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ORIGINAL ARTICLE

# Celiac Disease Presenting in a Community-Based Gastroenterology Practice: Obesity and Bone Disease Are Common

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## Abstract

**Background** The description of the clinical presentation of celiac disease (CeD) has usually come from studies at referral centers. Data about CeD presentation in the community are sparse.

**Aims** We aim to describe the clinical presentation of patients with biopsy-proven CeD at a community-based adult gastroenterology practice and compare it to a referral center.

**Methods** We performed a retrospective study of two cohorts of patients diagnosed with CeD between 2000–2007 ($n=117$) and 2013–2016 ($n=91$) in a community practice, and a third cohort ($n=188$) diagnosed between 2000 and 2007 in a tertiary referral center. The clinical presentation, body mass index, tissue-transglutaminase levels, DEXA scan, vitamin D levels, and vaccine recommendations were assessed.

**Results** Celiac disease presentation changed over time in the two community cohorts. Recently, fewer patients presented with diarrhea and anemia, but constipation and neurologic symptoms were more common. The most recent cohort had a higher proportion of patients who were overweight or obese than the first cohort. However, the body mass index in both community cohorts was higher than in the tertiary referral center. The frequency of osteopenia and osteoporosis was high in both community cohorts. The tertiary referral center patients were younger, presented with a higher proportion of diarrhea and a lower body mass index.

**Conclusions** The clinical presentation of CeD differs between the community setting and a tertiary referral center. Patients with CeD presenting to the community setting tended to be older, overweight, and to have a high proportion of mineral bone disease.

**Keywords** Celiac disease · Clinical presentation · Community practice · Overweight · Mineral bone disease

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## Introduction

Celiac disease (CeD) is an autoimmune enteropathy that affects patients with genetic susceptibility after exposure to gluten present in wheat, rye, and barley [1, 2]. There has been a significant rise in the incidence of CeD, especially in the latter half of the twentieth century, which is due to increased screening of at-risk populations, more diagnostic awareness, and the availability of accurate serologic testing [3–5]. In most Western populations, the current estimated seroprevalence rate is 1.4% and the prevalence of biopsy-diagnosed CeD is around 0.7% [6–9]. Celiac disease was thought to be a pediatric disease, but it is now well known that it can present at any age, including in the elderly population [10, 11]. Additionally, some studies report women have a higher incidence of CeD than men (17.0 vs 7.8 per

100,000 person-years), while other studies have shown that the seroprevalence might be equal, suggesting that men may be more likely to remain undiagnosed [3, 10, 12].

Celiac disease can manifest with a myriad of classical symptoms. The most common presentation includes diarrhea, bloating, chronic abdominal pain, weight loss, nutritional deficiencies, mineral bones disease, among others [13, 14]. Nevertheless, extra-intestinal symptoms are frequent and a subclinical phenotype may represent about 20% of cases, making the diagnosis challenging [15, 16]. The description of the clinical presentation of CeD has traditionally been derived from studies performed at tertiary referral centers [16–19]. The data from these centers are prone to referral bias and may not reflect the typical presentation of the majority of patients with CeD in a general gastroenterology community practice. Additionally, there is a paucity of data characterizing the presentation of CeD in the community setting. Thus, we sought to describe the clinical presentation of patients with biopsy-proven CeD who presented to a community-based adult gastroenterology practice, which may facilitate a prompt diagnosis and appropriate management in this setting. Additionally, we compared the data from a community practice to that of a tertiary celiac specialty clinic at a major academic center in the same geographic region. We also assessed the application of the guideline-recommended quality metrics for patients with CeD in a community practice.

## Methods

### Study Design, Population, and Data Collection

We defined biopsy-proven CeD if Marsh 2 or 3 findings were mentioned in the initial pathology report from a duodenal biopsy, with either positive celiac serology or a response to a gluten-free diet (GFD). We initially performed a retrospective study of patients diagnosed with biopsy-confirmed CeD between 2000 and 2007 in a community practice in Providence, Rhode Island. The practice is a single-specialty gastroenterology practice with physicians seeing adult patients 18 years of age and older. We performed an initial study assessing 117 patients, including demographics, presenting symptoms, body mass index (BMI), tissue-transglutaminase (TTG) levels (IgA anti-tTG serology upper limit of normal 20 units), and DEXA scan. Using our electronic medical record (which was not in place for the first cohort), we identified a second cohort of 91 newly diagnosed celiac patients from January 2013 to May 2016 in the same community practice using the above-mentioned criteria. In addition to the prior described variables, the update evaluated the quality of care provided upon diagnosis, assessed by reviewing the frequency of underlying bone disease, vitamin D level, nutrition referral, pneumococcal vaccine recommendation, and whether a follow-up appointment was made (Supplementary Table 1).

Furthermore, we identified a third cohort of 188 patients with CeD at a tertiary referral center in Boston, Massachusetts, during 2000–2007. All patients included in the study had biopsy-proven CeD**.** We excluded patients whose pathology did not confirm CeD diagnosis.

### Statistical Analysis

Continuous variables were compared using Student's t test, categorical variables were compared using Fisher's exact test, and to compare means between multiple groups, ANOVA was used, with Tukey HSD post hoc test when appropriate.

### Ethics

The study was approved by the two hospital IRBs where the community GI practice offers care and also the hospital IRB at the tertiary referral center.

## Results

The baseline characteristics of the cohorts are presented in Table 1. In general, the demographic characteristics of the community cohorts and the tertiary referral center were different, including the gender distribution and the age at diagnosis. The proportion of female patients was higher in the referral center when compared to the two community cohorts (81.9% vs. 65% and 70.3%, $p = 0.003$). Also, the patients at the referral center were diagnosed at a younger age than the community patients (41 years vs. 48.6 years and 46.1 years, $p = 0.003$).

From 2000–2007, 117 patients with biopsy-confirmed CeD were identified in the community-based gastroenterology practice. The mean age at diagnosis was 48.6 years, with a range from 18 to 88 years old. There were 76 (65%) females and 41 (35%) males. The most common reasons for referral were diarrhea (58.1%), abdominal pain/dyspepsia (47%), flatulence/bloating (29.9%), and anemia (46.2%). Malaise, weight loss, depression/anxiety, and elevated liver enzymes were also common symptoms reported at the initial assessment (Table 2). TTG levels were assessed in 112 (95.7%) of patients with biopsy-confirmed CeD. False-negative TTG results, considered if the level was less than 20 units per laboratory cutoff in both centers, were seen in 19 (17.0%) of the patients with biopsy-confirmed disease. The average BMI at diagnosis was 26.5 (range 16.5–51.7). Forty-four percent of patients were overweight or obese at diagnosis. Fifty-seven percent underwent DEXA testing. Of

**Table 1** Baseline characteristics of the cohorts

| | Community Cohort 2000–2007 ($n=117$) | Community Cohort 2013–2016 ($n=91$) | Tertiary referral center 2000–2007 ($n=188$) | $p$ value |
|---|---|---|---|---|
| Sex, $n$ (%) | | | | |
| Male | 41 (35.0) | 27 (29.7) | 34 (18.1) | 0.003 |
| Female | 76 (65.0) | 64 (70.3) | 154 (81.9) | |
| Age at diagnosis Mean ± SD, *years* | 48.6 ± 17.16 | 46.1 ± 18 | 41 ± 15 | < 0.001* |
| BMI at diagnosis, Mean ± SD | 26.5 ± 6.8 | 26.1 ± 5.1 | 23.1 ± 3.9 | < 0.001* |
| BMI > 25, $n$ (%) | 51 (44) | 49 (54.4) | 12/34 (35.3) | 0.13 |
| BMI ≤ 25, $n$ (%) | 65 (56) | 41 (45.6) | 22/34 (64.7) | 0.13 |
| TTG at diagnosis | | | | |
| TTG > 20U, $n$ (%) | 93/112 (83.0) | 71 (78.0) | 95/103 (92.2) | 0.02 |
| TTG ≤ 20U, $n$ (%) | 19/112 (17.0) | 20 (22.0) | 8/103 (7.8) | 0.02 |
| Bone mass measurement by DEXA scan at diagnosis | (n tested = 67) | (n tested = 17) | | |
| Normal bone density, $n$ (%) | 20 (29.8) | 7 (41.2) | – | 0.58 |
| Osteopenia, $n$ (%) | 31 (46.3) | 6 (35.3) | – | 1 |
| Osteoporosis, $n$ (%) | 16 (23.9) | 4 (23.5) | – | NA |

*ANOVA. Tukey HSD post hoc test: Community cohort (2000–2007) versus Community cohort (2013–2016). Diff = − 5.0000, 95%CI = − 10.3836 to 0.3836, $p=0.0750$

**Table 2** Characteristics of patients in the community cohorts

| | Community Cohort 2000–2007 ($n=117$) | Community Cohort 2013–2016 ($n=91$) | $p$ value |
|---|---|---|---|
| Diarrhea | 68 (58.1%) | 30 (33.0%) | < 0.001* |
| Abdominal pain/dyspepsia | 55 (47.0%) | 41 (45.1%) | 0.89 |
| Flatulence/bloating | 35 (29.9%) | 31 (34.1%) | 0.63 |
| Malaise/fatigue | 31 (26.5%) | 24 (26.4%) | 1 |
| Weight loss | 30 (25.6%) | 14 (15.4%) | 0.10 |
| Nausea/vomiting | 16 (13.7%) | 19 (20.9%) | 0.23 |
| Constipation | 0 (0%) | 16 (17.6%) | < 0.001* |
| Anxiety/depression | 13 (11.1%) | 11 (12.1%) | 1 |
| Rash | 11 (9.4%) | 9 (9.9%) | 1 |
| Iron deficiency anemia | 54 (46.2%) | 28 (30.8%) | 0.04* |
| Hypertransaminasemia | 7 (5.9%) | 3 (3.3%) | 0.57 |
| Neurologic symptoms | 5 (4.3%) | 16 (17.6%) | 0.003* |
| Positive family history | 2 (1.7%) | 16 (17.6%) | < 0.001* |

*$p$ value < 0.05

these, 46.3% had osteopenia, 23.9% were osteoporotic, and 29.9% had a normal bone density. Almost eighty percent had documented referrals to a nutritionist for counseling/teaching on a GFD. The treating gastroenterologist requested follow-up appointments after diagnosis in 95.7% of cases. Ninety percent of patients who had follow-up appointments had fewer symptoms, lower TTG levels, or both after therapy with a GFD.

In the second cohort seen in the community practice from 2013 to 2016, a total of 91 patients with biopsy-confirmed CeD were identified. Seventy-one percent were female. The average age was 46.1 years with a range from 18 to 93 years old, similar to the original community practice cohort ($t$ test $p=0.77$). The average BMI was 26.1 (range 14–43.1), with 54.4% being overweight or obese (BMI > 25) at presentation. In this more recent cohort, 71 of 91 (78%) were TTG positive; 20 patients had a negative TTG result. Before starting a GFD in this cohort, the average TTG level was 83.72 U/mL and after starting a GFD, it was 28.8 U/mL. Repeat TTG was positive in 24% of patients, negative in 33%, and 42% did not have a repeated TTG level. The recommendation and assessment of bone disease with DEXA testing were

ordered in 40.2% of patients, but only 17 patients had testing completed. There was no difference in the rate of osteopenia or osteoporosis between the two community cohorts.

Comparisons between the initial and the more recent community cohorts demonstrated that the most common reasons for referral to a gastroenterologist practice were, respectively, diarrhea (58.1% vs. 33.0%, $p < 0.001$), abdominal pain/dyspepsia (47% vs. 45.1%, $p = 0.89$), flatulence/bloating (29.9% vs. 34.1%, $p = 0.63$), and anemia (46.2% vs. 30.8%, $p = 0.04$). Other items that had a statistically significant difference between the two cohorts included family history of celiac disease, constipation, and neurologic symptoms (Table 2). In terms of family history, increased awareness of asking about family history of celiac in the second cohort may explain the difference observed between cohorts. When assessing quality measures in the new cohort in the community practice, we found that vitamin D testing was ordered for 74.7% of patients. However, a pneumococcal vaccine recommendation was documented in only 13.3% of patients. Eighty-six percent of the first community-diagnosed cohort was referred to a nutritionist, and 92% of these followed a GFD with symptomatic improvement. The recommendation for bone density assessment was the only measure with a significant change over time (62.4% vs. 38.9%, $p = 0.001$). The treating gastroenterologist requested follow-up appointments after diagnosis in 96% of cases of the first cohort. The quality assessment measures between the two cohorts are summarized in Table 3.

In the tertiary center cohort, 188 patients with biopsy-proven CeD were identified between 2000 and 2007. The mean age at diagnosis was 41 years, with a range between 18 and 74 years. There were 154 (82%) female and 34 (18%) male patients. The average BMI of this cohort was 23.1, with a range between 16.9 and 32.5.

Both the initial community cohort and the tertiary center patients were diagnosed between 2000 and 2007. In these two groups, the most common reasons for referral were the following, respectively: abdominal pain/dyspepsia (47% vs. 32.2%, $p = 0.06$), diarrhea (58.1% vs. 40%, $p = 0.008$), and anemia (46.2% vs. 19.4%, $p = 0.33$).

## Discussion

Celiac disease has a diverse and commonly non-specific clinical presentation in modern practice [10, 20]. Fewer patients now present with severe gastrointestinal symptoms, and the clinical face of CeD is no longer one of a malnourished individual with diarrhea and malabsorption [7, 9, 15, 20, 21]. We found a change in the clinical presentation over time in the community cohorts. Compared to the new community cohort, the initial cohort presented with more systemic and gastrointestinal symptoms, including diarrhea, a higher proportion of anemia, and neurologic symptoms. As previously observed by Abu Daya et al., patients presenting with anemia are more likely to have more severe villous atrophy than those with diarrhea as the initial presentation[22]. Thus, the initial cohort may have had more intestinal damage than the more recent community cohort, since the initial cohort also presented at an older age which might suggest that they remained undiagnosed for a longer period. In the later years, a prompter diagnosis has been attributed to greater awareness of CeD and the availability of serologic tests that have been clinically used in the USA since the early 1990s and were available for both of the study's time points [9].

Additionally, the community population's gastrointestinal complaints were frequent in both cohorts, but other non-gastrointestinal manifestations, including dermatologic and neurologic manifestations, were also noted. Contrary to classic descriptions of patients with CeD, both groups of patients in the community practice were older with a higher rate of being overweight or obese. In contrast, the tertiary referral center patients presented with a lower average BMI and with diarrhea. The referred patients' presentation might be explained as a more severe disease than patients in the primary or secondary settings. Multiple studies from tertiary referral centers have described patients with similar demographics characteristics (female proportion 60–75% and mean age 35–45 years) and clinical presentation (51–63% with

**Table 3** Quality Assessment Measures in the community cohort

| | Community Cohort 2000–2007 ($n = 117$) | Community Cohort 2013–2016 ($n = 91$) | $p$ value |
|---|---|---|---|
| Referral to nutritionist | 92 (78.6%) | 77 (86.5%) | 0.320 |
| DEXA recommendation recorded | 73 (62.4%) | 35 (38.9%) | 0.001 |
| Vitamin D testing | N/A$^+$ | 68 (74.7%) | |
| Pneumococcal vaccination | N/A$^+$ | 12 (13.3%) | |
| GFD following | N/A | 84 (93.3%) | |
| Follow-up appointment | 112 (95.7%) | N/A | N/A |

$^+$Vitamin D testing and pneumococcal vaccination were not assessed prior to 2013

*$p$ value < 0.05

gastrointestinal symptoms) [17, 23]. However, Rampertab et al. observed that the clinical presentation in a single referral center has changed since the early 1980s when compared to the early 2000s. There was a decline in the percentage of patients presenting with diarrhea over time, while the percentage of patients with silent celiac disease increased [9]. The contrasting data in the two settings is valuable when interpreting CeD studies conducted at tertiary care centers that are not necessarily similar to the findings of community-based internal medicine and gastroenterology practices.

Celiac disease is associated with significant osteoporotic bone loss [24]. Therefore, appropriate management of CeD warrants examination of bone mineral density and vitamin D levels. In our study, DEXA scans were done in 57.3% of patients in the initial community practice cohort and 18.7% of the new community cohort. One explanation for these low rates could be that DEXA scans were done by patients' primary care physicians or another healthcare provider and not reported to the gastroenterologist's documentation. The rate of osteoporosis was 23.9% and 23.5% in the community cohorts. Also, 46% and 35.3% of the patients tested had osteopenia in the initial and follow-up community practice cohorts, respectively. A recent meta-analysis found that 14.4% and 39.6% of patients with CeD have osteoporosis or osteopenia, respectively [24, 25]. Studies have shown that even 1 year of dietary treatment leads to significant bone mass improvement [26]. This supports the view that gluten withdrawal can improve bone derangements and highlights the importance of screening for coexisting bone disease.

Impaired splenic function affects more than one-third of adult patients with CeD, and it may predispose to a higher risk of infections by encapsulated bacteria [27, 28]. One prior study has shown a 28% increased risk of pneumonia in CeD unvaccinated patients compared to unvaccinated non-celiac controls [29]. In the community practice, only 14% of the initial cohort had a documented recommendation for the pneumococcal vaccine. The low numbers observed may, in part, be due to physicians verbally making the recommendation for vaccination without documentation in the chart. Also, the community practice could not offer pneumococcal vaccination due to a lack of insurance coverage of this vaccine in a specialist clinic. In contrast, hepatitis A and B vaccination was routinely given in the office when appropriate. Thus, in the community where the private practice is located, patients must get the vaccine from their primary care provider or a local pharmacy. This finding serves as a wake-up call to recommend and document the proper vaccination protocols. The community practice implemented a link to pneumococcal vaccination recommendation when a patient has an ICD-10 diagnosis of CeD. Also, there is a reminder embedded in the electronic medical record to ensure appropriate vaccination recommendations.

The American Gastroenterological Association recommends an initial screening with TTG in patients with suspected CeD, with a confirmatory endoscopy with duodenal biopsy [21, 30]. While the reported sensitivity of TTG is about 90–98%, a minority of patients may test negative for serology despite having histology changes [21]. This small subset of patients with negative serology may have a false negative result, patients who already started a GFD, or patients with IgA deficiency, or seronegative celiac with intestinal symptoms related to gluten ingestion [31]. Although seronegative CeD's prevalence is low, it can be a cause of villous atrophy [31]. The sensitivity of TTG in the community cohort was lower than expected. Only 83% of the first cohort and 78% of the second community cohort had a positive TTG. Meanwhile, at the tertiary center, 92% of patients had a positive TTG. The subgroup of seronegative CeD patients is commonly overlooked. Patients should be questioned as to whether they were following a GFD before TTG measurement and, ideally, patients should have a measure of total IgA and IgG deamidated gliadin antibody testing. It is important to have a high suspicion of CeD in patients with evidence of malabsorption, nutritional deficiencies, or dermatologic changes and also to continue with the workup of CeD with endoscopy and duodenal biopsy if clinical suspicion is high despite a negative TTG [20, 32]. If the suspicion of CeD is high in the setting of a negative TTG in patients on a GFD, HLA genotyping should be considered [10, 30, 33].

The major advantage of our study is the evaluation of two different cohorts of newly diagnosed patients with CeD in a community practice over two separate recent periods (2000–2007 and 2013–2016). Another strength is the comparison of the presentation of CeD in the community practice and a tertiary referral center. We are limited by the retrospective design of the study and by evaluating a single community practice. This limits the external validity of the study and potentially skews the data based on management patterns of the practice. Our study did not assess the initial workup done in a primary care physician practice to further evaluate the reason for referral to the community versus a tertiary center. Also, we found a high rate of false-negative TTG in the community cohort. Given the retrospective nature of the study, we were unable to differentiate whether a false-negative TTG in the community was due to self-treated CeD, incompletely treated CeD, a difference in the laboratory test, or due to IgA deficiency, a condition present in approximately 1 in 400 non-Hispanic whites[4, 27]. While our study looked at gender differences, we did not evaluate racial differences. Another weakness of this study was a lack of standardization of the pathologists' evaluation of the small intestinal biopsies. Community general pathologists read some biopsies in the earlier cohort, which raises the possibility of increased misinterpretation compared to

readings by a dedicated gastrointestinal pathologist in the second cohort and tertiary referral center.

In conclusion, we have found that patients presenting to the community setting differ from a tertiary referral center. Patients with CeD in the community setting tended to be older, overweight, and have a high mineral bone disease rate. Searching for CeD has become common in patients with iron deficiency anemia, unexplained osteoporosis, infertility, functional bowel disorders, and chronic diarrhea. Despite the increased awareness, the disease remains under-diagnosed, and patients may still have delayed diagnosis. Finally, using the electronic medical record tools, quality initiatives can be incorporated. Reminders can be automatically triggered to suggest the order of vitamin D level, DEXA scan, nutrition consultation, pneumococcal vaccination, and screening of 1st-degree family members, which help improve the care of patients with CeD.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10620-022-07521-9.

**Author's contributions** All authors contributed substantially to the manuscript and approved the final manuscript. The study was conceived by SAS, with input from ERF. KK and SAS wrote the protocol for IRB approval, and KK did the initial chart reviews and collection of data for the original community cohort. SJ performed the update and gathered the data for the second cohort. SAS did a second chart review of the second cohort for presenting symptoms. DL, GAR, and AC were involved with the data from the tertiary referral center for comparison and provided critical input for the poster and paper. The bulk of the manuscript was written by GAR, SJ, AC, and SAS with critical input from all the authors. Each author read and approved the final submitted manuscript.

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## Declarations

**Conflict of interest** There were no conflict of interest on behalf of all authors.

## References

1. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet.* 2018;391:70–81. https://doi.org/10.1016/S0140-6736(17)31796-8.
2. Lebwohl B, Ludvigsson JF, Green PHRR. Celiac disease and non-celiac gluten sensitivity. *BMJ.* 2015;351:1–11. https://doi.org/10.1136/bmj.h4347.
3. King JA, Jeong J, Underwood FE et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. *Am J Gastroenterol.* 2020;115:507–525. https://doi.org/10.14309/ajg.0000000000000523.
4. Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. *Gastroenterology.* 2015;148:1175–1186. https://doi.org/10.1053/j.gastro.2015.01.044.
5. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol.* 2012;107:1538–1544. https://doi.org/10.1038/ajg.2012.219.
6. Singh P, Arora A, Strand TA et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2018;16:823–836. https://doi.org/10.1016/j.cgh.2017.06.037.
7. Ludvigsson JF, Rubio-Tapia A, van Dyke CT et al. Increasing incidence of celiac disease in a North American population. *Am J Gastroenterol.* 2013;108:818–824. https://doi.org/10.1038/ajg.2013.60.
8. Rubio-Tapia A, Kyle RA, Kaplan EL et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology.* 2009;137:88–93. https://doi.org/10.1053/j.gastro.2009.03.059.
9. Rampertab SD, Pooran N, Brar P, Singh P, Green PHR. Trends in the presentation of celiac disease. *Am J Med.* 2006;119:9–14. https://doi.org/10.1016/j.amjmed.2005.08.044.
10. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. *Gastroenterology.* 2021;160:63–75. https://doi.org/10.1053/j.gastro.2020.06.098.
11. Popp A, Kivelä L, Fuchs V, Kurppa K. Diagnosing celiac disease: Towards wide-scale screening and serology-based criteria? *Gastroenterol Res Pract.* 2019;2019:1–10. https://doi.org/10.1155/2019/2916024.
12. Lebwohl B, Tennyson CA, Holub JL, Lieberman DA, Neugut AI, Green PHR. Sex and racial disparities in duodenal biopsy to evaluate for celiac disease. *Gastrointest Endosc.* 2012;76:779–785. https://doi.org/10.1016/j.gie.2012.05.011.
13. Hujoel IA, Reilly NR, Rubio-Tapia A. Celiac disease: clinical features and diagnosis. *Gastroenterol Clin North Am.* 2019;48:19–37. https://doi.org/10.1016/j.gtc.2018.09.001.
14. Schøsler L, Christensen LA, Hvas CL. Symptoms and findings in adult-onset celiac disease in a historical Danish patient cohort. *Scand J Gastroenterol.* 2016;51:288–294. https://doi.org/10.3109/00365521.2015.1092576.
15. Green PHRR. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. *Gastroenterology.* 2005;128:74–78. https://doi.org/10.1053/j.gastro.2005.02.016.
16. 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 Gastroenterol.* 2014;14:1–8. https://doi.org/10.1186/s12876-014-0194-x.
17. Binicier OB, Tosun F. Evaluation of adult celiac disease from a tertiary reference center: a retrospective analysis. *Rev Assoc Med Bras.* 2020;66:55–60. https://doi.org/10.1590/1806-9282.66.1.55.
18. Dominguez Castro P, Harkin G, Hussey M et al. Changes in presentation of celiac disease in Ireland from the 1960s to 2015. *Clin Gastroenterol Hepatol.* 2017;15:864-871.e3. https://doi.org/10.1016/j.cgh.2016.11.018.
19. Bhattacharya M, Kapoor S, Dubey AP. Celiac disease presentation in a tertiary referral centre in India: current scenario. *Indian J Gastroenterol.* 2013;32:98–102. https://doi.org/10.1007/s12664-012-0240-y.
20. Katz KD, Rashtak S, Lahr BD et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. *Am J Gastroenterol.* 2011;106:1333–1339. https://doi.org/10.1038/ajg.2011.21.
21. Benson BC, Mulder CJ, Laczek JT. Anti-gliadin antibodies identify celiac patients overlooked by tissue transglutaminase antibodies. *Hawaii J Med Public Health.* 2013;72:14–17.
22. Abu Daya H, Lebwohl B, Lewis SK, Green PH. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. *Clin Gastroenterol Hepatol.* 2013;11:1472–1477. https://doi.org/10.1016/j.cgh.2013.05.030.
23. Bledsoe AC, King KS, Larson JJ et al. Micronutrient deficiencies are common in contemporary celiac disease despite lack of overt

malabsorption symptoms. *Mayo Clin Proc.* 2019;94:1253–1260. https://doi.org/10.1016/j.mayocp.2018.11.036.
24. 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. *Nutr J.* 2019. https://doi.org/10.1186/s12937-019-0434-6.
25. Selby PL, Davies M, Adams JE, Barbara Mawer E, Mawer EB. Bone loss in celiac disease is related to secondary hyperparathyroidism. *J Bone Miner Res.* 1999;14:652–657. https://doi.org/10.1359/jbmr.1999.14.4.652.
26. Sategna-guidetti C, Grosso SB, Grosso SB et al. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult coeliac disease patients. *Aliment Pharmacol Ther.* 2000;14:35–43. https://doi.org/10.1046/j.1365-2036.2000.00671.x.
27. Di Sabatino A, Brunetti L, Maffè GC, Giuffrida P, Corazza GR. Is it worth investigating splenic function in patients with celiac disease? *World J Gastroenterol.* 2013;19:2313–2318. https://doi.org/10.3748/wjg.v19.i15.2313.
28. Simons M, Scott-Sheldon LAJ, Risech-Neyman Y, Moss SF, Ludvigsson JF, Green PHR. Celiac disease and increased risk of pneumococcal infection: a systematic review and meta-analysis. *Am J Med.* 2018;131:83–89. https://doi.org/10.1016/j.amjmed.2017.07.021.
29. Zingone F, Abdul Sultan A, Crooks CJ, Tata LJ, Ciacci C, West J. The risk of community-acquired pneumonia among 9803 patients with coeliac disease compared to the general population: a cohort study. *Aliment Pharmacol Ther.* 2016;44:57–67. https://doi.org/10.1111/apt.13652.
30. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol.* 2013;108:656–676. https://doi.org/10.1038/ajg.2013.79.
31. Volta U, Caio G, Boschetti E et al. Seronegative celiac disease: Shedding light on an obscure clinical entity. *Dig Liver Dis.* 2016;48:1018–1022. https://doi.org/10.1016/j.dld.2016.05.024.
32. Rewers M. Epidemiology of celiac disease: What are the prevalence, incidence, and progression of celiac disease? *Gastroenterology.* 2005;128:47–51. https://doi.org/10.1053/j.gastro.2005.02.030.
33. Kaukinen K, Lindfors K, Mäki M. Advances in the treatment of coeliac disease: an immunopathogenic perspective. *Nat Rev Gastroenterol Hepatol.* 2014;11:36–44. https://doi.org/10.1038/nrgastro.2013.141.