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Review

Gluten free diet and nutrient deficiencies: A review

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SUMMARY

Background & aims: The only available treatment for celiac disease (CD) is lifelong adherence to gluten free (GF)-diet. However, GF-diet may lead to possible nutrient unbalance resulting in improper nutritional quality of diet. The aim of this study is to evaluate the nutritional quality of GF-diet.
Methods: MEDLINE®/PubMed and Cochrane Library were electronically searched for articles published between 1990/01/01 and 2015/09/01.
Results: GF-diet was found to be poor in alimentary fiber due in particular to the necessary avoidance of several kinds of foods naturally rich in fiber (i.e. grain) and the low content of fiber of GF product that are usually made with starches and/or refined flours. Micronutrients are also found to be poor, in particular Vit. D, Vit. B12 and folate, in addition to some minerals such as iron, zinc, magnesium and calcium. Moreover, an inadequate macronutrient intake was reported related above all to the focus on the avoidance of gluten that often leaving back the importance of nutritional quality of the choice. In particular, it was found a higher content of both saturated and hydrogenated fatty acids and an increase in the glycemic index and glycemic load of the meal.
Conclusions: Despite the GF-diet is necessary in celiac disease treatment and the attention is on gluten avoidance, the evaluation of nutritional quality of the diet must be considered. Moreover, educational strategies based on the relationship between nutrients and food and human health could be developed to optimize the therapeutic approach in celiac patients.

1. Introduction

Celiac disease (CD) is a chronic enteropathy which affects approximately 1% of the general population [1]. Now, the only treatment is strict lifelong adherence to a gluten-free diet (GF-diet) which leads to disappearance of the signs/symptoms [1,2]. Removing completely gluten from the diet of celiac patients will result, in the majority of patients, in remission in terms of symptoms and serologic and histological aspects [3]. It is reported that many disease complication can be avoided with gluten removal and in children growth and development can return to normal with the adherence to the GF-diet [3,4].

However, it is not always simple for CD patient to strictly follow a GF-diet and to make the right nutritional choices [5].

Moreover, GF-diet may lead to possible nutrient deficiencies (such as fiber and specific micronutrients) or nutrient excess (i.e. saturated fats). Gluten-free products are usually lower in fiber, magnesium and folic acid and gluten-free cereals found in nature have a lower magnesium content compared with gluten-containing ones [6–8].

The aim of this study is to determine and evaluate the nutritional quality of GF-diet and the impact on specific nutrients such as iron, folate, fiber, vitamins (in particular Vit. B12 and Vit. D), zinc, magnesium and calcium.

2. Methods

2.1. Literature search

MEDLINE®/PubMed and Cochrane were electronically searched for articles published between 1990/01/01 and 2015/09/01. A combination of keywords addressing “gluten”, “gluten-free diet”, “gluten free”, “gluten free diet” OR “nutritional” OR “quality” were used.

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2.2. Inclusion criteria

Observation study, controlled clinical trial (CCT), meta-analysis, systematic review, and consensus conferences were included as random controlled trials (RCTs) with randomization at any level. Studies regarding gluten sensitivity were excluded. Papers with information on at least one nutrient of our interest were included.

2.3. Data extraction

Data extracted from each eligible study were specifically analyzed in term of nutrition quality of the diet, in particular excess or deficiency of particular nutrients.

Of the 281 identified articles, we excluded 211 on the basis of the title and abstract as they did not fit with our interest. The full text of the remaining 70 articles was extensively reviewed to determine whether the articles met the inclusion or exclusion criteria. 44 articles did not meet our inclusion criteria. We excluded another 5 articles because they did not report data for the use of at least one specific nutrient. The remaining 21 articles were considered for the review (Fig. 1.)

3. Results

As reported in Table 1, several studies reveal different nutrients inadequacies in GF-diet.

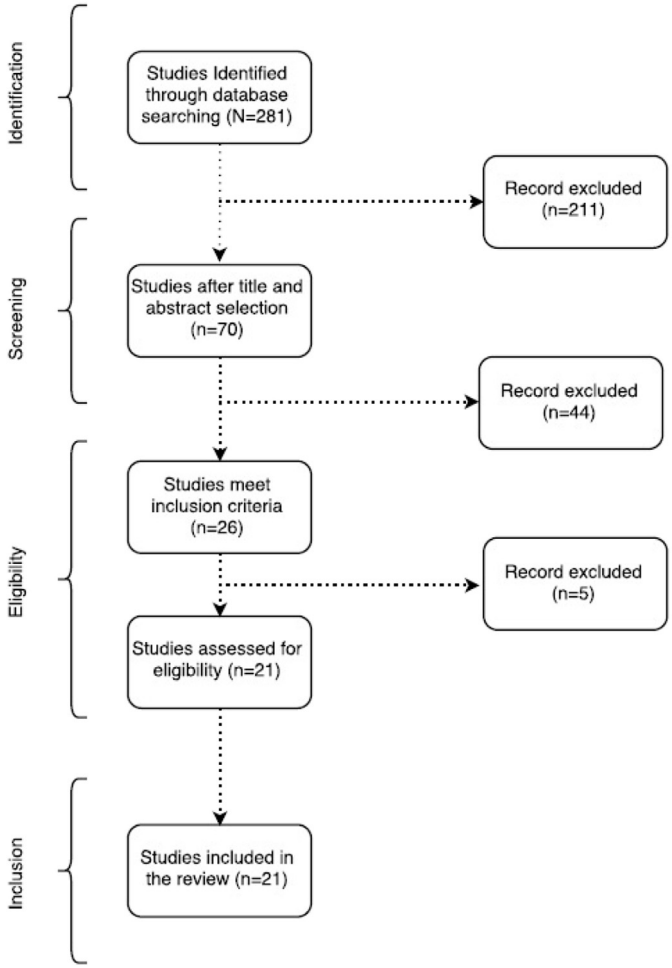

Fig. 1. Selection process schema.

3.1. Dietary fiber

As demonstrated by several studies, a GF-diet is often characterized by a lower intake of dietary fiber respect to normal diet containing gluten [9,10].

Fiber deficiency can be encountered both at the diagnosis and during the GF-diet. At the diagnosis, deficiency is related to malabsorption due to villi atrophy. During GF-diet, it could be related to poor quality of GF products, to patients' choice and, of course, to the avoidance of several kinds of foods naturally rich in fiber (i.e. grain).

The composition of GF product can be a reason for the lower intake of fiber. GF product is usually made with starches and or refined flours characterized by low content of fiber. During the production process, in particular the refined process, the outer layer of grains is removed leaving the starchy inner part. As is known, the outer layer containing the most of the fiber so the refined process is related with a decrease of fiber content [9].

Wild and co-workers conducted a study where they compared the nutritional value of GF-diet with data from the National Diet and Nutrition Survey of Adults and the UK Women's Cohort Study (UKWCS).

In particular, they found that there is a significant decrease in fiber content in women diet if compared with UKWCS [11].

Martin and co-workers compared data from 88 German CD patients to the DACH reference value and to the German National Diet and Nutrition Survey (NVSII) data and they observed that the content of fiber in male CD patients was significantly lower than the one of general population [12].

Mariani and co-workers examined the diet of 47 adolescents with CD and 47 healthy aged-matched control subjects. This study showed a lower consumption of carbohydrates and in particular a low content of fiber in the diet of CD adolescents than healthy adolescents [13].

As is known, a consumption of adequate amounts of dietary fiber is related to important health benefits such as prevention of colon cancer, diabetes and cardiovascular disease [9]. Indeed, the *Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases* stated that, by current evidence, an adequate amount of fiber in the diet is related to potential health benefits. In particular, they show their important role for preventing obesity, diabetes, cardiovascular diseases and various cancers [14].

Several studies underline the importance of choosing enriched-food and the use of pseudocereals [6,10]. Indeed, as underlined by Saturni and co-workers, pseudocereals are good sources of fibers with a fiber content ranges from 7 to 10 g/100 g. Comparing these with other plant foods, it is possible to observe that fiber content is higher in pseudocereal respect to other cereals and also to other plant foods such as fruits and nuts [6].

3.2. Vitamins

Usually, vitamins deficiencies are associated with untreated celiac disease due to malabsorption linked to villi atrophy. However, in some CD patients following a GF-diet, deficiencies of some vitamins may persist and this required a particular attention to the quality of the GF-diet [1,6,9,15].

Martin and co-workers demonstrated that CD patients showed significantly lower level of folic acid, vitamin C and vitamin B12 compared to DACH reference value and to NVSII data [12].

In addition, in a double blind placebo controlled multicentre trial, performed on 65 celiac subjects divided into two groups (supplemented with folic acid, cyanocobalamin and pyridoxine vs. no supplemented) the plasma total homocysteine (tHcy) was

Table 1
Nutritional deficiencies and excess of GF-diet.

	Country and year	Design	Study population	GF-diet nutritional evaluation method	Deficiencies	Excesses
Caruso et al. [1]	Italy, 2013	Review	–	–	Folate, Vit. B12, Vit. D	–
Saturni et al. [6]	Italy, 2010	Review	–	–	Dietary fiber, folate, niacin, Vit. B12	Total fat, saturated fat, energy intake
Zuccotti et al. [8]	Italy, 2013	Cross-sectional age-matched study	18 CD patients (mean age 7,6)	Food frequency questionnaire + 24-h dietary recall	Fat	Carbohydrate, energy intake
Penagini et al. [9]	Italy, 2013	Review	–	–	Vit. B, iron, folate, fiber, calcium, magnesium	Saturated fat, sugar, complex carbohydrates (high glycemic index)
Kupper et al. [10]	USA, 2010	Review	–	–	Vit. B, calcium, Vit. D, iron, zinc, magnesium, fiber	Lipids
Wild et al. [11]	UK, 2010	Observational study	139 CD patients	Validated 5-day food diary	Magnesium, iron, zinc, manganese, selenium, folate	Sugar
Martin et al. [12]	Germany, 2013	Observational Study	88 CD patients aged 45-80	7-day food diary + food questionnaire	Fiber, Vit.B, Folic Acid, Magnesium, Iron	Lipids
Mariani et al. [13]	Italy, 1998	Case–control study	47 CD adolescent patients	3-Day alimentary record	Calcium, fiber, iron, carbohydrates	Proteins, lipids
Samasca et al. [15]	Romania, 2014	Review	–	–	Dietary fiber, Vit. D, magnesium	Sucrose, saturated fat, energy intake
Hallert et al. [16]	Sweden, 2009	Double blind placebo controlled multicenter trial	65 CD patients aged 45–64	Randomized daily dose of 0.8 mg of folic scid, 0.5 mg Cyanocobalamin, 3 mg Pyridoxine or Placebo for 6 months	Vitamins status, Vit. B	–
Hallert et al. [19]	Sweden 2002	Observational study	30 CD patients (mean age 55, range 45–64)	Measure of total plasma homocysteine level + 4-day food record	Vitamins, Vit. B12	–
Grace-Farfaglia [21]	USA, 2015	Systematic review	–	–	Iron, Folate, Vit. B12, Vit. D, Vit. K, calcium, magnesium	–
Shepherd et al. [27]	Australia, 2013	Observational study	55 CD patients on GFD from more than 2 years + 50 newly diagnosed CD patients	7-Day food intake questionnaire	Dietary fiber, thiamine, folate, Vit. A, magnesium, calcium, iron, zinc	–
Öhlund et al. [28]	Sweden, 2010	Observational study	30 children aged 4–17 with CD on GFD	5-Day food record	Fiber, Vit. D, magnesium, selenium	Sucrose, saturated fat
Theethira et al. [29]	USA, 2014	Review	–	–	Dietary fiber, iron, Vit. B	Fats
Thompson et al. [31]	USA, 2005	Observational study	47 CD patients	3-Day self-reported food records	Iron, calcium, fiber	–

measured as marker of B vitamin status in addition to the general well-being. The study showed both the normalization of tHcy levels and a better situation of well-being in supplemented group [16].

As indicated by Penagini and co-workers, fish, meat, fruit and vegetables represent important sources of mineral in diet. So, due to the possible micronutrient deficiencies associated with GFPs, people with CD are recommended to consume an appropriate amount of these foods, above all fruit and vegetables that are also low in energy and rich in vitamins [9].

The intake of at least five portions of fruit and vegetables a day is fundamental and particularly applies to people with CD, indeed they contains antioxidant substances that have protective roles against problems associated with oxidative damage [1,17,18]. Deficiencies associated with GF-diet are related above all to folate, vitamin B12 and vitamin D [19]. Hallert and co-workers studied a group of 30 celiac patients and found that over 10 years of GF-diet a poor vitamins status was present. In particular, evaluating the total plasma homocysteine value and related plasma vitamins levels, they observed significant higher levels of total plasma homocysteine in CD patients compared to general population. Moreover, investigating the daily intake of vitamins through a 4-day food record, a lower intake of folic acid and Vit. B6 was found [19].

This lower intake can also be related to certain gluten-free cereal products. Some studies demonstrate that these products contain lower amounts of folate compared to their gluten-containing counterparts [9,19].

Hallert and co-workers suggest that routine folate measurements and supplementation should be recommended to those who have folate deficiency [16].

For these purposes, in agreement with Saturni, naturally gluten free products should be taken under consideration. Quinoa and amaranth contains a higher amount of folic acid, 78.1 μg/100 g and 102 μg/100g respectively, in comparison to wheat (40 μg/100 g). Moreover, these cereals are good sources of vitamins (riboflavin, vitamin C and vitamin E). Furthermore, gluten-free products are now being fortified with vitamins and minerals thanks also to the growing interest on improve the nutritional quality of GF-diet products by companies [6].

In CD patients malabsorption and inflammation contribute to a low bone mineral density (BMD) [20] (Table 2).

Indeed, Grace-Farfaglia reported that it is possible to find low BMD conditions in approximately 75% of newly diagnosed patients with CD. Moreover, celiac patients have a risk for bone fractures 40% higher than non-affected population [21].

Table 2
BMD (body mass density) in CD patients.

	Country and year	Design	Study population	Method	Outcomes
Pantaleoni et al. [20]	Italy, 2014	Prospective study	175 CD patients	Evalutation of BMD with DXA (Dual X-ray absorptiometry) at point 0 (newly diagnosed) and after 1 year of GF-diet	Significant improvement in lumbar spine and femoral neck BMD with GF-diet
Grace-Farfaglia [21]	USA, 2015	Review	–	–	75% of newly diagnosed patients with CD have low BMD. Celiac patients have a 40% greater risk for bone fracture compared to a non-affected population matched by age and gender
Sdepanian et al. [22]	Brazil, 2003	Case–control study	30 Asymptomatic CD patients (13 adolescents and 17 children) on a GF-diet, and 23 healthy subjects	Lumbar spine BMD food diaries for nine non-consecutive days Laboratory tests to evaluate calcium balance	Significantly lower BMD on adolescents than control group. High percentages of magnesium, calcium, and phosphorous deficiencies on CD patients' diets
Krupa-Kozak [23]	Poland, 2013	Review	–	–	GF-diet rarely normalizes BMD in adulthood Nutritional supplementation should be considered for CD patients
Lucendo et al. [25]	Spain, 2013	Review	–	–	Low body mass density Treatment of low BMD in CD should comprise gluten-free diet, calcium and vitamin D supplementation

Diet plays a crucial role in proper bones mineralization. Pantalleoni and co-worker demonstrated that 1 year of GF-diet leads to a significant improvement in lumbar spine and femoral neck mineral density [20].

Unfortunately, the only exclusion of gluten from the diet does not always normalize bone mineral density and GF-diet often results unbalanced in terms of calcium and Vit. D [1].

In this regard, several surveys reported that CD patients consume a level of calcium and vitamin D lower than the recommended one [1,6,9].

Even if, Caruso and co-workers reported that in most cases, Vit. D and calcium levels normalize leading to an improvement in BDM following 1–2 years of GF-diet [1]. Several studies showed that particular groups (i.e. children, women postmenopausal) are susceptible to low BMD even during GF-diet [1,21].

One study carried on by Sdepanian and co-workers demonstrated that adolescents with CD have a mean BDM was significantly lower than the control groups, moreover they showed an high percentages of magnesium, calcium, and phosphorous deficiencies [22].

In postmenopausal women, long-term Vit. D and calcium supplementation is still under discussion.

Some studies demonstrated that this kind of supplementation prevents further bone loss and improves BMD [1]. As underlined by Kozak, a GFD rarely normalizes BMD in adulthood, therefore, nutritional supplementation could be important for patients with CD [23].

There is also evidence that a combination of a GF-diet and vitamin D supplementation is effective in improving osteomalacia-related symptoms and normalizing calcium levels [1].

On the other hand, Mautalen and co-workers showed that calcium and vitamin D supplementation for a 12-month period did not provide additional benefit to that obtained by a GF-diet alone on BMD normalization [1,24].

Lucendo and Manzanares stated that low BMD in CD can be treated with GF-diet and supplementation of calcium and Vit. D, even if the effects have not been assessed yet and GF-diet is still considered to be the most rational treatment approach [25].

3.3. Minerals

As several studies have demonstrated, GF-diet could be poor in minerals [1,6,9,15,26].

Shepherd and Gibson studied nutritional inadequacies of GF-diet, it was found that more than 1 in 10 patients presents an inadequate intake of minerals, in particular magnesium, calcium in both sexes, zinc in male and iron in women [27].

Martin and co-workers demonstrated that the intake of micronutrient of male and female adult patients was significantly lower in comparison to NVSII especially for magnesium and iron [12].

Ohlund and co-workers assessed dietary intakes of nutrient in children and reported that CD children's diet follow the same trends as healthy children, in particular they reported a higher intake of simple sugars and saturated fat but a lower intake of fiber, Vit. D and magnesium [28].

One of the most common extra-intestinal manifestation of CD is iron deficiency anemia that can be found in 28–50% of patients at time of diagnosis and it is mainly related to malabsorption [29].

Annibale et al. stated that GF-diet is able to normalize the histological alterations of the intestinal mucosa and as a consequence to lead to a recovery from anemia that occurs in 6–12 months.

Nevertheless, after the healing of the small intestinal mucosa the repletion of iron stores may require a considerable amount of time (6–12 months) [1,30].

In this regard, it results very important to recommended CD patient to consume foods naturally gluten free and rich in iron as meat, vegetables and to carefully read food label of GF products to evaluate iron content.

Among minerals, different studies reported that zinc and magnesium can be deficient in GF-diet [1,6,26].

Zinc is an essential trace element involved in numerous reactions and biochemical functions. Zinc deficiency can affect protein synthesis and leads to growth arrest.

Magnesium is the main divalent intracellular cation essential for several enzymatic functions (e.g. DNA transcription and replication, mRNA translation, ionic pumps, and calcium channel function). Magnesium plays also a key role in the metabolism of proteins, nucleic acids, glucose, fats, and transmembrane transportation [1]. Several studies reported that zinc and magnesium levels in CD patients are improper above all in newly diagnosed [9,12,28]. A study conducted by Wild and co-workers compared data obtained from a 5-day food diary of 93 CD patients with National Diet and Nutrition Survey of Adults and the UK Women's Cohort Study (UKWCS) data.

Comparing the intake of micronutrients, in particular iron, magnesium, selenium, zinc and folate, it was found that in women

it was lower than in the control group. Moreover, in CD men, the achievement of magnesium and selenium RNI was present in a very low percentage [11].

Caruso et al. reported that zinc deficiency resolves usually after 1 year of a strict GF-diet, and long-term supplementation is not needed [1].

In treated patients can be encountered a magnesium deficiency linked probably with low-magnesium concentration of gluten-free cereal products [1].

As mentioned before, several studies reported that CD patients can easily have an inadequate intake of calcium, and Vit. D [6,13,19,26,31].

Sources of minerals and trace elements are both animal and vegetable foods. Some minor cereals and pseudo-cereals such as amaranth and quinoa have a mineral content that is twice the common cereals [6].

Furthermore, another study reported that minerals and trace elements are also contained in a significant amount in pseudo-cereals, in which the content can be twice as high as in other cereals. For example, in teff, iron and calcium contents (11–33 mg/100 g and 100–150 mg/100 g, respectively) are higher than those of wheat, barley, sorghum and rice [9].

3.4. Macronutrients

Macronutrients and energy intake is usually inadequate in CD patients not only at the diagnosis but also during GF-diet [1,6,8,9,27].

This could be related to the focus on the avoidance of gluten that often leaving back the importance of nutritional quality of the choice.

Indeed, Zuccotti et al. reported that 36.3% of the daily total energy intake is related to commercially available gluten-free products [8]. As is known, gluten free products usually have a greater carbohydrate and lipid (above all saturated fatty acids) content than their gluten counterpart [9].

The importance of minor cereals and pseudo-cereals is now increasing as they have been better characterized demonstrating that they are a good source of macronutrients such as carbohydrates and proteins, but also of vitamins and minerals [6].

Moreover, talking about carbohydrates, a key aspect is the glycemic index (GI) and the glycemic load (GL) of the meal.

It was demonstrated that the obesity risk is increased in CD people on GF-diet because of the high glycemic index of the gluten-free diet [32].

Comparing the nutritional composition of GF breads and their normal counterpart, a high glycemic index was found in GF-products (estimated between 83.3 and 96.1 *vs.* 71 for white wheat flour bread). Moreover, protein content was low with an increase of fat [9,33].

Talking about proteins, in GF-diet usually the most common source is animal food. However, several studies reported that some minor cereals and pseudo-cereals have a protein content higher than the common cereal. Moreover, the limiting amino acid, the lysine, was found in higher amount above all in pseudo-cereals as also arginine and histidine (essential for children) [6,7].

GF-products are usually richer in fat than their counterparts [9].

As it is known, the intake of monounsaturated and polyunsaturated fats should be preferred as they are associated with reduced cardiovascular disease risk [34].

It is crucial that CD patients pay attention to food label and to macronutrients content, in particular fat [3].

In pseudo-cereals the lipid content could be considered high if compared with other cereals but they are characterized by a higher content of unsaturated fatty acids [6].

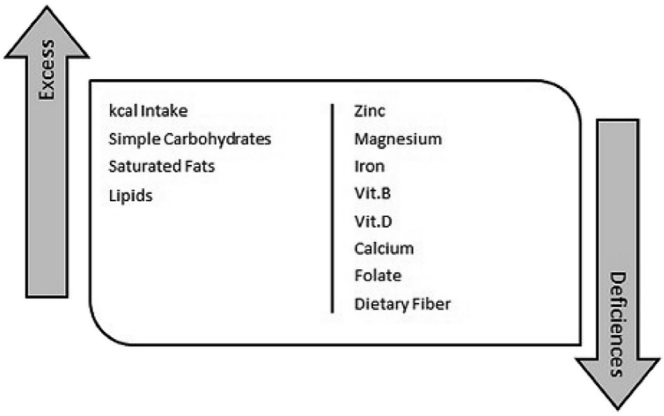

Fig. 2. Common nutrition inadequacies in GF-diet.

4. Conclusion

Analyzing the nutritional value of the GF-diet, it is common to identify remarkable inadequacies in terms of both macro- and micronutrients (Fig. 2).

In particular, it is observed a decrease in vitamins and minerals with an increase of obesity risk due to the high glycemic index of the gluten-free diet and the high content of saturated lipids.

Nutrient deficiencies, particularly low levels of fibers, folate, vitamin B12, vitamin D, calcium, iron, zinc and magnesium can persist in some subsets of treated CD patients.

In order to monitoring the health status and optimize the dietary plan of celiac patients on GF-diet, an annual screening for nutrient status results to be fundamental. Moreover, alimentary education should become part of the therapeutic pathway to understand the importance of labels, choice of food and combination of macro and micronutrients. Furthermore, the dietary-therapeutic approach should encourage the use of naturally gluten free products such as pseudo-cereals that have showed to have good nutritional quality.

Conflict of interest

None.

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