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REVIEW

Diagnosis and Treatment Patterns in Celiac Disease

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Abstract

Celiac disease (CD) is an immune-mediated gastrointestinal (GI) disorder driven by innate and adaptive immune responses to gluten. Presentation of CD has changed over time, with non-GI symptoms, such as anemia and osteoporosis, presenting more commonly. With improved screening and diagnostic methods, the reported prevalence of CD has increased globally, and there is considerable global variation in diagnostic and treatment practices. The objective of this study was to describe the current state of CD diagnosis and treatment patterns. A targeted review of literature from MEDLINE, Embase, the Cochrane Library, and screening of relevant conference abstracts was performed. The generally recommended diagnostic approach is GI endoscopy with small bowel biopsy; however, in selected patients, biopsy may be avoided and diagnosis based on positive serology and clinical symptoms. Diagnosis often is delayed; the average diagnostic delay after symptom onset is highly variable and can last up to 12 years. Barriers to accurate and timely diagnosis include atypical presentation, lack of physician awareness about current diagnostic criteria, misdiagnosis, and limited access to specialists. Currently, strict adherence to a gluten-free diet (GFD) is the only recommended treatment, which is not successful in all patients. Only one-third of patients are monitored regularly following diagnosis. Unmet needs for CD include improvements in the accuracy and timeliness of diagnosis, and the development of treatments for both refractory CD and GFD nonresponsive CD. Further research should investigate the impact of education about gluten-free eating and the availability of gluten-free foods support adherence and improve outcomes in patients with CD.

Keywords Celiac disease · Diagnosis · Treatment patterns · Review · Gluten-free diet · Adherence

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Introduction

Celiac disease (CD) is a chronic, immune-mediated enteropathy in which dietary gluten triggers an inflammatory reaction in the small intestine of genetically predisposed individuals [1–3]. Overall incidence in the USA and Europe has been reported at 11.8–17.4 per 100,000 person years [4–6]. Globally, CD is more prevalent in children (0.1–5.7%) than in adults (0–1.9%) and has been rising in recent years [7].

The clinical presentation of the disease varies broadly and may include an array of intestinal and extraintestinal manifestations (EIM) [8]. Classical CD refers to a disease course presenting with signs and symptoms of malabsorption, which include diarrhea, malnutrition, and growth failure [1, 3]; in contrast, patients with nonclassical CD present without symptoms and signs of malabsorption [1]. EIMs include iron deficiency anemia, neuropathy, aphthous ulcers, and dermatitis herpetiformis [3, 9]. CD also is classified by patient response to a gluten-free diet (GFD). Some patients with CD may be classified as nonresponsive to a GFD if both symptoms and enteropathy do not respond after 6–12 months on the diet, or classified as refractory if malabsorptive symptoms and intestinal atrophy are still present after 12 months on a strict GFD, with no other clear cause [1, 2].

Though increased awareness and the introduction of serologic testing have improved disease detection, CD remains significantly underdiagnosed worldwide and symptomatic individuals commonly experience considerable diagnostic delays, often of several years [10–12]. An estimated 10% to 20% of CD cases are identified following serological screening of high-risk individuals, most commonly family members of diagnosed patients [12, 13]. The average time to diagnosis after onset of symptoms for adults with CD ranges from 4 to 12 years [10, 12, 14, 15]. To improve detection of CD, active case finding (serologic testing for CD in patients with symptoms or conditions closely associated with CD) has been recommended worldwide, but is suboptimal [2, 16–18]. No consensus has been reached on which symptoms, associated diagnoses, or laboratory abnormalities should require a diagnostic evaluation. The generally recommended initial test of choice is tissue transglutaminase (tTG)-immunoglobulin A (IgA) due to its high sensitivity and specificity and wide availability. Endomysial antibody (EMA) testing may also be used but is less commonly available, and may not be as sensitive at tTG-IGA outside of reference laboratories. In cases of IgA deficiency, young children, and where CD is highly suspected despite normal tTG-IGA, IgA or immunoglobulin G (IgG) deamidated gliadin peptide (DGP) testing may be helpful [19].

While celiac serologies are highly accurate, seronegative CD does exist and may affect approximately 5% of the celiac population. Patients with very high suspicion of CD, such as those with malabsorption and no other etiology, those gastrointestinal (GI) symptoms and either a family history of CD or a personal history of other autoimmune disease duodenal biopsy should be considered even if celiac serologic tests are normal.

Despite duodenal biopsy serving as the cornerstone of CD diagnosis, biopsies can be avoided particularly in younger patients whose relatives have a diagnosis of CD, by using serology alone or more overall flexibility in the diagnostic approach [2, 20]. Currently, CD diagnosis without biopsy is still controversial; however, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines, which were developed by consensus, suggest that in children with classic celiac GI symptoms, IgA-tTG titers > 10 times the upper limit of normal (ULN) on two separate blood tests and human leukocyte antigen (HLA) serotype groups with DQ2/DQ8 positivity may be diagnosed without a biopsy. However, it is expected that these guidelines will evolve in the coming years [21].

The recommended treatment for CD is lifelong strict adherence to a GFD [2]. Regular, long-term monitoring of symptoms and GFD adherence is advised to decrease the risk of symptoms and disease complications. However, follow-up recommendations by American, British, and international gastroenterology associations vary considerably and both physicians and patients report diverse experiences with long-term CD follow-up [22, 23].

The variable presentation of CD and lack of consensus in the medical community regarding the best approaches to diagnosis and follow-up raise questions regarding the real-world experience of diagnosis and treatment of CD. This review describes the current state of knowledge regarding global CD diagnosis and treatment patterns.

Literature Search

A targeted literature review was performed to identify primary analyses, systematic reviews, and meta-analyses on diagnosis and treatment patterns of CD. Searches (limited to August 2012–December 2016) were performed in MEDLINE and replicated in Embase and the Cochrane Library. To augment database search results, manual searches of the literature were performed for information published between January 2016 and August 2018. Searches were also performed in meetings of the following conferences: Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week.

Diagnosis Patterns

Presentation Types and Symptomology by Age

CD has remarkable clinical variability, which can make the confirmation of diagnosis challenging. Classical symptoms include diarrhea, weight loss, or bloating, while a smaller proportion of patients with CD can present initially with subclinical or asymptomatic disease (Table 1) [24]. Adults are more likely than children to present with anemia, dyspepsia, osteoporosis, osteopenia, and hypertransaminasemia [25]. GI symptoms and growth failure are more common in young children, who also may present with vomiting, bowel movement changes, abdominal pain, and weight issues including failure to thrive. Fatigue and other symptoms related to the joints, skin, and nervous system are also common in children [26]. In a study of 1030 CD patients, children under 15 years of age primarily presented with GI symptoms (70–80%), while those over the age of 15 years were likely to present with either GI symptoms (59%) and/or EIM (43%) [27]. Of 511 Finnish children, most (60%) presenting with GI symptoms at diagnosis also had concomitant EIM [26].

There is also evidence of a change in the epidemiology of disease in children in recent years. A retrospective study of 1030 CD children diagnosed between 1973 and 2013 found a significant increase in the mean age at diagnosis from 2.2 years (1973–1982) to 8.2 years (1997–2013) due to increasing frequencies of patients presenting with only one type of CD symptom [27]. There was a decrease in the proportion of children with severe symptoms at diagnosis, dropping from 92.8 to 78% in recent decades [27]. This may result from earlier diagnosis and greater awareness of CD among physicians and laypersons, identifying and diagnosing children with milder disease, due to the greater availability of serological screening.

Nonresponsive Celiac Disease

Nonresponsive celiac disease (NRCD), defined as no improvement in symptoms after 6–12 months on a GFD, has been estimated to affect up to 30% of CD patients following a GFD [2]. Deliberate or accidental gluten ingestion is the most common cause of persistent symptoms of NRCD [2, 28], but it is not clear how commonly this occurs. The occurrence of purposeful or inadvertent gluten ingestion in patients initially suspected of having NRCD varies greatly in the literature from 7 to 50% [29], 35% [30], and 50% [31]. Adherence to a GFD is an extremely complex task; however, convenient clinical monitoring of gluten consumption can be assessed using noninvasive methods to detect gluten immunogenic peptides (GIP) in both urine [32] and stool samples [33]. This testing identifies more GFD noncompliance than by addressing adherence by dietary questionnaire or by the determination of tTG antibodies in serum alone [33].

If a patient suffering from persistent symptoms is thought to be strictly adhering to a GFD, several diagnostic investigations can be carried out to determine if the patient has developed complications of CD, associated NRCD conditions, or refractory CD (RCD). Associated NRCD conditions include microscopic colitis, small bowel bacterial overgrowth, exocrine pancreatic insufficiency, and irritable bowel syndrome (IBS) [28]. Clinicians also may attempt to determine if patients have concurrent conditions not directly associated with CD, such as lactose or fructose intolerance, protein-losing enteropathies, anal sphincter dysfunction, or Whipple disease which may mimic some of the signs or symptoms of CD [28]. It is important to consider small intestinal bacterial overgrowth in patients with persistent symptoms despite adherence to a GFD prior to making a diagnosis of RCD [28, 34]. Once other conditions are ruled out, it is then possible to be more certain of severe diagnoses

Table 1 Typical presentation and definitions of celiac disease

CD presentation	Description/symptoms
Classical	Signs and symptoms of malabsorption. Includes diarrhea, malnutrition, growth failure [1, 2]
Nonclassical	No signs and symptoms of malabsorption [1]
Potential	Normal small intestinal mucosa at increased risk of developing CD as indicated by positive CD serology [1]
Nonresponsive	No response to a GFD or a return of symptoms following 6–12 months on a GFD [3]
Refractory	Persistent or recurrent malabsorptive symptoms and signs with VA despite a strict GFD for more than 12 months [1, 3] Refractory type I resembles symptoms of classical CD, but with GFD resistance and poor prognosis [4–6] Refractory type II is characterized by abnormal IELs and is associated with poorer prognosis than type I [4–6]

CD celiac disease, *GFD* gluten-free diet, *IELs* intraepithelial lymphocytes, *VA* villous atrophy

References [1–3, 87]

which may include enteropathy-associated T-cell lymphoma (EATL) or RCD [2].

Identifying CD-associated conditions and comorbidities requires a biopsy of the small intestine, and the American College of Gastroenterology has recommended that the results of this second biopsy be compared with those of the initial, diagnostic biopsy [2]. Normal or near-normal small intestinal histology (after adherence to a GFD) suggests IBS, microscopic colitis, food intolerances, or pancreatic insufficiency, among other possible diagnoses [2]. Ongoing inflammatory enteropathy with villous atrophy (VA) is consistent with RCD, small intestinal bacterial overgrowth, and conditions such as CD with persistent symptoms [2].

RCD can be classified as primary (without response to diet) or secondary (relapse following response to diet), but is more commonly referred to as refractory CD type I (RCDI) or type II (RCDII). The diagnosis is challenging and is primarily a diagnosis of exclusion resulting from ruling out other conditions that could give rise to NRCD [28]. RCD presents with persistent or recurrent signs and symptoms of malabsorption accompanied by small intestinal VA occurring in the absence of other disorders like overt lymphoma [2]. The epidemiology of patients with RCDI and RCDII is not well understood, although RCDII may be less common than RCDI, with the former estimated to comprise approximately 15–23% of patients with RCD [35, 36]. These two types differ by expression of intestinal intraepithelial lymphocyte (iIEL) T cell receptors and associated T cell co-receptors [37]. RCDII patients present with more serious symptoms including malnutrition and can also suffer from ulcerative jejunitis and lymphocytic gastritis. Notably, ulcerative jejunitis may also occur in cases without clear evidence of RCDII [37, 38]. Patients with RCDI have improved survival compared with those diagnosed as RCDII: 44–58% of patients survive on average only five years following diagnosis with RCDII, compared with 80–96% for RCDI [39]. The increased mortality in patients with type RCDII is due to the higher risk of clonal expansion and transformation of abnormal iIELs into EATL. The development of EATL occurs in more than 50% of patients within 4–6 years after RCDII is diagnosed, and is the main cause of death in this population [40]. A multicenter, multinational study developed a simplified 3-factor risk score to predict 5-year mortality among patients with RCD that includes age at RCD diagnosis, albumin, and iIEL immunophenotype. EATL was the most common (35%) cause of mortality for all deaths ($n = 51$) among patients with RCD and was nearly exclusively observed in those with abnormal iIELs [38].

Undiagnosed CD

Despite growing awareness of the occurrence of CD in most countries, its diagnosis remains challenging. Large numbers of patients often go undiagnosed for several years, particularly if patients are asymptomatic or have nonspecific symptoms, and in most countries, the majority of patients never receive a diagnosis of CD. Patients with CD presenting with atypical symptoms are less likely to have had serology testing for CD after investigative GI endoscopy [41]. A US population-based survey reported that the estimated prevalence of undiagnosed CD fell from 0.6% of the US population in 2009–2010 to 0.3% in 2013–2014 [42]. Another population-based study in the US reported that the prevalence of undiagnosed CD among persons aged 18–50 years was 1.1% of the general population, with the highest prevalence among those aged 18–29 years (1.4%) [43].

Classifications and Technical Approaches for Diagnosis

Diagnostic approaches are variable, and several different systems are commonly used to classify biopsy results (Table 2). The Marsh–Oberhuber classification is the most common system, but there is no universal use of any system [1]. If other clinical indications warrant CD testing, opportunistic screening is a supported strategy to improve the efficiency of CD testing [44]. Generally, if the serologic assessments and a duodenal biopsy are both positive, then CD can be considered confirmed. Positive serologic assessments with high antibody titers and negative biopsy result in a diagnosis of potential CD, some of whom will progress to CD with VA over time [1, 21, 45]. However, the sensitivities and specificities of serologic tests vary, depending on the manufacturer (Table 3). There is also some variability in the sensitivity and specificity of different serologic tests, such that tTG-IgA tests are highly sensitive and specific, whereas EMA and DGP IgA tests only have high specificity (> 90%) [46]. Due to the varying study designs and high pretest probability of CD, many studies may overestimate the performance of serologic tests. Biomedical scientists have pointed out that the availability of multiple testing kits for the same antibody adds to inconsistencies across diagnostic methods as each has its own ULN range for detection [47]. Interpretation of CD pathology can be complex, which may lead to both false positives and false negatives in diagnostic assessment of biopsies [48].

American College of Gastroenterology guidelines recommend GI endoscopy, commonly referred to as esophagogastroduodenoscopy (EGD), with small bowel biopsy as the diagnostic approach for people with suspected CD [2]. The duodenum is the preferred site for biopsies conducted during EGD, but detection rates by biopsy are not 100% and multiple (4–6) sites of biopsy may be needed [2, 49]. Detection could also be increased by routine screening, particularly in relatives of patients with confirmed CD, but

Table 2 Celiac disease diagnosis based on intestinal biopsy

Morphology of duodenal mucosal biopsy	Marsh criteria [1]	Marsh–Oberhuber [2]	Corazza [3]
Normal	Type 0	Type 0	Normal
Normal architecture, IEL ≥ 25–40/100 enterocytes	Type 0	Type 0	Grade A
Normal architecture, increased IEL ≥ 40/100 enterocytes	Type 1	Type 1	Grade A
Normal architecture, increased IEL ≥ 40/100 enterocytes with crypt hyperplasia	Type 2	Type 2	Grade A
Partial VA, increased IEL ≥ 40/≥ 25/100 enterocytes	Type 2 hyperplastic lesion crypt hyperplasia, increased crypt height and influx of inflammatory cells	Type 3 destructive; Type 3a partial VA; villi blunt and shortened with a villous-to-crypt ratio of 1:1; Type 3b subtotal VA; villi atrophic but still separate and recognizable	Grade B1 atrophic, villous-to-crypt ratio is < 3:1
Total VA IEL ≥ 40/≥ 25/100 enterocytes	Type 3 destructive severe inflammation, flat villi; hyperplastic crypts	Type 3c total VA; villi rudimentary or absent; mucosa resembles colonic mucosa	Grade B2 atrophic, villi are no longer detectable
Atrophic hypoplastic lesion: flat mucosa, normal crypt height, no inflammation with normal IEL counts	No equivalent	Type 4	No equivalent

CD celiac disease, *IEL* intraepithelial lymphocytes, *VA* villous atrophy

Reprinted from [1, 112–114]

Table 3 Sensitivities and specificities of commonly commercially available serological kits using manufacturer-defined cutoffs [1]

Assay	Sensitivity (%)	Specificity (%)
Inova tTG-IgA	89.3	95.0
Binding site tTG-IgA	85.7	100
Eurospital tTG-IgA	92.9	100
Immco tTG-IgA	96.4	87.5

IgA immunoglobulin A, *tTG* tissue transglutaminase

Reference [115]

whether biopsies should be used for this purpose is controversial [50]. A task force of 16 physicians from seven different countries concluded that serologic tests for specific EMAs, tTG, or DGP antibodies may be used to diagnose CD together with biopsies of the duodenum which must be taken when patients are on a gluten-containing diet [1]. Recent evidence in both children and adults suggests that antibody testing in selected patients can accurately diagnose CD without duodenal biopsy [51]. Based on seminal studies in adults [52], ESPGHAN guidelines allow for diagnosis without biopsy in symptomatic children without a positive family history, when there are clear clinical signs and symptoms, high serologic titers, and permissive HLA type [21]. Advancements in gene expression profiling to identify at-risk infants demonstrated predictability of CD 9 months before clinical or serological signs were observed [53–55]. However, several studies have reported that serology alone is not sufficient to confirm a CD diagnosis, but rather is used to support a biopsy-confirmed diagnosis [24, 56–58].

Despite clinical recommendations, adherence to guidelines is suboptimal, particularly in children. A retrospective study of US children ($n = 9171$) found that 35% of diagnosed cases adhered to American Gastroenterology Association (AGA) recommendations for GI biopsy [59]. Diagnostic methods also differ in clinical practice among adult patients. In a US survey of adults with CD ($n = 1832$), only 78.8% were diagnosed using EGD small intestine biopsy. A small percentage (1.9%) of responders were unsure of their method of diagnosis [60]. Diagnostic methods were not mutually exclusive, so it is likely that many patients were diagnosed by both serology and biopsy.

Diagnosis of CD depends on biopsy collection and interpretation, and pathology follow-up, with the care team reaching a diagnostic consensus. Inadequate biopsy collection, inaccurate interpretation of biopsy results, and variability in biopsy reporting by histopathologists pose significant challenges to CD diagnosis. Pathologists may not provide enough relevant or uniform information to aid in the correct interpretation of results [61]. In addition, pathologic findings may not be specific for CD. While most VA in western

countries is related to CD, a number of other etiologies are possible [62–64]. More frequently, patients are found to have increased iIELs without VA, the so-called Marsh 1 lesion. While this finding can be seen in untreated celiac disease, it is highly nonspecific and most patients with this histologic diagnosis do not have celiac disease [65, 66].

Moreover, a lack of access to gastroenterology specialists for diagnosis and follow-up care contributes to under-and delayed diagnosis of CD. A US survey of 1832 patients with CD reported that only 57% of patients were diagnosed by a gastroenterologist [60]. Unlike specialists, primary care physicians may not properly interpret the pathological findings or adhere to clinical guidelines to diagnose CD. A survey of primary care physicians reported that only 72% were likely to refer their serology-positive CD patients to a gastroenterologist and 80% did not follow established recommended guidelines regarding biopsy to confirm diagnosis [67].

Even when a correct diagnosis of CD is given, it is often delayed by several years. A retrospective analysis of 101 US patients with biopsy-supported CD initially presenting with non-GI symptoms ($n=49$ [49%]) reported that they experienced median diagnostic delays of 42 months (3.5 years), compared with 2.3 months in patients presenting with GI symptoms ($n=52$ [51%]) ($P<0.001$) [68]. However, other non-US studies have reported significantly longer time to diagnosis even with most patients presenting with typical GI-related CD symptoms. The average time to diagnosis after symptom onset varies considerably in the literature. In a large nationwide survey of CD patients ($n=1689$) in Switzerland, the average diagnostic delay was 7.3 years (range, 0–65 years) with 84.7% of patients presenting with GI symptoms [69]. A Canadian survey of biopsy-confirmed CD patients ($n=5912$) reported average delays of 12 years with 84.9% of patients presenting with typical symptoms [15]. Another study of 825 CD patients in Finland also found considerable delays in CD diagnosis, with 32% of patients reporting delays of greater than 10 years and 68% presenting with GI symptoms [70].

Diagnostic delays may also vary between types of CD. In a retrospective analysis, RCD patients ($n=29$) had a significantly longer median time between symptom onset and CD diagnosis (6 years vs. 1 year for CD patients who did not go on to develop RCD) [24]. It can be difficult to diagnose RCD as it is a diagnosis of exclusion in many cases [71]. Living with undiagnosed and untreated disease for a longer period of time before diagnosis may cause longstanding immunological activity that could lead to refractory disease [24].

Treatment Patterns

GFD Adherence

Lifelong adherence to a GFD, the mainstay of treatment for CD, has been shown to promote mucosal healing, reduce serum levels of celiac antibodies, improve protein–energy deficiencies, improve bone health, and lead to increases in body fat [72, 73]. Nonadherent or partially adherent patients have been reported to have more fatigue, pruritus, and abdominal bloating than fully adherent patients [74, 75]. Similarly, the persistence of VA is less frequently reported in patients who adhere to their GFD [76]. However, not all patients adhere to a GFD and strict adherence rates in adults (aged ≥ 16 years) have been reported to range from 42 to 91% [77]. Specific types of patients who are less likely to adhere to a GFD have been examined in several studies (Table 4). Adherence may suffer when patients lack confidence about the diet or do not believe they understand it well [78, 79]. Cost may also be an issue for patients facing out-of-pocket purchases for gluten-free (GF) foods [78, 79].

Studies have shown that children have relatively high rates of GFD adherence, with factors impacting adherence differing from those of adults [33, 80]. Two studies reported that most preschool children were adherent to their GFD, with high adherence rates due to parent control over diet [33, 80]. A review of the pediatric literature suggested that

Table 4 Factors influencing gluten-free diet adherence in the US adults

Greater adherence [1–3]	Lesser adherence [1–3]
Belief that purposeful gluten exposure has important health consequences	High costs of GF foods
Belief that accidental gluten exposure has important health consequences	Perceived inability to follow diet
Reported greater understanding of GFD	Negative perception of own knowledge
Higher scores on GFD quiz	Lower educational level
Greater ability to follow GFD when traveling	Income < $200,000
Greater ability to follow a GFD when dining out	Increased severity of current symptoms
Greater ability to follow a GFD at social events	Lower perceived importance of treatment
Greater comfort in following a GFD at work	
Belief that avoiding gluten is important for health	
Ability to follow a GFD regardless of mood	

GF gluten-free, *GFD* gluten-free diet, *US* United States

References [72, 78, 79]

parental educational level and knowledge of GFDs can affect children's adherence [81]. Other factors acting as barriers to adherence in children include the availability of GF foods, especially at school and in restaurants [82]. Cost and labeling of GF foods impact adherence in children, but social pressure does not [82].

GF Foods on Prescription

Receiving GF foods on prescription improves dietary adherence, but similar barriers to adherence still exist in countries where patients can receive GF foods on prescription. In a retrospective study in the UK ($n=375$), dietary adherence was greater in patients with prescriptions: 62% of patients not receiving GF foods on prescription were nonadherent compared with 42% on prescriptions ($P<0.001$) [83]. Most nonadherent patients (73%) reported that they did not fully understand food labels, which affected their adherence. Regardless of prescription status, 80% of respondents thought that GF products were too expensive and 60% found them unpalatable. Rates of GF food prescriptions vary across UK patients, particularly across genders and age groups. Differences in management initiatives, attempts at cost savings, and unawareness of the prescribing guidelines among regional physicians were reported by a retrospective analysis in the UK to affect prescription of GF foods [84].

Pharmacologic Treatments

In RCDI and RCDII, pharmacologic treatment improves symptoms and histology in only 30–40% of patients [85]. In RCDI, symptoms often improve after treatment while RCDII is generally less responsive to available therapies. For both RCDI and RCDII, therapeutic options reported include budesonide, systemic corticosteroids, 6-mercaptopurine, cladribine, and mesalamine [35, 86–88]. Mycophenolate mofetil and methotrexate have also been reported as therapeutic options for RCDI [86]. Available treatments for RCDII do not appear to prevent progression to EATL, and mortality rates remain high even with aggressive therapy [28]. Interleukin 15 (IL-15) is felt to play a central role in pathogenesis of RCD, and recent data suggest a potential therapeutic effect of anti-IL-15 antibodies in this severe CD phenotype [89]. Currently, there is no standardized approach for RCDII, apart from aggressive nutritional support and strict GFD adherence [40].

While there are no current approved treatments for CD other than the GFD, there does appear to be an unmet medical need for adjunctive or alternate therapies, in particular, for patients not responding well to diet modification. There are currently many clinical trials in development targeting CD and RCD patients which are beyond the scope of this review [90]. In addition, there is some recent evidence that the use of wheat flour modified by microbial transglutaminase in patients with CD can be a suitable alternative to the GFD [91].

Follow-up Care, Monitoring, and Other Patterns of Care

Practice guidelines remain inconsistent about the type and timing of follow-up care after CD diagnosis, leading to significant practice variation. The AGA and US National Institutes of Health recommend periodic visits at regular intervals with GFD adherence to be assessed and reinforced with consultation with both a physician and a dietitian [92, 93]. A US study of CD patients ($n=122$) found that only 35% maintained regular follow-up visits over a four-year period [94]. In another US survey ($n=1832$), 65% of patients with CD had not followed up with a healthcare provider in the past 5 years [60].

Consultation with a dietitian does not always occur at diagnosis or during follow-up care, which conflicts with disease management recommendations to provide interview-based monitoring of GFD adherence. A US survey of CD patients ($n=122$) reported that 84% consulted with a dietitian at the time of diagnosis [94], and a patient survey ($n=1689$) in Switzerland reported that expert nutrition counseling was only given to 80% of CD patients after diagnosis [95]. This further illustrates disparities in care due to lack of access to specialists. CD patient ($n=122$) follow-up visits were reported to be conducted by primary care providers and gastroenterologists, 56% and 39%, respectively [94].

Discussion

The number of CD cases has increased in recent years and is projected to continue to increase across all affected regions, with the exception of Finland, possibly due to improved efforts to detect the disease [96, 97]. Greater awareness of CD and the use of serologic tests in its diagnosis have resulted in more accurate diagnoses. Biopsy confirmation of serological findings remains recommended for definitive diagnosis of CD, although diagnosis based on serology alone is becoming more common, and European pediatric guidelines list criteria for a biopsy-free serological diagnosis [21]. Most studies have followed these recommendations and used both serology and histopathology to diagnose CD, especially in adults.

The frequent long delay in accurate diagnosis after the onset of symptoms represents an unmet need in CD for both adults and children, who can suffer from significant symptoms prior to starting a GFD. Diagnostic delay is substantially longer among adult female and elderly patients [41, 98]. These delays partly stem from their physician's

insufficient awareness of CD, as well as atypical symptoms [41, 98]. In addition, while most celiac disease can be easily identified using modern diagnostic tests, there continue to be diagnostic dilemmas including seronegative celiac disease, intraepithelial lymphocytosis and potential CD [65, 66, 99]. Further study of these cohorts of patients is needed to improve diagnostic algorithms and facilitate effective therapy.

Patient management after diagnosis appears to vary significantly and can be suboptimal: Follow-up visits with both physicians and dietitians on the whole should become more frequent and consistent and should be based on national and international recommendations for treatment management [94]. With standardized and validated surveys of adherence to a GFD, such as the CD adherence test, it may be possible to determine whether certain components of follow-up, such as greater frequency of visits or consultations with a dietitian, may improve adherence and thus clinical outcomes [100]. Additionally, patients who knowingly consume gluten may not schedule regular follow-ups per provider recommendations. Moreover, many CD patients without complications choose to self-manage their disease without ongoing care from their health care providers [60].

Strict adherence to a GFD is believed to play an important role in patient outcomes; however, GFD adherence has not been studied extensively or reported well in the literature and study results are highly variable. Survey response return rates are 34–39% and are limited by small sample sizes and failure to use validated adherence measures [81, 83, 101]. Different measures of adherence, include dietary self-reports, interviews with dietitians, small bowel biopsies to assess mucosal inflammation or VA, and serological screening, do not necessarily generate comparable findings [79]. Self-reports are particularly questionable in their accuracy and do not correlate well with the results of dietitian's evaluations, serologic screening, or small bowel biopsy [33, 72]. More recently, a method examining stools for gluten immunologic peptides found that approximately 30% of adult patients on a GFD for at least a year had gluten immunologic peptides in their stools, suggesting recent gluten exposure [33]. In order to improve adherence to a GFD, an understanding of the factors that influence the patient's ability to follow it, both intentional and unintentional, is needed [102].

Other research initiatives are focusing on developing treatments for CD in combination with a GFD, as treatment based solely on a strict GFD is burdensome and can have poor efficacy. A recent survey of teenagers and adults reported that CD patients extremely adherent to a strict GFD had increased symptoms of anxiety and fatigue, and therefore significantly worse quality of life (QoL) than those who were less adherent [103]. Three alternative novel therapeutic strategies to improve CD patients' QoL and overall health have been proposed: gluten detoxification, reversal of increased intestinal permeability, and modulation of immune response [49]. The first two therapeutic modalities seek to directly modify the gluten antigen or its trafficking, while the latter modifies the immune response to the gluten exposure. Genetically engineered grains with the removal of α-gliadin locus, oral proteases (ALV003) to degrade gluten, and probiotic preparations are being explored in clinical trials to reduce gluten immunogenicity [104]. Preliminary results of the drug, larazotide, in multiple phase II randomized, placebo-controlled clinical trials have shown to restore the mucosal barrier in CD patients that suffer from increased intestinal permeability [105, 106]. Larazotide regulates tight junctions in the intestinal epithelium to reduce antigen, such as gliadin, trafficking [105, 106].

Modulation of the immune response to gluten is being widely investigated for novel CD treatments. Pathological targets for CD treatment include autoimmune, inflammatory, and innate responses after gluten exposure. To modulate the overactive immune response associated with autoimmunity, two treatments have been identified. First, the restoration of immune tolerance in CD was explored through gluten-specific vaccination (Nexvax2) in phase I trials with phase II studies initiating in 2018 (NCT00879749). Secondly, alternative therapy such as the inoculation of multiple species of parasitic roundworms is being used to counter pro-inflammatory responses in CD at multiple stages of clinical trials [107]. Reduction in inflammatory cytokine production by antibody-mediated therapy (Infliximab and Hu-MiK-Beta-1) and blockade of lymphocyte recruitment (anti-CCR9) are promising treatments as they have been successful in treating pathologically similar conditions, such as IBS and Crohn's disease, respectively [49].

Limitations

This literature review does not focus on the similarities or differences across countries, but offers global insight on diagnostic and treatment patterns. While it was designed as a targeted review with inclusion and exclusion criteria defined a priori, the screening and abstraction were not performed systematically, which is a limitation of the review. Recently published articles summarize the key aspects of epidemiology, diagnostic approaches and challenges, and management of the disease [108–111]. These reviews primarily focus on guidelines regarding diagnosis and treatment and the clinical aspects and implications of CD and its subtypes. This review augments these evaluations of current CD knowledge by presenting global patterns of diagnostic approaches, barriers to GFD adherence, and patterns of follow-up care.

Conclusion

The true prevalence of CD is estimated to be up to 1% of adults in developed countries, with incidence and prevalence rising in recent years, mainly due to improved identification of CD through greater awareness of symptoms and access to serological diagnostic methods. Regardless of methodology, improvements in the rate and process of diagnosis, particularly for adult women and the elderly, represent areas for improvement in CD and can result from atypical symptom presentations. Preventing CD complications from developing in all subtypes is an unmet need. Following diagnosis, patient management by both physician and dietitian appears to be suboptimal with inconsistent patterns of follow-up visits. Management should include GFD monitoring and support for patient adherence—a burden patients perceive as substantial, as dietary nonadherence is the most common reason for persistent symptoms of nonresponsive disease. Future research should expand clinical trials of pharmacological therapies to treat all forms of CD and investigate whether recent improvements in availability of GF foods and general awareness in society may aid adherence and thus outcomes in the CD population.

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Compliance with ethical standards

Conflict of interest ESM, TB, ABC, and KJC are or were employees of Truven Health Analytics, an IBM Company, during the completion of this study. AT, MG, JD, and DAL are or were employed by Takeda Pharmaceuticals International Co. BL and DSS serve as consultants for Takeda Pharmaceuticals International Co. No authors have any conflicts of interest germane to this study.

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