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MINIREVIEWS

Dyspepsia and celiac disease: Prevalence, diagnostic tools and therapy

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Abstract

The prevalence of dyspepsia is up to 40% in population-based study. Functional dyspepsia is an exclusion diagnosis and it is classified as a chronic abdominal pain-related functional disorder, characterized by the presence of persistent or recurrent pain or discomfort centered in the upper abdomen, neither relief by defecation, nor association with the onset of a change in stool frequency or form. Celiac disease (CD) is a common autoimmune enteropathy, with a prevalence around 1% in the general population. Its diagnosis includes a serological screening and an upper gastrointestinal endoscopy with multiple biopsies. Gluten-free diet is the only effective treatment. CD diagnosis is often delayed in asymptomatic patients or in individuals with less clinical gastrointestinal symptoms. Several studies performed coeliac disease screening in patients with symptoms suggestive of dyspepsia, showing a biopsy-proved prevalence that ranged from 0.5% to 2%. The typical endoscopic markers of villous atrophy are not sufficiently sensitive, so some endoscopic techniques, such as "water immersion" and confocal endomicroscopy were proposed to improve the diagnostic sensitivity and target biopsies. A recent meta-analysis estimated that the prevalence of CD was higher in patients with dyspepsia, but not in a statistically significant way. However this assumption should be confirmed further larger studies.

Key words: Dyspepsia; Coeliac disease; Upper endoscopy; Villus atrophy; Screening

Core tip: Dyspepsia is classified as a chronic abdominal pain-related functional disorder that affects almost 40% of the population. It can be also a manifestation of celiac disease, an immuno-mediated enteropathy, caused by the ingestion of gluten in genetically predisposed patients. The prevalence of celiac disease among dyspeptic patients has been investigated, with results ranging from 0.5% to 2%. Celiac disease diagnosis requires histological evaluation of villous atrophy on duodenal biopsies specimens. Screening for celiac disease in dyspeptic patients and routinely performing of biopsies during upper gastrointestinal endoscopy, may be useful as part of the diagnostic flow-chart of these patients.

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INTRODUCTION

Dyspepsia is one of the most common gastrointestinal disorders to be faced in clinical practice, with prevalence up to 40% in population-based study[1] so that the economic impact is very high.

When dyspepsia is not a manifestation of an organic

pathology, such as gastroesophageal reflux disease or peptic ulcer disease, then it is classified as functional dyspepsia (FD).

FD markedly reduces patients' quality of life, similarly to mild heart failure and menopause[2]. However FD is an exclusion diagnosis and on the basis of Rome Ⅲ criteria[3], it is defined as the presence of gastroduodenal symptom without evidence of structural disease able to explain the syptoms. Often patients refer to suffer from early satiation or postprandial fullness (postprandial distress syndrome), epigastric pain/discomfort or burning (epigastric pain syndrome).

Pathophysiology of FD is not completely understood yet and several pathophysiological mechanisms have been proposed to underlie symptoms. Central processing of visceral stimuli, low-grade inflammation in the duodenum and genetic factors are the main emerging hypothesis investigated[4]. FD is difficult to manage, because no medication is currently approved in the United States, Canada or the European Union. Many treatments have been proposed (diet, eradication of *H. pylori* and drugs such as prokinetic agents or protonic pump inhibitors)[5] but no one was satisfactory.

Celiac disease (CD) is an auto-immune enteropathy, whose diagnosis is often delayed in asymptomatic patients or in individuals with less clinical gastrointestinal symptoms, such as abdominal bloating, nausea and vomiting. CD diagnosis, according to the American Gastroenterology Association, consists of a serological screening (including anti-transglutaminase, anti-endomisium and anti-deamidated gliadin antibodies) and an upper gastrointestinal endoscopy with multiple duodenal biopsies. Gluten-free diet is the only effective treatment for the disease.

However, although dyspepsia may be a manifestation CD, most of FD patients do not perform serological screening for CD or duodenal biopsies and there are few data about the prevalence of CD in patients with dyspepsia.

Recent studies[6-10] demonstrates that the prevalence of silent CD in patients with dyspepsia is slightly higher than that of the general population, however in one study it resulted rather low[11].

The 40%-60% of subjects with dyspepsia resulted macroscopically normal when performing upper gastrointestinal endoscopy[12]. Unfortunately, the practice of performing biopsies, even in absence of endoscopic alteration of intestinal mucosa, is quite uncommon.

The typical endoscopic markers of villous atrophy include mosaic pattern, scalloping of folds, and a decrease of duodenal folds. However, mostly in less severe cases, CD diagnosis cannot only be performed on these parameters. So, considering that many authors describe these markers as not sufficiently sensitive, some endoscopic techniques, such as "water immersion" and confocal endomicroscopy (CEM) were proposed to improve the diagnostic sensitivity and target biopsies in most damaged mucosal areas[13,14].

DYSPEPSIA AND CELIAC DISEASE

Recent studies demonstrate that the prevalence of CD in patients with dyspepsia is higher than that of the general population[6-10].

Bardella *et al*[6] prospectively enrolled 517 patients suffering from dyspeptic symptoms. All patients were submitted to upper gastrointestinal endoscopy, and six were diagnosed to be celiac (1.2%). Interestingly three patients (50%) had a normal duodenal endoscopic pattern and five of the six celiac patients were young women aged between 20 to 37 years. The authors suggest to perform serological screening for celiac disease especially in young women suffering from dyspepsia.

Lima *et al*[7] reported a CD prevalence of 1.4% in a small series of patients with dyspepsia, both were young women, aged 19 and 25 years respectively. In the paper of Ozaslan *et al*[8] among the 196 investigated patients three were diagnosed to be celiac (1.5%). All were female younger than 52 years, and only two showed abnormal endoscopic findings.

In the manuscript by Giangreco *et al*[9], published in 2008, the role of upper gastrointestinal endoscopy in CD diagnosis was evaluated in patients suffering from FD. The prevalence of CD was 2% (15 patients out of 726 enrolled), higher than the general population one, also considering that patients with an increased risk for CD (such as first degree relatives) were excluded from the study. Among the 15 CD patients (age ranged 20 to 56): 10 were female and only 8 patients presented endoscopic findings suggestive for CD.

Keshavarz *et al*[10] investigated the prevalence of CD among 170 patients with FD. Twelve patients (10 female), suffering form dysmotility-type dyspepsia, tested positive for CD related antibodies, however only two of them showed villous atrophy at the histological evaluation.

Only in the paper by Heikkinen *et al*[11] published in 1995, among the 400 uselected dyspeptic patients enrolled to perform upper gastrointestinal endoscopy, serological evaluation and abdominal ultrasound, CD was diagnosed in 2 patients (both aged less than 64 years). The low prevalence (0.5%) could be due, maybe, to the eterogeneity of the population study, with a higher percentage of aged patients (77% were more than 44 years old) while the most frequent diagnosis in younger patients was lactose intolerance (9%).

In a recent meta-analysis by Ford *et al*[15], the authors provided a pooled prevalence of biopsy-proven CD of 1.0%, similar to that in the general population, when duodenum biopsy was performed as first-line investigation. However when the authors pooled the data from the studies that used the Rome Ⅱ criteria for dyspepsia, the biopsy proved CD was 2%, significantly higher.

CD

CD is a chronic, immuno-mediated enteropathy, caused by ingestion of gluten in susceptible individuals, carrying DQ2 and/or DQ8 HLA. It is characterised by a chronic inflammatory state of the small intestine that recover after gluten withdrawal. The typical changes of the duodenal mucosa include: raised intra-epithelial lymphocyte, crypt hyperplasia and various degree of villous atrophy

as classified by Marsh and modified by Oberhuber *et al*[16] in 1999, that decreased digestion of food and micro- and macronutrients absorption.

CD is common, with a prevalence around 1% in the general population of Western countries[17,18], more frequent in females than males.

Pathogenesis

The pathogenesis is multifactorial, including the interactions between environmental, genetic and immune factors. Gluten, a protein derived from wheat, barley and rye, represents the trigger factor of CD. The alcohol-soluble fraction of gluten, the alpha-gliadin, is rich in prolamine and glutenine that could trigger an immune response, mediated by both innate and adaptative arms of CD patients' mucosal immune system. Genetic susceptibility plays a crucial role in CD pathogenesis, as demonstrated by the increased prevalence in first-degree relatives (9.5%) and siblings (11%)[19]; in the homozygous twins it arises to 75%[20,21]. The genetic basis of celiac disease can be divided between *HLA* and *non-HLA* gene variants[22].

The HLA DQ2 heterodimer is present in 90% of celiac patients, in 5% of the cases the HLA DQ8 heterodimer is present. The HLA DQ2 heterodimer, present in 90% of celiac patients[23], is formed by a beta chain (β) encoded by the allele HLA DQB1 * 02 (HLA DQB1 * 0201 or * 0202) and by an alpha chain (α) encoded by the allele HLA DQA1 * 05. The heterodimer HLA DQ8 is formed by a β chain and an α chain encoded by HLA DQB1 * 0302 and HLA DQA1 * 03 respectively[24].

Genes of the HLA complex can contribute in only 36% of the increased risk of celiac disease in siblings[22], indicating the need for assistance from other *non-HLA* genes[25].

The frequent association of celiac disease with other monogenic diseases may demonstrate the existence of a link with other genes on chromosome 7 (short arm) implicated in Williams syndrome and on chromosome 21 involved in Down syndrome[26].

A fundamental role in the pathogenesis is carried out by an ubiquitous calcium-dependent enzyme, the transglutaminase type 2 (TG2). The TG2 catalyzes the acyl transfer between the γ-carboxamide group of glutamine and the ε-amino group of lysine or primary amine soluble. This mechanism forms gliadin-gliadin macromolecular complexes, which are considered neoepitopes, therefore non-self antigens against which the immune system reacts.

In the presence of a low pH, an abundance of glutamminic residues and scarcity of proteins that bind lysine, TG2 catalyses the deamidation of glutamine[27-29]. Some of these peptides of "deamidated" gluten, because of their negative charge, show a high affinity for the HLA-DQ2 or-DQ8 heterodimer. Once bound to these molecules they activate intestinal mucosa T cells[30-32] and they cause the cytokine production and the begins of the intestinal damage.

Clinical presentation

The first modern description of CD is due to Samuel Gee, an English paediatrician, published in the St. Bartholomew's Hospital Reports of 1888. He recognised CD as a chronic indigestion, occurring in people of all ages, presenting as diarrhoea.

Nowadays clinical presentations of CD may vary from silent to severe malabsorption symptoms (celiac crisis).

Didactically, CD manifestations are divided in: (1) typical: including gastrointestinal symptoms, such as diarrhoea, weight loss, abdominal pain, failure to thrive, abdominal distension and vomiting; (2) atypical: that is for example short stature, iron-deficiency anaemia, dermatitis herpetiformis, delayed puberty; and (3) silent: completely asymptomatic.

A delayed gastric empty and a slow oro-caecal transit has been observed in celiac patients on a gluten containing diet, probably due to abnormal exposure of small bowel unabsorbed starch and fats and to altered neuroimmunomodulation and hormonal deregulation (low levels of cholecystokinin and high levels of peptide YY)[33]. Some authors investigated the transit disorders in patients with untreated CD using the video-capsule endoscopy. Urgesi *et al*[34] found that there was no difference in gastric empting and small bowel transit time between CD patients and control group. However, Ciaccio *et al*[35] observed changes in motility of the small bowel and they speculated that the reduced folds can cause more rapid changes in the position and in the width of the luminal centre.

Diagnosis

CD diagnosis, according to the American Gastroenterology Association, consists of a serological screening and an upper gastrointestinal endoscopy[36].

Nowadays, CD serological screening is recommended for symptomatic patients, or for those people who are at high risk of CD (such as first degree relatives). It encompasses the total serum IgA, the IgA anti-transglutaminase antibodies (AbTG2), IgA anti-endomisium antibodies (EMA) and IgA anti-deamidated gliadin antibodies (DGP).

AbTG2 proved to have a very high sensitivity (98%-100%) and a very good specificity (94%-98%)[37], they are the most widely used for CD screening, even if they can be found in patients affected by other autoimmune diseases[38]. They can be determined both by ELISA or RIA, the latter technique showing a so high sensitivity[39] that it has been used to detect AbTG2 in saliva[40], demonstrating a correlation with CD histological grading and diffusion of duodenal lesions[41].

EMA have a very high specificity (100%), but a lower sensitivity than AbTG2[38]. They are determined by indirect immunofluorescence, using monkey oesophagus sections as substrate.

DGP have been demonstrated to be more sensitive and specific than the old antigliadin antibodies and they are useful especially in children younger than two years

of age[42].

In IgA deficient patients, it is recommended to perform the IgG antibodies, particularly IgG anti-deamidated gliadin antibodies.

The upper gastrointestinal endoscopy with multiple biopsies, both from duodenal bulb and distal duodenum, is the gold standard for diagnosis[36]. The standard endoscopy does not permit the visualization of villous atrophy, even if several macroscopic markers has been related to CD (Figure 1), such as reduction or absence of duodenal folds, scalloping, nodular appearance and mosaic pattern. However the power of these endoscopic markers to predict the villous atrophy is still debated[43,44]. This variability could be due to the absence of macroscopic sign in case of patchy or partial villous atrophy.

In the last few years, new methods have been developed to evaluate with more accuracy the macroscopic appearance of villous pattern during upper gastrointestinal endoscopy.

The water immersion technique (Figure 1C) is an easy procedure that can emphasize the villous pattern. It consist in a first phase of air suction from the lumen, then a second phase of injection of 90-150 mL of water[45]. It has the potential to target biopsies and, eventually, reduce the number of specimen, thanks to its capability of enhancing areas of villous atrophy. An alternative technique is represented by the chromoendoscopy, that uses the dye staining with indigo carmine in enhancing the visualization of the mucosal surface. This endoscopic tool has showed a better accuracy when combined with magnification endoscopy[14].

Narrow band imaging (NBI) is another technology that improves the visualization of the surface of the superficial mucosa and its vascular architecture.

NBI with optical magnification assists in detecting patients with villous atrophy without determining the level of intraepithelial lymphocytosis and crypt hyperplasia[46,47].

Cammarota *et al*[48] reported their experience in the use of I-scan technology during endoscopy for the evaluation of the duodenal villous pattern. It works in real time and permits to switch from standard endoscopy to I-scan view very quickly. The authors reported an accuracy of 100% in detecting total villous atrophy, and suggested a possible role of this technique in targeting biopsies in patchy distribution of lesions. However in the reported study, all the enrolled patients underwent upper gastrointestinal endoscopy for suspicion of malabsorption, so they had a high pre-test probability of duodenal atrophy.

Rokkas *et al*[49] recently published a meta-analysis about the role of video capsule endoscopy in CD diagnosis and reported a pooled sensitivity of the tool of 89%. A normal capsule endoscopy cannot exclude CD, however it could provide information on the extent of the disease, allowing the visualization of not accessible portion of small bowel, even thou the histological evaluation of bioptic samples still remain the gold standard for the diagnosis.

Biopsies taken during endoscopy must be oriented on filter paper, fixed in formalin and embedded in paraffine. After the cut and haematoxylin-eosin staining, an expert pathologist assesses the sections under light microscopy, evaluating the intraepithelial lymphocytes (IEL) count, the villo/crypta ratio and the villous atrophy using the Marsh modified by Oberhuber classification[16]: (1) type 0: normal mucosa with less than 40 IEL/100 enterocites (EC); (2) type 1: infiltrative, that is characterised by normal villous architecture, normal crypt height, but high IEL counts (> 40/100 EC); (3) type 2: hyperplastic, with a normal villous architecture, but but high IEL counts (> 40/100 EC) and crypt hyperplasia; (4) type 3: destructive, in which besides a high IEL counts (> 40/100 EC) and acrypt hyperplasia, it can be also observed a villous atrophy (3a: mild villous atrophy, 3b moderate villous atrophy, 3c: total villous atrophy).

Recently a new classification has ben proposed by Corazza *et al*[50], in order to reduce the inter and itra-observer disagreements and to facilitate the relationship between pathologists and gastroenterologist. It consists of two degrees: (1) A: non-atrophic lesions of the duodenum; and (2) B: atrophic lesions. It is divided into grade B1, that include mild and moderate villous atrophy, and grade B2, with a total villous atrophy.

The intestinal involvement, however, is not always confined to the duodenum. It has been demonstrated that other portions of the gastrointestinal tract are involved, such as the gastric[51], oral[52] and colonic mucosa[53].

The chronic superficial gastritis has been described as the most frequent form of gastritis that occurs in non treated celiac patients[54], followed by lymphocytic gastritis, a form of gastritis of uncertain pathogenesis[55].

Therapy

Gluten-free diet is, at this moment, the only effective treatment for coeliac disease, allowing the healing of intestinal mucosa, the improvement of symptoms and prevents the onset of long-term complications, such as osteoporosis[56] and autoimmune disorders[57,58].

However, many efforts have been made to find an alternative therapy for CD, involving the biotechnology field, which led to a better understanding of the molecular mechanisms of coeliac disease and the identification of pathogenetic pathways that could be targeted by new drugs. Currently the main targets under investigation are[27]: (1) endopeptidases capable to detoxify gluten in order to decrease its immunogenic power; (2) modulation of permeability by the pill AT-1001; (3) block of antigen presentation made by inhibitors of TG2 and HLA-DQ2; (4) inflammation modulation using monoclonal antibodies directed against inflammatory cytokines; (5) block of the recruitment of lymphocytes by molecules that inhibit the migration to the intestinal mucosa; and (6) immunomodulation and induction of gluten tolerance.

In the last few years a new gluten- related syndrome is increasing awareness: the non celiac gluten sensitivity (NCGS). NCGS often overlaps with irritable bowel disease syndrome and for both conditions the diagnosis is

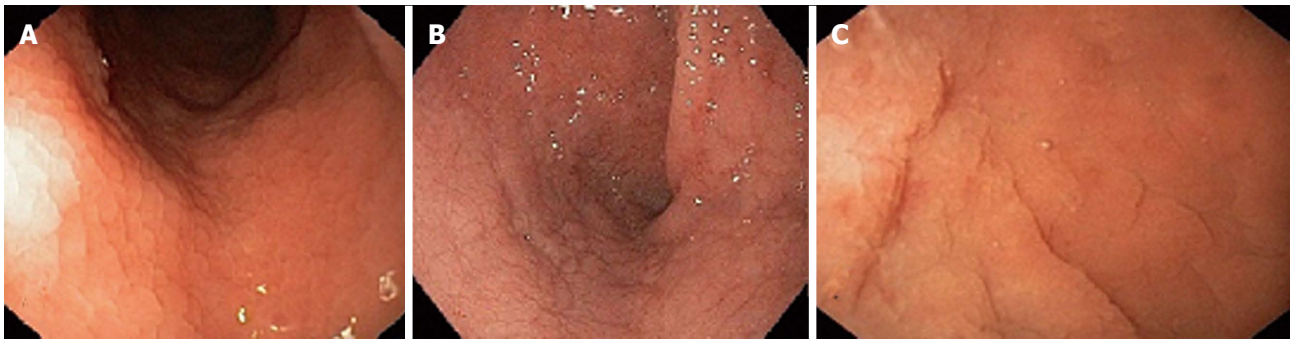

Figure 1 Endoscopic markers of celiac disease. A, B: The typical endoscopic markers of villous atrophy include mosaic pattern, scalloping of folds, and a decrease of duodenal folds; C: Appearance of the duodenum of a celiac patient using the water immersion technique.

based on clinical symptoms.

However it is a still poorly defined syndrome, characterized by the presence of gastrointestinal symptoms, such as bloating, abdominal pain, nausea, gastroesophageal reflux disease, and/or extraintestinal manifestation, tiredness, headache, anxiety, foggy mind and peripheral numbness[59]. The clinical presentation of these symptoms has been associates to the ingestion of gluten, however it has been hypothesize that other wheat proteins, such as amylase trypsin inhibitors, could play a role[60]. Also fermentable oligosaccharides, monosaccharides and disaccharides, contained in wheat, rye, but also in milk, legumes, honey and some vegetables (fennel, beetroot, and chicory) has been proposed to be important in NCGS[61]. NCGS is an exclusion diagnosis, so CD and wheat allergy should be rouled out. Its prevalence is still uncertain, ranging from 3.19%[59] in Italy, to 6% in United States[62] and it is more frequent in female than in male. Further study, including possibly a double blind gluten challenge, should be performed to assess the real prevalence of NCGS.

CONCLUSION

CD diagnosis is often delayed in asymptomatic patients or in individuals with less clinical gastrointestinal symptoms, such as abdominal bloating, nausea and vomiting, despite the many benefits deriving from a prompt identification.

Based on these assumptions, several studies performed coeliac disease screening in patients with symptoms suggestive of dyspepsia, showing a biopsy-proved prevalence that ranged from 0.5% to 2%[6-11]. Interestingly, the subgroup of dyspeptic patients at highest risk comprised young women, aged from 20 to 37 years (RR of CD 3.22)[6].

The 40%-60% of subjects with dyspepsia resulted macroscopically normal when performing upper gastrointestinal endoscopy[63,64]. Unfortunately, the practice of performing biopsies, even in absence of endoscopic alteration of intestinal mucosa, is quite uncommon.

The typical endoscopic markers of villous atrophy include mosaic pattern, scalloping of folds, and a decrease of duodenal folds (Figure 1). However, mostly in less severe cases, CD diagnosis cannot only be performed on these parameters. So, considering that many authors describe these markers as not sufficiently sensitive, some endoscopic techniques, such as "water immersion" and CEM were proposed to improve the diagnostic sensitivity and target biopsies in most damaged mucosal areas[12-14].

A recent meta-analysis by Ford *et al*[15] evaluated the yield of diagnostic testing for CD in patients affected by dyspepsia. The pooled prevalence of positive celiac serology ranged from 6% to 8%. The author pooled the data from literature and estimated that the prevalence of positive celiac serology ranged from 6% to 8%, the biopsy-proved CD prevalence was also higher in patients with dyspepsia, approximately 2%, than controls, but not in a statistically significant way. However, due to several limits that affected the paper, such as presence of study based only in tertiary care, this assumption should be confirmed further larger and, possibly, case-control studies.

In conclusion screening for CD in patients suffering from dyspeptic symptoms, as defined by Rome Ⅲ criteria, and routinely performing of biopsies during upper GI endoscopy, may be useful as part of the diagnostic flow-chart of these patients, considering the benefits of a promptly beginning of a gluten-free diet, even thou further, well-defined and case-control studies on a larger population could definitively assess if CD prevalence is higher in dyspeptic patients.

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