Nutrient intakes in adult and pediatric coeliac disease patients on gluten-free diet: a systematic review and meta-analysis

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The composition of gluten-free diet for coeliac patients: a systematic review and meta-analysis

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Abbreviations: CD, coeliac disease; CI, confidence interval; EFSA, European Food Safety Authority; GFD, gluten-free diet; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis.

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ABSTRACT

Background

Coeliac Disease (CD) continues to rely on strict lifetime gluten-free diet (GFD) adherence to maintain healthy status. Many studies have assessed the GFD nutritional adequacy in terms of macro- and micronutrient, but no quantitative synthesis has been provided.

Aim

To assess the nutritional suitability of GFD followed by CD patients.

Methods

Systematic review occurred across PubMed, Scopus and Scholar up to March 2021, including full-text studies which assessed the composition of GFD followed by CD, in terms of macro- and/or micronutrients (absolute or percentage daily average). Random-effect meta-analysis and univariable meta-regression was applied to obtain pooled estimates for proportions and influential variables on the outcome, respectively.

Results

Thirty-five studies with 1,984 patients were included. Overall, the daily energy intake was 2042 (CI 1921-2164) Kcal with 48.3% (CI, 46.2-50.4%) from carbohydrates, 15.4% (CI, 14.6-16.3%) from proteins, and 35.5% (CI, 34.1-37.0%) from fats. Of total fats, 13.5% (CI, 12.6-14.4%) were saturated fats. In particular, teenagers had the highest consumption of fats (95.2, CI 90.4-100.1 g), and adults insufficient dietary fibre intake (20.6 g, CI 15.6-25.6 g). Micronutrients were also poorly represented: calcium and vitamin D intakes were insufficient in children, iron intake was scanty in pediatric age and in women, whereas magnesium was insufficient among all age groups.

Conclusions

GFD may expose CD patients to high fat and low essential micronutrients' intakes. Given GFD is a lifelong therapy, chronic nutritional imbalances may favor the occurrence of diseases (e.g. cardiovascular or bone disorders). GFD quality needs to be assessed on long-term follow-up.

Keywords: Gluten-free diet, coeliac disease, nutrition, composition.

INTRODUCTION

Coeliac disease (CD) is an autoimmune condition which entails chronic enteropathy and affects approximately 1% of the general population [1]. It is triggered by the ingestion of gluten in genetically predisposed individuals, and it is characterized by specific serological and histological findings [1]. Currently, the only effective therapy available is a strict lifetime adherence to a gluten-free diet (GFD), which leads to symptoms' remission and normalization of serological and histological patterns in most patients [1].

Owing to the prevalence of CD and to recent identification and widespread mass-media spread of the non-coeliac gluten sensitivity (NCGS) condition, which has been self-reported by up to 13% of the population [2], a significant proportion of people in industrialized countries are currently eating GFDs. However, consuming a balanced GFD is not always simple. Numerous studies have analyzed the actual composition of GFDs followed by CD patients and have found mixed results [3,4]. Some studies, in particular, blamed GFD to be unbalanced toward high fat intake and especially saturated fats [5,6]. This aspect might increase cardiovascular risk throughout patients' life [7]. This is especially true for pediatric patients who may start GFD at a very early age.

The information on gluten-free diets composition mostly come from single-center studies which often included a limited number of patients. At present, there were no attempts to summarize these data.

Therefore, the primary aim of this systematic review and meta-analysis was to comprehensively assess the absolute and relative composition in terms of macro and micronutrients of GFDs followed by adult and pediatric CD patients.

METHODS

The present systematic review was performed according to the guidelines of the preferred reported items for systematic review and meta-analyses (PRISMA-P; see **Supplementary Table 1**) [8]. The methodological quality of included studies was rated through the Newcastle-Ottawa scale [9], which was simplified to two items (i.e. representativeness of the exposed cohort and assessment of outcome) given the outcome of interest, i.e. the absolute and relative proportion of macro- and micro-nutrients in GFD.

Literature search and study selection

A comprehensive literature search was independently performed by three investigators (MG; LF; US) up to March 2021 by querying PubMed, Scopus, and Scholar using controlled vocabulary, medical subject headings (MeSH) terms, and keywords including “gluten-free diet”, “composition”, “nutrition”, and “coeliac disease”. The PubMed search string was: ((diet, gluten free[MeSH Terms] OR (composition[All fields] OR (nutrition[All fields]) AND (coeliac disease[MeSH Terms]).

We included studies on coeliac patients on gluten-free diet providing data on the percentage or absolute average daily intake of nutrients, i.e. carbohydrates, proteins, fats, saturated fats, fibers, sodium, calcium, magnesium, and vitamin D. Prospective and retrospective studies, published in English language were considered for inclusion. We excluded studies published in abstract form.

Titles and abstracts were first screened. Therefore, authors assessed the full text of potentially relevant screened studies, and included those satisfying the inclusion criteria. Disputes were resolved by collegial discussion. The reason for excluding studies from the selection process was recorded.

Data extraction

The same three authors who performed the search (MG; LF; US) extracted data from included study on a pre-specified datasheet. The following data were extracted from each study: design and country, numbers of centers involved, study size, patients' demographics (i.e. mean age and proportion of male sex), absolute and relative macro- and micro-nutrients intake.

Outcome assessment

The primary outcome was the percentage average daily intake of nutrients provided by the GFD. The key secondary outcome was the absolute average daily intake of energy (Kcal) and nutrients for the GFD, according to age groups as defined by the dietary recommendations for children by the American Heart Association (i.e. <9, 9-13, 13-18, and >18) [10]. For the purpose of the analyses, data on absolute energy intake expressed as KJ or MJ were converted into Kcal. Values expressed as mmol were converted into mg or g, as appropriate. Studies providing outcome data separately for males and females were included on a *per*-arm basis.

Statistical analysis

Means were pooled through a random effects model, and presented as point estimate with 95% confidence interval (CI). Statistical heterogeneity was computed through the I^2 statistic, defined as high if I^2 >50%, and tested through the Q^2 test (statistical significance set as $p<0.1$). In order to explore possible sources of heterogeneity, we performed meta-regression and subgroup analyses. Variables potentially impacting on the outcomes were selected *a priori* and included: publication year, Country, study design, and mean patients' age. In meta-regression analysis, we computed the R^2 statistic, being the proportion of variance explained by the model for each potential predictor. In subgroup analysis, we compared subsets through a likelihood ratio test to assess for significant differences. In order to investigate for publication bias, we drew a funnel plot and performed the Egger regression test. All the analyses were performed with R statistical software [11] with package *metafor* [12].

RESULTS

Study characteristics and quality

The literature search yielded 3,512 articles (**Figure 1**). After applying the inclusion criteria, 35 published articles were included in the systematic review, for a total of 1,984 patients with coeliac disease on gluten-free diet. Patients mean age ranged from 8 to 59 years, whereas 32-94% were females. Twenty-seven studies with 1,670 patients were performed in Europe, and 8 studies with 314 patients were performed outside Europe. Twenty-one studies including 1,022 patients were retrospective in design, whereas 14 studies with 962 patients were prospective. The publication year ranged from 1994 to 2020. The mean years on gluten-free diet of included subjects ranged from 1 to 21. Details on the baseline characteristics of the included studies and on the main outcomes are summarized in **Table 1**, **Figure 2** and **Figure 3**, respectively.

Percentage composition of gluten-free diet

Main outcomes are reported in **Figure 2**. Seventeen studies including 1,213 coeliac subjects on GFD reported data on the daily average percentage intake of carbohydrates. The pooled result was 48.3% (CI, 46.2-50.4%) with high heterogeneity (I^2 = 97%) (see **Supplementary figure 1**). Seventeen studies including 1,162 coeliac subjects on GFD reported data on the daily average percentage intake of proteins. The pooled result was 15.4% (CI, 14.6-16.3%) with high heterogeneity (I^2 = 97%) (see **Supplementary figure 2**). Eighteen studies including 1,250 coeliac subjects on GFD reported data on the daily average percentage intake of fats. The pooled result was 35.5% (CI, 34.1-37.0%) with high heterogeneity (I^2 = 96%) (see **Supplementary figure 3**). Fourteen studies including 1,074 coeliac subjects on GFD reported data on the daily average percentage intake of saturated fats. The pooled result was 13.5% (CI, 12.6-14.4%) with high heterogeneity (I^2 = 98%) (see **Supplementary figure 4**).

Absolute composition of gluten-free diet

Main outcomes are reported in **Figure 3**. The overall pooled average daily energy intake was 2042 (CI 1921-2164) Kcal with high heterogeneity (I^2=97%). This figure was 1893 (CI 1462-2325) Kcal for children <9 years old, 1785 (CI 1645-1925) Kcal for children aged 9-13, 2198 (CI 2064-2332) Kcal for adolescents between 13 and 18 years old, and 2178 (CI 2009-2348) Kcal for adults (see **Supplementary figure 5**). The overall pooled average daily carbohydrate intake was 246.3 (CI 231.6-260.9) g with high heterogeneity (I^2=95%). This figure was 252.7 (CI 192.9-312.6) g for children <9 years old, 214.1 (CI 199.8-228.3) g for children aged 9-13, 240.4 (CI 216.1-264.7) g for adolescents between 13 and 18 years old, and 259.3 (CI 237.7-280.9) g for adults (see **Supplementary figure 6**). The overall pooled average daily protein intake was 76.6 (CI 78.6-90.1) g with high heterogeneity (I^2=98%). This figure was 63.3 (CI 58.3-68.2) g for children <9 years old, 63.8 (CI 57.6-70.1) g for children aged 9-13, 80.3 (CI 72.0-88.5) g for adolescents between 13 and 18 years old, and 84.4 (CI 78.6-90.1) g for adults (see **Supplementary figure 7**). The overall pooled average daily fat intake was 79.0 (CI 73.1-84.9) g with high heterogeneity (I^2=96%). This figure was 63.9 (CI 60.2-67.5) g for children <9 years old, 72.3 (CI 64.9-79.7) g for children aged 9-13, 95.2 (CI 90.4-100.1) g for adolescents between 13 and 18 years old, and 81.0 (CI 72.2-89.9) g for adults (see **Supplementary figure 8**). The overall pooled average daily saturated fat intake was 26.3 (CI 19.9-32.7) g with high heterogeneity (I^2=99%). This figure was 14.7 (CI 6.7-22.8) g for children <9 years old, 26.2 (CI 22.2-30.2) g for children aged 9-13, 28.5 (CI 26.2-30.8) g for adolescents between 13 and 18 years old, and 32.3 (CI 27.5-37.1) g for adults (see **Supplementary figure 9**).

The overall pooled average daily calcium intake was 874.4 (CI 787.4-961.5) mg with high heterogeneity (I^2=96%). This figure was 695.4 (CI 511.1-879.7) mg for children <9 years old, 737.9 (CI 621-854.8) mg for children aged 9-13, 756.2 (CI 557.4-955.1) for adolescents between 13 and 18 years old, and 985.4 (CI 935.4-1035.3) mg for adults (see **Supplementary figure 10**). The overall pooled average daily vitamin D intake was 2.9 (CI 2.2-3.6) mcg with high heterogeneity (I^2=95%). This figure was 0.8 (CI 0.5-1.1) mcg for children <9 years old, 3.6 (CI 2.5-4.6) mcg for children aged 9-13, 1.6 (CI 1.3-1.9) mcg for adolescents between 13 and 18 years old, and 3.1 (CI 2.6-3.6) mcg for adults (see **Supplementary figure 11**). The overall pooled average daily iron intake was 10.8 (CI 8.9-12.6) mg with high heterogeneity (I^2=99%). This figure was 6.4 (CI 5.3-7.5) mg for children <9 years old, 7.2 (CI 5.7-8.8) mg for children aged 9-13, 8.7 (CI 6.3-11.2) mg for adolescents between 13 and 18 years old, and 13.6 (CI 12.2-15) mg for adults (see **Supplementary figure 12**). The overall pooled average daily sodium intake was 1989.1 (CI 1381.2-2597) mg with high heterogeneity (I^2=98%). This figure was 1531.6 (CI 886-2177.1) mg for children aged 9-13, 1419 (CI 1272.7-1565.3) mg for adolescents between 13 and 18 years old, and 2989.5 (CI 2484.1-3494.9) mg for adults (see **Supplementary figure 13**). The overall pooled average daily magnesium intake was 261.4 (CI 204.9-317.8) mg with high heterogeneity (I^2=99%). This figure was 104.9 (CI 71-138.8) mg for children <9 years old, 147.9 (CI 114.6-181.1) mg for children aged 9-13, 184.6 (CI 170.4-198.8) mg for adolescents between 13 and 18 years old, and 336.9 (CI 296.1-377.8) mg for adults (see **Supplementary figure 14**). The overall pooled average daily fiber intake was 16.3 g (CI 14.1-18.6) with high heterogeneity (I^2=98%). This figure was 12.6 (CI 11.4-13.7) g for children <9 years old, 14.2 (CI 12.3-16.1) g for children aged 9-13, 15.6 (CI 11.5-19.7) g for adolescents between 13 and 18 years old, and 20.6 (CI 15.6-25.6) g for adults (see **Supplementary figure 15**).

Sensitivity analysis and publication bias

The impact on heterogeneity for study design, publication year, Country, and proportion of male patients is shown in **Table 2** and **Table 3**. Gluten-free diets provided in Northern Europe contained more saturated fats, both as relative and absolute quantity, and more calcium in absolute terms. Throughout years of publication, the absolute quantity of carbohydrates, sodium, calcium, and iron significantly decreased. Males consumed a higher relative proportion of saturated fats than females.

The methodological quality of included studies was judged as low, mostly due to retrospective design and unspecified adherence of patients to GFD. Study quality evaluation is detailed in **Table 4**. No significant publication bias was detected for the primary outcome (i.e. the percentage average daily intake of nutrients provided by the GFD), according to both visual inspection of funnel plots (see **Figure 4**) and regression test (p=0.547, p=0.333, p=0.952, and p=0.963 for carbohydrate, protein, fat, and saturated fat intake respectively).

DISCUSSION

In the present systematic review and meta-analysis, we found that GFD can expose to qualitative and quantitative variability in several nutrients. As the majority of studies were carried out in Europe, we decided to compare the data to the recommended intakes provided by the "Dietary Reference Values for nutrients - Summary Report" [13] of the European Food Safety Authority (EFSA), but also the "2020-2025 Dietary Guidelines for Americans" [14] of the U.S. Dept. of Health and Human services and U.S. Dept. of Agriculture were considered. The GFDs were abundant in fats and especially saturated fats, whereas fiber intake was insufficient. Further, calcium intake was inadequate among pediatric age groups, whereas vitamin D intake was scarce for both children and adults. Protein intakes were overrepresented in all patients. Most of these results are not unusual even in the general population living in Western countries [15]. What is peculiar is that GFD is a lifelong requirement for CD patients and this impies that long-term exposures to hazardous eating habits may lead to health consequences later in life. This is a potential source of harm if wrong eating habits take place early in life and are perpetuated throughout it.

Our comprehensive analysis showed that GFDs tend to display a reversal trend in carbohydrate content, leaning towards the lower end of the EFSA recommended range, while being rather rich in fats as represented by more than 40% of the daily caloric intake in some studies [16–18]. This shift is a mimic of the high-fat (>35 E%) and low-carbohydrates (<50 E%) diet, whose long-term effects are unknown although some metabolic derangements potentially dangerous for the vascular system were identified due to chronic lipid profile unbalance and hyperhomocysteinemia [17-20]. When classified by age, absolute figures showed that teenagers consumed the largest quantity of total fat among all age groups. This excessive intake was confirmed when considering saturated fat, even though the whole picture showed that abundancy started since 9 years of age and progressively increased, peaking in adulthood. Such eating patterns set the stage for early atherosclerosis and other metabolic dysfunctions in adulthood [19], even though adequately powered follow-up studies are not available. The meta-regression analysis suggested that males seemed to consume a higher proportion of saturated fats than females. This result is compatible with the hypothesis that men are motivated by the “strong taste” and are more prone to eat fatty and junk food than women [24]. This motivation may be even stronger when GFD has to be followed: future studies may investigate this interesting association.

The dietary fibre intake was between 12.6 and 20.6 g/day among all age groups, being in range for all but adults according to EFSA [13]. More specifically, average fibre intake reached the 97% of EFSA recommendations in children below 9 years of age and 84% in those below 13 years. When considering the USDA guidelines [13], fibre intakes did not reach two-third of the recommendations due to more generous reference values in all age groups. It is not easy to introduce fibre when adhering to a GFD especially if people tend to stick to commercial products and do not use naturally gluten-free cereals. A recent population-based study in Sweden highlighted how the change from gluten-containing to gluten-free diet led to a different food selection in adolescents [25]. This attitude can be seen as a protective behaviour made by patients and their families to protect themselves and can be modified by a proper nutritional counselling. Changes in eating habits in youth may prevent the occurrence of non-communicable diseases, as low-fibre diets, on top of being associated with constipation [26] may be an indirect cardiometabolic risk factor and expose to overweight due to a less satiating effect of food [27].

Our study tried to expand previous isolated evidence showing that GFD may lead to micro-nutrient deficiencies [3]. In our analysis, calcium intake was acceptable in adults, while being insufficient especially in preadolescents and adolescents. Vitamin D dietary intake was also slightly insufficient among all age groups, being the lowest for children under 9 years who did not reached the 20% of the recommended intakes. These findings are relevant, as they may imply both general and specific consequences such as skeletal alterations with reduced peak bone and increased risk of atopy and autoimmunity [28]. On the opposite, it was encouraging the finding of an acceptable sodium intake in children and adolescents, peaking in adults. This result was unexpected as saturated fat and sodium are often combinedly present in most commercial food items. It can be argued that the more appropriate fibre intake in youth may have limited those food items. As dietary content of sodium has been linked to increased cardiovascular risk [29], positive reinforcements towards selection of healthier food should be part of the training at GFD start. Iron intake was particularly inadequate in pediatric age, while in adulthood it was in line with daily requirement. Thus, dietary iron deficiency determined by GFDs, along with folate or Vitamin B12 deficiencies can explain the persistence of anemia (which is one of the most recurrent extra-intestinal manifestation of CD) even after diagnosis [30]. As for magnesium intake, this was poor in all age groups according to EFSA recommended intakes.

Insightful hints come from the sensitivity analyses. First, Northern Europe countries yielded GFDs richer in saturated fats and calcium, as compared to Southern Europe. One explanation might be related to higher dietary content in butter and margarine in Northern Europe, as compared to higher consumption of olive oil in Southern Europe. Similar results could not be carried out in studies performed in the United States of America. Second, the absolute daily content in total calories tended to decrease over time. In details, carbohydrates, sodium, calcium and iron reductions were statistically significant in most recent studies. This may reflect a tendency towards healthier GFD diets, even though the iron and calcium reductions might be explained by a decline in consumption of dairy products and red meat in recent years [31]. Nonetheless, such data should be taken cautiously, as metaregression and subgroup meta-analysis generally yield exploratory and not confirmatory results.

Our meta-analysis has strengths and limitations. The quality of most included studies included was low, owing to the retrospective nature and the limited sample size. Most of them were performed in Europe. Dietary intake assessment was not carried out uniformly across all studies, and not all studies reported exhaustive information on patients' characterization. Moreover, the analysis stratified by age groups was based on the mean age of included subjects as reported in the studies. Furthermore, the studies covering the youngest children were only two. Therefore, such results are exploratory and not confirmatory. Taken altogether, such limitations clearly affect the degree of confidence in our estimates. However, we followed the PRISMA recommendations [8] for conducting systematic reviews and meta-analyses. Further, our study is the first comprehensive overlook on gluten-free dietary patterns actually followed by CD patients belonging to all age groups, highlighting how such diets can be unbalanced.

In conclusion, GFDs can expose to nutrient unbalance with potential health consequences in the long run. Whether it is due to a specific nutrient or the whole diet is still to be determined. As recent evidence pointed out, the second option may be more reliable, but more studies and performed worldwide are needed [32]. Given that life-long adherence to a GFD is the only treatment for CD, a thorough nutritional guidance must be provided at any age but especially during youth, when disease prevention is possible and mandatory.

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Figures

Fig 1. Main steps performed in the study

Fig 2 Overall macronutrients' distribution

Fig 3 Composition of gluten-free diet in the analyzed studies

Fig 4 Funnel plot visual inspection of average daily intakes of nutrients (A. Carbohydrates; B. Proteins; C. Fats; D. Saturated fats)