# Effect of Gluten-Free Diets on Nutritional Status in celiac patients: a systematic review

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## Abstract

Introduction: Celiac disease (CD) is an autoimmune disease of the small intestine in which ingestion of gluten leads to destruction of intestinal areas in affected patients. Lifelong adherence to a gluten-free diet (GFD) is the only possible treatment for CD. It is less evident in adults considering the nutrient status in patients on GFD. Therefore, the aim of the study is to systematically evaluate the effect of GFD on the nutritional status of celiac patients.

Methodology: A comprehensive electronic search with time and language restrictions was done. Several known databases were included: “Google Scholar, PubMed, The Cochrane Library, Web of Science” from 2000 to 2022. Keywords used included “celiac disease”, “nutrient status”, “gluten-free diet”, “nutritional deficiencies”, “dietary deficiencies”, “nutrient intake”, “micronutrient”, “macronutrient”, “vitamin”, “mineral”, “fiber intake”, “Protein intake”, and “Fat intake”

Results: The electronic search strategy conducted in this review ended in 875 hits which after removing duplications reduced to 360 studies. These 360 studies were considered eligible for further evaluation, from which 346 studies were excluded for different reasons as 216 studies were based on title and abstract, 86 studies were not relevant to the subject of this study or of this review, 17 were considered replies of authors, 2 were books, and 27 were reviews. Finally , 12 articles were included in the qualitative synthesis of the present review.

Conclusion: The current review showed that gluten free diet is associated with unbalanced intake of macro and micronutrients in both, celiac women and men mainly because of the unhealthy dietary habits and difficulty eliminating gluten from the diet which leads to low cereal intake and high consumption of processed gluten free products.

Keywords: Gluten free diet, nutritional status, celiac disease, Saudi Arabia

## Introduction

Celiac disease (CD) is an autoimmune disease of the small intestine in which ingestion of gluten leads to destruction of intestinal areas in affected patients [1,2]. The main genes involved in CD development are HLA DQ2 and HLA DQ8 [1,3]. CD affects 1 to 2 out of every 100 people worldwide; however, systematic reviews have shown that CD prevalence in Saudi Arabia is high (about 3%) [4,5]. Patients with CD may present with a variety of gastrointestinal symptoms, malabsorption (classical CD) or extraintestinal symptoms (nonclassical CD) [6]. CD is a multifactorial disease characterized by the interaction between gluten intake and the immune response, as well as environmental and genetic factors [1,7]. Previously, CD was only considered in patients with overt malabsorption and gastrointestinal (GI) manifestations, including bloating, chronic diarrhea, abdominal pain, constipation, nausea, and vomiting [7–9]. However, at present, there are no signs of the classic symptoms in many patients, and extraintestinal symptoms such as growth retardation, dental enamel defects, and iron deficiency anemia have become predominant [7]. In fact, the clinical symptoms of CD go beyond gastrointestinal presentations [10]. Global assessments showed that CD affected approximately 1% of the European population [11]. In Iran, the serological assessments revealed a prevalence of CD of 1 per 167 children [12]. However, the prevalence of CD has been found to be higher in different diseases, such as irritable bowel syndrome (IBS), diabetes, and neurological disorders (11, 12, and 3.7%, respectively) [13].

According to the Oslo CD classification, different types of CD have been identified: classic, non-classic, subclinical, probable and refractory [14,15]. Classic CD is characterized by signs and symptoms of malabsorption and non-classical CD by extraintestinal symptoms. Subclinical CD is below the threshold of clinical detection. Potential CD identifies patients at high risk of developing the disease [16]. Proximal intestinal mucosal damage and fat malabsorption lead to nutrient, vitamin (D, K, and B9) and mineral (iron and zinc) deficiencies, which in turn may increase the risk of developing hypocalcemia. rickets and osteoporosis, coagulation disorders, anemia and poor nutrition [17–20]. As well as nutrient malabsorption, the reduced food intake is associated with poor growth in children with CD [21].

The lifelong adherence to the gluten-free diet (GFD) is the only possible treatment for CD [22]. A strict diet is very important to improve the duodenal mucosa and eliminate the symptoms [23,24]. Intestinal mucosa takes longer to heal in adults than in children, making it easier for children to achieve full recovery [25]. However, despite a strict GFD, total dietary gluten appears to be very difficult to avoid due to gluten cross-contamination, resulting in persistent intestinal atrophy [25–27]. In fact, apart from familiar wheat foods such as bread, pasta, cakes, and other processed foods such as snacks, gluten can also be used as a thickener in sauces or as a stabilizer or flavoring agent [27]. Therefore, inadvertent gluten loss and resulting nutritional deficiencies are common in people with CD who follow a theoretically strict GFD [25,28]. Finally, the dietary habits of this group clearly play an important role in their nutritional status. In addition to being gluten-free, DSG should be balanced, meeting all energy and nutrient requirements. Several studies have revealed an unbalanced GFD profile characterized by low intake of grains, fruits and vegetables and meat and meat products [29–31]. In addition, high consumption of specific gluten-free products (GFP) has been reported among children and adolescents. Considering that these products have been shown to be inferior to their gluten-containing counterparts [32,33], the observed imbalance in nutrient and energy intake may be explained, particularly by high fat intake, which can alter the amount of dietary fiber and complex carbohydrates [34]. These habits can lead to many micronutrient deficiencies [28], however, they are less evident in adults and need further investigation. Therefore, the aim of the study is to systematically evaluate the effect of GFD on the nutritional status of celiac patients.

## Methodology

This review was reported in the light of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

**Search methods for identification of studies:**
A comprehensive electronic search with time and language restrictions was done. Several known databases were included: “Google Scholar, PubMed, The Cochrane Library, Web of Science” from 2000 to 2022. Keywords that were used include “celiac disease”, “nutrient status”, “gluten-free diet”, “nutritional deficiencies”, “dietary deficiencies”, “nutrient intake”, “micronutrient”, “macronutrient”, “vitamin”, “mineral”, “fiber intake”, “Protein intake”, and “Fat intake”

**Eligibility criteria and study selection**
In the first step, two researchers reviewed the retrieved articles and removed the duplicates. In other steps, the researchers screened the title and abstract of the records and the ineligible studies were removed. Then, the authors surveyed the full text of the remaining studies based on inclusion and exclusion criteria and the eligible studies (case report, case series, and cross-sectional) were identified.

We excluded the articles which were topic to at least one of the following criteria:

- **Exclusion criteria:**
  - Unpublished studies
  - Non-original articles including reviews, protocols and editorials.
  - Animal studies
  - Unsupported opinion of expert.
  - Clinical trials which were in progress without yet published results.
  - Replies to the author/editor.
  - Books’/conferences’ abstracts.
  - Abstract papers, articles without obtainable full text

- Published in any language other than English
- Published or conduction of the study prior to 2020

**Data analysis:**
In several known databases which were searched Ex: Google Scholar, PubMed, The Cochrane Library, Web of Science we combined the search terms and limited the study to the English language. Depending on PRISMA checklist we removed duplicates, and articles were screened based on title, abstract, and full text.

## Results

**Study selection**
The electronic search strategy conducted in this review ended in 875 hits which after removing of duplications reduced to 360 studies. These 360 studies were considered eligible for further evaluation, from which 346 studies were excluded for different reasons as 216 studies were based on title and abstract, 86 studies were not relevant to the subject of this study or sitting of this review, 17 were considered replies of authors, and there were 2 books, and 27 reviews. Finally , 12 articles were included in the qualitative synthesis of the present review (Figure 1).

**Study characteristics:**
In the current review, we included 12 studies which were published between 2002 and 2021 in eight countries including five studies conducted in Spain [29,30,32,33,35] and one study conducted in each of the following countries: Italy [36], Netherlands [36], Sweden [36], UK [37], Germany [38], USA [33], and Canada [39]. Moreover, eight studies had study design of observational, transversal case-control design while one study was cross-sectional, two studies were observational, longitudinal cohort studies, and one study was randomized double blind-controlled study. The collected studies included 774 adult patients with celiac disease and who were on gluten free products. Among the sample, the age of the participants ranged between 25-80 years old with mean age of 41.26 years and 198 patients were males (25.58 %). The mean duration of intake of gluten free products was 8.157 years with at least 1 year (Table 1).

**Macronutrients intake:**
The intake of macronutrients and distribution in patients on gluten free foods and products is presented in table 2 where different imbalanced patterns were repeated across the studies which have been conducted in different patients from different countries who followed GFP of a different duration. All studies agree that intake of fat in celiac adults is considered unbalanced. Some of them reported high fat intakes in patients on GFP [29,36,39], however others studies reported high consumption of some types of fats including saturated fatty acids (SFA) or an excessive intake of cholesterol [30,35,40]. Considering intake of carbohydrates, several studies showed that patients with celiac disease who were on gluten free diet showed low carbohydrate intake [29,30,36,38,39,41]. Wild et al reported in their study low complex carbohydrate intake, however the total carbohydrate intake seemed to be enough because of the high consumption of simple sugars and processed food [37]. Considering consumption of fibers among patients with celiac disease who were on gluten free diet, it was found that most of the studies reported low fiber intakes which is in perfect agreement with the low CHO and high fat intakes reported previously [29,30,35,37–41]. Moreover, some studies including the study of Martin et al. [38], Gonzalez et al. [30], and Ballestero-Fernandez et al., [35] reported that the intake of protein is higher than recommended in celiac patients who follow a gluten free diet which may be associated with excessive meat intake (Table 2).

**Micronutrient Intake**
The results of the current review also reported an impairment in the intake of vitamins and minerals in patients with celiac disease who are on gluten free diet. When analyzing the vitamin intakes, several studies showed deficiencies for the same vitamins including vitamin D and vitamin E [29,30,35–37] followed by low intake of vitamin B groups such as vitamin B9 (folate), vitamin B1 (thiamine), vitamin B2 (riboflavin), and vitamin B6 (pyridoxine) [29,30,36–38,42]. Moreover, among the included studies, iron, calcium, and magnesium showed the highest deficiency [29,30,35–41]. Deficiencies in iodine, potassium and zinc were also reported [29,30,36–38], and some studies showed low intake of selenium, sodium, and manganese [29,36,37] (Table 2).

**Figure 1:The PRISMA figures showing the steps to choose the studies for systematic review**

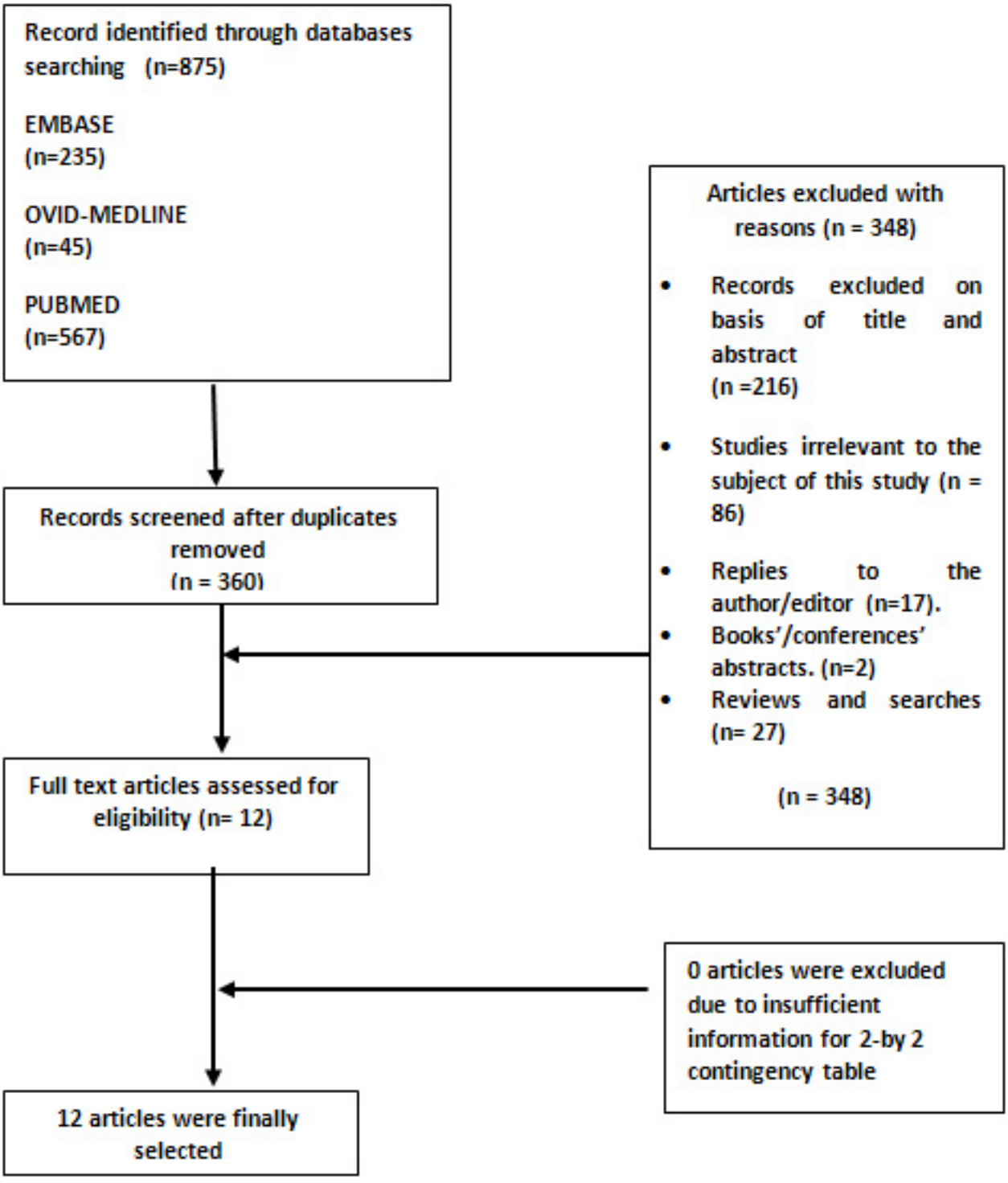

**Table 1: The general characteristics of studies and their samples**

| | Author | Year | Type of Study | Country | Sample size | Age (Mean ± SD) | Gender (M) | Duration of GFD (year) |
|---|---|---|---|---|---|---|---|---|
| 1 | González et al. [30] | 2018 | Observational, transversal cohort study | Spain | 42 | 31.5 ± 11.9 | 42 | >1 year |
| 2 | Churruca et al. [29] | 2015 | Observational, transversal cohort study | Spain | 54 | 34 ±13 | 0 | 10 |
| 3 | Bascuñán et al. [36] | 2019 | Randomized double bind controlled study | Italy | 46 | 41.1 ± 10.1 | 3 | >1 year |
| 4 | Hopman et al. [40] | 2006 | Observational, transversal cohort study | Netherlands | 132 | 16.6 ± 4.4 | 45 | 9.6 |
| 5 | Hallert et al.) [42] | 2002 | Observational, longitudinal cohort study | Sweden | 30 | 55 ±10 | 12 | 10 |
| 6 | Wild et al. [37] | 2010 | Observational, longitudinal cohort study | UK | 93 | 56 ±15 | 31 | 8 |
| 7 | Martin et al. [38] | 2013 | Observational, transversal cohort study | Germany | 73 | 18-80 | 18 | 7.5 |
| 8 | Thompson et al. [41] | 2005 | Observational, transversal cohort study | USA | 47 | 51 ±11 | 8 | 5.3 |
| 9 | Jamieson et al. [39] | 2020 | Observational, transversal cohort study | Canada | 35 | 47 ±11.5 | 6 | 6.7 |
| 10 | Miranda J. et al. [32] | 2014 | Observational, transversal cohort study | Spain | 58 | 18-75 | 12 | NA |
| 11 | Calvo-Lerma J et al [33] | 2019 | Cross-sectional study | Spain | 100 | NA | NA | NA |
| 12 | Ballestero-Fernández et al. [35] | 2021 | Observational, transversal case-control study | Spain | 64 | 39.17 ± 10.62 | 21 | >1 year |

| No. | Author | Macronutrients | | | | | | Micronutrients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fat | Protein | CHO | Fiber | Cholesterol | Energy | Folate | Vitamin E | Vitamin D | Iodine | Calcium | Zinc | Magnesium | Iron | Potassium | Vitamin B1, B2, B6 |
| 1 | [30] | High, especially SFA | High | Low | Low | High | NA | Low | Low | Low | Low | NA | NA | Low | NA | NA | NA |
| 2 | [29] | High | NA | Low | Low | NA | Low | Low | Low | Low | Low | Low | NA | Low | Low | Low | Low |
| 3 | [36] | High | NA | Low | NA | NA | NA | Low | Low | Low | NA | Low | Low | NA | Low | Low | NA |
| 4 | [40] | High saturated fat | NA | Low | NA | NA | NA | NA | NA | NA | NA | NA | Low | NA | Low | NA | NA |
| 5 | [42] | NA | NA | NA | NA | NA | NA | Low | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 6 | [37] | NA | NA | High sugar | Low | NA | NA | Low | NA | Low | NA | Low | Low | Low | Low | NA | NA |
| 7 | [38] | NA | NA | Low | Low | NA | NA | Low | NA | NA | NA | NA | NA | Low | Low | NA | Low |
| 8 | [41] | NA | NA | | Low | NA | NA | NA | NA | NA | NA | Low | NA | NA | Low | NA | NA |
| 9 | [39] | High | NA | Low | Low | NA | NA | NA | Low | NA | NA | Low | NA | NA | Low | NA | NA |
| 10 | [32] | High | Low | High | Low | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 11 | [35] | High | Low | High | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 12 | .[33] | High, low PUFA | High | Low | Low, high sugar | NA | NA | Low | Low | Low | Low | Low | Low | Low | Low | NA | NA |

**Table 2: The nutrient status in patients with celiac disease who are on gluten free diet**

## Discussion

Studies on nutritional deficiencies in the first year of a gluten free diet showed some possible deficiencies depending on biochemical data however, only a few main nutrients are described. When mucosa is recovered, it is assumed that strict gluten free diet has been followed in the long term therefore, measuring intake of different nutrients in celiac patients to assess their nutritional status with supposedly no absorption problem make sense [42,43]. In the current review, all included studies reported a high fat intake associated with gluten free product consumption. This result is similar to that reported in pediatric patients with celiac disease where it was found that GFP was associated with high fat intake with increased SFA/polyunsaturated (PUFA) ratio [28]. This could be explained due to the low intake of plant-based foods and high consumption of processed gluten free products [29,37]. In patients with celiac disease who follow a gluten free diet, it is common to consume gluten free products extensively and this tends to be generally higher in both total fat and SFA than their gluten containing analogues [28,32,33]. Moreover, the study of Wild et al compiled some records of gluten free products and reported that 47 % of the energy intake came from processed products thus, correct classification of GFP is needed so that celiac patients could be more informed and choose these products appropriately [37]. Moreover, consuming of unbalanced diets which are rich in SFA is associated with many different health problems including increased risk of cardiovascular disease, and/or insulin resistance in general and celiac patients [44–46]. In addition, consuming food with high fat content is associated with higher risk of death from cardiovascular disease in celiac patients [47].

Furthermore, consumption of processed products has been associated with higher mortality in patients with celiac disease [48] and chronic low grade inflammation [49].

Patients with celiac disease who are on a gluten free diet have to stop consuming cereal based foods which contain gluten which are the most commonly consumed cereals. Cereals are considered the basis of a balanced diet, therefore, without adequate guidelines, diet could be imbalanced [50]. In the current review, it was noticed that patients on gluten free diet showed low carbohydrate intakes which may be due to their fear of consuming gluten which makes them reject cereals which prevent them from consuming enough complex carbohydrates. This is consistent with the fact that gluten free products tend to increase the glycemic index in their products when compared with their gluten containing alternatives [45,51]. Therefore, it can be assumed that imbalances observed in the current review are not only associated with low- or non-existent consumption of gluten-containing cereals, but with the high intake of processed gluten free products and low consumption of vegetables and legumes [37]. This result is similar to that reported in children where it was found that children tend to consume less food rich in complex carbohydrates and increase the consumption of simple carbohydrates because of gluten free products [28].

Foods which are high in carbohydrates usually contain a high level of fibers [44], however, this is unusual in the diets of celiac patients [30,31,38]. The current review showed low fiber intake in patients with celiac disease which could be explained by the low consumption of fiber-rich plant foods and whole-grains [52], and by the high consumption of refined processed foods [28]. Low fiber intake is significantly associated with higher prevalence of constipation, increasing the risk of diverticulitis, and higher risk of gastrointestinal symptoms commonly present in patients with celiac disease [53]. Therefore, however while a direct relation between gluten free diet and constipation or diverticulitis has not been confirmed, it could be thought that increase in the intake of fibers among these patients could help in improvement of inflammation that is noticeable in those patients [54,55] and reduction if the symptoms of abdominal pain [56]. Moreover, the current review showed high intake of protein among patients on gluten free diet which is not consistent with the results of previous studies which showed higher protein consumption among non-celiac children [28,35,57].

Considering the intake of micronutrients, the current study reported a low intake of vitamin D among patients on a gluten free diet. Vitamin D deficiency reported in the current review has some indications since there is higher prevalence of osteoporosis reported in patients with celiac disease, and this vitamin is considered of vital importance in bone metabolism [58–60]. Therefore, vitamin D supplementation should be administered during the first year of a gluten free diet in order to recover its deficiency because of the low absorption associated with celiac disease. Considering deficiency in group B vitamins, this is in agreement with the biochemical data reported by Hallert et al who reported low B12 and low folate levels and reported that homocysteine levels were raised in those patients higher than in the general population [42,61]. High level of homocysteine is associated with higher risk of cardiovascular disease [62]. In order to reduce this problem, it is vital to highlight that the deficiency of vitamins is associated with low intake and not to the intestinal malabsorption [42]. Moreover, deficiency in vitamin B group is associated with worse sense of quality of life [42], and their supplementation is associated with better general well-being [61].

Iron deficiency is a major problem in non-treated active celiac disease and in patients with incompletely regenerated mucosa who have difficulties in reaching normal iron values [63]. Therefore, low levels of iron should be considered alarming, especially in women [38]. Moreover, it can worsen because of the observed low consumption of legumes and cereals [29,30]. In relation to calcium, different results could be found based on the reference intakes of different countries. Hopman et al. observed a low intake of calcium depending on the American recommendation [40] and Moreiras et al reported adequate results based on the Dutch recommendation [52]. Although calcium intakes are similar in celiac patients to the general population, it is considered that in recently diagnosed celiac patients, too little lactase is produced because of the damaged

mucosa and therefore they develop a secondary lactose intolerance. Calcium intake together with appropriate levels of vitamin D should be of benefit in newly diagnosed patients [64].

In conclusion, the current review showed that gluten free diet is associated with unbalanced intake of macro and micronutrients in both, celiac women, and men mainly because of the unhealthy dietary habits and difficulty in eliminating gluten from the diet which leads to low cereal intake and high consumption of processed gluten free products. It is vital to conduct a continuous and personalized follow-up of celiac patients from the moment of diagnosis in the presence of a nutritionist. Moreover, increasing the knowledge among patients through proper nutritional education will be the key for the long-term balanced diet.

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