

STATISTICAL RESEARCH ON THE CORRELATION BETWEEN CELIAC DISEASE AND OTHER AUTOIMMUNE DISEASES

Merije Elezi^{1*}, Namik Durmishi¹, Vlatko Tanevski¹, Enesa Nesimi¹, Mirsade Tairi¹

¹Faculty of food technology and nutrition, University of Tetovo,
Ilinden nn, 1200 Tetovo, Macedonia

*e-mail: merije.elezi@unite.edu.mk

Abstract

Number of people currently suffering from celiac disease is on the rise. The primary goal of this study is to statistically determine the correlation between celiac disease and the occurrence of other autoimmune diseases (Hashimoto's thyroiditis, rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, etc.) in the representative sample that was included in this study.

The research was conducted by the Faculty of Food Technology and Nutrition at the University of Tetovo, VT Diet Club - Bitola, and the Association of Celiacs - Gevgelija. The research was conducted in the period from 01 April 2023 until 30 April 2023 by using an online questionnaire. The research was conducted on a representative sample of 110 subjects suffering from celiac disease aged 3 to 68 years - 90 women and 20 men. Data on minors who were included in this study were obtained from their parents - guardians. As a statistical method of work student's t-test is used to test the significance of the difference between two proportions and to determine whether there is an association between celiac disease and other autoimmune diseases from which the subjects suffer.

The results indicate that 64.5% of the respondents suffer only from celiac disease, while 35.5% of the respondents suffer from some other autoimmune disease in addition to celiac disease. Since the obtained value for $t = 3.05$ is greater than the table value $t = 1.982$ for $n = 108$, and $p < 0.05$, it is concluded that the difference between the proportions in the two groups is significant. In this case, the working, i.e. alternative hypothesis is accepted that the celiac disease from which the subjects suffer and the intake of gluten are one of the main reasons that led to the appearance of other autoimmune diseases in the subjects.

From this study it can be concluded that celiac disease is a risk factor for the occurrence of a large number

of other autoimmune diseases, so celiac disease is a very important disease to be promptly diagnosed and timely start with the application of gluten-free diet in order to improve the health condition of patients and to prevent the occurrence of other autoimmune diseases.

Key words: Celiacia, Gluten, Autoimmunity, Disease, Diet.

1. Introduction

Wheat, rye, and barley can cause celiac disease in people with a genetic predisposition. The role of oats in this disease is not certain. Celiac disease affects both children and adolescents and in adults, it is called sprue. It is related to the villi structure of the intestinal mucosa. Epithelial cells show degenerative changes and the functions of absorption of nutrients are quite impaired. The incidence of the disease varies, e.g. 0.1% of children are affected in central Europe and 0.3% in Ireland. The prolaminic fractions of wheat, barley, or rye are the cause of the disease, which is therefore eliminated by changing the diet, where primary emphasis is placed on gluten-free grains and their products: rice, corn, millet, buckwheat, quinoa, amaranth, etc. [1].

The primary goal of this research is to statistically determine the correlation between celiac disease and the occurrence of other autoimmune diseases (Hashimoto's thyroiditis, rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, etc.) in the representative sample that was included in this study. Also, a detailed statistical analysis was made of data related to the diagnosis of celiac disease and other autoimmune diseases suffered by the respondents who were included in the study and the effect of the gluten-free diet on the health status of the respondents.

2. Materials and Methods

2.1. Materials

There is a rapid increase in the number of people suffering from celiac disease and other autoimmune diseases worldwide. That's why we decided to research the correlation between celiac disease and the occurrence of other autoimmune diseases (Hashimoto's thyroiditis, rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, etc.) in patients suffering from celiac disease. The research was conducted by: the Faculty of Food Technology and Nutrition at the University of Tetovo, VT Diet Club - Bitola and Association of celiac - Gevgelija. The research was conducted in the period from April 1, 2023, until 30.04.2023 by using an online questionnaire. The research we conducted is of a retrospective type.

To conduct this research we prepared a survey questionnaire with the following 10 questions: gender; age (in years); has your celiac disease been diagnosed by a qualified medical person - doctor?; How were you diagnosed with celiac disease?; At what age were you first diagnosed with celiac disease by a qualified medical professional - a doctor?; Do you suffer from any other autoimmune disease that has been diagnosed by a qualified medical person - a doctor?; Which of the following autoimmune diseases have you been diagnosed by a qualified medical person - a doctor?; At what age were you first diagnosed with the autoimmune disease you suffer from by a qualified medical professional - a doctor?; Are you receiving adequate drug therapy for your autoimmune disease prescribed by a qualified medical person - doctor?; Has practicing a gluten-free diet helped you reduce the symptoms of the autoimmune disease you suffer from and improve your overall health?

The research was conducted on a representative sample of 110 respondents. The study included male and female respondents aged from 3 to 68 years. To be able to use the obtained data in our study, we obtained written consent from the respondents who were included in the research and the parents - the guardians of the minor respondents.

2.2 Methods

The study was conducted with a quota sample: the number of female respondents was 90, and the number of male respondents was 20 respondents. The selection of the sample was systematic, i.e. it was necessary to meet certain criteria:

- The study should include both sexes;
- Respondents should be between the ages of 3 and 68;
- The respondents suffer from celiac disease.

We would also like to point out that the data for the minors who were included in this study were obtained from their parents - guardians.

2.3 Statistical method of data processing

As statistical methods of work, student's t-test was used to test the significance of the difference between two proportions to determine whether there is a connection between celiac disease and other autoimmune diseases from which the respondents suffer, as well as relative numbers for data processing that are related to the diagnosis of celiac disease and other autoimmune diseases and the effect of the gluten-free diet on the health status of the respondents.

3. Results and Discussion

3.1 Results

Table 1 shows information on the number of respondents who were included in this study, distributed by gender.

Table 1. Distribution of celiac disease patients by gender

Gender	Number of respondents
Men	20
Female	90
Total	110

Table 1 shows that the number of women suffering from celiac disease is 4.5 times higher than the number of men suffering from celiac disease.

Figure 1 shows information on the number of respondents who were included in the study, distributed by age group.

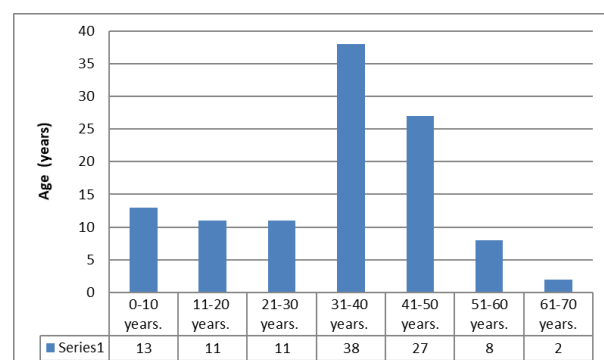


Figure 1. Distribution of patients with celiac disease by age group

From Figure 1, it can be seen that most of the respondents suffering from celiac disease (38 respondents) are aged 31 - 40 years.

Table 2 shows data on the percentage distribution of the number of respondents who answered the

question: "Have you been diagnosed with celiac disease by a qualified medical person - a doctor?"

Table 2. Percentage distribution of respondents who answered the question: "Have you been diagnosed with celiac disease by a qualified medical person - a doctor?"

Answers	Number of respondents (%)
Yes	92.6
No	7.4
Total	100

From Table 2 it can be seen that celiac disease in 92.6% of respondents was diagnosed by a qualified medical person - a doctor.

Figure 2 shows information on the diagnostic methods used to diagnose celiac disease among the respondents.

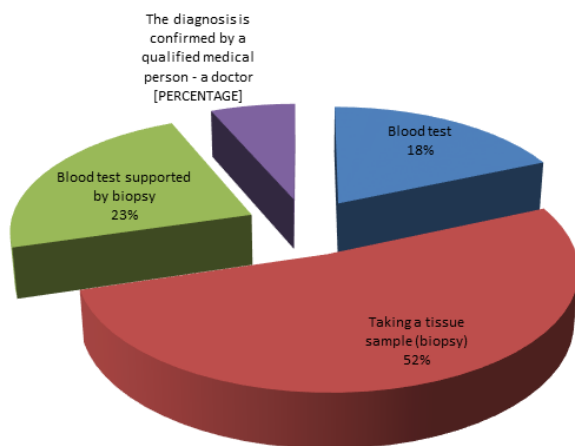


Figure 2. Diagnostic methods used to diagnose celiac disease in respondents

From Figure 2 it can be concluded that in 52% of the subjects suffering from celiac disease, a biopsy was used to diagnose celiac disease.

Table 3 provides information on the age at which celiac disease was first diagnosed for subjects included in this study.

From Table 3 it can be concluded that celiac disease in the majority of respondents (33.6%) was first diagnosed at the age of 31 - 40 years.

Table 4 shows information on the distribution of the number of respondents according to the diagnosis of other autoimmune diseases that they suffer from in addition to celiac disease.

From Table 4, it can be concluded that 35.5% of those suffering from celiac disease also suffer from some other autoimmune disease, and 64.5% of the respondents suffer only from celiac disease.

To see if there is significance in the difference between the two proportions, we used the student's t-test. Testing was performed according to the formula:

$$t = \frac{p_1 - p_2}{\delta p_1 - p_2}$$

Where: p1 represents the proportion of a certain attribute in the first sample, p2 the proportion in the second sample, and $\delta p_1 - p_2$ represents the standard error between the two proportions.

The standard error of the difference between the two proportions is determined by the formula:

$$\delta p_1 - p_2 = \sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}}$$

The value of q is determined in the following way $q_1 = 1 - p_1$; $q_2 = 1 - p_2$. n1 represents the size of the first sample and n2 is the size of the second sample [2].

Table 3. Percentage distribution of respondents according to the age at which they were first diagnosed with celiac disease

Parameters	Diagnosed by the doctor								The diagnosis has not been confirmed by a doctor
	Age								
	0 - 10	11 - 20	21 - 30	31 - 40	41 - 50	51 - 60	61 - 70	Over 70	
% of respondents	20.6%	12.1	14%	33.6	9.3	2.8	0	0	7.6

Table 4. Distribution of patients with celiac disease according to diagnosis of other autoimmune diseases from which they suffer

Number (%) of respondents who...	
Suffer from another autoimmune disease besides celiac disease	Do not suffer from any other autoimmune disease besides celiac disease
39 (35.5)	71 (64.5)
Total: 110 respondents (100%)	

If the values are replaced in the previous formulas, we get:

$$\begin{aligned} \delta p_1 - p_2 &= \sqrt{\frac{0.645 \times 0.355}{71} + \frac{0.355 \times 0.645}{39}} = 0.095 \\ &= \frac{0,645 - 0,355}{0,095} = 3.0 \end{aligned}$$

The obtained result for $t = 3.05$ is compared with tabular value (Table 5 and Figure 3) for the t-test, for a certain degree of freedom n ($n_1 + n_2 - 2$) and $p = 0.05$. Since the obtained value for $t = 3.05$ is greater than the table value $t = 1.982$ for $n = 108$ and $p < 0.05$, it is concluded that the difference between the proportions in the two groups is significant. In this case, the working, i.e. alternative hypothesis is accepted that the celiac disease from which the subjects suffer and the intake of gluten are one of the main reasons that led to the appearance of other autoimmune diseases in the subjects.

Table 5. Table of t-distribution

cum. prob	t.50	t.75	t.80	t.85	t.90	t.95	t.975	t.99	t.995	t.999	t.9995
one-tail	0.50	0.25	0.20	0.15	0.10	0.05	0.025	0.01	0.005	0.001	0.0005
two-tails	1.00	0.50	0.40	0.30	0.20	0.10	0.05	0.02	0.01	0.002	0.001
df											
1	0.000	1.000	1.376	1.963	3.078	6.314	12.71	31.82	63.66	318.31	636.62
2	0.000	0.816	1.061	1.386	1.886	2.920	4.303	6.965	9.925	22.327	31.599
3	0.000	0.765	0.978	1.250	1.638	2.353	3.182	4.541	5.841	10.215	12.924
4	0.000	0.741	0.941	1.190	1.533	2.132	2.776	3.747	4.604	7.173	8.610
5	0.000	0.727	0.920	1.156	1.476	2.015	2.571	3.365	4.032	5.893	6.869
6	0.000	0.718	0.906	1.134	1.440	1.943	2.447	3.143	3.707	5.208	5.959
7	0.000	0.711	0.896	1.119	1.415	1.895	2.365	2.998	3.499	4.785	5.408
8	0.000	0.706	0.889	1.108	1.397	1.860	2.306	2.896	3.355	4.501	5.041
9	0.000	0.703	0.883	1.100	1.383	1.833	2.262	2.821	3.250	4.297	4.781
10	0.000	0.700	0.879	1.093	1.372	1.812	2.228	2.764	3.169	4.144	4.587
11	0.000	0.697	0.876	1.088	1.363	1.796	2.201	2.718	3.106	4.025	4.437
12	0.000	0.695	0.873	1.083	1.356	1.782	2.179	2.681	3.055	3.930	4.318
13	0.000	0.694	0.870	1.079	1.350	1.771	2.160	2.650	3.012	3.852	4.221
14	0.000	0.692	0.868	1.076	1.345	1.761	2.145	2.624	2.977	3.787	4.140
15	0.000	0.691	0.866	1.074	1.341	1.753	2.131	2.602	2.947	3.733	4.073
16	0.000	0.690	0.865	1.071	1.337	1.746	2.120	2.583	2.921	3.686	4.015
17	0.000	0.689	0.863	1.069	1.333	1.740	2.110	2.567	2.898	3.646	3.965
18	0.000	0.688	0.862	1.067	1.330	1.734	2.101	2.552	2.878	3.610	3.922
19	0.000	0.688	0.861	1.066	1.328	1.729	2.093	2.539	2.861	3.579	3.883
20	0.000	0.687	0.860	1.064	1.325	1.725	2.086	2.528	2.845	3.552	3.850
21	0.000	0.686	0.859	1.063	1.323	1.721	2.080	2.518	2.831	3.527	3.819
22	0.000	0.686	0.858	1.061	1.321	1.717	2.074	2.508	2.819	3.505	3.792
23	0.000	0.685	0.858	1.060	1.319	1.714	2.069	2.500	2.807	3.485	3.768
24	0.000	0.685	0.857	1.059	1.318	1.711	2.064	2.492	2.797	3.467	3.745
25	0.000	0.684	0.856	1.058	1.316	1.708	2.060	2.485	2.787	3.450	3.725
26	0.000	0.684	0.856	1.058	1.315	1.706	2.056	2.479	2.779	3.435	3.707
27	0.000	0.684	0.855	1.057	1.314	1.703	2.052	2.473	2.771	3.421	3.690
28	0.000	0.683	0.855	1.056	1.313	1.701	2.048	2.467	2.763	3.408	3.674
29	0.000	0.683	0.854	1.055	1.311	1.699	2.045	2.462	2.756	3.396	3.659
30	0.000	0.683	0.854	1.055	1.310	1.697	2.042	2.457	2.750	3.385	3.646
40	0.000	0.681	0.851	1.050	1.303	1.684	2.021	2.423	2.704	3.307	3.551
60	0.000	0.679	0.848	1.045	1.296	1.671	2.000	2.390	2.660	3.232	3.460
80	0.000	0.678	0.846	1.043	1.292	1.664	1.990	2.374	2.639	3.195	3.416
100	0.000	0.677	0.845	1.042	1.290	1.660	1.984	2.364	2.626	3.174	3.390
1000	0.000	0.675	0.842	1.037	1.282	1.646	1.962	2.330	2.581	3.098	3.300
z	0.000	0.674	0.842	1.036	1.282	1.645	1.960	2.326	2.576	3.090	3.291
	0%	50%	60%	70%	80%	90%	95%	98%	99%	99.8%	99.9%
	Confidence Level										

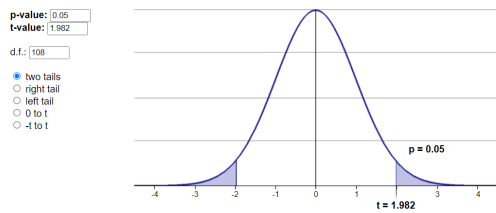


Figure 3. Determining a tabular value for a t-test

Figure 4 shows the percentage representation of other autoimmune diseases suffered by respondents who have celiac disease.

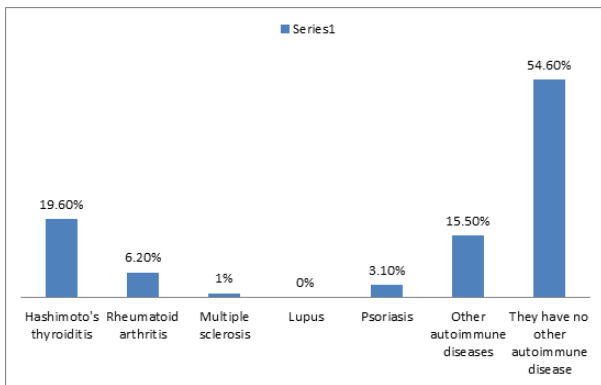


Figure 4. Percentage representation of other autoimmune diseases suffered by celiac disease sufferers

From Figure 4, it can be seen that Hashimoto's thyroiditis is the most common autoimmune disease that celiac disease sufferers suffer from. 19.6% of respondents suffering from celiac disease indicated that they also suffer from Hashimoto's thyroiditis.

Figure 5 provides information on the age at which the other autoimmune disease was first diagnosed in subjects with celiac disease.

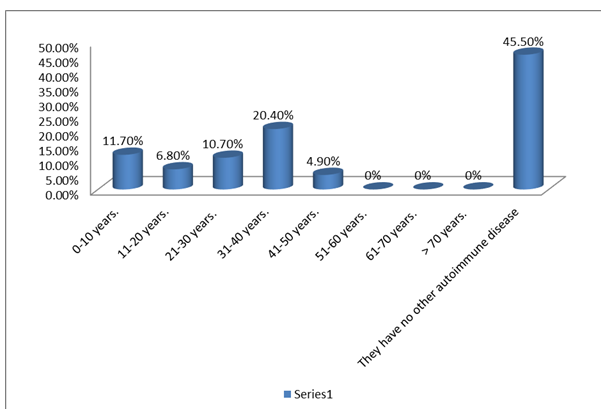


Figure 5. Percentage distribution of subjects suffering from celiac disease according to the age at which they were first diagnosed with another autoimmune disease

From Figure 5, it can be concluded that the majority of respondents suffering from celiac disease (20.4%)

were diagnosed with some other autoimmune disease at the age of 31 - 40.

Table 6 shows data on the percentage distribution of the number of patients with celiac disease who receive and do not receive drug therapy prescribed by a doctor for some other autoimmune disease from which they suffer.

Table 6. Distribution of patients with celiac disease according to whether or not they receive drug therapy for another autoimmune disease

Parameters	Drug therapy for another autoimmune disease		Do not suffer from another autoimmune disease
	Receiving	Not receiving	
% of respondents	27.9	31.7	40.4

From Table 6, it can be concluded that 31.7% of respondents who suffer from celiac disease and who are diagnosed with some other autoimmune disease do not receive any medical therapy prescribed by a qualified medical person - a doctor.

Figure 6 shows the percentage distribution of the respondents who were included in the study according to the effect of the gluten-free diet in terms of improving their health and reducing the symptoms of other autoimmune diseases that the respondents suffer from.

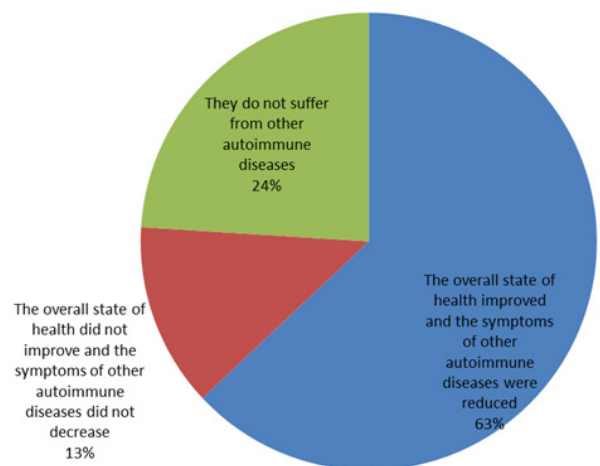


Figure 6. Percentage distribution of subjects suffering from celiac disease according to the effect of the gluten-free diet

As can be seen from Figure 6, it is encouraging that 63% of the respondents who were included in this study declared that the gluten-free diet helped them to reduce (reduce) the symptoms of other autoimmune diseases that the respondents suffered from and improved their overall well-being and health state.

3.2 Discussion

Today, it is considered that 1% of the entire population of the globe suffers from gluten enteropathy (celiac disease), that is, in Europe even 1 in 130 to 1 in 300 people in different countries have this disease. The risk of the disease in family members, where there is a celiac patient, is 10 times higher [3].

Today, it has been proven that celiac disease is equally prevalent in both sexes [3]. But it is interesting to note that in our study we found that the number of women suffering from celiac disease is 4.5 times higher than the number of men suffering from celiac disease (90 female subjects suffer from celiac disease, while the number of men suffering from celiac disease is 20).

Celiac disease is most common in the elderly [4]. Most of the subjects suffering from celiac disease (38 subjects) are between the ages of 31 and 40 according to the results of this research. It is also not to be underestimated the number of celiac disease sufferers who are between the ages of 41 and 50 (27 respondents).

92.6% of celiac disease sufferers who were included in this study indicated that the disease was diagnosed by a qualified medical person - a doctor. To determine if someone has this disease, a blood analysis is done for gluten antibodies, tissue transglutaminase, and determination of genetic predisposition, with which 80% confirmation of the diagnosis can be obtained. For 100% confirmation of the diagnosis, a biopsy of the mucosa of the small intestine is necessary [5]. Diagnosis, which involves a blood test as well as taking a tissue sample (biopsy), has become much more sophisticated in the last decade. Blood tests usually come first, but the results sometimes show false negative or false positive readings. Therefore, the blood test should be accompanied by a biopsy that will help establish the diagnosis. Also, although it may seem counterintuitive, it is important to stick to a standard diet until the diagnosis is complete. That's because if you decide to cut out gluten a few weeks before testing, signs of celiac disease may not show up in the results, and it's important to have a firm diagnosis [6]. In our study, in 52% of patients suffering from celiac disease, the diagnosis was made based on a biopsy of the mucosa of the small intestine. Only in 23% of subjects suffering from celiac disease, the diagnosis was established through blood tests accompanied by a biopsy.

It is interesting to note that the majority of respondents who were included in this study (33.6%) were diagnosed with celiac disease for the first time between the ages of 31 and 40. Late diagnosis is because atypical forms of the disease predominate in adults, which is why it is

diagnosed less often [3]. According to the literature, a large proportion of people suffering from this disease are not diagnosed. That is, about 80% of people who suffer from celiac disease are not aware that they have it [4].

The second age category in which celiac disease was diagnosed for the first time is 0 - 10 years (20.6% of respondents). Typical forms of the disease are more common in children aged 0 to 10 years, which are easier to diagnose, so it was previously thought that it is a disease that begins in childhood [3]. The clinical features of the typical forms of the disease are generally due to the malabsorption of important nutritional substances (carbohydrates, proteins, fats, minerals, and vitamins) [5].

35.5% of those suffering from celiac disease also suffer from some other autoimmune disease, and 64.5% of the respondents suffer only from celiac disease. Student's t-test to test the significance of the difference between the two proportions indicated that the obtained value for $t = 3.05$ was greater than the table value $t = 1.982$ for $n = 108$ and $p < 0.05$ indicating the conclusion that the difference between the proportions in both groups is significant. In this case, the working, i.e. alternative hypothesis is accepted that the celiac disease from which the subjects suffer and the intake of gluten are one of the main reasons that led to the appearance of other autoimmune diseases in the subjects.

The intolerance of gluten and the creation of antibodies to gluten does not necessarily lead to the destruction of the intestinal walls and intestinal villi, at least not to the same extent as in diagnosed celiac disease, but it also leads to the gradual destruction of other tissues, organs, hormones, glands or nerves in the body which causes numerous autoimmune diseases, which doctors do not associate with gluten at all. For example, some research shows that type 1 diabetes is an autoimmune disease, the possible cause of which is gluten intolerance, i.e. antibodies to gluten attack and destroy the cells of the pancreas, which otherwise produce insulin. If these cells are destroyed, their production of insulin is disabled, and then type 1 diabetes is diagnosed, which is why the patient is condemned to take insulin injections for life. Isn't it logical to ask: why are type 1 diabetics not necessarily sent for laboratory tests to detect celiac disease? However, doctors do not link this, as they do not link other autoimmune diseases to gluten intolerance [7].

Another possible mechanism by which celiac disease can lead to other autoimmune diseases is that people with celiac disease who follow a gluten-free diet are often found to be deficient in certain vitamins and nutrients. The most common deficiency

is observed in terms of calcium, iron, fiber, vitamins B1, B2, and B3 (thiamine, riboflavin, and niacin), and folates [8]. There is an inverse correlation between homocysteine and folate values. Decreased values of folate (which is often manifest in patients with celiac disease) lead to increased values of homocysteine (hyperhomocysteinemia) and *vice versa* [9]. There is a two-way relationship between homocysteine and the immuno-inflammatory reaction that is characteristic of autoimmune diseases, whereby the immuno-inflammatory reaction can contribute to an increase in homocysteine, and homocysteine, in turn, can act as a pro-inflammatory and immunostimulatory molecule that contributes to damage to specific target organs the disease, which is especially significant for rheumatoid arthritis and inflammatory bowel disease. Moreover, homocysteine can also be a trigger of autoimmune reactions through its ability to bind and structurally modify specific proteins resulting in the formation of neoantigens that may be key to the onset and development of a specific autoimmune disease. In summary: in celiac disease, as a result of the autoimmune reaction from the disease itself and folate deficiency, increased levels of homocysteine (hyperhomocysteinemia) occur which can contribute to the occurrence of other autoimmune diseases. However, we believe that more clinical research is needed to fully define these pathophysiological mechanisms [10].

The three most common autoimmune diseases in patients with celiac disease in our study were: Hashimoto's thyroiditis (19.6% of subjects), rheumatoid arthritis (6.2% of subjects), and other autoimmune diseases (15.5% of subjects). Other scientific studies have noted that Hashimoto's thyroiditis and Graves' disease, which are mainly autoimmune thyroid diseases characterized by lymphocytic infiltration of the thyroid parenchyma, are often associated with celiac disease. It is thought that the underlying mechanism for the association of these diseases lies in the common genetic background [11]. According to a Swedish study that included 24,014 respondents in the period from 2004 to 2017, it was determined that juvenile idiopathic arthritis develops almost 3 times more often in children with celiac disease than in the general population, and in adults with celiac disease, rheumatic arthritis occurs almost 2 times more often than in the general population [12]. Other autoimmune diseases that occur very often in patients with celiac disease are diabetes mellitus type 1, psoriasis, Sjogren's syndrome, autoimmune hepatitis, vitiligo, etc. [3].

Most (20.4%) of those suffering from celiac disease declared that the other autoimmune diseases from which they suffer were first diagnosed at the age of 31 - 40. It has been proven that the later the diagnosis

of celiac disease is made, the greater the chance of developing an autoimmune disease [3].

According to our study, 31.7% of respondents who suffer from celiac disease and who are diagnosed with some other autoimmune disease do not receive any medical therapy prescribed by a qualified medical person - a doctor. Also, 63% of the subjects included in this study stated that the gluten-free diet helped them reduce (reduce) the symptoms of other autoimmune diseases that the subjects suffered from and improved their overall well-being and health state. According to a scientific study, the implementation of a gluten-free diet improves the overall clinical course and affects the evolution of associated diseases. In some cases, such as anemia followed by iron deficiency, a gluten-free diet contributes to its disappearance. In other disorders, such as type 1 diabetes mellitus, a gluten-free diet provides better control of the disease. In several other complications and/or accompanying diseases (including other autoimmune diseases), appropriate adherence to a gluten-free diet, especially if implemented at an early stage, can slow down their evolution [13].

4. Conclusions

- To explain the connection between celiac disease and other autoimmune diseases, the English proverb can be used: "The two peas in a pod". With this proverb, we want to point out to you that these two things (celiac disease and autoimmune diseases) are very similar to each other.

- Since the obtained value for $t = 3.05$ is greater than the table value $t = 1.982$ for $n = 108$ and $p < 0.05$, it is concluded that the difference between the proportions in the two groups is significant. In this case, the working, i.e. alternative hypothesis is accepted that the celiac disease from which the subjects suffer and the intake of gluten are one of the main reasons that led to the appearance of other autoimmune diseases in the subjects.

- According to the results of this study, it can be concluded that celiac disease is a risk factor for the occurrence of a large number of other autoimmune diseases, so celiac disease is a very important disease to be promptly diagnosed and timely start with the application of gluten-free diet in order to improve the health condition of patients and to prevent the occurrence of other autoimmune diseases.

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