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EDITORIAL

- 627 Colon capsule endoscopy: Can it contribute to green endoscopy?
Nakaji K
- 632 Physical and psychological symptoms and survey importance in celiac disease
Ciaccio EJ, Lee AR, Lebovits J, Wolf RL, Lewis SK
- 640 Endoscopic ultrasound-guided therapies in the treatment of gastric varices: An in-depth examination of associated adverse events
Manolakis A, Tsagkidou K, Koumarelas KE

MINIREVIEWS

- 647 Water-assisted colonoscopy in inflammatory bowel diseases: From technical implications to diagnostic and therapeutic potentials
Pellegrino R, Palladino G, Izzo M, De Costanzo I, Landa F, Federico A, Gravina AG

ORIGINAL ARTICLE**Prospective Study**

- 661 Extended 72-hour patency capsule protocol improves functional patency rates in high-risk patients undergoing capsule endoscopy
O'Hara FJ, Costigan C, McNamara D
- 668 High Joule heat as a risk factor for post-endoscopic submucosal dissection electrocoagulation syndrome: A multicenter prospective study
Ochi M, Yamamoto A, Suematsu S, Fukuda K, Morishige K, Oka Y, Ishikawa Y, Ueyama S, Hiroshima Y, Omae Y, Kusano F, Kamoshida T

CASE REPORT

- 678 Endoscopic resection of a giant irregular leiomyoma in fundus and cardia: A case report
Li P, Tang GM, Li PL, Zhang C, Wang WQ

LETTER TO THE EDITOR

- 686 Emerging strategies in outpatient endoscopy sedation management: Recent trends and developments
Chen MQ, Zhang QS
- 691 Endoscopic ultrasound guided-gastroenterostomy is the best choice in the treatment of gastric outlet obstruction
Jagielski M

ABOUT COVER

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Physical and psychological symptoms and survey importance in celiac disease

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Abstract

Celiac disease is an autoimmune condition that affects approximately 1% of the worldwide community. Originally thought to be confined mostly to the small intestine, resulting in villous atrophy and nutrient malabsorption, it has more recently been implicated in systemic manifestations as well, particularly when undiagnosed or left untreated. Herein, the physical and psychological symptoms of celiac disease are described and explored. An emphasis is placed on efforts to query prospective and confirmed celiac disease patients *via* the use of surveys. Suggestions are made regarding the development of efficacious surveys for the purpose of screening for celiac disease in undiagnosed persons, and monitoring efficacy of the gluten-free diet in persons diagnosed with celiac disease. There are broad categories of physical and psychological symptoms associated with celiac disease. There is also an essential interaction between such physical and the psychological symptoms. It is important to capture the association between symptoms, *via* queries directed toward suspected and confirmed persons with celiac disease. The use of anonymous online surveys can be helpful to determine the qualities and characteristics which may be associated with this condition. It is suggested that personal surveys should be given a greater role in screening and to lessen the time for diagnosis. Querying the subject directly *via* a survey can provide clues as to the types of symptoms being experienced by those with celiac disease currently, as well as to determine the salient aspects of the symptomatology, which will be useful for rapid screening and monitoring in future work.

Key Words: Villous atrophy; Celiac disease; Digestive; Psychological; Survey

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Core Tip: In this article, the current symptoms and issues of celiac disease are discussed. The study focuses on the use and utility of surveys to query persons during the screening process for celiac disease, and to assess efficacy of the treatment in persons confirmed to have celiac disease. The symptoms are subdivided into those which are physical *vs* psychological, and their impact on quality of life is discussed.

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INTRODUCTION

The most common classical clinical presentation of celiac disease is characterized by overt gastrointestinal involvement[1, 2] including signs and symptoms of malabsorption[3], chronic diarrhea, and malnutrition[4,5]. Yet, more frequently in recent years, patients are experiencing nonclassical gastrointestinal symptoms, including constipation and abdominal pain, as well as extraintestinal manifestations[6]. When systemic features are present, these can include neurological manifestations with or without overt gastrointestinal symptoms[7]. The most common neurologic symptoms include ataxia, epilepsy, cerebral calcification and white matter lesions, peripheral neuropathy, and brain fog[8]. Contrarily, individuals with celiac disease may even be asymptomatic at diagnosis[9]. Due to the notoriously variable clinical presentation-classical, nonclassical, and asymptomatic, celiac disease diagnosis is often delayed, with the duration between symptom onset being highly variable in adults, and a definitive diagnosis sometimes taking several years[6]. Although there is considerable interest in developing new therapies for the disease, to date these have focused primarily on controlling the intestinal symptoms and enteropathy[10]. Complicating matters pertaining to symptomatology however, a lesser burden of symptoms may not increase the quality of life (QOL)[11]. Moreover, other modes of treatment may be equally important to improve patient health. For example, increased physical activity has recently been associated with a decrease in anxiety, depression, and an increase in dietary adherence in adults with celiac disease[12].

Overall, there are currently difficulties in both diagnostic and treatment processes for celiac disease. To improve understanding, patient-centric studies and analysis may be a viable option, which can be done simply and efficiently by querying the patient. Collection of self-report metrics *via* a survey can enhance the simplicity and brevity of an investigation as compared with using a standardized dietetic assessment, which may be limited in availability of trained specialist dietitians and is also time-consuming. Self-report metrics may furthermore provide nuance to objective, but time-consuming and expensive measures of gluten intake, such as urine or stool sampling. An overall goal in querying persons with celiac disease should be to detect patterns in the physical and psychiatric symptoms, and the relationship between those patterns *vs* adherence to the diet and QOL[11]. Of high importance is to identify patterns of persistent symptoms both intestinal and extra intestinal, which can reflect underlying condition, as well as to score subjective health ratings provided during querying, which can reflect both physical and mental health status. The presence of a persistent symptom profile and a particular health rating may be reflective of gluten-free diet adherence, the presence of any psychiatric symptoms, QOL, and functioning[11,13].

For development of self-report instruments, tiers of symptomatology can be included in the criteria utilized for analysis and diagnostics. For example, patients can be categorized at diagnosis as having: (1) Classical; (2) Nonclassical, or (3) Asymptomatic symptoms[6]. Following the definitive diagnosis, a tiered system of reporting may then be useful, thereby categorizing persons with: (1) Minor to no symptoms and excellent health; (2) Infrequent symptoms and good health; (3) Occasional symptoms and fair health; and (4) Frequent symptoms and poor health[11]. These aspects of physical health are assessed by querying the symptoms experienced by the patient. Alternatively, a tiered system could differentiate between typical gastrointestinal symptoms and other symptoms, *i.e.*, minor to no gastrointestinal symptoms and excellent health, *vs* minor to no *extraintestinal* symptoms and excellent health. All self-reported data obtained by querying, when scored, could then be compared with ground truth. Rates of health disorders can be calculated from queries using a formulaic method that is compared with national health statistics[1,2]. Queries can be directed toward the person with celiac disease, or for paediatric reporting, parents often complete electronic surveys about children's physical and psychological symptoms, and their QOL on the gluten-free diet.

Assessment procedures

Celiac disease can be categorized by the presence of classical *vs* nonclassical symptoms. Any psychological symptoms of the disease are often subclassified in terms of the presence of brain fog, anxiety, depression, and QOL. Psychologists should provide feedback and recommendations as clinically appropriate and referrals for follow-up mental health services when necessary[2]. All questionnaires should be formulated based on an extensive literature review and expert experience[14]. Below are listed a few of the more common procedures utilized for symptom measurement.

Beck depression inventory: This consists of a series of 21 multiple choice questions which concern mood, sleep, and appetite[15]. The components of each question are scored by integer numbers. The early response choices for each question (for example, 1 and 2 of a 5-part question) are less likely to indicate clinical depression, while later parts (for

example, 4 and 5 of a 5-part question) are more likely to indicate clinical depression. Hence, a greater overall score is obtained, indicative of depression, if the Survey Participant often selects from the later response choices.

Brain fog: This is a subjective cognitive impairment, yet of great importance and perhaps becoming more common or at least better known as a symptom. It is a type of mental health disorders (MHD), and is often reported in celiac disease [16]. Currently, the means are being developed to define and quantify this issue based on a better self-reporting of the issues involved.

CD-QOL survey: This is a reliable and valid measure of celiac disease related QOL[17]. It consists of 20 items which encompass four clinically relevant subscales (limitations, dysphoria, health concerns, and inadequate treatment). The CD-QOL has been shown to have high internal consistency, reliability, and psychometric validation.

Food insecurity: This is a condition with both economic and social implications that leads to restricted access to nutrient-rich food[18]. Food insecurity is an integration of the concepts of affordability, availability, and the cultural acceptability of foods[19]. Food security is obtained when an individual has the monetary, physical, and societal access to adequate food in order to maintain one's nutritional status for healthiness[20].

Multidisciplinary clinic models: Typically, this consists of a multifaceted provider team including a gastroenterologist, dietitian, and mental health counselor, employed to reduce symptoms and speed recovery. This model has as a main objective to enhance traditional medical doctor-only approaches to more completely and efficaciously optimize wellness and health status for individuals and families affected by chronic illness^{1,2}. Multidisciplinary care models have been useful to highlight the role of registered dietitians and mental health counselors in support of a gluten-free diet, which is an overriding component for treatment[21].

Rome IV criteria: These are typically utilized to analyze functional gastrointestinal disorders[22]. The criteria consist of a system of disorders including esophageal, gastroduodenal, bowel, gallbladder, anorectal, and paediatric, with clinical descriptions included to measure the degree and severity of each disorder.

Short form health survey: Short form health survey (SF-36) was developed by RAND[23] and consists of 36 questions. It is a combination of generic, coherent, and readily administered quality-of-life measures that depend on patient self-reporting. The questions inquire about work and life activities, and how much time is devoted to them. Each question is multiple choice, and questions have a number of response choices. For example, the first question asks[24]: 'In general, would you say your health is: 1 excellent, 2 very good, 3 good, 4 fair, or 5 poor'.

State-trait anxiety inventory: This is a 20-item validated and self-reported assessment tool which includes components for state and trait anxiety[25]. It is an ideal measure for studying anxiety in clinical and research settings[26]. For example, the first question is: 'I feel calm,' and the response choices, scored by integer numbers, are: 1 not at all, 2 a little, 3 somewhat, 4 very much so. The scores for positive questions like 'I feel calm' are reversed for those of negative questions such as 'I feel tense' in summing to form the overall score for all queries combined.

Detection of pathology

Celiac disease may present with classical signs and symptoms of malabsorption including diarrhea, steatorrhea, and loss of weight[27]. These symptoms and the underlying gastrointestinal pathologic process result from gluten and gliadin-mediated damage to the small intestine. Villous atrophy is common in classical celiac disease, and the intestinal villi can be effectively evaluated with methods such as narrow-band imaging[28]. Wireless capsule endoscopy and artificial intelligence may also be helpful for assessment[29]. Improved featuring for villous atrophy is being developed, to detect subtle, varying patterns in the small intestinal mucosa[30]. Assessment of villous atrophy and prediction of disease can also be done *via* a majority voting protocol[31]. Use of shape-from-shading to characterize the three-dimensional mucosal topography is useful to improve classification[32]. Although classical signs and symptoms still occur, the presentation of celiac disease has undergone alteration, since there is often earlier detection and serologic testing[33] resulting in the screening of more at-risk patients[34]. Nonclassical celiac disease is becoming more common and typically presents as extraintestinal symptoms including anemia, stomatitis, ataxia, and fatigue[35]. It also tends to be associated with less severe and more subtle symptoms. Both persons with the classical and nonclassical symptoms of celiac disease obtain an improved QOL and achieve a similar overall QOL scoring after they begin a strict gluten-free diet. A challenge will be to develop tools to detect and quantify these changing aspects of the disease.

Persistent symptoms

Symptoms exhibited by persons with celiac disease can evolve and are complex. Even with adherence to the gluten-free diet, a third of adult patients will have ongoing symptoms, the cause of which can be unclear[11,36,37]. A possible instigator of persistent symptoms for those on a gluten-free diet is ongoing gluten exposure. Trace amounts or unreported contamination means complete gluten removal from the diet is not achievable. The presence of minute gluten content contributes to persistent symptoms and an incomplete recovery from villous atrophy of the small intestine[38,39]. Persistent symptoms may also flag the presence of other food sensitivities, or of co-occurring medical disorders such as irritable bowel syndrome, as characterized by overlapping gastrointestinal issues including abdominal pain, bloating, bowel movement pain, diarrhea and constipation[40,41]. Persistent symptoms are also evident in refractory-type celiac disease[42]. Typically women[43] and those with more recently diagnosed disease[13] are more likely to exhibit persistent symptoms. The persistent symptoms include those associated with poorer physical functioning, lower QOL, and an

increased likelihood of anxiety and depression[11]. The degree of ongoing gastrointestinal symptoms is affiliated with reduced social functioning and greater anxiety and depression[44,45]. Some persistent symptoms may even emerge after intestinal recovery. These may be interrelated with the burden of the disease and or therapy, for example the cost of the gluten free diet, feelings of isolation, fear of contamination of one's food, and worry about future health. There is a connection between persistent physical and psychiatric symptoms, as yet to be fully understood[46]. Patient-centric querying may be helpful to better understand the correlation between physical and psychiatric symptoms and their persistence. However, a lower persistent symptom burden does not necessarily correlate to reduced MHD or to increased QOL. Hence, behavioral intervention can be important even for those with a low celiac symptom burden[11].

QOL in celiac disease

Generally, celiac disease treatment results in significant improvement in the QOL of symptomatic patients[47]. Patients with classical presentation tend to have a lower QOL as compared with nonclassical patients. Diagnostic delay, symptomatic presentation, and gender may all negatively affect QOL and the psychological metrics in celiac disease[6]. Women with celiac disease have an overall lower self-perceived QOL. Even in those patients with a more silent or asymptomatic screening-detected celiac disease, improvements in both symptoms and QOL occurs after onset of the gluten-free diet[48,49]. Besides the gluten-free diet, the number of symptoms, associated medical conditions, older age at diagnosis, and the duration of symptoms influence QOL[50]. Existing evidence also suggests that QOL can significantly vary over time since diagnosis[51,52]. A low QOL may contribute to and be impacted by psychological outcome, such as presence of anxiety, depression, and sleep disorder[53]. Anxiety may improve after diagnosis and onset of the gluten-free diet, although depression and sleep disorders may exist before and persist after diagnosis[6,54].

Comorbidities

Left untreated, celiac disease is associated with various comorbidities including osteoporosis, neurologic disorders, and cancer[1,2,55]. There is also a high prevalence of joint and bone pain in celiac disease[56]. Individuals with celiac disease may have a higher risk for mental disorders, a diminished QOL, and increased stress levels[57].

MHDs

Comorbid MHDs are typical in persons with celiac disease. A strict diet is often a source of psychosocial stress[1,2]. Since celiac disease is a chronic condition with a burdensome treatment, psychological distress may persist for a long time. The mental health comorbidities often associated with celiac disease include depression, anxiety, panic, suicide, and poor QOL[58]. Mental health comorbidities have been linked to lower adherence to the gluten-free diet[55,59]. In pediatric cases, they are associated with increased child and parent psychosocial distress[60,61], and health complications[53]. One third of children with celiac disease may have at least one MHD, and anxiety and attention-deficit/hyperactivity disorder are more common than in the general population[1,2]. About one third of parents report child psychosocial distress, and half report parental stress and a financial burden that is associated with the gluten-free diet. Caregivers may experience burnout due to the significant cost of gluten-free foods and questions regarding child health and safety, with the continued need for professional support and guidance relating to management of the disease[60].

Lack of dietary adherence

Lack of adherence to the diet is commonly associated with increased depression and anxiety, social pressures, and social relationship issues[62], and it can influence QOL. This underlines the importance of querying confirmed celiac disease individuals regularly, thereby ascertaining and understanding information concerning dietary adherence[63]. Lack of adherence to the gluten-free diet has many possible causes. It may be difficult due to a higher cost and limited availability of gluten-free products[64,65]. Food insecurity in general reduces gluten-free diet adherence, and it is associated with lower emotional well-being and issues with mental health[66]. Decreased physical health caused by gastrointestinal symptoms may also impact adherence[67]. Economic status can alter social and emotional states, additionally leading to decreased adherence[68]. When gastrointestinal symptoms prolong, there is a diminishment in self-reported scores for physical health, social functioning, and general health[34]. The presentation and treatment of celiac disease may affect QOL differently for classical *vs* nonclassical cases, depending on symptoms. Yet, adherence to the gluten-free diet is similar between the groups, suggesting that a nonclassical celiac disease presentation does not negatively affect adherence even though the symptoms are less evident. Untreated CD results in poor HR QoL, which improves to the level of the general population if diagnosed and treated[69]. By shortening the diagnostic delay it is possible to reduce this unnecessary burden of disease.

Brain fog

Brain fog has been implicated as a frequent indicator of celiac disease. A standardized tool to define and assess brain fog is an important but as yet unmet need[16]. The absence of a consensus definition for brain fog hampers research efforts to measure and quantify this complex symptom, and it impedes the development of novel drug treatments[70,71]. Despite the negative impact of brain fog on some celiac patients, its mechanism and clinical implications are poorly understood and researched. Although it is commonly reported in the context of gluten ingestion, it is unclear if gluten is always necessary to trigger this symptom, and whether it results from gluten-induced systemic immune activation, primary central nervous system pathology, or a combination[16]. As the negative impact of brain fog on patient function and QOL is increasingly noted, attempts to query patients as to status, and to eliminate this symptom therapeutically, will become more urgent[53,72]. To do this, a clinical outcome assessment utilizing a patient reported outcome measure should be specifically developed and validated in the celiac population for brain fog[70,71]. Development of such a brain fog

assessment and severity scale to be used as part of the Survey query process would be helpful to create a patient-centric clinical outcomes assessment tool. To implement, a series of celiac patient-derived definitions for brain fog should first be established, and then utilized with validated scales to assess a large cohort of patients, focusing on specific domains of mental disorder, including fatigue, slowness, psychological wellbeing, and the negative impact of brain fog. The relationship between brain fog, gluten intake, and gastrointestinal symptomatology should also be assessed. This would provide a blueprint for validation studies and to ascertain correlations to various celiac biomarkers.

Limitations and future directions

Surveys can have limitations in terms of accuracy; as many as ¼ of survey respondents claiming to have celiac disease may have not undergone a biopsy[73]. Recall bias may result from the Survey Participants having a preconceived view that a certain exposure may be a risk factor for the disease, and thereby overestimating the exposure in question[74]. Inclusion of empirical data from Survey responses or case studies, and providing detailed Survey design guidelines should be considered for future investigations. These enhancements could provide a more comprehensive resource for healthcare professionals who treat persons with celiac disease.

CONCLUSION

Celiac disease is associated with many differing symptoms, and its evolution after gluten-free diet onset can be complex [75]. After diet onset, the improvements among celiac disease patients with classical symptoms are similar to those observed in patients with nonclassical symptoms, except for anxiety, which tends to improve only in patients with a classical presentation at diagnosis[11]. The development of refined query surveys will be important to improve patient-centric diagnosis and treatment, and to elucidate differences between symptom types. Subsequent research investigations should query with a greater selection of symptoms, along with assessment of histological findings, and with an objective measurement of gluten intake, such as urine or stool analysis, to explore the Survey-derived relationships more robustly [76]. Since there is a well-established connection between chronic pain, depression and anxiety, and a lower QOL[77], some individuals with celiac disease may benefit from additional behavioral or clinical intervention for managing such symptoms as pain[78], as well as nutritional education, thus requiring a multidisciplinary clinical model. Even patients with a low gastrointestinal symptoms burden may benefit from additional treatment to address fatigue, pain, headache, and nutrition, and those with other symptom types may require different care. Furthermore, education and knowledge of skills for coping with the disease may help patients with greater gastrointestinal symptoms to have better QOL outcomes.

Multidisciplinary models in celiac disease that include psychology are to date uncommon, and are not well evaluated. Yet, psychological services can offer essential support to families and medical providers. The incorporation of a psychologist and a nutritionist in a team-based treatment may assist, along with results from Survey queries, to provide screening for and intervention to psychological conditions and issues with gluten-free diet adherence. Children with celiac disease may have increased risk of psychological disorders, both before or after definitive diagnosis, and may not improve after diet onset[55]. Supporting successful child and family education is essential for coping with the diagnosis and the symptoms, and to adhere to prescribed treatments.

FOOTNOTES

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