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How much of celiac disease is in dyspeptic syndrome?

Quanto há de doença celíaca na síndrome dispéptica?

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ABSTRACT

Introduction: Celiac disease is an autoimmune condition triggered by the ingestion of and contact with gluten in genetically predisposed individuals. Dyspeptic syndrome, on the other hand, is characterized by chronic upper digestive symptoms. The relationship between these two conditions is the main focus of this review.

Objective: To investigate the prevalence of celiac disease in patients with dyspeptic syndrome based on the analysis of epidemiological characteristics, upper digestive endoscopy, duodenal histology and serology.

Methods: Narrative review carried out with information published on virtual platforms in Portuguese and English and analyzed during the period from January 2022 to August 2023. The material for reading and analysis was selected from the SciELO platforms – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus using the following terms: "dyspepsia, celiac disease, gluten, prevalence" with AND or OR search, considering the title and/or abstract. Afterwards, the full texts were read, including 18 articles.

Results: In dyspeptic patients, the average age was 45.13 years and the female gender was predominant. Symptoms associated with gluten were reported in 6%. The antitransglutaminase antibody was positive, with an estimated prevalence of 1.5%. Considering the Brazilian sample of 100 patients, the diagnosis of celiac disease was made with a prevalence of 3%.

Conclusion: Although the prevalence of celiac disease in dyspeptic patients may be higher than in the general population, results are variable and depend on several factors, including testing methodologies and regional characteristics. This review also highlights the importance of an individualized approach in the investigation of celiac disease in dyspeptic patients, considering aspects such as family history, gluten-related symptoms and autoimmune comorbidities.

KEYWORDS: Dyspepsia. Celiac disease. Gluten. Prevalence

Central message

Celiac disease is an autoimmune condition triggered by the ingestion of gluten in genetically predisposed individuals. Dyspeptic syndrome, on the other hand, is characterized by chronic upper digestive symptoms. The relationship between these two conditions is the main focus of this study.

Perspective

Although the prevalence of celiac disease in dyspeptic patients may be higher than in the general population, the results are variable and depend on several factors, including testing methodologies and regional characteristics. This review highlights the importance of an individualized approach in the investigation of celiac disease in dyspeptic patients, considering aspects such as family history, gluten-related symptoms, and autoimmune comorbidities.

RESUMO

Introdução: A doença celíaca é uma condição autoimune desencadeada pela ingestão e/ou contato com o glúten em indivíduos geneticamente predispostos. A síndrome dispéptica, por outro lado, é caracterizada por sintomas digestivos superiores crônicos. A relação entre estas duas condições é o foco principal deste estudo.

Objetivo: Investigar a prevalência da doença celíaca em pacientes com síndrome dispéptica com base da análise de características epidemiológicas, endoscopia digestiva alta, histologia duodenal e sorologia.

Métodos: Revisão narrativa feita com informações publicadas em plataformas virtuais em português e inglês, e analisada durante o período de janeiro de 2022 a novembro de 2023. O material para leitura e análise foi selecionado das plataformas SciELO – *Scientific Electronic Library Online*, *Google Scholar*, *Pubmed* e *Scopus* utilizando os seguintes termos: "dispepsia, doença celíaca, glúten, prevalência" com busca *AND* ou *OR*, considerando o título e/ou resumo. Após, foi realizada a leitura da íntegra dos textos incluindo 18 artigos.

Resultados: A idade média dos pacientes com dispepsia foi de 45,13 anos e o sexo feminino foi predominante. Os sintomas associados ao glúten foram relatados em 6%. O anticorpo antitransglutaminase foi positivo com prevalência estimada de 1,5%. Considerando a amostra brasileira de 100 pacientes, o diagnóstico de doença celíaca foi prevalente em 3%.

Conclusão: Embora a prevalência de doença celíaca em pacientes dispépticos possa ser maior do que na população em geral, os resultados são variáveis e dependem de vários fatores, incluindo metodologias de teste e características regionais. Esta revisão também ressalta a importância de abordagem individualizada na investigação da doença celíaca em pacientes dispépticos, considerando aspectos como história familiar, sintomas relacionados ao glúten e comorbidades autoimunes.

PALAVRAS-CHAVE: Dispepsia. Doença celíaca. Glúten. Prevalência.

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INTRODUCTION

Dyspepsia means "difficult digestion".[1,2] It is a term derived from Greek, coined in the eighteenth century, marking an increase in interest in upper digestive diseases in developed countries. In parallel, celiac disease — a gluten-related autoimmune condition affecting the small intestine — was first described in the first century and recognized as gluten-related only in the 1940s. During World War II, grain shortages led to improved symptoms in affected children, which returned after the war.[3,4] Thus, interest in the relationship between symptoms and dietary conditions, especially cereals, was initiated.

Dyspepsia is characterized by pain or discomfort in the upper abdomen and affects approximately 10-45% of the world's population. On the other hand, the global prevalence of celiac disease is about 0.7%[7] and is apparently increasing. The pathophysiology is complex and includes genetic susceptibility and environmental factors. Its symptoms include intestinal changes and malabsorption. 3,5,6

It's unclear whether people with dyspepsia have a higher risk of celiac disease. Studies present contradictory results regarding the prevalence of dyspeptic in dyspeptic patients.[7-10] This uncertainty influences the decision to investigate celiac disease in these cases.[11,12] Therefore, there is a need for further epidemiological studies to determine when investigation of celiac disease is necessary in patients with dyspepsia.

Thus, this review aimed to evaluate the prevalence of celiac disease in individuals with dyspeptic syndrome; investigate demographic, clinical, risk and family factors; evaluate the symptoms presented, aiming to identify possible specific indicators of celiac disease; explore endoscopic findings; identify specific histological changes and evaluate serological tests to detect associated antibodies, providing a more comprehensive analysis.

METHOD

The literature review was carried out by collecting information published on virtual platforms in Portuguese and English and analyzed during the period from January 2022 to November 2023. The material for reading and analysis was selected from the SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus platforms. Initially, a search was carried out for descriptors related to the theme, which were identified through DeCS using the following terms: "dyspepsia, celiac disease, gluten, prevalence" with AND or OR search, considering the title and/or abstract. Afterwards, considering only those that were more related to the theme, the full texts were read and finally 18 articles were included.

DISCUSSION

Tack in 20212 defined dyspepsia as a heterogeneous group of symptoms of the upper abdomen, characterized by epigastric pain or discomfort, epigastric burning, early satiety, and postprandial fullness, and may include various symptoms such as belching, nausea, vomiting, heartburn, regurgitation, anorexia, and distension in the upper abdomen. It is a common condition that affects 10-45% of the population. In most cases, there is no underlying organic disease, which is called functional dyspepsia. However, in 20%, these symptoms may be due to peptic ulcer disease, digestive malignancy, gastroesophageal reflux disease, Helicobacter pylori infection, biliopancreatic diseases, or celiac disease. The term "uninvestigated dyspepsia" is used to describe cases that have not yet been investigated to reveal the underlying cause. The same author suggested starting the evaluation of uninvestigated dyspepsia with anamnesis and physical examination. The sequence depends on clinical suspicion, presence of alarm signs (weight loss, anemia, bleeding, dysphagia) and age (especially over 45 years), and may follow one of the following strategies: empirical treatment with proton pump inhibitor, upper gastrointestinal endoscopy with Helicobacter pylori (gold standard) or non-invasive tests to detect the bacteria. Celiac serology and abdominal imaging should be considered to complement the evaluation.

Coeliac disease

Singh, Arora, Lal, Strand, and Makharia in 201513 conducted a meta-analysis and systematic review on the risk of celiac disease in first-degree relatives. They included 54 articles in an initial sample of 2,259 people and observed that these family members, especially sisters and daughters, had a higher prevalence than the general population, around 7.5%.

In 2018, Lebwohl, Sanders, and Green5 defined celiac disease as an autoimmune disorder of the small intestine caused by gluten ingestion in genetically predisposed individuals. Its pathophysiology results from a complex of interactions between genetic susceptibility (HLA DQ2 and DQ8) and environmental factors with activation of innate and adaptive immunity. Its consequences are immune aggression to the small intestine and a range of intestinal and extraintestinal clinical presentations. The gastrointestinal presentation can be varied and characterized by osmotic diarrhea, steatorrhea, constipation, dyspeptic symptoms, aphthous stomatitis, abdominal bloating, flatulence, weight loss, abdominal pain, and secondary lactose intolerance.

Also, in 2018, Singh, Arora, Strand, Leffler, Catassi, Green, Kelly, Ahuja and Makharia14 conducted a systematic review and meta-analysis to describe the epidemiology of the disease. They included 96 articles out of a total of 3843. Serology was positive in 1.4% of the world population and diagnosis confirmed by biopsy in 0.7%. They concluded that there was a need for prevalence studies in several countries.

Lebwohl and Rubio-Tapia6, in 2021, in a review article, described the global seroprevalence at 1.4% and South American seroprevalence at 1.3%. After histological analysis and confirmation of the diagnosis of celiac disease, the prevalence was 0.7%.

In 2021, Lebwohl and Green3 described the extraintestinal manifestations of the disease according to the affected system, as follows: 1) mucocutaneous manifestations - ecchymosis, petechiae, edema, follicular

hyperkeratosis, and dermatitis; dermatitis herpetiformis highly related to the disease by the mechanism of autoimmunity and characterized by the presence of multiple pruritic papules and vesicles that are grouped in arrangements on the elbows, dorsal aspect of the forearm, knees, scalp, back, and buttocks; 2) endocrinological - growth retardation, short stature, amenorrhea, infertility, sexual impotence and secondary hyperparathyroidism (secondary to vitamin D deficiency); 3) hematological - anemia, bleeding and thrombocytosis; 4) hepatic - alteration of liver enzymes (lymphocytic hepatitis); 5) musculoskeletal - fatigue, weakness, muscle atrophy and osteoporosis; 6) neurological - headache, ataxia, peripheral neuropathy and mood disorders.

In addition to extraintestinal manifestations, celiac disease has other medical conditions that may be associated. Schuppan and Dieterich[15] described such conditions: selective immunoglobulin A deficiency, type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune polyglandular syndrome type III (autoimmune thyroiditis and immune-mediated diabetes), atopic dermatitis, gastroesophageal reflux disease, eosinophilic esophagitis, inflammatory bowel disease, microscopic colitis, cholestatic and autoimmune liver disease, idiopathic pulmonary hemosiderosis, and immunoglobulin A nephropathy.

Based on the latest global updates and the largest groups of studies in gastrointestinal diseases, Kelly in 2022[16] described the diagnostic resources for celiac disease. Your research should be carried out during the consumption of gluten, as the gluten-free diet reduces the sensitivity of the tests. Diagnostic resources involve serology and histology. The preferentially performed antibody is the anti-tissue transglutaminase of the IgA class. When compared with antibodies directed to gliadin and endomysium, antitransglutaminase is the antibody with the highest sensitivity and specificity (95% to 97%), in addition to being operator-dependent and enabling quantitative values, which will be used to evaluate the response to treatment. All measurements should be accompanied by total IgA measurements, as IgA deficiency is a condition that can result in false-negative tests. Histology of the small intestine is accessible via upper GI endoscopy. Macroscopically, the duodenal mucosa may be atrophic, irregular, nodular, fissure-like, or mosaic-like. Histology is performed regardless of the endoscopic appearance, as it does not have good sensitivity for detecting the disease. At least 4 postbulbar and 2 bulbar biopsies are recommended. Intraepithelial lymphocytosis, cryptic hyperplasia, and villous atrophy may be found. Since none of these findings are specific to celiac disease, the Marsh-Oberhuber classification is used, which stratifies histological findings into types 0, 1, 2, and 3, with types 2 and 3 being consistent with celiac disease. Therefore, the author reports that the diagnosis of celiac disease is established in the positivity of the anti-transglutaminase IgA antibody with the presence of normal total IgA and the histological findings of Marsh types 2 and 3.

Celiac disease and dyspepsia

Bardella, Minoli, Ravizza, Radaelli, Velio, Quatrini, Bianchi and Conte[9] in 2000 studied the prevalence of celiac disease in dyspeptic individuals in a prospective study. Patients who were going to undergo upper gastrointestinal endoscopy to evaluate dyspepsia were included. Patients under 12 years of age, known gastrointestinal tract disease, suspected celiac disease, malabsorption and/or iron deficiency anemia were excluded. A total of 3019 patients were evaluated, 517 of whom were included and evaluated with upper gastrointestinal endoscopy and duodenal histology. If they presented histological signs of celiac disease - such as villus atrophy, cryptic hyperplasia and epithelial lymphocytosis - immunoglobulin A and antiendomysium antibody IgA were measured for diagnostic confirmation. They observed that patients with dyspepsia have an elevated risk of celiac disease (relative risk for celiac disease of 2.32%), higher than expected for the general population. In addition, the study also indicated that endoscopic findings of the duodenum were not sufficient to confirm or not the presence of histological alteration. The study concluded with the recommendation of screening in this context.

A 2005 Brazilian study conducted by Lima, Gandolfi, Pires, and Pratesi10 prospectively evaluated patients treated for dyspepsia to determine the prevalence of celiac disease. Those with malabsorption, chronic diarrhea, celiac disease, or known diseases that cause dyspepsia were excluded. One hundred and forty-two patients participated in the study. These patients underwent endoscopy with duodenal histological analysis and collection of IgG antigliadin. If the antibody was positive, antiendomysium IgA was collected for confirmation. They found a prevalence of celiac disease of 1.4%, concluding that it was a high prevalence in this scenario.

In 2009, Ford, Ching and Moayyedi[7] conducted a meta-analysis of studies that studied the prevalence of celiac disease in dyspepsia up to February 2009. They included case-series and case-control studies that evaluated 90 or more patients and used serological analysis and/or duodenal biopsies in dyspeptic adults. We included 15 studies covering 9105 individuals. The seroprevalence found was 7.9% and the diagnosis confirmed by biopsy was 3.2% in dyspeptic patients. In controls, seroprevalence was 3.9% and diagnosis was 1.3%. They concluded that the seroprevalence and diagnosis of celiac disease are higher in dyspeptic individuals than in controls, but in this meta-analysis, there was no statistical significance.

In 2012, Nejad, Dabiri, Ehsani-Ardakani, Mojarad, Derakhsan, Telkabadi, and Rostami[8] conducted a study in Iran to assess the prevalence of celiac disease in dyspeptic individuals. They studied 407 dyspeptic patients from November 2007 to October 2008. All patients underwent upper gastrointestinal endoscopy with duodenal histology, total IgA and anti-transglutaminase IgA antibody dosage. In the case of IgA deficiency, they were tested with IgG class serology. They found a seroprevalence of 8% and a prevalence of celiac disease of 2.5%, concluding that the prevalence of celiac disease is significantly higher than the general population (1%), suggesting the investigation in these patients.

Lasa, Spallone, Gandara, Chaar, Berman and Zagalsky[11] in 2007 conducted a prospective study to evaluate the prevalence of celiac disease in dyspeptic individuals and compare it with the prevalence of celiac disease in healthy individuals without dyspepsia. The patients were initially submitted to upper gastrointestinal endoscopy with histology. If there were signs of atrophy in histology, the investigation was followed by serological analysis (anti-transglutaminase and/or anti-endomysium IgA). A total of 320 patients were included in each group and the diagnosis of celiac disease was made in 1.25% of dyspeptic individuals and 0.62% of asymptomatic individuals (p = 0.2), concluding that there was no higher prevalence of celiac disease in dyspeptic individuals compared to healthy individuals.

In 2020, Behforouz, Esmaeelzadeh, Mozzafari, Mokhtarifar, Faravani, Amoueian, Khooeim Jarahi, and Goshayeshi17 conducted a study to assess the prevalence of celiac disease in dyspepsia and determine the need for routine duodenal biopsies during upper GI endoscopy of dyspeptic patients as a screening for celiac disease. The patients underwent duodenal histology and serological analysis with anti-transglutaminase IgA antibody. Of the 530 patients included, 2.8% were diagnosed with celiac disease. The study concluded that despite the prevalent, routine duodenal biopsy is not the best strategy, but rather individualizing for better cost-effectiveness.

In 2022, Singh, Ellias, Singh, Ahuja and Makharia 12 conducted a systematic review and meta-analysis on the prevalence of celiac disease in patients with dyspepsia. They included surveys from January 1991 to May 2021. This resulted in 21 studies and 10,275 patients with dyspepsia. The seroprevalence of the disease based on the positivity of anti-transglutaminase IgA and/or antiendomysium IgA antibodies was 4.8%. When the diagnosis was confirmed by biopsy, the prevalence of celiac disease was 1.5%. Both results were not higher than those presented in controls, but the study highlights the risk of selection bias and significant heterogeneity in the results. Finally, the study does not support screening for celiac disease in these patients.

Cruz M A et al.[18] in a study in southern Brazil in 2023 with 200 patients, addressed the relationship between dyspepsia and celiac disease, focusing on exclusively dyspeptic patients and excluding those with other signs and symptoms suggestive of celiac disease, to identify individuals at higher risk of this condition. Regarding the 200 dyspeptic patients, the research observed a predominance of women (78%), a mean age of 45.[13] years, and hypothyroidism as the only autoimmune comorbidity reported that was related to celiac disease. Only 2.5% of patients had first-degree relatives with celiac disease, but there was no direct positive association between family history and diagnosis of celiac disease. Lactose intolerance was reported in 29%. Although there was a reference of dyspeptic symptoms with gluten ingestion, only 1 was diagnosed with celiac disease, indicating the possibility of non-celiac gluten sensitivity in the remaining cases. Helicobacter pylori infection was identified in 15%, but 80% had no organic causes for dyspepsia. Alterations suggestive of celiac disease were observed in 5 patients undergoing upper gastrointestinal endoscopy, but only 1 had the diagnosis confirmed by histology and serology. All patients had normal IgA levels, ruling out the possibility of false negatives in celiac serology due to IgA deficiency. The prevalence of anti-IgA transglutaminase antibodies was 1.5%.

Celiac disease was evaluated in 100 dyspeptic patients with a prevalence of 3%, a value above the world and Brazilian average, suggesting a higher prevalence of celiac disease in dyspeptic individuals compared to the general population. No cases of seronegative celiac disease, a condition in which serology is negative, but duodenal histology and genetics are compatible with the disease, have been identified.

CONCLUSIONS

Although the prevalence of celiac disease in dyspeptic patients may be higher than in the general population, the results are variable and depend on several factors, including testing methodologies and regional characteristics. The research highlights the importance of an individualized approach in the investigation of celiac disease in dyspeptic patients, considering aspects such as family history, gluten-related symptoms, and autoimmune comorbidities.

Authors' contributions

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