ORIGINAL INVESTIGATION

Increased Prevalence of Celiac Disease in Patients With Dyspepsia

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Background: Although 30% to 40% of patients with celiac disease (CD) (which affects 1 in 200 individuals) have dyspeptic symptoms, there is a lack of data concerning the prevalence of CD in patients with dyspepsia.

Methods: In this prospective series, we enrolled all consecutive outpatients undergoing endoscopy of the upper gastrointestinal tract for dyspepsia at our centers between January and June 1998. The exclusion criteria were age younger than 12 years, workup or follow-up of an already known disease of the gastrointestinal tract, suspected CD, malabsorption, and/or iron-deficiency anemia.

Results: Of the 3019 patients who were evaluated, 517 (17%) were eligible for the study. Endoscopic findings suggested CD in 5 cases. Celiac disease was histologically diagnosed in 6 patients (5 women and 1 man; mean age, 31.3 years; age range, 20-46 years), 3 of whom had a normal endoscopic pattern and 3 of whom had an endoscopic pattern that was consistent with CD. In the patients with histologically diagnosed CD, antiendomysium antibody positivity supported the diagnosis. The relative risk for CD was 2.32 (95% confidence interval, 1.06-5.07) in comparison with the general population and higher among females (3.22; 95% confidence interval, 1.37-7.56).

Conclusions: The present results indicate that the prevalence of CD in patients with dyspepsia is twice that of the general population. Thus, serological screening for CD should be considered in the early workup of these patients to allow diagnosis and treatment of an eminently treatable disease.

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CELIAC DISEASE (CD) is characterized by a wide range of intestinal and/or extraintestinal manifestations that, in susceptible individuals, are attributable to the toxic action of the gluten present in wheat, rye, and barley.[1] As defined according to recent reviews,[2,3] dyspeptic symptoms are reported by a number of patients with CD[4] and may represent the only manifestation of a disease that affects 1 in 200 subjects in most series from Western countries[5-7]; the prevalence is similar in Italy.[8,9] However, despite this, there are no data concerning the prevalence of CD in patients with dyspepsia, to our knowledge. This fact is surprising given that a gluten-free diet is highly successful in normalizing clinical and histologic abnormalities,[10] thus preventing severe and life-threatening CD complications, such as lymphoma or ulcerative jejunoileitis,[11] and avoiding further useless examinations and/or empirical management.

The present prospective study was therefore designed to evaluate the prevalence of CD in a large series of patients with dyspepsia who were undergoing duodenal biopsy and endoscopy of the upper gastrointestinal tract (GI).

RESULTS

Five hundred thirty-three of the 3019 prospectively evaluated patients complied with the inclusion criteria, but 16 were excluded because of the inadequacy of the duodenal samples taken for histologic processing. The analysis was therefore based on the biopsy specimens obtained from 517 patients, representing 17% of the entire group (207 males and 310 females; mean ± SD age, 49.9 ± 16 years; age range, 14-88 years).

The endoscopic findings were normal in 311 cases (60%), showed peptic lesion(s) in 132 (26%), demonstrated polyp(s) or tumors in 13 (2%), were suggestive of CD in 5 (1%), and were miscellaneous in 56 (11%). Celiac disease was histologically diagnosed in 6 patients (1.2%), 3 of whom had a normal duodenal endoscopic pattern (false-negative results), and 3 of whom had an endoscopic pattern suggestive of CD. The sensitivity of the endoscopic markers for CD was therefore 50%. The loss of duodenal folds

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PATIENTS AND METHODS

STUDY POPULATION

Between January and June 1998, all the outpatients attending the GI units of 2 tertiary centers in Lombardy (northern Italy) for upper GI tract endoscopy because of dyspeptic symptoms (chronic or recurrent pain or discomfort centered in the upper area of the abdomen) were prospectively studied. Excluded were patients younger than 12 years; those undergoing clinical workup for an upper GI tract disease suggested by previous radiographic or ultrasonographic findings; those referred for malabsorption, suspected celiac disease, or iron deficiency anemia; those receiving regular follow-up for a known disease (eg, peptic ulcer); and those with classic heartburn or acid regurgitation. All patients who fulfilled the inclusion criteria gave their informed consent for upper GI tract endoscopy and histologic sampling. The study was approved by the Ethics Committee of both centers. The endoscopic findings were classified as normal, consistent with peptic lesions (in the presence of esophagitis, mucosal reddening with erosions, or ulcers), positive for polyps and/or tumors, suggestive of CD (in the case of a loss or reduction in duodenal folds, a nodular or mosaic mucosal pattern, or duodenal fold scalloping),[12,13] or miscellaneous (hiatal hernia, varices, etc). Four duodenal mucosal samples (2 from 2 cm above and 2 from 2 cm below the major duodenal papilla) were obtained from all patients during upper GI tract endoscopy (using GIF-100; Olympus Optical Co, Tokyo, Japan), with further samples being obtained when considered necessary, ie, in the presence of macroscopic appearances consistent with esophagitis, gastritis, and/or duodenitis. The biopsy specimens were oriented, routinely processed, stained with hematoxylin-eosin and periodic acid–Schiff, and blindly examined by two of us (M.T.B. and P.V.) independently. The diagnosis of CD was based on the presence of villous atrophy, crypt hyperplasia, and an increased number of lymphocytes in the epithelium and lamina propria[14]; the presence of *Helicobacter pylori* was also always searched for histologically. All patients with a histologic diagnosis of CD also underwent standard nephelometric serological immunoglobulin determinations and IgA antiendomysium antibody measurements obtained by indirect immunofluorescence (Eurospital, Trieste, Italy) and were put on a gluten-free diet and followed up.

STATISTICAL METHODS

Descriptive statistics (mean, SD, minimum, and maximum) were calculated together with relative risks and 95% confidence intervals.[15]

in 2 other cases suggested CD, but the diagnosis was not histologically confirmed.

The demographic, endoscopic, histologic, and serological characteristics of the 6 patients with CD (3 diagnosed in Milan and 3 in Como) are shown in the **Table**.

Characteristics of the 6 Patients With Celiac Disease

Patient No./Sex/Age, y	Duodenal Findings	
	Endoscopic	Histologic*
1/F/26	Loss of fold, mosaic pattern	SVA
2/F/37	Normal	SVA
3/F/34	Reduction in folds, bulbar nodular pattern	TVA
4/M/46	Normal	SVA
5/F/20	Normal	IIELs/SVA
6/F/25	Reduction in folds	TVA

**SVA indicates subtotal villous atrophy; TVA; total villous atrophy; and IIELs, increased number of intraepithelial lymphocytes.*

All 6 patients were antiendomysium antibody positive; their ages ranged from 20 to 46 years (mean ± SD age, 31.3 ± 9.5 years); and 5 were female. None of them presented any histologic evidence of *H pylori*. There was absolute agreement between the 2 pathologists in diagnosing or excluding CD.

COMMENT

The present results indicate that patients with dyspepsia have an increased risk for CD and that the endoscopic duodenal markers suggestive of the disease are not sufficient to confirm or rule out its presence.

Over recent years, in addition to serological markers,[16] increased attention has been given to some endoscopic findings that may be suggestive of CD (eg, loss, reduction, or scalloping of duodenal folds and/or a nodular or mosaic mucosal pattern). The data from different studies indicate a sensitivity of 73% to 100%, a specificity of 83% to 99%, and a positive predictive value of 85% to 91% for the above-mentioned markers.[12,13,17-19] However, some of these results may reflect a selection bias (most of the studies included patients undergoing specific workup for overt malabsorption and/or suspected CD), and the series that included patients without CD were strongly biased because duodenal biopsy specimens were obtained only in the presence of one or more of the so-called typical endoscopic CD markers.

In our study, multiple duodenal samples were obtained from all patients who underwent upper GI endoscopy for dyspepsia, and, despite the long training of the endoscopists involved, the overall diagnostic sensitivity of the endoscopic marker(s) was only 50%.

Celiac disease has a wide spectrum of clinical manifestations, ranging from symptomless to atypical forms and even severe malabsorption,[1,20,21] and dyspepsia may be one of its symptoms.[4,13] Our data clearly indicate that patients with dyspepsia are at definite risk for CD: its prevalence was more than twice that reported in general populations from the same geographical areas and most Western countries.[5-9] Interestingly, the subgroup of dyspeptic patients at the highest risk comprised young women: 5 of the 6 patients with CD were women aged 20 to 37 years, and compared with the general population, their relative risk of CD was 3.22 (95% confidence interval, 1.37-7.56). The early diagnosis of CD is advisable because of the high prevalence of the disease and the beneficial ef-

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fect of a gluten-free diet in decreasing the risk of intestinal lymphoma[11] and other complications,[10,22,23] which worsen the quality of life and lead to an increase in costs owing to useless examinations or supportive therapies.[24,25]

Our results suggest that the workup of patients with dyspepsia could be modified. It is well known that an organic cause is found in only 40% of cases[26] and that the findings of clinical history and physical examination cannot reliably help in differentiating organic from functional dyspepsia,[27] which explains the current controversy as to whether all patients with dyspepsia should undergo early endoscopy or start with empirical therapy.[27-30] In fact, although 30% to 60% of these patients have *H pylori*–related gastritis, there is still uncertainty as to whether the infection is responsible for the symptoms or whether eradication treatment induces a clinical improvement.[31-33]

Although it is beyond the scope of this study to discuss the approach to dyspepsia (which needs to be evaluated by means of prospective studies based on cost-benefit analysis), we believe that our results justify modifying the guidelines recommended by recently reported consensus statements.[27] In the case of patients with dyspepsia who are older than 45 years or those considered to be at risk for gastric cancer and for whom early endoscopy is advisable, it would be useful to obtain additional duodenal samples because of the possibility of false-negative endoscopic results: this simple procedure can rule out CD on the basis of subsequent histologic findings. Patients who are younger than 45 years and who show no signs or symptoms of an underlying organic disorder should be serologically examined for CD before costly and empirical treatment is begun. As shown by our results and those of a study based on data from an open-access endoscopy unit,[34] this approach seems to be particularly appropriate for females. Serological CD screening can be based on the determination of antiendomysium antibodies, which, in addition to being the most sensitive and specific test currently available,[35] is relatively inexpensive, even for screening large series of patients, because of the possibility of detecting antiendomysium antibodies using human umbilical cord or umbilical vein endothelial cells.[36]

In conclusion, serological CD screening should be considered in the early diagnostic workup of patients with dyspepsia (especially female patients) who are younger than 45 years to ensure that such a frequent disorder as CD is not missed.

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REFERENCES

1. Trier JS. Celiac sprue. *N Engl J Med.* 1991;325:1709-1719.
2. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology.* 1992;102:1259-1268.
3. Friedman LS. *Helicobacter pylori* and nonulcer dyspepsia. *N Engl J Med.* 1998; 339:1928-1930.
4. Ciacci C, Cirillo M, Sollazzo R, Savino G, Sabbatini F, Mazzacca G. Gender and clinical presentation in adult celiac disease. *Scand J Gastroenterol.* 1995;30: 1077-1081.
5. Grodzinsky E, Franzen L, Hed J, Strom M. High prevalence of celiac disease in healthy adults revealed by antigliadin antibodies. *Ann Allergy.* 1992;69:66-70.
6. Ascher H, Kristiansson B. Childhood coeliac disease in Sweden. *Lancet.* 1994; 344:340-341.
7. Fasano A. Where have all the American celiacs gone? *Acta Paediatr Suppl.* 1996; 412:20-24.
8. Catassi C, Ratsch IM, Fabiani E, et al. Coeliac disease in the year 2000: exploring the iceberg. *Lancet.* 1994;343:200-203.
9. Catassi C, Fabiani E, Ratsch IM, et al. The coeliac iceberg in Italy: a multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl.* 1996;412:29-35.
10. Bardella MT, Molteni N, Prampolini L, et al. Need for follow up in coeliac disease. *Arch Dis Child.* 1994;70:211-213.
11. Holmes GKT, Prior P, Lane MR, et al. Malignancy in coeliac disease: effect of a gluten-free diet. *Gut.* 1989;30:333-338.
12. Brocchi E, Corazza GR, Caletti G, Treggiari EA, Barbara L, Gasbarrini G. Endoscopic demonstration of loss of duodenal folds in the diagnosis of celiac disease. *N Engl J Med.* 1988;319:741-744.
13. Jabbari M, Wild G, Goresky CA, et al. Scalloped valvulae conniventes: an endoscopic marker of celiac sprue. *Gastroenterology.* 1988;95:1518-1522.
14. Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. *Baillieres Clin Gastroenterol.* 1995;9:273-293.
15. Kahn HA, Sempos CT. Relative risk and odds ratio. In: *Statistical Methods in Epidemiology.* New York, NY: Oxford University Press Inc; 1989:45-71.
16. Maki M, Collin P. Coeliac disease. *Lancet.* 1997;349:1755-1759.
17. McIntyre AS, Ng DPK, Smith JA, Amoah J, Long RG. The endoscopic appearance of duodenal folds is predictive of untreated adult celiac disease. *Gastrointest Endosc.* 1992;38:148-151.
18. Maurino E, Capizzano H, Niveloni S, et al. Value of endoscopic markers in celiac disease. *Dig Dis Sci.* 1993;38:2028-2033.
19. Magazzù G, Bottari M, Tuccari G, et al. Upper gastrointestinal endoscopy can be a reliable screening tool for celiac sprue in adults. *J Clin Gastroenterol.* 1994; 19:255-258.
20. Corazza GR, Frisoni M, Treggiari EA, et al. Subclinical celiac sprue. *J Clin Gastroenterol.* 1993;16:16-21.
21. Bardella MT, Fraquelli M, Quatrini M, Molteni N, Bianchi P, Conte D. Prevalence of hypertransaminasemia in adult celiac disease and effect of gluten-free diet. *Hepatology.* 1995;22:833-836.
22. Wright DH. The major complications of coeliac disease. *Baillieres Clin Gastroenterol.* 1995;9:351-369.
23. Molteni N, Caraceni MP, Bardella MT, Ortolani S, Gandolini GG, Bianchi P. Bone mineral density in adult celiac patients and the effect of gluten-free diet from childhood. *Am J Gastroenterol.* 1990;85:51-53.
24. Dickey W, McConnell JB. How many hospital visits does it take before celiac sprue is diagnosed? *J Clin Gastroenterol.* 1996;23:21-23.
25. Hin H, Bird G, Fisher P, Mahy N, Jewell D. Coeliac disease in primary care: a case finding study. *BMJ.* 1999;318:164-167.
26. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology.* 1998;114:579-581.
27. Fisher RS, Parkman HP. Management of nonulcer dyspepsia. *N Engl J Med.* 1998; 339:1376-1381.
28. Talley NJ, Colin-Jones D, Koch KL, Koch M, Nyren O, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. *Gastroenterol Int.* 1991;4:145-146.
29. Talley NJ, Silverstein MD, Agréus L, Nyren O, Sonnenberg A, Holtmann G. Evaluation of dyspepsia. *Gastroenterology.* 1998;114:582-595.
30. Mullins PD, Colin-Jones DG. Guidelines for the management of dyspepsia. *Eur J Gastrointerol Hepatol.* 1999;11:215-217.
31. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med.* 1998; 339:1869-1874.
32. Blum AL, Talley NJ, O'Morain C, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med.* 1998;339:1875-1881.
33. Friedman LS. *Helicobacter pylori* and nonulcer dyspepsia. *N Engl J Med.* 1998; 339:1928-1930.
34. Dickey W. Diagnosis of coeliac disease at open-access endoscopy. *Scand J Gastroenterol.* 1998;33:612-615.
35. Volta U, Molinaro N, De Franceschi L, Fratangelo D, Bianchi FB. IgA antiendomysial antibodies on human umbilical cord tissue for celiac disease screening. *Dig Dis Sci.* 1995;40:1902-1905.
36. Whelan A, Willoughby R, Weir D. Human umbilical vein endothelial cells: a new easily available source of endomysial antigens. *Eur J Gastroenterol Hepatol.* 1996; 8:961-966.

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