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## **Screening for Celiac Disease in Individuals with Symptoms Suggestive of Irritable Bowel Syndrome: Still a Worthwhile Exercise.**

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**Comment on: L.A. Sánchez-Vargas, P. Thomas-Dupont, M. Torres-Aguilera *et al.* Prevalence of celiac disease and related antibodies in patient diagnosed with irritable bowel syndrome according to the Rome III criteria. A case-control study. *Neurogastroenterol Motil* 2016 Feb 23. doi: 10.1111/nmo.12799**

Irritable bowel syndrome is a chronic functional gastrointestinal (GI) disorder with a prevalence of 10-20%, depending on the criteria used for diagnosis (*Clin Gastroenterol Hepatol* 2012;10:712–721). It is characterized by symptoms such as altered bowel habit, lower abdominal pain, bloating, or distention (*Gastroenterology* 2006;130:1480–1491). As a functional GI disorder, diagnosis is largely based on clinical presentation and current guidelines do not recommend extensive investigation to rule out organic pathology, in the absence of alarm features. However, symptoms of IBS are not specific (*Gastroenterology* 2013;145:1262–1270), and may overlap with those of other organic GI conditions.

Celiac disease or gluten-sensitive enteropathy, is an autoimmune condition with an estimated prevalence of 1% in the United States (*Arch Intern Med* 2003;163:286-292). The initial presentation can be similar to IBS (*Lancet* 2001; 358: 1504–1508), making the two conditions difficult to distinguish clinically. This can lead to mislabeling, and concern that some patients in whom IBS has been diagnosed may in fact have celiac disease (*Dig Dis Sci* 2003;48:761-764). A

systematic review and meta-analysis demonstrated that the prevalence of biopsy-proven celiac disease among patients with symptoms suggestive of IBS was four-fold higher than healthy controls (Arch Int Med 2009;169:651-8). Further, decision-analytic models have reported that screening for celiac disease in IBS patients has an acceptable cost, and is beneficial, if disease prevalence is greater than 1% (Gastroenterology 2004;126:1721-32).

Following these findings, current guidelines advise routine serological screening for celiac disease in patients presenting with IBS-type symptoms, in particular diarrhea-predominant IBS (IBS-D) and mixed IBS (IBS-M) subtypes (Am J Gastroenterol 2013;108:656-76). However, findings from two recent studies conducted in the United States challenge these recommendations. In a multicenter study of patients with non-constipated IBS, the prevalence of biopsy-proven celiac disease was 0.4%, which was similar to the prevalence in the control population (Gastroenterology 2011;141:1187-93). More recently, a population-based study assessing individuals with symptoms suggestive of functional GI disorders demonstrated a prevalence of celiac disease, as based on serological markers, of 3% among those meeting criteria for IBS compared with 14% among controls without symptoms suggestive of IBS (Clin Gastroenterol Hepatol 2015;13:1937-43).

The authors of the present study undertook a case-control study to determine the prevalence of celiac disease, and related antibodies, in individuals diagnosed with IBS. Consecutive patients seeking medical attention for symptoms suggestive of the condition were prospectively evaluated at a single tertiary center in Mexico from December 2010 through to June 2012. Those included met the Rome III criteria for IBS diagnosis, and had alarm symptoms ruled out at clinical evaluation. Subjects with previous diagnoses of cancer, thyroid diseases, diabetes mellitus, inflammatory bowel disease, or major abdominal surgery were excluded. IBS patients were then compared with an asymptomatic control group matched by age and sex, recruited from an open population within the

same geographical region. Control subjects answered the Rome III questionnaire to confirm the absence of functional GI symptoms.

All subjects underwent serological testing for celiac disease, including IgA class antihuman tissue transglutaminase (h-tTG IgA) and deamidated gliadin peptide (DGP II IgA and DGP II IgG) antibody tests. Those with positive results were offered endoscopy, with duodenal biopsies evaluated by an expert pathologist to confirm a histological diagnosis of celiac disease. In total, 400 asymptomatic controls and 400 IBS subjects were evaluated, of which 220 patients had IBS-M (55%), 56 IBS-D (14%), and 124 constipation-predominant IBS (IBS-C; 31%). The mean age of the study population was  $44.47 \pm 18.01$  years and 335 (82%) were female. The mean duration of IBS symptoms was  $76.4 \pm 33$  months.

In terms of antibody detection, 21 patients and 6 healthy controls were positive for at least one serological test for celiac disease (5.25% vs 1.5%, OR 3.63; 95% CI 1.4-9.11,  $p=0.003$ ). The IBS patients had a significantly higher prevalence of seropositivity for h-tTG IgA antibodies (3.5% vs 0.75%, OR 4.79; 95% CI 1.3-16.4,  $p=0.014$ ), as well as DGP II IgA antibodies (3.0% vs 0.75%, OR 4.09; 95% CI 1.14-14.6,  $p=0.018$ ), compared with controls. However, no difference was found when comparing the prevalence of DGP II IgG antibodies between the two groups. The IBS-D subtype had the highest prevalence for seropositivity for both h-tTG IgA (12.7%) and DGP II IgA antibodies (12.7%), compared with the other subtypes. Furthermore, the multivariable regression analysis including age, sex, duration of symptoms, and IBS subtypes demonstrated a statistically significant difference only for the IBS-D subgroup. Histologically confirmed celiac disease was found in 2.5% of the IBS group, compared with 0.5% in the control group ( $p=0.04$ , OR 5.21).

## Comment

IBS and celiac disease are both prevalent conditions that share a common set of symptoms. However management of the two conditions is vastly different. Diagnosis of celiac disease, in particular implies treatment with a gluten-free diet over a lifetime. Furthermore, although IBS is known to negatively impact health-related quality of life (*Aliment Pharmacol Ther* 2007;26:227–236), it is generally considered a benign condition. In contrast, celiac disease has important sequelae, with a risk of long-term complications including osteoporosis (*Gut* 1995;36:710-714) and gastrointestinal malignancies, in particular T-cell lymphoma (*BMJ* 2004;329:716- 719). A gluten-free diet is protective, and alleviates symptoms (*Gut* 1989;30:333-8). Hence identifying underlying celiac disease in individuals reporting symptoms compatible with IBS has important health implications.

The present study demonstrates a prevalence of 2.5% for biopsy confirmed celiac disease in subjects with IBS, with up to 5.2% of patients showing seropositivity for at least one celiac disease-related antibody. In light of recent controversial studies questioning the approach of routine celiac screening in IBS subjects, these data are relevant in justifying screening in this population, particularly in cases of IBS-D. However, there are some limitations of the study. The authors have selected a population sample of IBS subjects regarded as ‘typical’ for the disease, and have further matched the control population by age and sex. Although results were correctly adjusted according to age, sex, and IBS subtype through logistic regression, it is difficult to ascertain the extent to which results are limited by residual confounding variables such as family history, diet, and concomitant autoimmune conditions. It can also be noted that patients with a history of thyroid disease or diabetes mellitus were excluded. It is possible that the exclusion of individuals with these associated autoimmune conditions could result in missed cases of celiac disease.

In addition, the nature of the case-control study predisposes it to spectrum bias by excluding difficult to diagnose clinically mild cases, thereby perhaps overestimating the sensitivity of diagnostic tests for celiac disease. Furthermore, as a single tertiary center study, the population is more likely to consist of patients with more severe symptoms, or those with refractory IBS. These patients may therefore be more likely to have underlying organic GI disease. This creates selection bias and could increase the likelihood for detecting celiac disease in the study population, as compared with primary care detection rates. Hence, the spectrum of disease in the trial population may not be a true representation of that among individuals with IBS in the community.

Due to the high prevalence rates of both IBS and celiac disease, it is possible that both conditions can co-exist with each other independently, and without necessarily sharing a common pathophysiological basis. Hence the diagnosis of celiac disease in IBS patients may be incidental in such cases, and symptoms may not improve solely by adherence to a gluten-free diet. Moreover the study did not evaluate information regarding diet prior to serological screening or endoscopy. There is a possibility that individuals with IBS-type symptoms may already have been excluding gluten from their diet prior to testing, hence underestimating the prevalence of celiac disease in the study cohort. For these reasons, it would be interesting to see whether commencing a gluten-free diet ameliorated symptoms in this population, as well as to know the number of patients on a gluten-free diet prior to serological testing.

In conclusion, and despite these limitations, this is an important study that provides some evidence for opportunistic celiac screening among Hispanic patients presenting with symptoms of IBS. The findings reinforce current guidelines, and are particularly useful in emphasizing the role of screening in those with presumed refractory IBS. However, it is important to consider the geographical variability in the prevalence of celiac disease among persons with IBS symptoms, especially given the results of recent conflicting studies in the United States. Given the high

numbers of Hispanics in the United States, these individuals should perhaps be targeted in future studies. It may therefore be necessary to have knowledge of local prevalence data to fully understand the likely costs and benefits of serological screening in a specific population. Recommendations for management in other countries should be based on local prevalence data.