Original
ISSN 2413-0516

Common Clinical Symptoms and Concomitant Disease in Celiac Patients – A Large Cohort Study in the North-East of Iran

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(Submitted: 12 September 2021 – Revised version received: 29 September 2021 – Accepted: 21 October 2021 – Published online: 26 December 2021)

Abstract

Objectives: This study aimed to provides an overview of large cohort focusing in different clinical symptoms and concomitant disease in CD patients.

Methods: Out of total 1,164 cases, 78.86% of cases were adults, mean age 29.67 ± 15.94 and sex ratio (f/m) was 2.40. Evaluated clinical characteristics included BMI, Marsh, TGA-IgA titer, main symptoms and concomitant disease.

Result: 96.86% of CD cases were seropositive and more than 88% of patients had villous atrophy that 48.89% of them were type c. Dyspepsia 35.23%, diarrhea 18.52%, were main CD clinical symptoms. The common concomitant diseases were including nervous problems 57.43%, anemia 54.25%, osteopenia 28.23% and skin disease 23.54%.

Conclusion: The classic type is common type of CD in northeast Iran. Dyspepsia and diarrhea main clinical symptoms in these patients, consequence we recommended to screening for CD in cases whiteout classic symptoms (such as dyspepsia). Also recommended to screening for concomitant disease such as nervous problems, bon disease and anemia in female CD patients in first visit.

Keywords: Celiac disease, concomitant disease, main clinical symptoms

Introduction

Celiac disease is an autoimmune disorder characterized by mucosal injury in response to gluten in genetically predisposed individuals.[1] CD accounts for about 1% of the population worldwide and is rapidly increasing because of availability of serologic tests which have high sensitivity and specificity.

The clinical manifestations of CD can vary from asymptomatic CD to classic or typical intestinal symptoms such as diarrhea, weight loss, and abdominal pain and atypical or non-classical symptoms including iron deficiency, bloating, constipation, chronic fatigue, headache, osteoporosis, neurologic disorders (e.g., depression and gluten ataxia), reproductive disorders (e.g., menarche disorders and menopausal disorders), and oral/cutaneous disorders (e.g., dermatitis herpetiform).[2–5]

By knowing wide variety of clinical presentation, early diagnosis and treatment of CD by gluten free diet (GFD) is important in patient out come and long term complications of disease. The prevalence of autoimmune diseases and malignancies has been reported to be higher in CD patients and even in their first-degree relatives.[6–8] These patients are at risk of long-term complications, such as gastrointestinal and extra-intestinal malignancies and autoimmune disorders.[6,9] Up to 30% of concomitant immune-mediated diseases have been reported in CD patients compared to (3–11.6%) in the general population.[2,6,9] Moreover, CD has been described as a risk factor for enteropathy-associated T-cell lymphoma (EATL), non-Hodgkin lymphoma, and gastrointestinal tumors and a protective factor for other types of malignancies such as breast and lung cancers.[10–12]

The etiology of this disease is multifactorial, including environmental (gluten and intestinal infections), genetic, and immunological factors with a high genetic susceptibility, proposed by studies on HLA-DQ2 and HLA-DQ8 haplotype associations with CD.[7,10] A significant proportion of CD patients are diagnosed through screening at-risk populations such as family members of patients with CD and insulin-dependent diabetics, but mostly remain undiagnosed.[7,13,14]

A combination of serology testing and duodenal biopsy (increase intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy) is required to diagnose CD in adults.[3,15,16] Currently, the only approved treatment for CD patients is a strict GFD. Improvement and resolution of symptoms occur after days or weeks after a GFD is implemented and often leads to normalization of serological markers and duodenal villous atrophy.[1,3,17]

There are studies about risk factor, clinical finding and presentation and association of CD with other disorders in cohorts all over the world.[2,18,19] Despite the high prevalence of CD in Iran due to the high rate of gluten and bread consumption, no previous well-designed cohort study was conducted in this region.[20] Therefore, establishing the demographic characteristics and different clinical manifestations of this disease may provide important information regarding its timely diagnosis and proper management.

To the best of our knowledge, this is the first large cohort study of CD patients done in the Northeastern Iranian province of Khorasan Razavi, extensively exploring the clinical manifestations and co-occurrence of immune-mediated diseases in these patients.

Methods

Study Setting & Design

This retrospective study includes a cohort of celiac patients registered in the Celiac Disease Center of Mashhad University of Medical Sciences (MUMS), located in the Northeastern Iran. This cohort was comprised of the records of all patients (with signs or symptoms of celiac) that were referred for diagnosis to the Celiac Disease Center from Khorasan and other neighboring provinces between 2010 and 2020. The data was analyzed using STATA version 12 (STATA, USA, 2009). The level of significance was less than 0.05 for all statistical tests. This study has been approved by the ethics committee of Mashhad University of Medical Sciences (Code: IRMUMSREC.1396.112). Furthermore, a written informed consent has been obtained from all participants.

Study Population

Study population was a cohort of 1164 patients with definite or clinical diagnosis of Celiac Disease. Diagnosis of CD was ascertained by positive celiac serology (TGA-IgA) and Marsh ≥ 2 histology on duodenal biopsy. TGA-IgA were assessed by enzyme-linked immunosorbent assay,[14] Kit (Euro immune, Germany) in a research laboratory. Biopsy reports based on Marsh and modified Marsh Oberhuber Classification.[21] Seronegative CD cases was diagnosed based on mucosal atrophy and HLA typing or challenge test after ruling out all other cause of mucosal atrophy including Crohn's, infection, radiation, HIV, CVID, malignancy and peptic deodenitis and drug use. IgA deficiency patients were diagnosed based on pathology and IgG base serology of TGA and anti DGP. Seropositive CD cases were included in this cohort without biopsy, if had raised TGA-IgA and response to GFD and compatible HLA and typical presentation. Also patients without villous atrophy were included, if they were symptomatic and had high serology titer more than 10 times of normal and compatible HLA.

Data Collection

Clinical and demographic variables were included age, gender, height, weight, symptoms, Type of diseases (seropositive, seronegative or others), thyroid function, liver function and immune mediated diseases and other concomitant diseases such as Skin problem and Nervous problem were extracted from the database. Main symptoms that assessed in these patients were including dyspepsia, diarrhea, weight loss, flatulence, reflux, abdominal pain and others symptoms. TGA-IgA levels were reported in unit per milliliter using the manufacturer's supplied reference ranges: 0–20 negative, >20 positive. The highest standard in the assay was >200, (10 times upper limit of normal).

Results

Characteristics of the Patients

Of the total of 1,164 cases, 78.86% of cases were adults (age 14 or older). 70.64% were female (n = 811) and sex ratio was (F/M) 2.40. The mean age at the time of the first visit was 29.67 ± 15.94 years (ranging from 1 to 76 years) and mean age not different between genders (male = 28.99, female = 29.95, P = 0.35). However 23.63% of patients (age >15 years old) had lower weight, but 48.49% of them had normal BMI (n = 353) (Table 1), and fortunately only 3.88% of this cohort were smoker (n = 32).

Table 1. **Baseline characteristics of celiac patients**

Variables		Total	Gender/female	Sig
BMI (age >15 years)	<19	172 (23.63)	122 (70.93)	$P = 0.10^{b}$
	19–25	353 (48.49)	249 (70.54)	
	25–30	147 (20.19)	98 (66.67)	
	>30	56 (7.69)	47 (83.93)	
Pathology (Marsh)	1	54 (5.12)	47 (87.04)	$P = 0.02^{a*}$
	2	71 (6.73)	47 (66.20)	
	3	964 (88.15)	653 (70.29)	
	3 a	138 (17.95)	97 (70.29)	$P = 0.37^{b}$
	3 b	253 (32.90)	169 (66.80)	
	3 c	376 (48.89)	270 (27.00)	
Type of diseases	Seropositive CD	1111 (96.86)	784 (70.63)	$P = 0.87^{a}$
	Seronegative CD	28 (2.44)	20 (71.43)	
	IgA deficiency CD	4 (0.35)	3 (75.00)	
	Others	4 (0.35)	2 (50.00)	
Patients classification	Gastrointestinal	668 (61.12)	497 (74.40)	$P < 0.001^{b*}$
	Non-gastrointestinal	396 (36.23)	264 (66.67)	
	Screening	29 (2.65)	15 (51.72)	
TGA-IgA titer	190.84 ± 121.01 (rang 0.8, 834)		191.04 ± 4.39	$P > 0.05$

[a]Fisher's exact test, [b]Pearson chi 2 test.

In this cohort 1,111 (96.86%) patients were seropositive celiac cases (positive by serology) and 28 (2.44%) were seronegative CD, this status not related to genders ($P = 0.87$). The mean ± SD of TGA-IgA titer was 190.84 ± 121.01 (rang 0.8, 834), mean difference of TGA-IgA titer not significant between two genders ($P > 0.05$). Based on the results of the biopsies, more than 88% ($n = 930$) of patients had villous atrophy and 48.89% of them were type c ($n = 376$ Marsh 3c). This cohort classified to three presentations of celiac disease: typical 61.12%, atypical 36.23% and screened patients 2.65%, the presentations of CD related to gender ($P < 0.001$). The baseline characteristics of this celiac cohort are displayed in Table 1.

Mostly patients (68.99%) presented by one clinical symptom and one third of them ($n = 361$) presented by 2 or more clinical symptoms at the time of diagnosis. The first common GI symptoms of CD were dyspepsia 22.26% and diarrhea 12.94%. Growing problem 9.92%, weight loss 8.80% and anemia 7.51% were others first clinical symptoms in these patients. Also dyspepsia 12.97%, diarrhea 5.58%, anemia 5.24% and constipation 2.49% were secondly main clinical symptoms in this cohort. The main symptoms (chief complaint) at the time of their diagnosis are shown in Table 2.

The nervous problems were the most concomitant disorders in celiac patients, as 57.76% of evaluated cases ($n = 779$) had a psychiatric disorder. Anxiety disorder (9.07%) and depression (8.31%) were the most common type of these psychiatric disorders. Unadjusted models show females more likely have nervous problems (OR = 1.37, CI 95% 1.00, 1.87) than male patients. Liver disease were seen in more than 22% of evaluated cases ($n = 724$), and this disorder not related to gender (OR = 0.88, CI 95% 0.54, 1.16), the most common of liver disease, was nonspecific abnormal alanine aminotransferase (ALT) (53.70%). Osteopenia have seen in 28.23% of CD patients, although odds of female are more likely to bone loss than male (OR = 1.51, CI 95% 1.01, 2.27). Other common disease in this cohort were oral aphtha ($n = 301$, 31.85%), and this not related to gender of patients (OR = 0.94, CI 95% 0.69, 1.27).

More than half of evaluated cases ($n = 485$, 54%) were anemic, based on their laboratory tests; and odds of anemia in female were two time more than male (OR = 2.09, CI 95% 1.56, 2.81).

The skin problems was seen in 23.53% of CD patients, that were include dermatitis herpetiformis (3.98%) and others skin problems (19.55%). Some concomitant immune and nonimmune disorders are shown in Table 3.

Table 2. **Common clinical presenting symptoms in celiac patients**

Variables	Main clinical symptoms	
	First *n* %	Secondly *n* %
Dyspepsia	258 (22.26)	151 (12.97)
Diarrhea	150 (12.94)	65 (5.58)
Weight loss	102 (8.80)	–
Flatulence	78 (6.73)	–
Reflux	47 (4.06)	–
Abdominal pain	42 (3.62)	–
Nausea	25 (2.16)	–
IBS	17 (1.47)	–
Vomiting	15 (1.29)	–
Growing problem	115 (9.92)	–
Constipation	35 (3.02)	29 (2.49)
Dermatitis	34 (2.93)	–
Anemia	87 (7.51)	61 (5.24)
Others atypical symptoms	188	55 (4.73)
Without symptoms	53 (4.57)	803 (68.99)

Discussion

This is the first large cohort study in the northeastern region of Iran evaluating the clinical manifestations and concomitant conditions in 1,164 celiac disease patients. In this study, most of our cases were among adults with the mean first visit age of 29.67 years, ranging from 1 to 76. CD can present in all ages, and gluten intolerance can happen later in life even after age 60.[22] As expected, CD was predominate in female in our cohort (F:M ratio 2.40).[1,2]

In our cohort common type of CD disease was gastrointestinal, interestingly, 2.65% of total cohort was diagnosed by CD screening, which is lower than previous reports (5–21%).[2,4,23] The most common GI symptom was dyspepsia. which is different from the dominant presentation in children.[24] These results are in line with other studies, which reported CD classic symptoms prevalence ranging from 34 to 85.2%.[2,4,23,25] There are some reports of a notable trend of changing presentation of CD from classic to non-classic. For instance, reports in 1985 found 85.2% of patients to present with diarrhea, whereas in 2003–2013, presentation with diarrhea was estimated at 37.4%. This trend could be explained by the increasing awareness of clinicians from the atypical presentations of CD.[2,4,25] In our study, only 12.94% had presented by diarrhea.

In our study, 31.01% of patients reported more than one specific clinical symptoms of CD disease. The main symptom that presented as first or secondary clinical symptoms were include dyspepsia (35.23%), diarrhea (18.52%), anemia (12.75%), growing problems (9.92%), weight loss (8.80%), and flatulence (6.73%). Dyspepsia is not fully investigated in the literature as a symptom of CD. A notable percentage of CD patients are diagnosed incidentally through endoscopy for dyspepsia. Therefore, it could be concluded that our present knowledge of CD presentation is inadequate. Although there is some evidence of a high prevalence of dyspepsia in CD patients, especially in our region, most previous cohorts have not considered dyspepsia as a CD symptom.[26–29] The occurrence of other presentations in our cohort were lower than previous finding, estimating the prevalence for diarrhea, weight loss, and abdominal pain to be at 27–64%, 28–56%, and 30–34%, respectively.[2,4,23,30] Additionally, constipation and reflux were 5.51% and 4.06% although ranged between 1–13% and 12–14% in other studies.[2,4,23]

Type of disease was seropositive in 96.86% of CD patients, 2.44% of CD patients was seronegative which is in line with other studies that estimated prevalence of seronegative patients between 1.7–5%.[31,32] The prevalence of IgA deficiency in our general population is not determined, but 0.35% of these patients had IgA deficient.

Table 3. **Concomitant diseases in related sex of celiac patients**

No. of evaluated patients	Type of diseases	*n* %	Unadjusted OR CI 95% (f/m)
Thyroid diseases *n* = 623	Without disease	516 (82.83)	1
	Hypo Thyroid	94 (15.09)	0.77 (0.49, 1.20)
	Hyper Thyroid	13 (2.09)	
Skin problem *n* = 578	Without disease	442 (76.47)	1
	Dermatitis herpetiformis	23 (3.98)	0.79 (0.52, 1.21)
	Others skin problem	113 (19.55)	
Nervous problem *n* = 779	Without disease	338 (42.57)	1
	Depression	66 (8.31)	1.37 (1.00, 1.87)*
	Anxiety disorder	72 (9.07)	
	Headache	44 (5.54)	
	Others	98 (12.34)	
	Undetected problems	176 (22.17)	
Liver disease *n* = 724	Without disease	562 (77.62)	1
	1 ALT abnormality	87 (12.02)	0.80 (0.54, 1.16)
	Fatty liver	42 (5.80)	
	2 AIH	14 (1.93)	
	3 PBC	5 (0.69)	
	4 PSC	2 (0.28)	
	Others	12 (1.66)	
Bone disease *n* = 627	Without disease	450 (71.77)	1
	Osteopenia	177 (28.23)	1.51 (1.01, 2.27)*
Oral disease *n* = 945	Without disease	644 (68.15)	1
	Aphthae	301 (31.85)	0.94 (0.69, 1.27)
Diabetes *n* = 1159	Without disease	1092 (94.22)	1
	Type 1	67 (5.78)	1.32 (0.74, 2.35)
Anemia *n* = 894	Without disease	409 (45.75)	1
	Anemic	489 (54.25)	2.09 (1.56, 2.81)*

Although most previous studies report 5–10% DH cases within CD patients, two larger studies reported percentages of 9.8%[33] to 3.2%[2] and decreasing prevalence of DH during last decade, probably because of early diagnosis of celiac disease. In our study 3.98% of patients had DH.

There has been a lot of research done investigating the association of CD in other autoimmune disorders such as diabetes and hypothyroidism, but few studies evaluate the prevalence of such autoimmune disorders in CD patients. In this study prevalence of hypothyroidism was estimated 15.09%, which is in accordance with the current literature (10–30%).[6,9,30,34] The association between diabetes type 1 and CD is widely explored, Our study showed a high prevalence of diabetes type 1 in CD patients (5.78%), which is supported by previous findings (3.2 to 10%) of CD patients.[2,4,23] Clinical guidelines recommend screening for CD in patients with type 1 diabetes which results in a large proportion of CD patients being diagnosed through screening at-risk populations.[35,36] Thyroid disorders were seen in 17.18% of patients that hypothyroidism was common type of them. Studies have shown autoimmune thyroid diseases to be found in between 2.4% to 40.4% of CD patients.[2,7,37] The high prevalence of autoimmune disorders in CD patients can be explained by the sharing of a common genetic background in immunological pathways between CD and other immune-mediated diseases.[34,38]

In this cohort 22.38% of patients had liver disorders, which more than half of them had abnormal ALT (12.02%). The simultaneous clinical presentation of CD with liver disorders is well-documented. CD can damage the liver directly or may be associated with other autoimmune liver disease. Hypertransaminas is seen in (13–60%) of CD patients,[39,40] even screening for CD is recommended for patients with autoimmune liver disease or chronic liver disease.[41]

In this cohort nervous problems were common concomitant disorders (57.43%) in CD patients that more reported in female than male (OR = 1.37). the common nervous problems include anxiety disorder (9.07%) and depression (8.31%), although previous studies have higher estimate of anxiety disorder (of 41 to 84%) and depression (of 34 to 60%) in CD patients.[42–44]

Few studies have evaluated bone diseases in CD patients. In our cohort, 28.23% of patients had osteopenia, odds of bone diseases more in female than male (OR = 1.5). Some previous studies have found an increased risk of osteopenia and fragility fractures in celiac patients.[45–47] A meta-analysis

on postmenopausal female and male with celiac disease reported the prevalence of osteopenia 39.6%.[48] Bone loss is explained through malabsorption of calcium and vitamin D, leading to secondary hyperparathyroidism and metabolic bone disease.[49] In addition, anemia was common in more than half of CD patients, in accordance to previous reports (8–50%).[4,23,30,45,50] Also odds of anemia in female patients was twice more than male (OR = 2.01).

Conclusion

The classic type is common type of CD in northeast Iran. Dyspepsia, diarrhea and anemia main clinical symptoms in these patients, consequence we recommended to screening for CD in cases whiteout classic symptoms, such as dyspepsia. Nervous problem, bon disease and anemia important concomitant disorders that more seen in female CD patients.

Acknowledgements

Thanks to the Mashhad University of Medical Sciences for supporting this project.

Appendices

List of Abbreviations

Celiac disease (CD), Irritable bowel syndrome (IBS), Tissue transglutaminase (TGA), Anti-tissue Transglutaminase-IgA (TGA-IgA), Deamidated gliadin peptide (DGP), Common variable immunodeficiency (CVID), Gluten free diet (GFD), Alanine amino transferase (ALT), Gastrointestinal (GI)

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Funding

None.

Authors' Contributions

- Conceptualization; A. G.
- Data curtain; AG
- Funding acquisition; A.G.
- Methodology; F.A.
- Data analysis; F.A.
- Supervision & Validation; A.G.
- Roles/Writing original draft; A.G.K.R, F.A., B.Sh.
- All authors have read and approved the final manuscript.

References

1. Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, et al. Celiac disease: a comprehensive current review. BMC Medicine. 2019;17(1):1-20.
2. Spijkerman M, Tan IL, Kolkman JJ, Withoff S, Wijmenga C, Visschedijk MC, et al. A large variety of clinical features and concomitant disorders in celiac disease–a cohort study in the Netherlands. Digestive and Liver Disease. 2016;48(5):499-505.
3. Lebwohl B, Sanders DS, Green PH. Coeliac disease. The Lancet. 2018;391(10115):70-81.
4. Dominguez Castro P, Harkin G, Hussey M, Christopher B, Kiat C, Liong Chin J, et al. Changes in presentation of celiac disease in Ireland from the 1960s to 2015. Clinical Gastroenterology and Hepatology. 2017 2017/06/01/;15(6):864-71.e3.
5. Reilly NR, Fasano A, Green PH. Presentation of celiac disease. Gastrointestinal Endoscopy Clinics. 2012;22(4):613-21.
6. Lauret E, Rodrigo L. Celiac disease and autoimmune-associated conditions. BioMed Research International. 2013;2013.
7. Neuhausen SL, Steele L, Ryan S, Mousavi M, Pinto M, Osann KE, et al. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. Journal of Autoimmunity. 2008;31(2):160-5.
8. Stagi S, Giani T, Simonini G, Falcini F. Thyroid function, autoimmune thyroiditis and coeliac disease in juvenile idiopathic arthritis. Rheumatology. 2005;44(4):517-20.
9. Diamanti A, Capriati T, Bizzarri C, Panetta F, Ferretti F, Ancinelli M, et al. Celiac disease and endocrine autoimmune disorders in children: an update. Expert Review of Clinical Immunology. 2013;9(12):1289-301.
10. Stein J, Schuppan D. Coeliac disease-new pathophysiological findings and their implications for therapy. Visceral Medicine. 2014;30(3):156-65.
11. Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Alimentary Pharmacology & Therapeutics. 2012;35(5):540-51.
12. Ilus T, Kaukinen K, Virta LJ, Pukkala E, Collin P. Incidence of malignancies in diagnosed celiac patients: a population-based estimate. Official Journal of the American College of Gastroenterology | ACG. 2014;109(9):1471-7. PubMed PMID: 00000434-201409000-00025.
13. Guandalini S, Assiri A. Celiac disease: a review. JAMA Pediatrics. 2014;168(3):272-8.
14. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Annals of Medicine. 2010 2010/12/01;42(8):587-95.
15. Schuppan D, Zimmer KP. The diagnosis and treatment of celiac disease. Deutsches Ärzteblatt International. 2013;110(49):835.
16. Tack GJ, Verbeek WH, Schreurs MW, Mulder CJ. The spectrum of celiac disease: epidemiology, clinical aspects and treatment. Nature Reviews Gastroenterology & Hepatology. 2010;7(4):204.
17. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World Journal of Gastroenterology: WJG. 2012;18(42):6036.
18. Odeh R, Alassaf A, Gharaibeh L, Ibrahim S, Khdair Ahmad F, Ajlouni K. Prevalence of celiac disease and celiac-related antibody status in pediatric patients with type 1 diabetes in Jordan. Endocr Connect. 2019 Jun 13;8(6):780-7. PubMed PMID: 31085767. Pubmed Central PMCID: PMC6590199. Epub 2019/05/16. eng.
19. Rönnblom A, Holmström T, Tanghöj H, Wanders A, Sjöberg D. Celiac disease, collagenous sprue and microscopic colitis in IBD. Observations from a population-based cohort of IBD (ICURE). Scand J Gastroenterol. 2015;50(10):1234-40. PubMed PMID: 25921772. Epub 2015/04/30. eng.
20. Mohammadibakhsh R, Sohrabi R, Salemi M, Mirghaed MT, Behzadifar M. Celiac disease in Iran: a systematic review and meta-analysis. Electron Physician. 2017 Mar;9(3):3883-95. PubMed PMID: 28461861. Pubmed Central PMCID: PMC5407219. Epub 2017/05/04. eng.
21. Oberhuber G. Histopathology of celiac disease. Biomedicine & Pharmacotherapy. 2000;54(7):368-72.
22. Collin P, Vilppula A, Luostarinen L, Holmes GKT, Kaukinen K. Review article: coeliac disease in later life must not be missed. Alimentary Pharmacology & Therapeutics. 2018;47(5):563-72.
23. Volta U, Caio G, Stanghellini V, De Giorgio R. The changing clinical profile of celiac disease: a 15-year experience (1998-2012) in an Italian referral center. BMC Gastroenterology. 2014 2014/11/18;14(1):194.

24. Vivas S, Vaquero L, Rodríguez-Martín L, Caminero A. Age-related differences in celiac disease: specific characteristics of adult presentation. World J Gastrointest Pharmacol Ther. 2015;6(4):207-12. PubMed PMID: 26558154. eng.
25. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. The American Journal of Medicine. 2006; 119(4):355. e9–e14.
26. Petrarca L, Nenna R, Mastrogiorgio G, Florio M, Brighi M, Pontone S. Dyspepsia and celiac disease: prevalence, diagnostic tools and therapy. World J Methodol. 2014;4(3):189-96. PubMed PMID: 25332916. eng.
27. Rostami Nejad M, Mahbobipour H, Fazeli Z, Mashayekhi R, Mirsattari D, Nazemalhosseini Mojarad E, et al. Celiac disease in dyspeptic patients. Koomesh. 2011;12(2 (38))209–214.
28. Ford A, Ching E, Moayyedi P. Meta-analysis: yield of diagnostic tests for coeliac disease in dyspepsia. Alimentary Pharmacology & Therapeutics. 2009;30(1):28-36.
29. Ghahramani R, Abbasian AS, Shafaee S. Prevelence of celiac disease in patients with different types of dyspepsia. Journal of Isfahan Medical School. 2009;27(93):65-73.
30. Green PHR. The many faces of celiac disease: Clinical presentation of celiac disease in the adult population. Gastroenterology. 2005 2005/04/01/;128 (4, Supplement 1):S74-S8.
31. Schiepatti A, Sanders DS, Biagi F. Seronegative coeliac disease: clearing the diagnostic dilemma. Current Opinion in Gastroenterology. 2018;34(3): 154-8.
32. Volta U, Caio G, Boschetti E, Giancola F, Rhoden KJ, Ruggeri E, et al. Seronegative celiac disease: shedding light on an obscure clinical entity. Digestive and Liver Disease. 2016;48(9):1018-22.
33. Green PHR, Stavropoulos SN, Panagi SG, Goldstein SL, McMahon DJ, Absan H, et al. Characteristics of adult celiac disease in the USA: results of a national survey. The American Journal of Gastroenterology. 2001 2001/01/01/;96(1):126-31.
34. Kahaly GJ, Frommer L, Schuppan D. Celiac disease and endocrine autoimmunity - the genetic link. Autoimmun Rev. 2018 Dec;17(12):1169-75. PubMed PMID: 30316996. Epub 2018/10/15. eng.
35. Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. Journal of Pediatric Gastroenterology and Nutrition. 2020;70(1):141-56.
36. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut. 2014;63(8):1210-28.
37. Roberta M, Federica G, Stefano K, Francesco DM, Fabiola F, Gioacchino L, et al. Thyroid and celiac disease in pediatric age: a literature review. Acta Bio Medica: Atenei Parmensis. 2018;89(Suppl 9):11.
38. Zhernakova A, Van Diemen CC, Wijmenga C. Detecting shared pathogenesis from the shared genetics of immune-related diseases. Nature Reviews Genetics. 2009;10(1):43-55.
39. Rubio-Tapia A, Murray JA. The liver and celiac disease. Clin Liver Dis. 2019 May;23(2):167-76. PubMed PMID: 30947869. Pubmed Central PMCID: PMC6588186. Epub 2019/04/06. eng.
40. Hoffmanová I, Sánchez D, Tučková L, Tlaskalová-Hogenová H. Celiac disease and liver disorders: from putative pathogenesis to clinical implications. Nutrients. 2018 Jul 12;10(7). PubMed PMID: 30002342. Pubmed Central PMCID: PMC6073476. Epub 2018/07/14. eng.
41. Cvetkovic L, Bernard G, Galette N, Hétu PO, Vincent C, Bouin M, et al. Discordance between serology and histology for celiac disease in a cohort with coexisting liver disorders. J Can Assoc Gastroenterol. 2020 Aug;3(4):185-93. PubMed PMID: 32671328. Pubmed Central PMCID: PMC7338843. Epub 2020/07/17. eng.
42. Guedes NG, Silva LAd, Bessa CC, Santos JCd, Silva VMd, Lopes MVdO. Anxiety and depression: a study of psychoaffective, family-related, and daily-life factors in celiac individuals. Revista Brasileira de Enfermagem. 2020;73.
43. Häuser W, Janke K-H, Klump B, Gregor M, Hinz A. Anxiety and depression in adult patients with celiac disease on a gluten-free diet. World Journal of Gastroenterology: WJG. 2010;16(22):2780.
44. Audrey S, Procter S. Employers' views of promoting walking to work: a qualitative study. International Journal of Behavioral Nutrition and Physical Activity. 2015;12(1):1-10.
45. Schøsler L, Christensen LA, Hvas CL. Symptoms and findings in adult-onset celiac disease in a historical Danish patient cohort. Scandinavian Journal of Gastroenterology. 2016;51(3):288-94.
46. Fedewa MV, Bentley JL, Higgins S, Kindler JM, Esco MR, MacDonald HV. Celiac disease and bone health in children and adolescents: a systematic review and meta-analysis. J Clin Densitom. 2020 Apr-Jun;23(2):200-11. PubMed PMID: 30833087. Epub 2019/03/06. eng.
47. Zanchetta MB, Longobardi V, Bai JC. Bone and celiac disease. Curr Osteoporos Rep. 2016 Apr;14(2):43-8. PubMed PMID: 26875096. Epub 2016/02/15. eng.
48. Ganji R, Moghbeli M, Sadeghi R, Bayat G, Ganji A. Prevalence of osteoporosis and osteopenia in men and premenopausal women with celiac disease: a systematic review. Nutrition Journal. 2019 Feb 7;18(1):9. PubMed PMID: 30732599. Pubmed Central PMCID: PMC6504166. Epub 2019/02/09. eng.
49. Micic D, Rao VL, Semrad CE. Celiac disease and its role in the development of metabolic bone disease. J Clin Densitom. 2020 Apr-Jun;23(2):190-9. PubMed PMID: 31320223. Epub 2019/07/20. eng.
50. Bergamaschi G, Markopoulos K, Albertini R, Di Sabatino A, Biagi F, Ciccocioppo R, et al. Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. Haematologica. 2008;93(12):1785-91.