THE PREVALENCE OF CELIAC DISEASE IN ADULT AND ADOLESCENT ROMANIAN PATIENTS WITH TYPE 1 DIABETES MELLITUS

Elena Z. Cev[1], Oliviu Pascu[2], Viorel Serban[3], C.J.J Mulder[4], Sorina Taban[5], Gabriel Samasca[6]

REZUMAT

Introducere: Coexistența dintre boala celiacă (BC) și diabetul zaharat tip 1(DZ) a fost frecvent descrisă, asocierea celor două boli fiind posibilă datorită predispoziției genetice comune. **Obiectiv:** Obiectivele studiului au fost de a determina prevalența bolii celiace la pacienții adolescenți și adulți cu DZ tip 1 în România și de a evalua caracteristicile clinice, biologice și histopatologice ale BC la pacienții luați în screening. **Pacienți și metode:** Au fost incluși în studiu un număr de 307 pacienți cu DZ tip 1 (158 femei, 149 bărbați), vârsta medie a fost de 27 de ani (limite 14-38 ani). Screeningul BC s-a efectuat prin determinarea anticorpilor totali anti-transglutaminază tisulară. La cazurile pozitive s-a efectuat endoscopie digestivă superioară cu biopsie duodenală. Pacienții au fost evaluați ca vârstă, sex, vârsta de debut și vechimea diabetului. Controlul metabolic a fost evaluat prin determinarea hemoglobinei A1c, a necesarului de insulină și cuantificarea anamnestică a episoadelor hipoglicemice sau hiperglicemice cât și a prezenței complicațiilor cronice. **Rezultate:** Anticorpii antitransglutaminază tisulară au fost pozitivi la șaptesprezece pacienți (5,5%). Endoscopia digestivă superioară cu biopsie duodenală s-a efectutat la 16 pacienți. Conform clasificării histopatologice Marsh, patru pacienți nu au prezentat modificări ale mucoasei, doi au fost Marsh 1, unul Marsh 2 și nouă Marsh 3. Prevalența BC dovedită bioptic la lotul studiat a fost de 3,9%. BC a fost mai frecventă la femei (83,3%). Doar doi pacienți (16,7%) au prezentat tabloul clinic classic al BC, patru (33,33%) au fost asimptomatici și șase (50%) au avut simptome gastrointestinale nespecifice. Cinci pacienți (41,7%) cu BC au fost diagnosticați cu anemie prin deficit de fier, iar 3 (25%) cu osteopenie. **Concluzii:** Studiul de față confirmă prevalența crescută a BC la pacienții cu DZ tip 1 în Romania. Boala celiacă asimptomatică apare frecvent la pacienții cu DZ tip 1 și este frecvent asociată cu sindrom de malabsorbție subclinic. Screeningul BC ar trebui să fie inclus în evaluarea de rutină DZ tip datorită prevalenței crescute a bolii la acest grup de pacienți.
Cuvinte cheie: boala celiaca, diabet zaharat tip 1, screening, anticorpi antitransglutaminaza

ABSTRACT

Background: Celiac disease (CD) and type 1 diabetes mellitus (T1DM) can frequently coexist, presumably due to a common genetic predisposition. **Aims:** to determine the prevalence of celiac disease among Romanian adolescents and adults with T1DM and to describe clinical, and histopathology features of celiac disease in screened patients with T1DM. **Patients and methods:** A total of 307 T1DM patients (158 females, 149 males) age range 14-38 years, median 27 years, were prospectively screened for CD by determination of total anti-tissue transglutaminase antibodies (t-TGA). In the positive cases, upper gastrointestinal endoscopy with duodenal biopsies was performed and gluten free diet was recommended if CD was confirmed. Patients were evaluated for age, sex, age of the onset, duration of T1DM. Metabolic control was assessed by hemoglobin A1c, frequency of hypoglycemic and hyperglycemic episodes, insulin requirements and chronic complications of T1DM. **Results:** Seventeen patients (5.5%) were positive for total t-TGA. Sixteen patients underwent upper endoscopy with duodenal biopsies. According to the Marsh histopathological classification, four patients had no mucosal modification (Marsh 0), two were Marsh 1, one was Marsh 2, and nine were with Marsh 3. The prevalence of biopsy-confirmed CD was 3.9%. CD was more frequently diagnosed in females (83.3%). Only two (16.7%) patients had typical clinical features for CD, foue (33.3%) were asymptomatic and six (50%) had nonspecific mild gastrointestinal symptoms. Five patients with CD (41.7%) presented iron deficiency anemia and three (25%) osteopenia. **Conclusions:** The present study confirms that CD is prevalent in T1DM in Romania. Asymptomatic celiac disease occurs frequently in T1DM patients, and is often associated with subclinical malabsorption. Because of the high prevalence of CD in T1DM patients screening should be part of routine evaluation of T1DM.
Key Words: celiac disease, type 1 diabetes mellitus, screening, anti-tissue transglutaminase antibodies

[1] Department of Gastroenterology, Municipal Hospital Lugoj, [2] Department of Gastroenterology, 3rd Medical Clinic, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, [3] Department of Diabetes and Internal Medicine, Victor Babes University of medicine and Pharmacy, Timisoara, [4] Department of Gastroenterology, VU University Medical Center, Amsterdam, [5]Department of Pathology, Victor Babes University of Medicine and Pharmacy, Timisoara, [6] Department of Imunology, Clinical Children Emergency Hospital Cluj

Correspondence to:
Elena Cev, Department of Gastroenterology, Municipal Hospital Lugoj,
Tel. +40723676298.
Email: elenac21@yahoo.com

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INTRODUCTION

Celiac disease is a chronic autoimmune disorder characterized by immune-mediated damage to the mucosa of the small intestine, triggered by ingestion of gluten and related proteins found in cereal grains such as wheat, barley and rye.[1]

Type 1 diabetes mellitus (DM) is also a chronic autoimmune disorder with varying degrees of insulin deficiency resulting from an immune-mediated destruction of pancreatic β-cells, usually presenting in young individuals.[2]

Celiac disease is the second most prevalent autoimmune condition accompanying type 1 diabetes after autoimmune thyroid disease.[3] Coexistence of the diseases has been previously described since the late 1960's. In several studies the figures reported for its prevalence have range from 1% to 8%, approximately 10 times higher than expected.[4-7]

The co-occurrence of both diseases may be explained by a similar genetic background and similar trigger mechanisms associated with HLA DQ2 and DQ8 for the autoimmune process. More than 90% of patients with CD and approximately 60% to 70% of type 1 diabetics carry the human leukocyte antigen heterodimer DQA1*0501DQB10201.[8,9]

Like the "iceberg" trend described in general population, the majority patients with CD are asymptomatic, or are not aware of symptoms.[10] Some patients present problems recognized only retrospectively as resulting from celiac disease; it is common for "asymptomatic" patients to report improved health or sense of well-being when following a gluten-free diet.[11]

More controversial is the question of whether CD affects blood glucose control. It has been observed that patients with CD have hypoglycemic episodes and reduced insulin needs before diagnosis, presumably because of malabsorption but the results are conflicting.[12,13] In a case controlled study of the incidence of hypoglycemia in patients with untreated CD, Mohn et al. found that there were significantly more episodes of hypoglycemia in CD patients than in controls. Institution of a gluten-free diet reduced hypoglycemia, but only after several months from initiation.[14]

Serological screening as part of routine diabetes care provides an opportunity to diagnose celiac disease at an early preclinical silent stage. However, screening in this population has not been universally adopted, and controversy exists as to whether it is of any clinical benefit.

AIMS

The present study was designed to evaluate the prevalence of CD among the adolescent and adult Romanian type 1 DM patients using total t-TGA as a screening test and to evaluate the metabolic control, clinical and histopathology features of CD in this population.

PATIENTS AND METHODS

Three hundred and seven patients with type 1 DM were prospectively enrolled in the study during the period between January 2004 and December 2008. Patients were admitted in the "Cristian Serban" Clinical Medical Center of Evaluation and Rehabilitation for Children and Adolescent from Buzias, and came from different areas of Romania. The study was explained to the patients and written consent was obtained. All patients were interviewed for full medical history of diabetes including age at onset of illness, duration of disease, metabolic control, daily insulin requirements, and chronic complications. Also a questionnaire was filled out about any history and symptoms compatible with celiac disease. Presence of typical or atypical symptoms, metabolic control in terms of values of hemoglobin A1c, frequency of hypoglycemic or hyperglycemic episodes were compared between diabetic patients with CD and without CD. The presence of the second or third autoimmune disease in the two groups was also investigated.

Serological screening

After formal consenting, 5 ml of blood was collected from each subject. Samples were centrifuged and the serum was separated, and immediately stored at -70 °C. Total anti-tissue transglutaminase (IgA and IgG) antibodies (t-TGA) were determined by enzyme-linked immunosorbent assay (ELISA) with human recombinant t-TG as antigen, using a commercial kit (Test AESKULISA, CeliCheck, Germany). Results were considered positive when the t-TGA levels were greater than 24 U/mL.

The patients with positive t-TGA were tested for antiendomisium antibodies IgA (EMA) measured by indirect immunoflorescence using unfixed cryosections of monkey esophagus (EMA), anti deamidated gliadin antibodies IgA and IgG determined by ELISA method.

Intestinal Biopsy Procedure

The patients with t-TGA positive were clinically evaluated and submitted to upper gastrointestinal endoscopy. Four specimens were obtained from the distal part of the duodenum. The specimens were put in formaldehyde solution and hematoxylin and eosin-stained sections were histologically examined.

The intestinal mucosa was assessed according to the mucosal changes described by Marsh and Oberhuber scoring system. The infiltrative (type 1 lesion) comprises normal mucosal architecture in which the villous epithelium is markedly infiltrated by intraepithelial lymphocytes (IEL) (more than 30 IELs /100 enterocytes). The hyperplastic (type 2) lesion is similar to the type 1 lesion but with the addition of enlarged crypts. The destructive (type 3) lesion is characterized by some degree of villous atrophy (3a mild villous atrophy, 3b moderate villous atrophy, 3c total villous atrophy), with inflammation and hyperplastic crypts.[15,16]

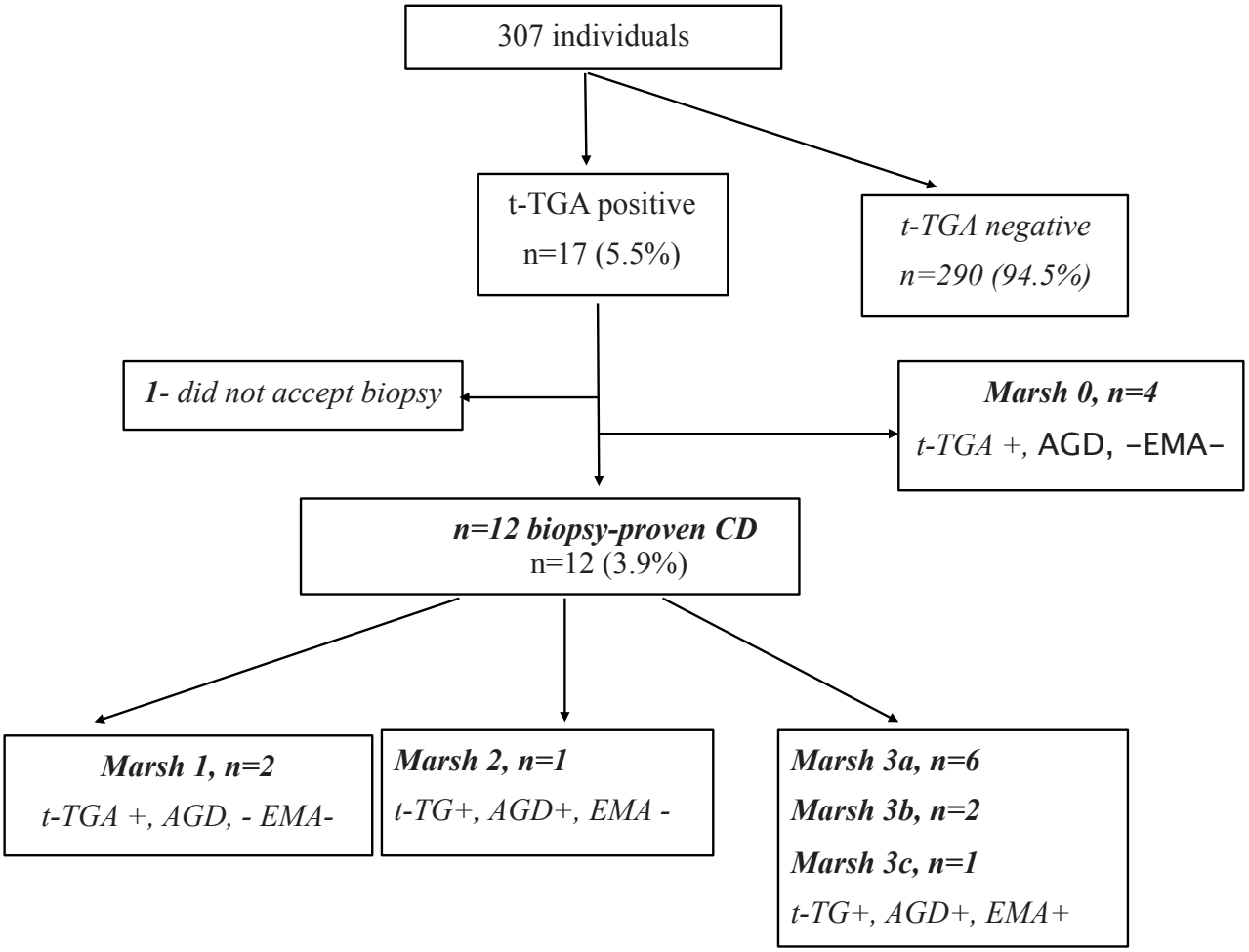


Figure 1. Flow diagram of the evaluated patients.

The diagnosis of CD was confirmed by the histopathologic demonstration of the mucosal lesions followed by serologic response to a gluten free diet and by clinical remission in symptomatic patients.

Patient follow-up and response to gluten-free diet

Gluten free diet (GFD) was recommended to all patients with histological abnormality. Clinical, histological, and serological assessments were carried out in all patients who adhered to a GFD at least one year after starting the diet. For the remaining individuals with mild positive tTGA but no histological abnormality at baseline, which were on a gluten-containing diet, clinical, and serological assessments were requested.

A complete histological response was defined as a decrease from Marsh 3 to Marsh 1 or Marsh 0, and in Marsh 1 cases, normalization in the IEL count or a reduction of at least 50% from the basal biopsy.

A partial histological response was considered an improvement in the degree of atrophy. In patients who did not accept a biopsy after GFD, negative serology was considered partial response. Patients with Marsh 1 were particularly encouraged to undergo serological and histological retesting during follow-up.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS), version 16. Simple statistics such as frequency, mean and standard deviation were used and chi-square, t-test and Mann-Whitney U test were performed for comparison. The results were considered to have a statistical significance when the P values were less than 0.05.

RESULTS

Prevalence of CD

Serological screening for CD based for total t-TGA was performed in 307 patients with T1DM with a nearly equal sex distribution 158 females and 149 males. The mean age at diagnosis of T1DM was 14 years (range 1-33 years) and the mean duration of DM was 7 years (range 1-29).

Seventeen patients (5.5%) were positive for t-TGA (median value 98 UI/ml, range 26-1150 UI/ml, the cut-off value was established at 24 U/ml). Of the 17 patients positive for t-TGA, 11 were positive

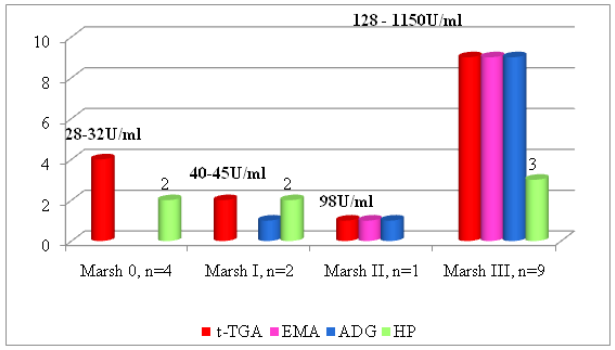
for AGD (IgG and IgA) and 9 for EMA. Selective IgA deficiency was not observed. Sixteen of these 17 underwent an upper endoscopy with intestinal biopsy, which disclosed the following histological findings: four Marsh 0, two Marsh 1, one Marsh 2, and nine with Marsh 3 (six 3a, two 3b, one 3c). Seven cases had Helicobacter pylori infection (two Marsh 0, one Marsh 1, and three Marsh 3).

The estimated sensitivity of t-TGA was 100% and the specificity was 98% ($p<0.0001$).

Thus the prevalence of biopsy-proven lesions of the CD spectrum was 3.9% (12 patients).

The value of t-TGA increases with the severity of the mucosal lesions. The patients with Marsh 0 and 1 were negative for EMA and ADG and the value of t-TGA was between 28 and 45 U/ml. The patient with Marsh 2 was positive for ADG but negative for EMA. All Marsh 3 patients were positive for ADG and EMA, in this cases the values of antibodies were correlated with higher titer of t-TGA (128-1150U/ml). There were four false positive values of t-TG, two of them where with positive Helicobacter Pylori.

Values of tTGA, ADG and EMA related to the degree of mucosal damage are shown in Figure 2.



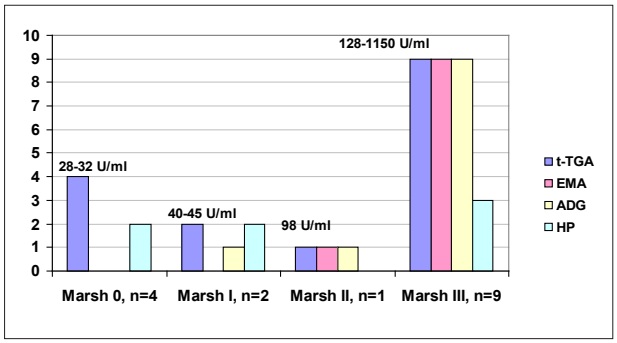


Figure 2. Values of t-TG related to the degree of histological damage.

Clinical feature of CD and T1DM

Twelve patients, 10 (83.4%) women and 2 (16.6%) men were identified with CD. The mean age of the patients with CD was 27 years (range 15-35 years) significantly higher than the control group T1DM (mean 23 years, range 7-38 years) ($p=0.003$). The mean duration of diabetes was 10 years (range 5-27 years) significantly higher than in patients with T1DM (mean 7 years, range: 1-29 years) ($p=0.041$).

Three (25%) of the 12 patients had associated autoimmune disorders, two were with hypothyroidism due to autoimmune thyroiditis and one with vitiligo. One patient was with Down syndrome.

There were no significant differences between the two groups regarding body mass index, insulin requirement and hemoglobin A_{1c} (HbA_{1c}). The mean HbA_{1c} was greater than 8% for both groups and revealed a poor metabolic control of diabetes in the previous three months.

In addition, the patients with CD had more hypoglycemic episodes in the previous 6 months than the control group (8/12 *vs.* 27/295, $p=0.001$) including severe hypoglycemia (hypoglycemic coma) (6/12 *vs.* 79/295, $p=0.0024$). The incidence of ketoacidosis episodes was significantly higher in patients with CD compared with control group (7/12 *vs.* 43/295 $p=0.0008$). The frequency of hypoglycemic or hyperglycemic episodes was not correlated the degree of severity of the mucosal lesions.

Regarding the chronic complications of diabetes, the presence of diabetic nephropathy, retinopathy, distal symmetrical polyneuropathy and vegetative neuropathy (nocturnal diarrhea, asymptomatic hypoglycemia, gastroparesis) was evaluated comparatively for the two groups.

Diabetic nephropathy, retinopathy and gastroparesis were significantly more frequent in the patients with CD ($p<0.05$) than the control group. This aspect can be interpreted in correlation with higher mean diabetes duration in the CD group (10 years vs. 7 years).

The chronic complications were not correlated with the degrees of severity of mucosal lesions. Five (41.7%) patients (four Marsh 3 and one Marsh 1) had no chronic complications and seven patients (58.3%) presented with chronic complications (one Marsh 1, one Marsh 2 and five with Marsh 3).

All patients were also assessed for the presence of gastrointestinal symptoms of CD. Four patients (33.3%) had no gastrointestinal symptom, one case had Down disease and vitiligo and in another one low level of serum ferritin was found.

Typical clinical features of CD including diarrhea, abdominal pain and weight loss were present in just two cases (16.7%), three patients (25%) had chronic constipation, six patients (50%) complained of abdominal discomfort, and five (41.7%) presented recurrent symptoms like nausea or vomiting.

Table 1. Clinical characteristics of diabetic patients with CD compared with control group

Characteristics	T1DM with CD	T1DM	p value
n	12	295	
Sex	2/10	110/126	0.037
Age(years)	27(15-35)	23 (14-38)	0.013
Duration of diabetes (years)	10 (5-27)	7 (1-29)	0.041
HbA1c (%)	9.85%	8,53%	0,64
Insulin requirements (U/Kg/day)	0.80	0.79	0.418
Hypoglycemia (6 months)	8 (66.66%)	27 (9.15%)	<0.0001
Hypoglycemic coma	6 (50%)	79(26.67%)	0.024
Ketoacidosis	7 (58.33%)	43(14.57%)	0.008
Diarrhea	2 (16.66%)	12 (4.06%)	0.100
Abdominal pain	4 (33.33%)	13 (5.38%)	0.003
Weight loss	3 (25%)	15 (5.08)	0.0004
Abdominal discomfort	6 (50%)	37(12.54%)	0.0006
Constipation	3 (25%)	15 (5.08)	0.024
Vomiting and nausea	4 (33.33%)	9 (3.50%)	0.0008
Anemia	5 (41.66%)	-	-
Osteopenia	3 (25%)	-	-
Recurrent abortion	2 (20%)	-	-
Autoimune tyroiditis	2	8	-
Vitiligo	1	1	-
Pssoriazis	0	3	-

Gastrointestinal complaints like abdominal pain, abdominal discomfort, chronic constipation, recurrent nausea and vomiting were significantly frequent in the patients with CD than in control group ($p<0.05$).

Atypical symptoms and signs of CD were present in 10 (83.4%) patients with CD. Iron deficiency anemia was present in six cases (60%), osteopenia in three cases (25%), recurrent abortion in two patients (16.7%), and hypocalcemia and hypomagnesemia were found in four patients (33.3%). The patients with typical symptoms of CD had also iron deficiency anemia, hypocalcemia, and mildly elevated liver enzyme levels were found in one patient.

Clinical characteristics of diabetic patients with CD compared with control group are shown in Table 1.

A progressive increase in severity of most symptoms from Marsh 1 to Marsh 3 was observed. One patient with Marsh 1 and the Marsh 2 patient were asymptomatic. Another patient with Marsh 1 was with mild gastrointestinal symptoms and also Helicobacter Pylori infection.

Follow up after 1 year of gluten free diet

There were 16 patients with positive serology. At baseline, four patients had mild elevation of t-TGA and no mucosal lesions (Marsh 0), two of them were with positive Helicobacter Pylori. One of them agreed to repeat the serology after one year and the t-TGA was negative.

The patient with Marsh 1 and Helicobacter Pylory infection and mild dyspeptic-like symptoms was not under GFD, the Helicobacter Pylori eradication was done and the patient returned after one year with negative serology and biopsy . One patient with Marsh 1 refused GFD and the follow-up.

From the eight patients (66.7%) (one with Marsh 2 and six with Marsh 3) who maintained the GFD for a year, in six cases the t-TGA values were negative at follow-up. Two patients with Marsh 3 lesions did not agree with GFD or one year follow-up and were excluded from the study.

A complete histological response as a decrease in severity of mucosal lesions from Marsh 3 to Marsh 1 or Marsh 0 was observed in 6 cases. All cases were asymptomatic after first year and had a significant improvement in the metabolic control (assessed through HbA_{1c} and hypoglycemic ore ketoacidosis episodes). In these cases the mean value of HbA1c decrease after one year from 9.4% to 7.8%.

A partial histological response was observed in two cases, one from Marsh 3c to Marsh 3a and another one from Marsh 3b to Marsh 2 in which the GFD was intermittently maintained. The clinical improvement and metabolic control for both cases were poor.

DISSCUSSIONS

An association between CD and type 1 diabetes mellitus has been recognized for more than 40 years.[5]

European studies in diabetic populations have estimated the prevalence of CD to be 1.5% to 4.6% in children and 2% to 4.1% in adults, significantly higher than the estimated 0.5% to 1% overall prevalence of CD observed in the general population. The literature published in the last 5 years reported a higher prevalence - 4.4% to 13.8%, this is probably due to more specific screening methods used in the last years than in the past.[4-7,18-21]

In Eastern Europe and in Romania few data is available regarding the prevalence of CD in general or in high risk population. In Romania in 2002 one study was performed in a selected population referred for endoscopy and the prevalence of CD was 2.22%.[22]

The prevalence of the biopsy-proven of CD in T1DM in this study was 3.9% with a majority of cases in females (83.4%). These data are similar that reported in previous studies in adult patients.

The celiac disease may develop at any age both during childhood or adolescence and is relatively common in the adult and elderly patients.[23]

In present study the age of the patients with CD and the mean diabetes duration were significantly higher than in control patients. Longitudinal studies, mostly performed in children, reported a mean time of 2 to 6 years between onset of T1DM and CD diagnosis and suggested that the screening for CD might be reduced in frequency with increasing duration of T1DM.[9,24] We cannot comment this aspect because our study was in adult population and the mean duration of T1DM for entire group of diabetics was 7 years.

Related to the duration of T1DM, the chronic specific complications of diabetes were more frequently encountered in CD patients, similar to other reports.[25]

There were no significant differences between the groups regarding body mass index, insulin requirements and HbA_{1c}.

The patients with CD had more frequent hypoglycemic episodes in the previous 6 months than the control group, including severe hypoglycemia. The incidence of ketoacidosis episodes was significantly higher at the patients with CD compared with control group.

A study by Acerini et al in a T1DM population found no difference between the celiac and non-celiac population in terms of HbA1c ant insulin requirements.[13] Another study of adults with T1DM found no difference in metabolic control of diabetes. Some studies have outlined the increased rate of hypoglycemic crises in DM1 patients with untreated CD owing to an erratic absorption of nutrients.[26] An Italian study demonstrated that the number of hypoglycemic episodes was twofold increased in celiac patients between 6 months before diagnosis and six months after initiation of GFD.[14]

Four patients were asymptomatic. Only two patients with CD identified by screening complained of suggestive symptoms of CD like diarrhea, abdominal pain and weight loss. More frequently nonspecific, mild gastrointestinal symptoms like constipation, abdominal discomfort, vomiting and nausea were reported. Extra-intestinal symptoms were present, the iron deficiency anemia was detected in six patients, and two of them had no gastrointestinal symptoms. Two patients had recurrent abortion, and osteopenia was found in three cases.

In three cases the third autoimmune disorder was previously diagnosed (two with autoimmune thyroiditis and one with vitiligo). The patient with vitiligo had also Down syndrome.

It has been shown that the most patients with CD and T1DM have few or no symptoms related to malabsorption, and when gastrointestinal complaints are present, they are often mild and appreciated only retrospectively.[10] Extraintestinal symptoms like iron deficiency anemia, osteopenia, infertility and recurrent abortion, mild hepatocellular dysfunction are frequently present in patients with both T1DM and CD.[26,27] "Asymptomatic" patients or with problems recognized only retrospectively as caused by CD report improvement of the quality of life when following the GFD.[28]

Eight (66.7%) patients with T1DM and CD agreed with GFD, six of them had complete clinical and histological response the metabolic control of diabetes was also improved and they reported that blood glucose control was easier to maintain. At the baseline just one of them was with suggestive symptoms of CD, another five patients were asymptomatic, with mild gastrointestinal complains or with extraintestinal signs of malabsorbtion. These patients with "silent" celiac disease recognized retrospectively the symptoms and report improved health or sense of well-being after following the GFD. In two cases just a partial histological response was obtained, with slight improvement of clinical and metabolic control but they admitted to only follow GFD intermittently.

The high prevalence of CD in T1DM patients worldwide described, furthermore the presence of silent or subclinical forms of CD and also the impact of GFD on the metabolic control and resolution of atypical symptoms, support the recommendation of regular screening for CD starting at the onset of T1DM.[29]

CONCLUSIONS

In this study the prevalence of CD among the T1DM patients in Romania was 3.9%, which is comparable with European studies in adult patient with CD. Unfortunately we don't have screening studies in general population or in another risk group to compare the data.

The gastroenterologist and diabetologist must be aware of atypical clinical feature of CD and the screening of CD at T1DM patients in Romania must be intensified.

REFERENCES

1. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med 2002;346:180-8.
2. Atkynson MA, Eisenbarth GS. Type 1 diabetes: New perspectives on disease pathogenesis and treatment. Lancet 2001;358:221-9.
3. Chang CL, Biswas M, Benton A, et al. Prospective screening for coeliac disease in patients with Graves' hyperthyroidism using anti-gliadin and tissue transglutaminase antibodies. ClinEndocrinol 2005;62:303-6.
4. Cronin CC, Shanahan F. Insulin-dependent diabetes mellitus and celiac disease. Lancet 1997;349:1096–7.
5. Lamapasona V, Bonfanti R, Bazzigaluppi E, et al. Antibodies to tissue transglutaminase C in type I diabetes. Diabetologia 1999;42:1195–8.
6. Seissler J, Schott M, Boms S, et al. Autoantibodies to human tissue transglutaminase identify silent coeliac disease in type I diabetes. Diabetologia 1999;42:1440–1.
7. Schober E, Bittmann B, Granditsch G, et al. Screening by antiendomysium antibodies for celiac disease in diabetic children and adolescents in Austria. J Pediatr Gastroenterol Nutr 2000;30:391–6.
8. Gorodezky C, Alaez C, Murguia A, et al. HLA and autoimmune diseases: Type 1 diabetes(T1D) as an example. Autoimmun Rev 2006;5:187-94.
9. Saukkonen T, Savilahti E, Reijonen H, et al. Coeliac disease: frequent occurrence after clinical onset of insulin-dependent diabetes mellitus. Childhood Diabetes in Finland Study Group. Diabet Med 1996;13:464-70.
10. Cronin CC, Feighery A, Ferriss JB, et al. High prevalence of celiac disease among patients with insulin-dependent (type I) diabetes mellitus. Am J Gastroenterol 1997;92:2210–2.
11. Madacsy L, Arato A, Korner A. Celiac disease as a frequent cause of abdominal symptoms in children with insulin-dependent diabetes mellitus. Clin Pediatr (Phila) 1997;36:185–6.
12. Iafusco D, Rea F, Chiarelli F, et al. Effect of gluten-free diet on the metabolic control of type 1 diabetes in patients with diabetes and celiac disease. Diabetes Care 2000;23:712–3.
13. Acerini CL, Ahmed ML, Ross KM, et al. Coeliac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. Diabet Med 1998;15:38–44.
14. Mohn A, Cerruto M, Lafusco D, et al. Celiac disease in children and adolescents with type I diabetes: importance of hypoglycemia. J Pediatr Gastroenterol Nutr 2001;32:37–40.
15. Marsh MN. Grains of truth: evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. Gut 1990;31(1):111-4.
16. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999;11(10):1185-94.
17. Payne WW. Coeliac disease and diabetes mellitus in the same patient. Great Ormond St J. 1954-1955;8:118-122.
18. Bouguerra R, Ben Salem L, Chaabouni H, et al. Celiac disease in adult patients with type 1 diabetes mellitus in Tunisia. Diabetes Metab 2005;31:83-6.
19. Sanchez-Albisua I, Wolf J, Neu A, et al. Coeliac disease in children with type 1 diabetes mellitus: the effect of the gluten free diet. Diabet Med 2005;22:1079-82.
20. Buysschaert M, Tomasi JP, Hermans MP. Prospective screening for biopsy proven celiac disease, auto-immunity and malabsorption markers in Belgian subjects with type 1 diabetes. Diabet Med 2005;22:889-92.
21. Mahmud FH, Murray JA, Kudva YC, et al. Celiac disease in type 1 diabetes mellitus in a North American community: prevalence, serologic screening, and clinical features. Mayo Clin Proc 2005;80:1429-34.
22. Dobru D, Pascu O, Tantau M, et al. The prevalence of celiac disease at endoscopy units in Romania: routine biopsies during gastroscopy are mandatory. Romanian Journal of Gastroenterology 2003,12(2):97-100.
23. van Heel DA, West J. Recent advances in celiac disease. Gut 2006;55:1037-46.
24. Maki M, Huupponen T, Holm K, Hallstrom O. Seroconversion of reticulinautoantibodies predicts coeliac disease in insulin dependent diabete smellitus. Gut 1995;36:239–42.
25. Rodrigo Saez L. Celiac disease in the adult. Rev Esp Enferm Dig 2006;98:397-407.
26. Iafusco D, Rea F, Prisco F. Hypoglycemia and reduction of the insulin requirement as a sign of celiac disease in children with IDDM. Diabetes Care 2000;23:712-3.
27. Holmes G K. Screening for celiac disease in type 1 diabetes. Arch Dis Child 2002;87:495-8.
28. Schwarzenberg S J, Brunzell C. Type 1 diabetes and celiac disease: overview and medical nutrition therapy. Diabetes Spectrum 2002;15(3):197-201.
29. Hansen D, Brock-Iacobsen B, Lund E, et al. Clinical benefit of gluten free diet in type 1 diabetic children with screening-detected celiac disease. Diabetes Care 2006;11:2452-6.