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Original article

Coeliac disease in a 15-year period of observation (1997 and 2011) in a Hungarian referral centre

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ABSTRACT

Aims: The aim of this study is to evaluate the experience of a single coeliac centre over a 15-year-long study period (between November of 1997 and September of 2011).
Patients and methods: Charts of 178 patients (139 females) with coeliac disease were retrospectively evaluated. Tests performed: multiple duodenal biopsies, anti-tissue transglutaminase and anti-endomysium antibodies, body mass index calculation, osteodensitometry, evaluation of disorders associated with coeliac disease, and implementation of family screening.
Results: Histological samples were available in 133 cases, distribution according to Marsh–Oberhuber classification: M0 in 7%, M1–M2 in 4%, M3a in 26%, M3b in 13%, and M3c in 50% of cases, respectively. Anti-tissue transglutaminase and anti-endomysium antibody tests were available in 158 cases, 132/158 showed seropositivity. Mean body mass index values were 23.05 kg/m^2 for males, and 21.07 kg/m^2 for females, respectively. Osteodensitometry showed normal values in 46%, osteopenia in 36%, and osteoporosis in 18% of cases, respectively. Coeliac disease associated disorders was present in 63/178 (35%) patients. Ninety coeliacs brought 197 first degree relatives for screening, with 47/197 (23%) relatives proving to have coeliac disease. Correlations between anti-tissue transglutaminase antibody titres and Marsh–Oberhuber classification, and anti-tissue transglutaminase antibody titres and bone mineral density values were found to be statistically significant ($p = 0.0011$, and $p = 0.001$, respectively).
Conclusions: Coeliac disease can become overt at any age. Female predominance is significant. Histology usually showed advanced villous atrophy. Mean body mass index values were within normal range. The high prevalence of associated disorders is also noted. The prevalence of 24% of coeliac disease among first degree relatives underlines the necessity of family screening.

1. Introduction

Coeliac disease is used to be considered as a chronic disorder of the small bowel leading to malabsorption, induced by cereal prolamins (mostly gluten) in genetically predisposed individuals. In recent decades, this common and variable disease has received increased attention from both physicians' and the general population's side. Thanks to the growing knowledge in the field, it has become evident that coeliac disease can be present at any age with the potential involvement of any organs, and is therefore currently considered as a systemic disorder. These novel observations were summarized in the ESPGHAN and the Oslo definitions [1,2]. According to the ESPGHAN definition, "Coeliac disease is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals, characterised by the presence of a variable combination of gluten dependent clinical manifestations, coeliac disease specific antibodies, HLA-DQ2 and DQ8 haplotypes and enteropathy" [1]. The Oslo definition was intended to be more straightforward for the convenience of the physicians by stating that coeliac disease was defined as "a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals" [2].

Despite huge interest towards coeliac disease, there is a clear shortage of publications regarding the analysis of all the major parameters of a coeliac patient cohort in total. Recently, we performed a retrospective evaluation on the charts of all coeliac disease patients diagnosed and followed at our coeliac centre in the last 10 years in order to see if the trends experienced in our material are reflected in literature as well [3]. In the past five years since then, the size of coeliac disease patient population in our centre has been growing rapidly, with an increase of 30%, presenting still the same trends, however in some aspects in even more pronounced ways, concerning the huge prevalence of coeliac disease among first degree relatives and the unequivocal female predominance. Considering the volume and the spectrum of experience obtained in this one-and-a-half-decade-long period, we found that the major features and the key interdisciplinary messages of our material are worthy of presentation

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and discussion on an international level, not only for gastroenterologists but also for physicians working in other fields of internal medicine as well. We would like to draw special attention to our most striking findings such as the unusually high prevalence of coeliac disease among first degree relatives (23%) and also unusually pronounced female predominance (78%) and high prevalence of associated disorders (35%). Certainly, these tendencies are well-known for the experts of the field, however, the extent of these trends in our material concerning the first two parameters in particular, is unique and we have not found such high figures in literature.

2. Patients and methods

Results of patients totalling 178 attending the centre between November of 1997 and September of 2011 with coeliac disease were analysed. The annual distribution of enrollment of coeliacs to the patients' cohort of our centre is shown in Fig. 1. There were 139 female and 39 male patients (78% vs. 22%), with a mean age of 38 years, a median of 36 years and a range between 18 and 78 years (Fig. 2). Notably, being a referral centre, in some cases, the diagnostic work-up of patients was launched in the primary care or at other settings. These patients were then referred to our centre for revision and confirmation of the suspected diagnosis.

Marsh–Oberhuber classification was implemented for the description of duodenal histological findings [4–6]. Duodenum histology samples were taken in 133 cases. Histological evaluation was performed mostly at the 1st Department of Pathology and Experimental Cancer Research of the Semmelweis University.

Serological results were based on measuring tissue transglutaminase antibody (anti-tissue transglutaminase antibody; IgA and IgG normal range: 0–10 U/ml) and anti-endomysium antibody tests. The IgG-anti-tissue transglutaminase antibody and IgG-anti-gliadin antibody results were applied for cases of selective IgA-deficiency. Baseline serological data of 158 patients were available. Serological tests were carried out at Semmelweis University and the Coeliac Disease Center of Heim Pal Children's Hospital.

The body mass index, also known as Quetelet-index is calculated by dividing the weight by the square of the height measured in meters (body mass index: bodyweight [kg] / height $[m]^2$).

Dual energy X-ray absorptiometry for measuring bone mineral density was performed on 113 coeliac patients at the 2nd Department of Medicine of Semmelweis University.

2.1. Statistical analyses

The correlations between histological damage according to Marsh–Oberhuber classification and anti-tissue transglutaminase antibody titres, body mass index values, and bone mineral density values were analysed by using nonparametric correlation (Spearman r). The correlation between anti-tissue transglutaminase antibody titres and bone mineral density values was analysed by using linear regression. All tests were two-sided, and a p-value of <0.05 was considered statistically significant. All analyses were performed using GraphPad InStat 3.0® (San Diego, CA) software.

3. Results

3.1. Serology

Baseline serology tests were performed in 158 patients. Results were based on measuring anti-tissue transglutaminase antibody (normal range: 0–10 U/ml) and anti-endomysium antibody titres. In 5 cases of selective IgA-deficiency, the IgG-anti-tissue transglutaminase antibody-examination tests were performed. Eighty-eight out of 158 patients had only anti-tissue transglutaminase antibody, 34 patients had only anti-endomysium antibody test, and 36 patients had both anti-tissue transglutaminase and anti-endomysium antibody tests, respectively. Seropositivity was detected in 132/158 (83, 5%) of cases.

3.2. Histology

Histological samples from multiple biopsies taken from the duodenum, were available in 133 cases. Distribution of data according to the Marsh–Oberhuber classification was as follows: negative in 10 patients, Marsh 1–2 in 5 patients, Marsh 3a in 34 patients, Marsh 3b in 18 patients, and Marsh 3c in 66 patients, respectively.

3.3. Associations between histological damage and serological results

Baseline serological coupled with histological results were available in 123 of the total 178 coeliac disease patients at our centre (69%). Serological along with histological positivity was detected in 103/123 cases (83%). Negative serology along with positive histological results were present in 17 cases (14%), and positive serology with negative histology was observed in 5 cases (3%), respectively. In cases of conflicting histological and serological results, diagnosis of coeliac

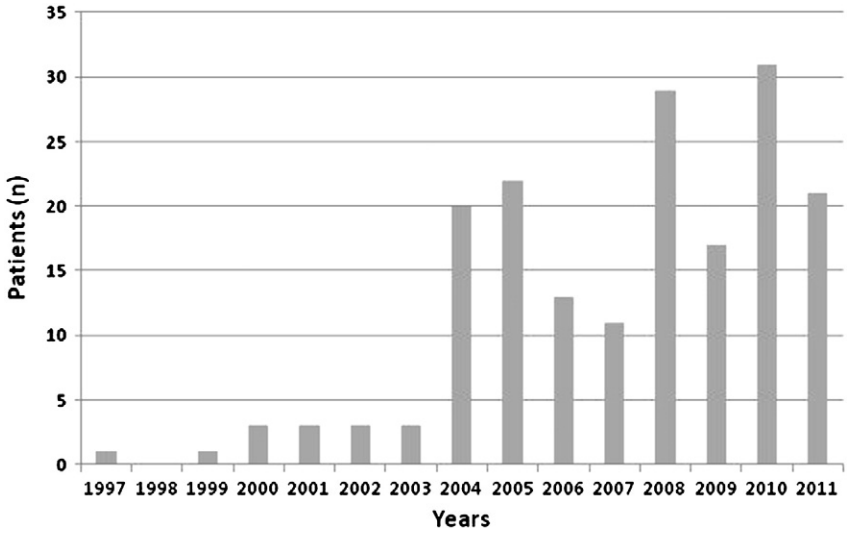

Fig. 1. The annual distribution of enrollment of coeliacs to the patients' cohort of our centre.

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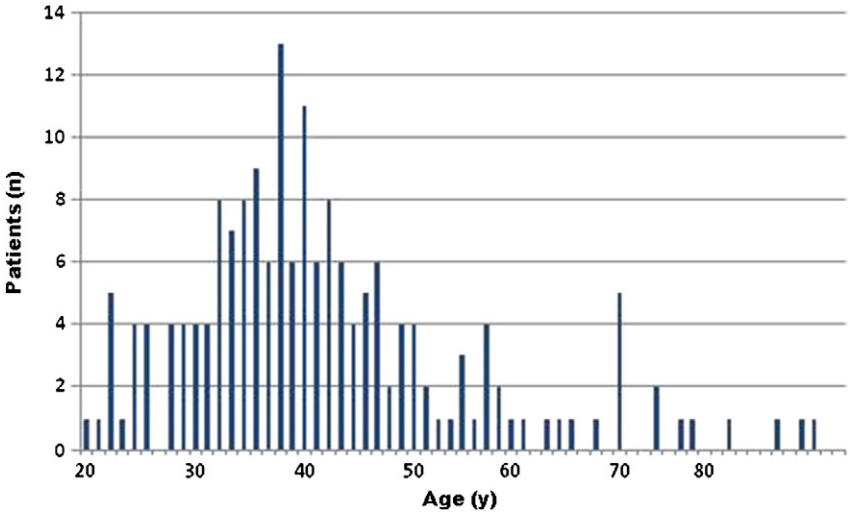

Fig. 2. Age distribution of 178 patients.

disease was made based on the clinical data, results of routine laboratory tests and imaging techniques, family history, and HLA phenotyping. The correlation between the extent of histological damage and anti-tissue transglutaminase antibody titre increase was examined in 106 cases (Table 1). Currently the fact that anti-tissue transglutaminase antibody titres correlate linearly with the stage of the histological lesion, with a higher sensitivity and specificity for coeliac disease diagnosis in patients with villous atrophy is considered evident and been reported by several experts [7–10]. This phenomenon is clearly present in our material as well, with the correlation between Marsh–Oberhuber classification and anti-tissue transglutaminase antibody titres being very significant ($p = 0.0011$).

3.4. Body mass index

Body mass index values for 158 patients were calculated. The mean body mass index result was 21.6 kg/m^2, range: 15.2 kg/m^2–33.4 kg/m^2. In accordance to gender, the mean body mass index result of the 32 male coeliac patients was 23.05 kg/m^2, range: 17.0 kg/m^2–31.5 kg/m^2. Among males, body mass index was lower than 18 kg/m^2 in 3 cases, whereas 21 patients were between 18 kg/m^2 and 25 kg/m^2, and 8 patients were over 25 kg/m^2. The mean body mass index result of the 95 female coeliac patients was 21.07 kg/m^2, range: 15.2 kg/m^2–33.5 kg/m^2. Among females, body mass index was lower than 18 kg/m^2 in 19 cases, whereas 66 patients were between 18 kg/m^2 and 25 kg/m^2, and 10 patients over 25 kg/m^2.

3.5. Associations between histological damage and body mass index in coeliac disease patients

Correlations between body mass index and Marsh–Oberhuber classification were evaluated on a sample of 99 coeliac patients (Table 2). In case of body mass index <18, Marsh 3c was the predominant level of histological damage. For patients with a normal body mass index, Marsh 1–2, Marsh 3a and Marsh 3b together were more common, than Marsh 3c alone. In case of body mass index >25, Marsh 3a lesion proved to be the most common finding. There was no statistically significant correlation between Marsh–Oberhuber classification and body mass index values ($p = 0.3601$).

3.6. Osteodensitometry

Osteodensitometry was performed on 124 coeliac patients. Data of female patients aged above 50 years were excluded, since decrease in bone mineral density in this group can be explained with decreased oestrogen levels related to menopause. Having therefore excluded results of 11 female patients, records of 113 coeliac patients (83 female, 30 male) were evaluated; normal bone mineral density was detected in 52 cases (46%), osteopenia in 41 patients (36%), and osteoporosis and in 20 patients (18%), respectively. In the subgroup of 30 males (mean age 37 years), normal bone mineral density was detected in 12 patients, osteopenia in 11 patients, and osteoporosis in 7 patients, respectively. The correlation between results obtained with osteodensitometry diagnoses and histological damage is presented in Table 3. There was no statistically significant correlation between Marsh–Oberhuber classification and bone mineral density values ($p = 0.2742$). However, by performing a linear regression test on the correlation between anti-tissue transglutaminase antibody titres and bone mineral density values, the correlation proved to be very significant ($p = 0.001$).

3.7. Associated diseases

Sixty-three out of 178 coeliac patients (13 male, 50 female) also suffered from at least one disease known to be associated with coeliac disease (Table 4). In our material, dermatitis herpetiformis was the most common associated disease ($n = 23$). However, this high prevalence of dermatitis herpetiformis is a bias resulting from the close cooperation between the Department of Dermatology,

Table 1
Distribution of tTG serum levels contrasted with histological damage.

tTG level U/ml	Negative	Marsh 1–2	Marsh 3a	Marsh 3b	Marsh 3c
0–10 U/ml	4	0	9	0	3
11–50 U/ml	3	1	6	2	14
51–100 U/ml	0	1	4	1	6
101–150 U/ml	1	0	2	1	4
151–200 U/ml	0	1	0	1	4
201 < U/ml	1	1	5	8	23
Total:	9	4	26	13	54

Table 2
Association between BMI and histological results.

BMI (kg/m^2)	Negative	Marsh 1–2	Marsh 3a	Marsh 3b	Marsh 3c
18 > x	0	1	2	2	11
18 ≤ x < 25	5	2	17	14	33
25 ≤ x	1	0	6	0	5
Total:	6	3	25	16	49

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Table 3
Correlation between bone mineral density and severity of histological damage.

	Negative	Marsh 1–2	Marsh 3a	Marsh 3b	Marsh 3c
Normal	4	0	9	6	20
Osteopenia	2	2	10	4	16
Osteoporosis	1	0	1	5	6
Total:	7	2	20	15	42

Dermatooncology and the 2nd Department of Internal Medicine of Semmelweis University. The methodology of collecting, preparing, and interpreting samples from dermatitis herpetiformis patients has been previously reported [11,12]. Thyroid-disorders are further common entities worth mentioning besides dermatitis herpetiformis. In our setting, 6 patients proved to have hypothyroidism, and 14 patients have hyperthyroidism, respectively. Selective IgA-deficiency occurred in 2.8% of cases. Finally, the increasing appearance of Crohn's disease among coeliac patients is also noticeable.

3.8. Family screening

In our centre, family screening for all the first-degree relatives of index coeliac patients is available. Until recently, according to guidelines, the first step of screening has been serology [13,14]. Formerly the test of choice was the measurement of the titres of the anti-endomysium antibody, recently replaced by anti-tissue transglutaminase antibody. In cases of increased anti-tissue transglutaminase antibody level or other anamnestic data or clinical symptoms suggesting coeliac disease, duodenum biopsy samples are taken. Out of the 178 coeliac patients at our centre, 90 coeliac patients (51%) have brought a total of 197 first-degree relatives (80 males). Seropositivity was detected in 47 first-degree relatives (23.8%), 14 males and 33 females (30% versus 70%).

However, in the latest ESPGHAN guideline, the first test for asymptomatic people belonging to any known risk group is HLA phenotyping [1]. Unfortunately, for the time being, this practice cannot be followed in Hungary, since this method is poorly available and even where available, then mostly it is not covered by health insurance in contrast to the nowadays widely available serological methods — notably these tests are not of the same quality and diagnostic accuracy.

3.9. Clinical symptoms

The clinical symptoms of coeliac patients belonging to our cohort, upon which the diagnosis of coeliac disease was made are presented in Table 5.

Table 4
Characteristics of coeliac disease associated diseases in our patients' cohort.

Disease	Patients number	Male/female	Prevalence at our centre
Dermatitis herpetiformis Duhring (DHD)	23	6/17	13%
Hyperthyroidism	14	2/12	8%
Crohn's disease	7	3/4	4%
Hypothyroidism	6	0/6	3.4%
Selective IgA deficiency	5	2/3	2.8%
M. Gilbert	3	1/2	1.6%
M. Scheuermann	2	0/2	1%
Endometriosis	2		1%
Systemic lupus erythematosus	1	0/1	<1%
Myasthaenia gravis	1	0/1	<1%
Type 1 diabetes mellitus	1	0/1	<1%

4. Discussion

In our retrospective study, serological, histological and family screening data, as well as the body mass index and osteodensitometry records of the 178 coeliac patients treated at our department between November of 1997 and September of 2011 were evaluated. A number of studies have shown that coeliac disease is at least twice as common among females [15–17]. In our patients' cohort, female predominance was almost 4-fold, and such a difference between the prevalence of male and female patients has not yet been published in literature.

The mean age of 38 years in our study also underlines the fact that coeliac disease is not solely a paediatric disorder, but can emerge, or more precisely, get diagnosed at higher age as well. The majority of our patients are diagnosed with coeliac disease in a 20-year-long interval, between the ages of 26 and 45 years, as shown in Fig. 2. However, we diagnosed patients with coeliac disease well over the age of 70 years, whose disease is supposed to have been active for decades. Other studies carried out among adult coeliac patients also suggest a similar age distribution, with the mean age being 33 years in a Spanish, and 39.9 years in an Italian study, respectively [18,19]. In the past 3 decades, one can clearly observe a trend among adult celiacs and that is an increasing incidence of patients presenting only minor symptoms instead of heavy malabsorption-related symptoms and complications [20,21]. This phenomenon could be at least partly responsible for the shift in age distribution of adult coeliac disease patients [22]. Interestingly, our patients' cohort is fairly young in comparison to the ones in literature, with a mean age of 38 years and only 21% of patients being over 50 years of age.

Currently, the two-step serological testing is recommended, with anti-tissue transglutaminase antibody being the first line test, and in case of seropositivity, and anti-endomysium antibody test is performed for confirmation [23,24]. The current ESPGHAN guideline renders duodenal biopsy redundant only for patients with HLA-positivity, and anti-tissue transglutaminase antibody titre with at least 10 times over the upper limit of normal range, confirmed with anti-endomysium antibody positivity [1].

In our patients' cohort, baseline anti-tissue transglutaminase and anti-endomysium antibody tests proved to be positive in a total of 86% of the cases, which is in line with data in literature [23–25]. These results provide further evidence for the necessity of duodenal biopsies. In our material, 17% of coeliac disease patients were seronegative. In these cases, histology, HLA phenotyping, anamnestic and clinical data are required for diagnosis. That means that relying exclusively on serology, we would have failed to diagnose coeliac disease in 26 patients. It is advisable to look at the serological results in accordance with the histological records, comparing the increased titres with the severity of the histological damage (Table 1).

Histology was available for 133 patients. At the time of the diagnosis, the majority of patients presented advanced stage according to Marsh–Oberhuber classification (Marsh 3b 13%, Marsh 3c: 50% versus Marsh 1–3a, a total of 30%). These results correspond well with results from previous studies [19,26,27]. This finding suggests that adult patients with coeliac disease are diagnosed with their disease

Table 5
Clinical symptoms of coeliac disease experienced in our patients' cohort.

Clinical symptoms of coeliac disease:
1. General symptoms: *fatigue, weight loss*
2. Gastrointestinal symptoms: *diarrhea, steatorrhea, bloating, nausea, vomiting, abdominal pain, aphthous lesions in oral cavity*
3. Bone and joint symptoms: *osteopenia, osteoporosis, arthralgia*
4. Hematopoietic symptoms: *iron deficiency anaemia*
5. Obstetrical and gynecological: *menstrual disturbances, amenorrhoea, infertility, recurrent miscarriages*
6. Urological symptoms: *male infertility*
7. Neurological symptoms: *peripheral neuropathy*

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having been active for years, or even decades. This tendency of late diagnosis can be changed by continuously raising awareness of the disease both among doctors and the public. Furthermore, by accomplishing family screening among first-degree relatives of index coeliac patients, family members will be provided with the chance of being diagnosed at an earlier stage of the disease, with a more moderate activity.

In our setting, 83% of coeliac patients had both seropositivity and villous atrophy. In the subgroup of coeliac disease patients with conflicting histological and serological results, seronegativity was accompanied with histological positivity 3 times more frequently, than seropositivity with negative histology. This result is in line with the observation, that serology can be false-negative in patients with mild histological lesions [26–28]. Seropositivity with negative histology is deemed to be a consequence of either a sampling error upon taking the biopsy or misinterpretation. Statistical analysis showed significant correlation between anti-tissue transglutaminase antibody-titres and the severity of histological lesions ($p = 0.0011$), in line with the corresponding literature [7–10].

Unlike coeliac children, the vast majority of adult coeliacs are not malnourished, even overweight patients are not uncommon [29–31]. In our study, the mean body mass index value of 21.6 kg/m^2 also falls within the normal range provided by the WHO. The ratio of patients with low body mass index (14%) and the ratio of overweight and obese patients (11.8%) are both significant. Separating the data according to gender, males presented a mean body mass index value of 23.05 kg/m^2 and females a mean body mass index value of 21.07 kg/m^2, respectively. The rate of overweight patients was higher among male patients. Bardella and his colleagues observed the opposite correlation [16].

Not surprisingly, the majority of coeliac disease patients with a body mass index under 18 kg/m^2 presented Marsh 3c lesions. Notably, patients with normal body mass index values showed almost equally as much Marsh 3c lesions than less severe mucosa damage. Moreover, even in the subgroup of overweight coeliacs, Marsh 3c lesions were marginally less frequent than the histologically milder lesions (Table 2). Based on this observation, the main role of body mass index calculation is not to support the diagnosis, but, besides serology, to serve as a follow-up marker of dietary adherence for patients showing overt malabsorption before starting the glutenfree diet.

Normal bone mineral density was the most common osteodensitometry result, followed by osteopenia and osteoporosis. An opposite tendency is reported in the literature, with osteoporosis being reported to be more common for newly diagnosed patients than osteopenia, and patients with normal bone mineral density are also represented by lower rates, than patients with decreased bone mineral density [32–34]. In our records, osteoporosis was the most common osteodensitometry result only in the subset of patients with a body mass index value under 18 kg/m^2. Possible causes for this phenomenon are the decreased absorption of vitamin D and calcium caused by malabsorption due to villous atrophy, the decreased intake of calcium due to secondary lactose intolerance, and the consequent secondary hyperparathyroidism [35,36]. When evaluating the correlation between decreased bone mineral density and the severity of villous atrophy, osteoporosis was more commonly associated with more advanced histological damage (Marsh 3b and 3c), whereas osteopenia was more frequent in patients with less severe villous atrophy (Marsh 3a), in accordance with data in literature [18]. Notably, linear regression test provided a statistically significant correlation between anti-tissue transglutaminase antibody titres and bone mineral density values ($p = 0.001$), similarly to the results reported by Albulova et al. [37].

At the time of diagnosis, 63 coeliac patients (35%) previously diagnosed with or were newly discovered to suffer from diseases known to be associated with coeliac disease (Table 4). Female dominance in presenting associated diseases was prominent in our patient cohort (79%), in accordance with experience reported from other centres [18,38,39]. Notably, the high prevalence of dermatitis herpetiformis in our material is a bias, due to the result of an intense cooperation with the Department of Dermatology, Dermatooncology and Venerology. However, other studies also reported dermatitis herpetiformis occurrence exceeding 10% for young adult coeliac patients [40–42]. Thyroid diseases were in the forefront of associated disorders (11.4%), that is in total accordance with the prevalence of 10–15% reported in previous publications [43–46]. The rate of selective IgA-deficiency in our sample (2.8%) is also consistent with previous results (3%) [47,48]. In addition, the number of patients suffering from both Crohn's disease and coeliac disease has been recently on the rise [23,49,50].

The prevalence of coeliac disease in the general population is over 1% in Hungary [51]. The prevalence in the most exposed risk group, namely the first degree relatives is more than 10%, but even among second degree relatives, prevalence rates of 2.6–5.5% were reported [24,30,52,53]. In our experience, there is an improving tendency of participation in family-screening among the relatives of index coeliac patients (51%), knowing that this figure is still far from being optimal. In the light of these marked prevalence rates, family screening is mandatory among first-degree relatives of coeliac patients [1]. Following this policy, the emergence of complications and associated diseases can be prevented, or their progression can be diminished, which leads to a significant reduction of diagnostic and therapeutic expenses.

The retrospective analysis of the charts in our coeliac centre inevitably has some limitations. The evaluation of histological samples was performed mainly, but not in all cases, at the 1st Department of Pathology and Experimental Cancer Research of the Semmelweis University by several histologists, who were blinded to clinical data. Histological records received from external pathology departments often lacked some of the crucial parameters (IEL/EC rate, crypta-villi rate, etc.) making the exact definition of Marsh–Oberhuber classification impossible. Another bias to be mentioned is that our coeliac centre, being a referral centre for coeliac disease, is often expected to provide second opinion for coeliac patients whose histological and serological results originate from external sources. According to our experience, these results need to be handled with care meaning they frequently require reconsideration. Moreover, patients sent to our centre are on glutenfree diet with rising frequency and already have been for a couple of months at the time of our first encounter, thereby causing serious difficulties in decision making. Furthermore, differences between the sensitivity and diagnostic accuracy of ELISA kits are also potential sources of error, although the extent of these errors does not reach the level of significance.

In conclusion, there are surprisingly few publications in literature reviewing the charts of coeliac patients of a single coeliac centre in total. The few papers that are available describe the characteristics of smaller patients' cohort, than the one we presented. Similarly to other studies, age distribution proves that coeliac disease can become overt at every age. Also in line with previous reports, female dominance is remarkable, especially in the field of decreased bone mineral density and associated diseases. At the time of diagnosis, histological results mostly show severe villous atrophy, suggesting years or even decades of latency of the disease. Serological examinations are vital in making the diagnosis along with histological results, and furthermore, these methods are indispensable for monitoring dietary adherence and performing family screening and epidemiological examinations. The mean body mass index value of our sample is within normal range proving that adult coeliacs are not necessarily malnourished, therefore awareness of the disease should not be limited to abnormally thin patients. The high prevalence of associated disorders clearly demonstrates that coeliac disease is a true systemic disorder. The 24% prevalence of coeliac disease obtained at family screening clearly demonstrates the necessity of family screening among first degree relatives.

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Learning points

- This is the first publication from our country on an adult coeliac population.
- Female predominance was highly significant.
- Coeliac disease associated disorders were present in 35% of our patients confirming that coeliac disease is indeed a systemic autoimmune disorder.
- The prevalence of 24% of coeliac disease among first degree relatives underlines the necessity of family screening.

Conflict of interests

The authors declare to have no conflict of interest. This work was not supported by any academic grant, scholarships, etc. This manuscript has not been published previously and is currently not even under consideration (in whole or in part) for publication elsewhere. The manuscript is approved by all Authors. We understand that in case of acceptance of the manuscript the copyright is transferred to European Journal of Internal Medicine.

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