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ACCIDENTAL EXPOSURE TO GLUTEN IS LINKED WITH MORE SEVERE DRY EYE DISEASE IN CELIAC DISEASE PATIENTS ON A GLUTEN-FREE DIET

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ABSTRACT

Dry eye disease is the most common condition in ophthalmology, which is particularly affecting people with health conditions having underlying inflammation and malnutrition in the pathology. One of these conditions is celiac disease.

We aimed to analyse the prevalence of dry eye symptoms and the quality of tear film in celiac disease patients following a gluten-free diet. This is the first stage research for the randomized clinical trial aiming to assess the effect of omega-3 fatty acid supplementation on the tear film quality and dry eye disease in celiac disease patients following a gluten-free diet (ClinicalTrials.gov ID NCT05825978). One hundred celiac disease patients following a gluten-free diet completed general questionnaire, modified Celiac Disease Questionnaire, and semi-quantitative food frequency questionnaire which included foods potentially contaminated with gluten i.e. risky foods. The presence of dry eye symptoms and the quality of the tear film were assessed with two objective (Schirmer test I and TBUT) and one subjective (OSDI test) measurement. Subjective and objective measures of dry eye were lower in celiac disease patients who consumed more risky foods. However, average values for all measurements did not fit the criteria for dry eye diagnosis, but point out the need to educate celiac disease patients of the risks posed on eye health with exposure to gluten, even accidental.

KEYWORDS: Celiac disease; gluten-free diet; accidental exposure to gluten; tear film quality; dry eye disease

INTRODUCTION

Celiac disease is an immune-mediated chronic disease of proximal parts of the small intestine that occurs in genetically predisposed people as a consequence of intolerance to gluten, protein fragments found in wheat, barley, rye and hybrids such as kamamute and triticale [Farrel JR & Kelly CP, 2002]. The prevalence is estimated to about 1% of global population, with significant variations

across the world [Makharia GK et al., 2022].

Classic form of celiac disease is most commonly manifested in children during the first two years of life, and typical symptoms include diarrhoea, flatulence, stomach ache, vomiting and weight loss [Makharia GK et al., 2022]. More studies show that the atypical symptoms of celiac disease are becoming more prominent in the popu-

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lation, and more people are diagnosed with various forms of the disease [Almallouhi E et al., 2017; Makharia GK et al., 2022]

The only effective treatment for celiac disease is a lifelong, strict, gluten-free diet, but patients face numerous challenges, especially with regard of getting access to safe, gluten-free products [Makharia GK et al., 2022]. Despite the interest for commercially available gluten-free products increased drastically [Food Industry Executive, 2019] primarily as a result of gluten-free products promoted as a weight-loss strategy, nutritional quality of these products is often debated [Rostami K et al., 2017]. This is especially concerning given that people who follow a strict gluten-free diet for a minimum of 2 years face numerous nutritional deficiencies, especially zinc, iron, potassium, vitamin D, magnesium and vitamin B12 [Rondanelli M et al., 2019]. Additionally, chronic conditions affect large share of celiac disease patients, from gastrointestinal problems, migraines, fibromyalgia, dermatological problems to increased risk of other autoimmune disorders [Bibbò S et al., 2017]. In some cases, certain ophthalmological issues, such as night blindness, dry eye, cataract, uveitis, thyroid gland related orbitopathy, optical neuromyelitis, orbital miozitis and central retinal vein occlusion can be the first symptoms of celiac disease [Fousekis FS et al., 2020].

Dry eye disease or dry eye syndrome (DED) is one of the most common diagnosis in ophthalmology affecting 10% to 30% of population worldwide [Hodžić N et al., 2024], and the prevalence is considered to be even higher in some population groups, including celiac disease patients [Huang R et al., 2022]. Many studies have shown connection between celiac disease and diseases affecting eye surface, like DED [Karatepe Hashas AS et al., 2017; Uzel MM et al., 2017; Martins TGDS et al., 2021]. In people with celiac disease DED is a result of inflammation of the eye, which is further exacerbated with micronutrient deficiencies typical for celiac disease malabsorption [Bolukbasi S et al., 2019].

We aimed to analyse how many celiac disease patients on a gluten-free diet are exposed to gluten, either accidentally or intentionally and whether this is reflected on the tear film quality, i.e. symptoms of DED.

MATERIAL AND METHODS

This is the first stage of the randomized clinical trial (ClinicalTrials.gov ID NCT05825978) in which we aim to determine whether celiac disease patients benefit from omega-3 fatty acid supplementation in comparison to placebo, with regard to their eye health, i.e. the tear film quality and presence of DED symptoms.

For the first stage of the research, we recruited 100 celiac disease patients at the private health institution Plava Medical Group Tuzla, in Tuzla, Bosnia and Herzegovina, from March 2023 to June 2023.

Ethical approval was obtained from the ethical committee of the private health institution Plava Medical Group Tuzla (decision number 312-1/23 dated February 8, 2023).

Study subjects: People diagnosed with celiac disease (K50) by gastroenterologist specialist, both gender, age 18 to 50 years were eligible to participate in the study.

Patients using medications (antidiabetics, antihypertensive, antidepressants, thyroid medicines, antihistamines, antiepileptic, antipsychotics, antiparkinsonian, glaucoma, or oral contraceptives) were excluded. Also, misuse of alcohol, as well as consuming alcohol on the day of testing as it was proven to negatively affect tear film [You et al., 2016], especially in women [Magno MS et al., 2021]. Women in menopause were also excluded due to negative effect of hormonal misbalance on tear film [Hodžić N et al., 2024]. Eye trauma, acute infection, glaucoma, eye surgery and contact lenses use were also excluding criteria [Huang R et al., 2022]. Given the primary aim of this RCT, and due to protective effect of omega-3 fatty acids on inflammation in DED [Hyon J, Han S, 2021; Hodžić N et al., 2024], people who used supplements of omega-3 fatty acids during the last 3 months were also excluded.

A total of 100 people fit the criteria and were enrolled to complete ophthalmological screening for the quality of tear film, i.e. presence of DED symptoms.

Research methods: All 100 celiac disease patients completed one general questionnaire (age, gender, education and employment status, year of diagnosis, medication use, etc.), modified version of Celiac Disease Questionnaire we used previously [Dragoje M, 2023] and a semi-quantitative

food frequency (sFFQ) questionnaire covering foods potentially problematic for celiac disease patients [Dragoje M, 2023]. Basic anthropometric measurements (body weight and height) were measured with body scale with integrated stadiometer (Seca 700), at recruitment, with head positioned in Frankfurter position and patient wearing no shoes and light clothes. Based on these measurements, Body Mass Index (BMI) was calculated to determine state of nourishment.

To examine the quality of the tear film, one subjective and two objective methods were selected based on literature overview and recommendations [Okumura Y et al., 2020].

Subjective DED evaluation was done by the Ocular Surface Disease Index (OSDI), and the two methods for the objective evaluation selected for this study were Schirmer test I and Tear Break-up Time test (TBUT).

OSDI test consists of 12 questions used to evaluate the frequency of subjective nuisances that occur during Ocular Surface Disease. OSDI questionnaire is divided in three parts: the first part refers to subjective symptoms of the dry eye (A), second part refers to sight function (B) and third part refers to environment triggers (C) [Grubbs JR et al., 2014]. Patient answers to each question by circling the number on a scale from 0 to 4 which presents the frequency of certain symptom in the last seven days where zero means no symptoms are present and 4 means that the symptoms are constantly present. The total sum of answers from every part is added, multiplied with 25 and then divided with the number of all answered questions. The results are interpreted as follows: Normal values of the question results are from 0 to 12.00; mild case of dry eye are considered values from 13.00 to 22.00; moderate case are values from 23.00 to 32.00. Values higher than 33.00 are considered severe case of Ocular Surface Disease [Jeng BH, 2013].

Schirmer test I is one of the most commonly used tests for DED diagnosis and decreased secretion of tear water component [Karampatakis V et al., 2010]. Filter tape 5 mm width and 35 mm length is inserted in the lateral third of the lower fornix of the both eyes simultaneously. Anaesthesia is not pre-applied. The results can be interpreted after five minutes; if the length of the tear-damped tape exceeds 10 mm it is considered as a

normal result, under 5 mm is considered DED, while the result between 5 mm and 10 mm is indicated for dry eye [Saleh TA et al., 2006].

TBUT is used for evaluating the stability of the tear film and is the main criteria for the dry eye. It is defined as the time interval between the complete blink of an eye and the first appearance of the dry spot in the tear film [Lan W et al., 2014]. To measure TBUT, the respondent is looking down while upper eye lid is mildly lifted, and the fluorescent tape is covered in saline. The excess of the fluid is removed from the tape and then the tape is used to dye the surface of the eye. Patient is looking straight forward with both eyes open. The stopwatch is started after the last blink and we keep track of the dry stains on the surface of the cornea with cobalt blue light from the flashlight. With the appearance of the first dry stains the stopwatch is stopped. The time interval between the last blink and first appearance of the dry stain is recorded as TBUT. The procedure is repeated three times on both eyes, right eye first, then the left. Middle value of all three measurements is considered as a relevant value for TBUT [VidasPauk S et al., 2019]. Less than 10 seconds indicates abnormal tear film, values from 5 to 10 seconds are borderline values, and less than 5 seconds is indicator for dry eye [VidasPauk S et al., 2019].

Data analysis

Statistica software (TIBCO Software Inc., version 14.0) was used for all statistical analyses. Level of statistical significance was set to 0.05. Data plotting and graphic presentation of the data was done with MS Office Excel package (version 2016, Microsoft Corp., USA). All numeric data were normally distributed and are shown as mean and standard deviation while categorical data are shown as absolute frequencies. Pearson's correlation coefficients were calculated for numeric data.

RESULTS

The study included 100 celiac disease patients, of whom 19 were male and 81 were female, with a mean age of 38.0 ± 9.3 years, ranging from 19 to 49 years. Average BMI of $23.3 \pm 2.8 \text{ kg/m}^2$, ranging from 17.0 to 33.7 kg/m^2 . Generally, patients had a normal state of nourishment, but 22% of patients had $\text{BMI} \geq 25.0 \text{ kg/m}^2$ which was more common in older patients (correlation coefficient $r=0.371$; not

shown). Genetic predisposition for celiac disease was reported by 36% of patients, while 64% had no genetic predisposition for celiac disease.

Interestingly, the majority of patients were diagnosed late in life (44% were diagnosed between 31 and 50 years of age) and only 3% fit the classic celiac disease (diagnosed by 10 years of age, **Fig. 1**). Symptom duration prior to the diagnosis varied greatly; from 20% of those saying they had no symptoms to 27% of patients saying the symptoms lasted between one and 4 years prior to the diagnosis (**Fig. 1**).

No significant difference was found in subjective and objective measures of dry eye regarding genetic predisposition, or age at diagnosis.

Gluten consumption was calculated based on the reported consumption frequency of foods listed in sFFQ which covers risky foods (potato chips, dried fruits, fruit yoghurt, pudding, cream cheese spread etc.). Patients were asked to indicate their consumption frequency within the last 30 days, starting from two or more times a day, once a day, 4 to 6 times a week, 2 to 3 times a week, once a week, 2 to 3 times a month, once a month and never. Based on the consumption frequency and foods consumed, gluten exposure was calculated and is reported as a number of servings per day. Additionally, they were asked to assess how much they consider gluten exposure to be a problem while dining out or eating commercially available gluten-free products. To do this, the modified version of Celiac Disease Questionnaire included the following questions:

QUESTION 1: How many times in the past 4 weeks did you consume foods containing gluten?

QUESTION 2: I comply with gluten-free diet even when dining out.

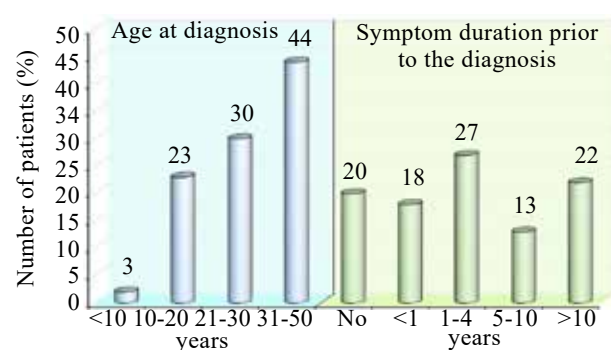


FIGURE 1. Distribution of celiac disease patients (N=100) regarding the age when the diagnosis was confirmed and the duration of symptoms prior to the diagnosis

QUESTION 3: Before you consume food, do you consider the consequence?

QUESTION 4: How important is accidental exposure health?

Average consumption of gluten through foods listed in the sFFQ was 2.2 ± 1.8 servings (**Table 1**) over the last month, ranging from no consumption to striking 13 servings of risky foods per day. The majority of patients (81%) on Question 1 answered that over the past month they avoided gluten completely but there was 17% of patients who expose themselves to gluten 3 to 5 times a month and 2% of patients who expose themselves more than 10 times over the last month (**Fig. 2**). Dining out is just one of potentially risky situations when it comes to gluten exposure, and 96% of patients said that they do consider gluten exposure while dining out (Question 2) while 4% said that they are not concerned about it. The majority of patients (96%) said they do think about potential health consequences when consuming foods (Question 3) but 4% do not think there will be any health consequences. Finally, despite the majority of patients consider accidental exposure to gluten very impor-

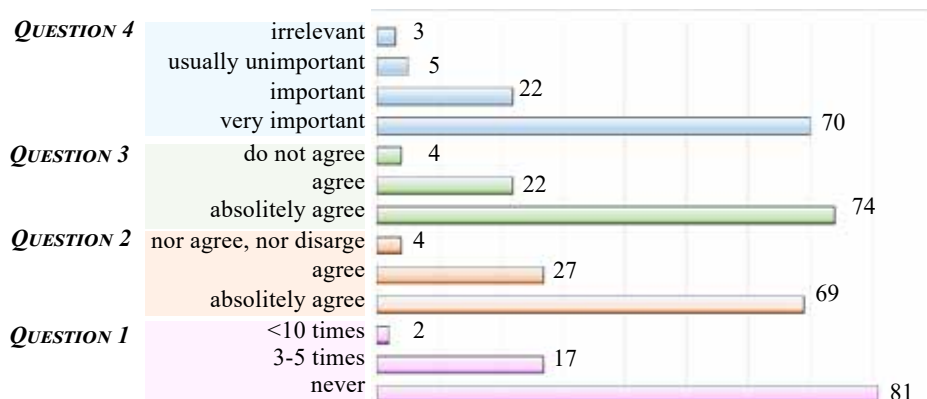


FIGURE 2. Distribution of celiac disease patients (N=100) regarding their subjective opinion on gluten and diet

tant (70%) or important (22%) for their health (Question 4), there was 8% of patients who did not consider accidental exposure to gluten problematic (**Fig. 2**).

According to our research, TBUT for right eye was 15.0 ± 4.2 and 14.6 ± 4.7 for left eye (**Table 1**). Despite TBUT nor Schirmer test I results do not indicate the presence of dry eye, their values are negatively correlated with higher consumption of risky foods (**Table 1**), and statistical significance was achieved only for TBUT. Based on the average OSDI score, patients can be considered to have a mild form of DED, however, maximum values show that some patients experience major symptoms for DED (**Table 1**). Subjective symptoms indicative of dry eye (OSDI score) are more expressed in patients who consumed risky foods (**Table 1**; $r=0.229$).

DISCUSSION

The results on general characteristics and disease presentation are in line with previously conducted studies on celiac disease. One study found that accidental exposure to gluten through dining out or consumption of potentially contaminated foods in celiac disease patients following gluten-free diet is 66% and occurs less than once a month, but all experienced clinically significant symptoms, some even within 1 hour after food was consumed [Silvester JA et al., 2016]. Our results confirm that even rare exposure to potentially contaminated foods could result in worsening of the eye health, specifically more symptoms of dry eye, which is further worsened by our lifestyle and prolonged time spend indoors and in front of screens [Hodžić N et al., 2024].

For healthy population, the average TBUT is 27 seconds [VidasPauket S et al., 2019] and our patients have lower values, but they do not fulfil the criteria for the diagnosis of dry eye, which has been proven in several other studies [Uzel MM et al., 2017; Hazar L et al., 2020]. Possible explanation lies in the fact that patients enrolled in the study took care of their gluten exposure, and that they took extra precaution when buying and consuming potentially risky foods.

As previously noted, gluten-free diet is the only medicine for celiac disease patients [Bascunan KA et al., 2017]. Most people with celiac disease can

TABLE 1.
Consumption of risky foods and ophthalmological indicators of dry eye in celiac disease patients enrolled in the study (N=100) and corresponding correlation coefficients

	Mean \pm SD	Min – Max	r
Risky food (serving/day)	2.2 ± 1.8	0.0 – 13.0	-
OSDI score	14.8 ± 6.8	0.0 – 37.0	0.229*
Schirmer right eye	28.7 ± 6.3	9.0 – 35.0	-0.053
Schirmer left eye	28.3 ± 4.2	7.0 – 22.0	-0.109
TBUT right eye	15.0 ± 4.2	4.0 – 22.0	-0.334*
TBUT left eye	14.6 ± 4.7	4.0 – 23.0	-0.303*

NOTES: OSDI – Ocular Surface Disease Index; TBUT – Tear Break-up Time; *indicates statistically significant result at $p < 0.05$

tolerate well ingestion of about 10 mg of gluten or 500 g of food containing around 20 mg of gluten per kg of product. However, there is a high degree of sensitivity variability among this population, as some patient's histological changes can worsen even with the small daily amount of gluten exposure [Wieser H et al., 2021]. Having in mind over presence of commercial gluten-free products and dine out options, the risk of (unintentional) gluten ingestion is a real, and a very concerning possibility [Wieser H et al., 2021], especially for highly sensitive population. Labels (and declarations) of gluten-free products has become unreliable [Falcomer AL et al., 2020]. Along with that, many commercially available gluten-free products (made from corn, rice, millet), ready-to eat meals and meals prepared in restaurants can be cross-contaminated with gluten [Wieser H et al., 2021]. Systematic review of 24 cross-sectional studies by Falcomer AL et al. [2020] showed that the prevalence of contamination in industrial food products offered by food services is 13.2%, and increases to 41.5% in non-industrial food products labelled as gluten-free.

CONCLUSION

This is one of the few studies focused on dry eye disease symptoms in celiac disease patients on a gluten-free diet. The results show that celiac disease patients following a gluten-free diet, when consuming higher amounts of potentially risky foods experience deterioration in eye health, specifically dry eye disease.

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