Introduction

Celiac disease (CD) is a chronic immune-mediated disorder characterized by malabsorption and growth retardation in children as a result of gluten exposure. In CD treatment, clinical, histological and serological improvement is possible with gluten-free diet. Thus, we aimed to assess the vitamin and trace element levels of CD patients in regard to their compliance with gluten-free diet. Materials and methods. In our study, 77 patients diagnosed with CD were evaluated retrospectively. All individuals were assessed with Marsh classification histopathologically and surveyed when they follow a gluten-free diet. Demographic features, age of disease onset, physical examination findings, anthropometric measurements and laboratory findings along with clinical and laboratory outcomes of patients after a gluten-free diet were compared between compliant to diet and non-compliant to diet groups. Results. A total of 77 individuals, 48 females and 29 males with a diagnosis of CD and mean age of 9.81 ± 4.73 years on admission, were required in our study. Patients were mostly found to have Marsh type 3a (n = 22) and Marsh type 3b (n = 20) histopathologically. The results of serological screening revealed that 40.3% of people (n = 31) were compliant with diet whereas 59.7% (n = 46) — non-compliant. Non-compliant group had significantly lower mean vitamin B12, vitamin D, folate, zinc and selenium levels compared to compliant group (p = 0.000; 0.000; 0.000; 0.000 and 0.031, respectively). In addition, a significantly higher mean serum total IgA level was detected in non-compliant group in comparison to compliant group (p = 0.027). Conclusions. High efficacy of gluten-free diet in correcting nutritional insufficiencies and deficiencies was shown. Thus, there is no doubt that informing patients and their families about lifelong gluten-free diet in detail is beneficial although this treatment contains many social and practical difficulties.

Keywords: celiac disease; gluten-free diet; gluten; malabsorption; vitamin D; vitamin B12

Impact of compliance to a gluten-free diet on vitamin and trace element deficiencies in celiac patients

Abstract. Background. Celiac disease (CD) is a chronic immune-mediated disorder characterized by growth retardation and malabsorption related to mucosal damage and inflammation of small intestine in genetically predisposed people as a result of gluten exposure. In CD treatment, clinical, histological and serological improvement is possible with gluten-free diet. Thus, we aimed to assess the vitamin and trace element levels of CD patients in regard to their compliance with gluten-free diet. Materials and methods. In our study, 77 patients diagnosed with CD were evaluated retrospectively. All individuals were assessed with Marsh classification histopathologically and surveyed when they follow a gluten-free diet. Demographic features, age of disease onset, physical examination findings, anthropometric measurements and laboratory findings along with clinical and laboratory outcomes of patients after a gluten-free diet were compared between compliant to diet and non-compliant to diet groups. Results. A total of 77 individuals, 48 females and 29 males with a diagnosis of CD and mean age of 9.81 ± 4.73 years on admission, were required in our study. Patients were mostly found to have Marsh type 3a (n = 22) and Marsh type 3b (n = 20) histopathologically. The results of serological screening revealed that 40.3% of people (n = 31) were compliant with diet whereas 59.7% (n = 46) — non-compliant. Non-compliant group had significantly lower mean vitamin B12, vitamin D, folate, zinc and selenium levels compared to compliant group (p = 0.000; 0.000; 0.000; 0.000 and 0.031, respectively). In addition, a significantly higher mean serum total IgA level was detected in non-compliant group in comparison to compliant group (p = 0.027). Conclusions. High efficacy of gluten-free diet in correcting nutritional insufficiencies and deficiencies was shown. Thus, there is no doubt that informing patients and their families about lifelong gluten-free diet in detail is beneficial although this treatment contains many social and practical difficulties.

Keywords: celiac disease; gluten-free diet; gluten; malabsorption; vitamin D; vitamin B12

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does not develop in absence of allelle coding HLA-DQ2 or HLA-DQ8 proteins while presence of that allelle does not always suffice for the disease to emerge. In addition, a mild gluten exposure of celiac patients may lead to mucosal damage, however clinical, histological or even serological (TGA/G) improvement is likely after a gluten-free diet [1, 2].

Thus, we purposed to analyze the vitamin and trace element levels of patients we followed up with a diagnosis of CD, in regard to dietary compliance after a gluten free diet (GFD) therapy.

Materials and methods

This study was conducted in pediatric gastroenterology outpatient clinics of Istanbul Training and Research Hospital between January 2017 and June 2018 in accordance with the local ethics committee approval of 07.01.2019/201-01-24.

A total of 77 patients being between 1 to 18 years of age diagnosed with CD who have no other chronic illness leading to additional malabsorption were investigated retrospectively. Demographic features of patients, age of disease onset, physical examination findings, anthropometric measurements and laboratory findings along with clinical and laboratory outcomes of patients after a GFD were compared between compliant to diet and non-compliant to diet groups. Biochemical analysis of serum derived from patients was performed with the Abbott Architect c8000 autoanalyzer (Abbott Diagnostics, Illinois, USA) by using electrochemiluminescence method whereas serum 25-hydroxyvitamin D3, vitamin B12, and folate levels were measured and reported by using test kits compatible with chemiluminescence method in Roche Cobas 6000 (Tokyo, Japan) immunological autoanalyzer device.

Serological screening for CD was carried out with enzyme-linked immunosorbent assay by using anti tissue transglutaminase antibodies (TGAb). All patients were also screened with immunoﬂuorescence method (INOVA, San Diego, Calif., USA) for anti-endomysial antibodies, umbilical cord and fluorescein isothiocyanate conjugated anti-human IgA. To detect serum IgA deficiency, total serum IgA levels were assessed with nephelometric method. In addition, presence of HLA antigens (DQ2 and DQ8) were investigated by using polymerase chain reaction (PCR) technique on genomic DNA isolated from peripheral blood of all patients. Patients with positive TGA and EMA antibodies got a definite diagnosis after the endoscopic biopsy of all patients. Patients with positive TGA and EMA antibodies were noted in non-compliant group compared to compliant group (p = 0.381). Additionally, overall mean age of cases at diagnosis was 2.28 ± 2.37 years (range of distribution: 0–11 years) (Table 1). A total of 57 patients from our study population who underwent gastroduodenoscopy and intestinal biopsy were investigated histopathologically which revealed that 22 of those had Marsh type 3a, 20 Marsh type 3b, 13 Marsh type 3c and two Marsh type 1 and 2 disease.

As a result of serological screening in our study carried out upon TG IgA, TG IgG, EMA-IgA and EMA-IgG levels, 40.3 % of cases (n = 31) were compliant to diet and the remaining 59.7 % (n = 46) were non-compliant. In the non-compliant group, mean serum IgA level was 137.94 ± 66.02 mg/dl, vitamin B12 level 328.43 ± 167.22 pg/ml, vitamin D level 21.70 ± 13.38 ng/ml, folate 9.46 ± 5.37 mg/l, zinc 70.61 ± 11.25 µg/dl and selenium 42.83 ± 8.47 µg/dl. Conversely, mean serum total IgA level was found to be 109.55 ± 64.17 mg/dl, vitamin B12 level 496.71 ± 179.94 pg/ml, vitamin D 31.24 ± 10.90 ng/ml, folate 15.03 ± 5.08 mg/l, zinc 82.32 ± 9.84 µg/dl and selenium 49.91 ± 5.77 µg/dl in the group compliant to diet. Hence significantly higher mean serum total IgA levels were observed in non-compliant group compared to compliant group (p = 0.027). In addition, significantly lower mean serum vitamin B12, vitamin D, folate, zinc and selenium levels were noted in non-compliant group compared to compliant group (p values; 0.000; 0.000; 0.000; 0.000 and 0.031, respectively).

Discussion

CD developed into a crucial global health issue as its prevalence increases in recent years and its atypical and asymptomatic presentations suggest presence of many undiagnosed cases. Accordingly, current data show that children and adolescents with a higher mean age compared to that of past reports are diagnosed with CD [6]. Predominance of female gender in CD was also reported many times [7]. N.R. Reilly et al. reported a mean age of 8.3 years based on 318 pediatric patients of whom 57 % were female and diagnosed with CD histopathologically [8]. E. Lurz et al. also reported a group of 94 pediatric patients at a mean age of 6.8 years diagnosed with CD, which displayed a female predominance of 62 % [9]. Consistent with the published data, female/male ratio in our study was calculated as 1.65 and the mean age on admission was found to be 9.81 ± 4.73 years.

Celiac patients frequently face nutritional deficiencies resulting from malabsorption of macro- and micronutrients induced by basal enteropathy. Micro-nutritional insufficien-
cies and deficiencies mostly comprise iron, zinc, copper, calcium and selenium elements accompanied by vitamin E, D, B12 and B6 [10]. Iron deficiency is so widespread in adult patients without a diagnosis of CD yet that it is worth to perform serological screening [11].

Systemic and neurological disorders may also develop in celiac patients without treatment, leading a decline in quality of life [12]. At the present day, most effective treatment for celiac patients is GFD whereby clinical symptoms and morbidity lessen along with a quick improvement in body weight, bone density and nutritional parameters [13]. For the efficacy of GFD, one should strictly avoid all products of wheat, rye and barley [14]. Since enteropathy may worsen even with as low as 50 mg of gluten, patients also have to abstain from products such as oat which may be contaminated with gluten although it is essentially gluten-free [15]. With an appropriate GFD, iron deficiency is corrected in 6–12 weeks and zinc deficiency in a few weeks [16].

S. Terlemez et al. investigated the influence of a 6 months GFD followed by 66 pediatric CD patients on their laboratory parameters. Researchers detected iron deficiency anemia in 36.6 % of patients, folate deficiency in 3 % and vitamin B12 deficiency in 1.5 %. By means of GFD, however, vitamin B12, and folate deficiencies were completely corrected and iron deficiency anemia significantly improved [17].

P. Rawal et al. randomized 134 patients with CD into two groups and treated them with GFD or GFD accompanied by zinc supplementation. While final plasma zinc levels in both groups were significantly increased compared to initial values, researchers concluded that this rise in zinc levels occurred solely due to GFD independent of supplementation [18]. Additionally, several neurological and thyroid disorders related to copper and selenium deficiency were reported in patients with CD from previous studies. After the GFD, serum copper and selenium levels were observed approaching the normal ranges despite a minimum improvement in neurological disturbance [19, 20].

E. Topal et al. reported the rate of vitamin D and zinc deficiency in 52 newly-diagnosed pediatric celiac patients as 51.9 % and 67.3 %, respectively [21]. Moreover, K. Öhlund et al. notified in their study that vitamin D absorption was significantly lower than required amount in 17 of 25 patients diagnosed with CD whereas none of the children being 12 years old and younger could achieve normal serum levels of vitamin D in this group [22]. In addition, M. Unubol et al. showed that vitamin D deficiency of celiac patients is corrected by taking vitamin D supplementation along with GFD therapy [23]. A. Dahele et al., on the other hand, detected vitamin B12 deficiency in 41 % of 39 patients with CD and folate deficiency in 31 %. After an 11-months GFD therapy, normal serum vitamin B12 and folate levels were achieved in all patients except one whose data were unavailable [24]. Correspondingly, our study has also demonstrated a significantly lower mean serum vitamin B12, vitamin D, folate, zinc and selenium levels in non-compliant to diet group compared to compliant ones, supporting all these data.

**Conclusions**

High efficacy of GFD on CD was also shown in our results even if GFD treatment contains lots of social and practical difficulties due to low satisfaction and high costs for the patient and his family. Thus, it is undoubted that informing patients and their families in depth about lifelong GFD may contribute both to abate CD-related morbidity for patients’ safety and to use health resources productively.

**Conflicts of interests.** Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.
Вплив дотримання безглютенової дієти на дефіцит вітамінів і мікроелементів у хворих на целіакію

Резюме. Актуальність. Целіакія — хронічне захворювання імунного генезу, що характеризується затримкою росту та мальборообсягом, пов’язаною з пошкодженням слизової оболонки і запаленням тонкої кишки у генетично схильних людей. Ця хвороба спостерігається у відомих народів у всьому світі. Це стосується хворих з рядом відомих народів у всьому світі. Це стосується хворих з рядом відомих народів у всьому світі. Це стосується хворих з рядом відомих народів у всьому світі. Це стосується хворих з рядом відомих народів у всьому світі.

Целі дослідження. Визначити, що впливає на дефіцит вітамінів і мікроелементів у хворих на целіакію за умов дотримання безглютенової дієти. Матеріали і методи. Групи дослідження складалися з хворих на целіакію, які дотримувались безглютенової дієти. Дослідження проводилося в течіні 3 місяці. Результати: У хворих на целіакію, які дотримувалися безглютенової дієти, виявлено дефіцит вітамінів і мікроелементів. Заключення: Дотримання безглютенової дієти стимулює процеси розвитку і відновлення слизової оболонки тонкої кишки.

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середній вік яких становив 9,81 ± 4,73 року. Переважно у пацієнтів виявлені гістологічно за класифікацією Marsh типи 3а (n = 22) і 3б (n = 20). Результати серологічного скринінга показали, що у 40,3 % випадків (n = 31) хворі дотримувалися безглютенової дієти, тоді як у 59,7 % (n = 46) — не дотримувалися. У хворих цієї групи відзначалися вірогідно нижчі показники вмісту вітаміну B12, вітаміну D, фолатів, цинку та селену порівняно з групою хворих, які дотримувалися відповідної дієти (p = 0,000; 0,000; 0,000; 0,000 та 0,031 відповідно). Крім того, був виявлений вірогідно вищий середній рівень загального IgA в сироватці крові у групі хворих без дотримання дієти порівняно з групою хворих, які дотримувалися безглютенової дієти (p = 0,027). Висновки. Встановлено висока ефективність безглютенової дієти для корекції недостатності та дефіциту вітамінів і мікроелементів. Необхідно детально інформувати пацієнтів з целиакією та їх родини про неухильне пожиттєве дотримання безглютенової дієти, хоча дотримання такого харчування створює чимало соціальних і практичних труднощів.

**Ключові слова:** целиакія; безглютенова дієта; мальабсорбція; вітамін D; вітамін B12