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Celiac Disease

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Abstract

Purpose of review—To summarize recent advances in celiac disease (CD) published between August 2008 and July 2009.

Recent findings—CD affects ~1% of most populations but remains largely unrecognized. In the last year, work has shown that the prevalence of CD has increased dramatically, not simply due to increased detection. Also, undiagnosed CD may be associated with increased mortality. Significant progress has been made in understanding how gliadin peptides can cross the intestinal border and access the immune system. New genetic loci and candidate genes that may contribute to the risk of CD and its overlap with type 1 diabetes mellitus have been identified. New deamidated gliadin peptides antibodies have better diagnostic accuracy over native gliadin-based tests. The inclusion of duodenal bulb biopsy specimens may increase the rate of CD detection. The spectrum of CD likely includes a minority of patients with mild enteropathy. A practical 7-item instrument may facilitate standardized evaluation of gluten-free diet adherence. Finally, refractory CD, whilst rare, is associated with a poor prognosis.

Summary—Celiac disease is a global health problem that requires a multidisciplinary and increasingly cooperative multinational research effort.

Keywords

undiagnosed celiac disease; mortality; autoimmunity; gluten

Introduction

This review summarizes the basic and clinical advances in CD published between August 2008 and July 2009 including Epub ahead of print listed by July 2009 at the time of PubMed search. During the study period, a total of 557 publications were identified in PubMed using the keyword “Celiac Disease”. We exclude review articles (n=77), case reports (n=67), letters or editorials (n=48), and those articles not written in English language (n=48). Thus, 317 original articles, metaanalysis, or systematic reviews were considered for inclusion. Citations were chosen on relevance by authors’ subjective selection.

Epidemiology

Celiac disease (CD) now affects ~1% of most populations. This was not always so. In fact, at least two studies have shown that over time there has been a substantial increase in background prevalence of the disease.[1, 2] In addition to an increase in background prevalence, serologic testing for CD has impacted the rate of diagnosis as well as our understanding of the epidemiology of CD. The incidence of CD in children <2 years of age showed an epidemic

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pattern in Sweden during the period of 1984–1996.[3] A population-based incidence register of CD covering epidemic and post-epidemic birth cohorts revealed that the cumulative incidence at 2 years of age was almost 3 times higher during the epidemic, compared to the years before and after the epidemic.[4] Also, a significant successive increase in incidence rates among children <2 years of age was once again revealed during the last years of follow-up monitoring rising the question of a new epidemic approaching.[4] Furthermore, a study that followed up the fate of children born during the Swedish epidemic of infant CD showed an increasing prevalence of CD in these children reaching 3% by the age of 12.[5]

Whilst CD was traditionally considered a childhood disease, most patients are diagnosed in adulthood. Indeed, the prevalence of CD in Finland adults aged 52 to 74 years was 2.1%, higher than the prevalence reported in the general population.[6] Virta[7] reported that the nation-wide point prevalence of adult diagnosed CD in Finland is 0.55%, the highest reported to date for clinically-diagnosed CD. Therefore, awareness of CD diagnosis and active case-finding are encouraged in all ages.

Why the prevalence of celiac disease may have increased over time is not clear. This is too short a time period for substantial changes in human genetics and likely represents some major and pervasive environmental influence. Concepts such as the hygiene hypothesis, perhaps changes in wheat or other cereals may influence this. One study suggesting a pervasive environmental influence identified a higher rate of celiac disease in Finland compared to the adjacent, but less developed, Karelia.[8] Immunoreactivity to dietary proteins in CD appears to be age-related; specifically IgA immunoreactivity to bovine milk caseins was lower in CD patients under 2 years of age than older children or young adults suggesting that the proteins in infant formulas and foods could be associated with the risk for CD prevalence.[9]

Abu-Zekry[10] demonstrated that CD is a frequent disorder among not-at risk (general population) and at-risk (type 1 DM, diarrhea) Egyptian children, similar to the rate in Iceland.[11] These data and previous reports of high prevalence of CD in the “Fertile Crescent” challenges the hypothesis of a Middle East-Europe CD prevalence gradient attributable to a lack of exposure to cereals until relatively recently (Simoons’ hypothesis).

Undiagnosed Celiac Disease is not benign

Delay in diagnosis, especially in patients who have severe symptoms at presentation, is associated with increased mortality, primarily because of malignancy. A major question relates to what is the ultimate outcome of undiagnosed, presumed silent CD. Two studies suggested a significantly increased risk of mortality in patients with undiagnosed CD.[1, 12] However, the association with increased mortality is not universal nor is the association with increased malignancy.[13, 14] For example, CD detected in an older population is not necessarily associated with increased risk of either malignancy or general mortality (author’s unpublished data). However, the longest follow-up study over 45 years showed the accumulated excess mortality does not occur until 25 years after the serum sampling date,[1] suggesting that if one got CD later in life it may take much longer follow-up to determine excess mortality if it occurs.

Pathogenesis

Celiac disease results from innate and adaptive immune system dysregulation. Activation of the adaptive immune system implies that gliadin (the toxic component of gluten) cross the intestinal epithelium. It has been hypothesized that increased intestinal permeability is an early event in CD pathogenesis. Lammers et al[15] demonstrated that gliadin bind to the chemokine receptor CXCR3, the interaction gliadin-CXCR3 may induce release of zonulin that may lead to tight junction disassembly and subsequent paracellular passage of gliadin to the gut mucosa. Other mechanisms of gliadin transport in CD have been postulated. Matysiak-Budnik et al[16]

and Heyman et al[17] demonstrated the overexpression of the transferrin receptor CD71 in patients with active CD; this receptor may transport gliadin across the intestinal mucosa through retro-transcytosis of secretory immunoglobulin A-gliadin complexes. Finally, Schumann et al [18] demonstrated that epithelial translocation of the intact or partially degraded α2-gliadin-33mer (an important trigger of CD) occurs by apical-to-basal transcytosis and that this process is stimulated by interferon-γ, a key cytokine involved in CD immunopathogenesis. In summary, these novel findings suggest that gliadin transport through the epithelial barrier in CD may involve paracellular as well as transcellular mechanisms. Better understanding of the complex mechanisms associated to gliadin transport might lead to novel therapeutic strategies for CD in the future.

Fina D et al[19] demonstrated a gluten-dependent increased expression of both RNA and protein interleukin 21 in duodenal samples of patients with untreated CD as well as the relevance of this cytokine to sustain T-bet expression and interferon-γ production. Bas et al[20] showed that patients with CD may fail to regulate T cell response to gluten because of an impaired capacity for extra-thymic T cell receptor gene rearrangement.

Grose et al[21] demonstrated that invariant NK T cells were both systemically deficient and with defective cytokine production in CD, this observation suggest that a deficiency on immunoregulatory NK T cells may play a role in loss of immunological tolerance in CD.

Cytosolic phospholipase A2 is a central molecule in NKG2D-mediated cytolysis in cytotoxic T lymphocytes.[22]

Di Sabatino[23] demonstrated that mucosal addressin cell adhesion molecule 1 (a critical molecule in lymphocyte homing to the gut) is strongly up-regulated in untreated CD dependent on interferon α and may be involved in the mucosal damage in CD.

Serological responses to commensal enteric bacteria (either anti-Saccharomyces cerevisiae antibodies, Pseudomonas fluorescens associated sequence I2 or Bacteroides caccae TonB-linked outer membrane protein) are frequent in CD.[24] Serum levels of microbial antigens decreased significantly during GFD, also ASCA levels correlated with the grade of mucosal injury, thus, these markers may be gluten dependent in CD patients.[25]

Clinical manifestations and Associated conditions

Celiac disease has a wide spectrum of gastrointestinal and extraintestinal manifestations. In a prospective Spanish cohort,[26] female preponderance, presence of typical symptoms, marked villous atrophy, and higher titer of tissue transglutaminase antibodies were more frequently observed in children than adults. Time to diagnosis was shorter in children than in adults. [26] Dental enamel defects were more prevalent in celiac children than non-CD controls (83.3% vs. 53.3%, p=.02).[27]

Many conditions occur in association with CD. CD is associated with diabetes mellitus type 1 (T1DM), although most children had a silent presentation and yearly screening for CD may be necessary to detect the majority of cases. [28] Children and adults with CD may have a modest increased risk of sepsis; however, the risk is higher for pneumococcal-related sepsis.[29] Increased risk of pneumococcal infection in CD was also suggested by a British study that included a cohort of 18 928 CD patients, although risk was not as high as for splenectomized subjects.[30] The risk of non-Hodgkin lymphoma is higher in patients with CD and also among individuals with a sibling affected with CD.[31] Neurologic dysfunction can be the sole presenting feature of gluten sensitivity, antibodies to transglutaminase 6 IgG and IgA are prevalent in gluten ataxia and these antibodies can serve as a marker of CD-associated neurological disorder. [32]

The increased risk of autoimmune conditions such as T1DM or juvenile rheumatoid arthritis/juvenile idiopathic arthritis is not limited to CD cases but also present among first-degree relatives of celiacs.[33] The risk of CD in first-degree relatives of CD patients may be higher than previously though especially for siblings.[34] The prevalence of depression is higher in patients with both T1DM and CD.[35]

Patients with CD have a 70-fold increased risk to have microscopic colitis compared with the general population.[36] Patients with concurrent microscopic colitis and CD frequently required steroids or immunosuppressive drugs to control diarrhea and may have more severe villous atrophy.[36]

The prevalence of biopsy-proven CD was 2.8% among 251 patients with Turner‘s syndrome.[37] Small-bowel bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate was observed in 9.3% patients with symptomatic treated or untreated CD.[38]

A systematic review and meta-analysis demonstrated that the prevalence of CD in patients meeting diagnostic criteria for irritable bowel syndrome was more than 4-fold that in controls.[39]

Genetics

A large genome-wide association study demonstrated that seven chromosome regions are shared between CD and T1DM such as RGS1 (1q31), IL18RAP (2q12), TAGAP (6q25), the 32-bp insertion-deletion variant (3p21), PTPN2 (18p11), CTLA4 (2q33), and SH2B3 (12q24).[40] These data further supports extensive epidemiological evidence of association between CD and type 1 DM and future evaluation of gluten consumption as a shared etiologic factor.

Two novel CD risk regions were identified at chromosomes 6q23.3 (OLIG3-TNFAIP3) and 2p16.1 (REL) by testing large case-control European cohorts, both genes are key mediators in the nuclear factor kappa B pathway, an innate-immunity via that has not been reported to be heritably altered in CD before.[41]

In the first follow-up study of CD cases from the United States, five of the eight regions identified in a previous large UK GWAS study were strongly associated with CD, including regions on 1q31, 3q25, 3q28, 4q27, and 12q24. In addition, new evidence for association in the region 2q31 (ITGA4) was reported. [42]

Although human leukocyte antigen (HLA)-DQ2 is the principal genetic risk factor for CD, Romanos et al [43] demonstrated that CD cases carrying ≥13 non-HLA risk alleles had a higher CD risk compared with those carrying 0–5 risk alleles, this model increased sensitivity by 6.2% in relation to the use of HLA only.

Diagnosis

The availability of highly accurate serologic tests greatly facilitates the diagnosis of CD. A large multinational study demonstrated significant variability in sensitivity (69% to 93%) and specificity (96% to 100%) for tTGA assays among 20 laboratories that support the necessity of better standardization of the tTGA assays.[44] A changing pattern of CD serology request has been observed in United Kingdom during the last decade with a significant increase on general practitioner requests of CD serologies (from 3.3% to 52%) and a decrease on the proportion of positive serological results (from 5.7% to 2.6%).[45] Deamidated gliadin peptides may replace native anti-gliadin antibodies, though they are not necessarily any better than tissue transglutaminase antibodies. [46] In addition, combination testing (such as multiplex immunoassay) provides both opportunities and challenges for improving the accurate diagnosis of celiac disease, though there also may be increased or decreased specificity in this context

when tests of intrinsically lower specificity are combined with those of higher specificity.[47] Detection of anti-transglutaminase antibodies in human saliva is possible and may be useful to monitor adherence to GFD with a good correlation between saliva and serum titers ($r = 0.75$, $p = 0.0001$).[48] The diagnostic accuracy of serologic kits (either tTGA or deamidated gliadin peptide) for the detection of CD may be lower in routine clinical practice than that reported in the literature, especially in patients with lower grades of villous atrophy.[49] Immunoglobulin A antibodies directed at epidermal transglutaminase (TG3) are elevated in patients with dermatitis herpetiformis (a papulovesicular eruption caused by ingestion of gluten) and adults with CD. [50]

Endoscopy and Biopsy of the Small Intestine

Confocal endomicroscopy effectively evaluated CD severity “in vivo” before and after treatment with a gluten-free diet.[51] High-resolution magnification with optimal band imaging system had an almost perfect diagnostic accuracy for detection of partial/total villous atrophy or normal mucosa.[52] Endocytoscopy at 450x magnification accurately identified villous atrophy but not minimal change CD.[53]

Despite advances on endoscopic “in vivo” diagnosis, histology examination of the small intestine remains the diagnostic gold standard for CD. In a multicenter study, the lesion was limited to the duodenal bulb in 2.4% of 665 children with CD.[54] These data suggests that biopsy specimens should be obtained from both the duodenal bulb and the distal duodenum.

Vande Voort et al[55] compared 124 systematically assessed patients with lymphocytic duodenosis (defined as >40 intraepithelial lymphocytes per 100 epithelial nuclei) with 454 CD patients, this study demonstrated that lymphocytic duodenosis differs significantly in terms of HLA type, serology, and clinical features to CD patients, suggesting that the majority (52%) of patients with lymphocytic duodenosis do not belong in the spectrum of CD. Therefore, serologic and HLA genotyping are necessary to determine if mild enteropathy is part of the spectrum of CD.[55] Biagi et al[56] showed that minimal intestinal lesions in the absence of endomysial antibodies are most often unrelated to CD. IgA anti-tissue transglutaminase 2 antibody deposits in the small-bowel mucosa may suggest gluten-sensitivity in subjects with normal villous architecture and either CD-associated antibodies in serum or greater density of γδ intraepithelial lymphocytes.[57] Koskinen et al[58] demonstrated that the response of small bowel mucosal transglutaminase 2 IgA deposits after GFD was similar in overt and mild enteropathy CD. Thus, detection of such IgA deposits may improve detection of mild enteropathy CD but ultimately proof would be the clinical response to gluten withdrawal.

Treatment with a Gluten-free diet

The treatment of choice in CD is a lifelong gluten-free diet (GFD). Although expected, complete recovery of intestinal mucosa is rare in adults with CD despite adherence to GFD, clinical response, and disappearance of CD-specific serology.[59] The histological spectrum of CD recognizes that mucosal damage develops gradually over time. Kurppa et al[60] demonstrated using a randomized, controlled design that patients with mild enteropathy (defined by Marsh type I-II) with positive endomysial antibodies may have a benefit from GFD in terms of improving symptoms, antibody response, and mucosal inflammation. Thus, EMA positivity in the absence of enteropathy may be an early predictor for later development of villous atrophy. [61]

Identification of CD by mass screening led 10 year later to health improvement in 66% of children (aged 2–4 years) without deterioration of quality of life.[62] Quality of life is more severely affected in patients with classical CD than those with atypical/silent CD, treatment with a GFD improved quality of life in symptomatic cases but not in silent patients.[63]

The ingestion for 24 weeks of wheat-based starch hydrolysates, glucose syrups and maltodextrines did not have harmful effect on histology or inflammation in CD patients in remission as compared with placebo.[64]

A systematic review concluded that adherence to GFD and mucosal healing may prevent or ameliorate CD-associated complications.[65] Serology, dietitian interview, and re-biopsy have been utilized for assessment of adherence to GFD. Leffler et al [66] proposed a 7-item instrument that allows standarized evaluation of GFD adherence with a superior performance than tissue transglutaminase antibodies (areas under the curve of 0.830 vs 0.652 respectively). Compliance to GFD in adolescents represents a particular challenge that may require specific clinical interventions for optimum clinical outcomes.[67] Meal appearance and the poor availability of gluten-free food that make their condition obvous in public are recurrent stigma-related themes in adolescents with CD.[68] Adherence to GFD may prevent osteopenic status in children and adolescents with CD and concurrent Type 1 DM. [69]

A double-blind placebo controlled multicenter trial showed that the supplementation of B vitamins for 6 months normalized total homocysteine and improved general well-being in patients with CD following a GFD.[70] Copper deficiency in CD may be associated with neurologic or hematologic abnormalities that can be treated with adequate supplementation. [71] Patients with CD and GFD may have inadequate intake of calcium, non-starch polysaccharides, and vitamin D.[72]

On average, gluten-free products were 242 % more expensive than comparable regular products in Canada.[73] This excess cost may affect adherence to the GFD.

Basic Research behind Potential Alternative Therapies for the Future

Huibregtse et al[74] demonstrated that oral administration of Lactococcus lactis-delivered DQ8-specific gliadin epitope induced suppression of local and systemic DQ8-restricted T cell response in a NOD AB° DQ8 transgenic mice. These data provides experimental support for potential therapeutic approaches to induce oral tolerance in CD. Gliadin was neutralized by formation of complexes with a linear co-polymer of hydroxyethylmethacrylate and sodium 4-styerne sulfonate; even more, polymeric binders prevent gliadin-induced epithelial toxicity and barrier dysfunction in HLA-HCD4/DQ8 transgenic mice.[75] Proteases from germinating wheat degraded gliadin into small peptide fragments that did not increase epithelial permeability or stimulate T-cell proliferation in vitro at the same extent as unprocessed pepsin and trypsin digested gliadin.[76] New improved variants of Sphingomonas capsulata prolyl endopeptidases (enzymes that may cleave immunogenic gluten peptides) with as much as 20% enhanced activity at pH 4.5 and 200-fold greater resistance to pepsine were identified by protein engineering.[77]

Refractory Celiac Disease

Refractory celiac disease is a rare condition characterized by a symptomatic severe enteropathy and villous atrophy despite strict adherence to GFD for at least 6–12 months after exclusion of other causes of non-responsive CD and malignancy.

Refractory CD was associated with poor prognosis in two large cases series from France and US, with clonal (type 2 subtype) having a worse outcome because of progression to overt lymphoma.[78, 79] A novel clinically-based staging system based on the additive effect of the following 5 prognostic factors scored at the time of refractory CD has been proposed using single-center data: older age (>65), low albumin (<3.2), low hemoglobin (<11), total villous atrophy on the diagnostic biopsy, and presence of T-cell clone in the intestine.[78]

Verbeek et al[80] demonstrated that aberrant T-lymphocytes, the hallmark of type 2 refractory CD are not strictly confined to a small intestinal intraepithelial localization.

Conclusions

Celiac disease is a global health problem that requires a multidisciplinary and increasingly cooperative multinational research effort.

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