, M., et al., *Living with coeliac disease and a gluten-free diet: a Canadian perspective.* J Hum Nutr Diet, 2013. **26**(1): p. 10-23.

53. Silvester, J.A., et al., *Living gluten-free: adherence, knowledge, lifestyle adaptations and feelings towards a gluten-free diet.* J Hum Nutr Diet, 2016. **29**(3): p. 374-82.

54. Sdepanian, V.L., M.B. de Morais, and U. Fagundes-Neto, *[Celiac disease: evaluation of compliance to gluten-free diet and knowledge of disease in patients registered at the Brazilian Celiac Association (ACA)].* Arq Gastroenterol, 2001. **38**(4): p. 232-9.

55. Hopman, E.G., et al., *Dietary compliance and health-related quality of life in patients with coeliac disease.* Eur J Gastroenterol Hepatol, 2009. **21**(9): p. 1056-61.

56. Hauser, W., et al., *Health-related quality of life in adult coeliac disease in Germany: results of a national survey.* Eur J Gastroenterol Hepatol, 2006. **18**(7): p. 747-54.

57. Chauhan, J.C., et al., *Assessment of dietary compliance to gluten free diet and psychosocial problems in Indian children with celiac disease.* Indian J Pediatr, 2010. **77**(6): p. 649-54.

58. Rashid, M., et al., *Celiac disease: evaluation of the diagnosis and dietary compliance in Canadian children.* Pediatrics, 2005. **116**(6): p. e754-9.

59. Crocker, H., et al., *The affordability and obtainability of gluten-free foods for adults with coeliac disease following their withdrawal on prescription in England: A qualitative study.* J Hum Nutr Diet, 2024. **37**(1): p. 47-56.

60. Kurppa, K., et al., *Factors associated with dietary adherence in celiac disease: a nationwide study.* Digestion, 2012. **86**(4): p. 309-14.

61. Webb, C., et al., *High adherence to a gluten-free diet in adolescents with screening-detected celiac disease.* J Pediatr Gastroenterol Nutr, 2015. **60**(1): p. 54-9.

62. Ferreira, S., et al., *[Anti-transglutaminase antibody in adults with celiac disease and their relation to the presence and duration of gluten-free diet].* Rev Gastroenterol Peru, 2018. **38**(3): p. 228-233.

63. Głodyś, K., et al., *Celiac Dietary Adherence Test and Standardized Dietician Evaluation in Assessment of Adherence to a Gluten-Free Diet in Patients with Celiac Disease.* Nutrients, 2020. **12**(8).

64. Tursi, A., G. Brandimarte, and G.M. Giorgetti, *Lack of usefulness of anti-transglutaminase antibodies in assessing histologic recovery after gluten-free diet in celiac disease.* J Clin Gastroenterol, 2003. **37**(5): p. 387-91.

65. Burgin-Wolff, A., et al., *Antibodies against human tissue transglutaminase and endomysium in diagnosing and monitoring coeliac disease.* Scand J Gastroenterol, 2002. **37**(6): p. 685-91.

66. Vahedi, K., et al., *Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease.* Am J Gastroenterol, 2003. **98**(5): p. 1079-87.

67. Matysiak-Budnik, T., et al., *Long-term follow-up of 61 coeliac patients diagnosed in childhood: evolution toward latency is possible on a normal diet.* Gut, 2007. **56**(10): p. 1379-86.

68. Kaukinen, K., et al., *IgA-class transglutaminase antibodies in evaluating the efficacy of gluten-free diet in coeliac disease.* Eur J Gastroenterol Hepatol, 2002. **14**(3): p. 311-5.

69. Bufler, P., et al., *Diagnostic performance of three serologic tests in childhood celiac disease.* Z Gastroenterol, 2015. **53**(2): p. 108-14.

70. Bannister, E.G., et al., *Can celiac serology alone be used as a marker of duodenal mucosal recovery in children with celiac disease on a gluten-free diet?* Am J Gastroenterol, 2014. **109**(9): p. 1478-83.

71. Galli, G., et al., *Comparison of Clinical, Biochemical and Histological Features between Adult Celiac Patients with High and Low Anti-Transglutaminase IgA Titer at Diagnosis and Follow-Up.* Nutrients, 2023. **15**(9).

72. Qureshi, M.H., *The Correlation Between Serum Anti-tissue Transglutaminase (Anti-tTG) Antibody Levels and Histological Severity of Celiac Disease in Adolescents and Adults: A Meta-Analysis.* Cureus, 2023. **15**(12): p. e51169.

73. Selby, W.S., et al., *Persistent mucosal abnormalities in coeliac disease are not related to the ingestion of trace amounts of gluten.* Scand J Gastroenterol, 1999. **34**(9): p. 909-14.

74. Sugai, E., et al., *Dynamics of celiac disease-specific serology after initiation of a gluten-free diet and use in the assessment of compliance with treatment.* Dig Liver Dis, 2010. **42**(5): p. 352-8.

75. Leffler, D.A., et al., *A prospective comparative study of five measures of gluten-free diet adherence in adults with coeliac disease.* Aliment Pharmacol Ther, 2007. **26**(9): p. 1227-35.

76. Leonard, M.M., et al., *Value of IgA tTG in Predicting Mucosal Recovery in Children With Celiac Disease on a Gluten-Free Diet.* J Pediatr Gastroenterol Nutr, 2017. **64**(2): p. 286-291.

77. Silvester, J.A., et al., *Tests for Serum Transglutaminase and Endomysial Antibodies Do Not Detect Most Patients With Celiac Disease and Persistent Villous Atrophy on Gluten-free Diets: a Meta-analysis.* Gastroenterology, 2017. **153**(3): p. 689-701.e1.

78. Rubio-Tapia, A., et al., *Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet.* Am J Gastroenterol, 2010. **105**(6): p. 1412-20.

79. Nazario, E., et al., *IgA Deficiency Is Not Systematically Ruled Out in Patients Undergoing Celiac Disease Testing.* Dig Dis Sci, 2022. **67**(4): p. 1238-1243.

80. Choung, R.S., et al., *Synthetic Neoepitopes of the Transglutaminase-Deamidated Gliadin Complex as Biomarkers for Diagnosing and Monitoring Celiac Disease.* Gastroenterology, 2019. **156**(3): p. 582-591.e1.

81. Ramírez-Sánchez, A.D., et al., *Molecular Biomarkers for Celiac Disease: Past, Present and Future.* Int J Mol Sci, 2020. **21**(22).

82. Singh, A., et al., *Non-Invasive Biomarkers for Celiac Disease.* J Clin Med, 2019. **8**(6).

83. Ruiz-Carnicer, Á., et al., *Negative predictive value of the repeated absence of gluten immunogenic peptides in the urine of treated celiac patients in predicting mucosal healing: new proposals for follow-up in celiac disease.* Am J Clin Nutr, 2020. **112**(5): p. 1240-1251.

84. Bascunan, K.A., M.C. Vespa, and M. Araya, *Celiac disease: understanding the gluten-free diet.* Eur J Nutr, 2016.

85. Samasca, G., et al., *Gluten-free diet and quality of life in celiac disease.* Gastroenterol Hepatol Bed Bench, 2014. **7**(3): p. 139-43.

86. Balamtekin, N., et al., *Is compliance with gluten-free diet sufficient? Diet composition of celiac patients.* Turk J Pediatr, 2015. **57**(4): p. 374-9.

87. Churruca, I., et al., *Analysis of Body Composition and Food Habits of Spanish Celiac Women.* Nutrients, 2015. **7**(7): p. 5515-31.

88. Kautto, E., et al., *Nutrient intake in adolescent girls and boys diagnosed with coeliac disease at an early age is mostly comparable to their non-coeliac contemporaries.* J Hum Nutr Diet, 2014. **27**(1): p. 41-53.

89. Wu, J.H., et al., *Are gluten-free foods healthier than non-gluten-free foods? An evaluation of supermarket products in Australia.* Br J Nutr, 2015. **114**(3): p. 448-54.

90. Shepherd, S.J. and P.R. Gibson, *Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease.* J Hum Nutr Diet, 2013. **26**(4): p. 349-58.
91. Miranda, J., et al., *Nutritional differences between a gluten-free diet and a diet containing equivalent products with gluten.* Plant Foods Hum Nutr, 2014. **69**(2): p. 182-7.
92. Vici, G., et al., *Gluten free diet and nutrient deficiencies: A review.* Clin Nutr, 2016.
93. Martin, J., et al., *Inadequate nutrient intake in patients with celiac disease: results from a German dietary survey.* Digestion, 2013. **87**(4): p. 240-6.
94. MacCulloch, K. and M. Rashid, *Factors affecting adherence to a gluten-free diet in children with celiac disease.* Paediatr Child Health, 2014. **19**(6): p. 305-9.
95. Burden, M., et al., *Cost and availability of gluten-free food in the UK: in store and online.* Postgrad Med J, 2015. **91**(1081): p. 622-6.
96. Missbach, B., et al., *Gluten-free food database: the nutritional quality and cost of packaged gluten-free foods.* PeerJ, 2015. **3**: p. e1337.
97. Leffler, D., et al., *Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease.* Gut, 2013. **62**(7): p. 996-1004.
98. Pedoto, D., et al., *Adherence to Gluten-Free Diet in Coeliac Paediatric Patients Assessed through a Questionnaire Positively Influences Growth and Quality of Life.* Nutrients, 2020. **12**(12).
99. Elsahoryi, N.A., M.O. Ibrahim, and O.A. Alhaj, *Adherence to the Gluten-Free Diet Role as a Mediating and Moderating of the Relationship between Food Insecurity and Health-Related Quality of Life in Adults with Celiac Disease: Cross-Sectional Study.* Nutrients, 2024. **16**(14).