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**ARTICLE**

**Is there a relationship between occult celiac disease and functional dyspepsia?**

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Hanaa Kh. Fath-Elbab, Magdy Fouad, Elham Ahmed Mohammed, Nehad M. Reda  
And Hend Mones

*Full Length Research Paper*

## Is there a relationship between occult celiac disease and functional dyspepsia?

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**This is a study to answer the question: Is there a relationship between occult celiac disease and functional dyspepsia? The study was carried out on 400 dyspeptic patients. Upper gastrointestinal tract (GIT) endoscopy was done for all patients and those with non-functional dyspepsia were excluded from the study. Duodenal biopsies with histopathological examination according to the Marsh-Oberhuber criteria were done. Serum tissue transglutaminase IgA antibody (anti-tTG-IgA) was done for patients with histopathological findings suggestive to have celiac disease (subtotal and total villous atrophy). 172 patients with endoscopic findings explaining their dyspeptic symptoms were excluded. Only patients with functional dyspepsia were enrolled in this study (228 patients). Bloating was the most common symptom (46.5%). Normal villous pattern was found in 199 cases (87.2%). Villous atrophy was found in 29 patients, subtotal atrophy in 20 cases (8.7%) and total atrophy in 9 cases (3.9%). Age group of 14-20 years (20/29, 90.9% patients) with villous atrophy was reported to have statistically significant difference (P value =0.000). Serum anti-tTG-IgA level was measured in all cases of abnormal villous pattern. Nine patients (3.9%) were proved to have a celiac disease (total villous atrophy and high serum anti-tTG-IgA) and fourteen dyspeptic patients (6.1%) had subtotal villous atrophy with high anti-tTG-IgA level could be diagnosed as occult celiac disease. Occult celiac disease should be suspected among patients with functional dyspepsia complaining of bloating, especially in age 14 to 20. Subtotal villous atrophy and high anti-tTG-IgA could be considered as occult celiac disease.**

**Key words:** Celiac disease, endoscopy, duodenal biopsy, functional dyspepsia.

### INTRODUCTION

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamins ingestion in genetically susceptible individuals and characterized by atrophy of the proximal small intestinal villi, presence

of a variable combination of gluten-dependent clinical manifestations and celiac disease specific antibodies (Abadie et al., 2011).

It has been considered for years to be a rare pathology

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that affects, in particular, pediatric patients who present with a clinical picture of malabsorption. During the past years, researches have shown that the prevalence of celiac disease has increased dramatically, especially with the development of sensitive and specific serological tests and their administration to subjects who are apparently healthy (Corazza and Villanacci, 2005). CD is still under diagnosed in all age groups and the form with clear symptoms is found in a limited number of cases; in most patients, the disease has atypical symptoms or completely asymptomatic (Gujral et al., 2012).

CD is reported to be associated with many functional gastrointestinal tract (GIT) disorders especially in its occult form; so many studies discussed the prevalence of CD in such functional disorders such as irritable bowel syndrome and functional dyspepsia. In comparison with the general population, it was observed that CD had a greater prevalence in dyspeptic patients and that 30 to 40% of CD patients have dyspeptic symptoms. These findings suggested that it would be useful to carry out, in subjects undergoing esophago-gastro-duodenoscopy (EGD), biopsies of the descending duodenum independently of the endoscopic aspect of the mucosa (Keshavarz et al., 2010).

Until the year 2000, CD was almost unknown in Egypt, to the authors' knowledge, few data are available on its prevalence in Egypt and the relationship between dyspepsia and CD. The diagnosis of celiac disease is based on demonstrating characteristic villous abnormality of duodenal biopsy together with positive celiac serology. Among the serological tests, endomysial antibody (EMA) and anti-tissue transglutaminase antibodies (anti-tTG-IgA or IgG) are commonly used (Gujral et al., 2012).

Tissue transglutaminase is an intracellular enzyme present in many tissues. It has been found that it is not only increased in patients with celiac disease but also correlated with duodenal histology and confirmed that this enzyme is a target in the autoimmune process of celiac disease (Rahmati et al., 2014).

## MATERIALS and METHODS

The study was carried out on 400 patients complaining of dyspepsia and attending the Gastroenterology Unit of Endemic Diseases and Internal Medicine Departments, Minia University Hospital, Egypt. Patients already diagnosed with CD, with family history of celiac disease, with inflammatory bowel disease or irritable bowel syndrome, diarrhea or malabsorption, significant weight loss, any organ failure or refusing to be entitled in the study were excluded.

All patients were subjected to written informed consent before participation in the study, full history taking, clinical examination and underwent EGD using Pentax EPM-5000 after using the standard technique. Patients with endoscopic findings explaining their dyspeptic symptoms were also excluded from the study while patients with no endoscopic findings explaining their dyspeptic symptoms were diagnosed as functional dyspepsia according to Rome III criteria (Jung, 2011).

Duodenal biopsies were obtained by UGI endoscopy from those

patients with functional dyspepsia. 3-5 biopsies were taken from the distal duodenum and sent for histopathological examination according to "Marsh" Criteria for diagnosis of CD as follows:

Stage 0: Preinfiltrative mucosa (small-intestinal biopsy specimens that appear normal).

Stage 1: Increase in the number of intraepithelial lymphocytes (IELs) to more than 30 per 100 enterocytes.

Stage 2: Crypt hyperplasia: In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height.

Stage 3: Villous atrophy: A, partial; B, subtotal; C, total. This is the classic celiac lesion.

Despite marked mucosal changes, many individuals are asymptomatic and therefore classified as having occult or silent cases. This lesion is characteristic, but not diagnostic, of celiac disease and can also be seen with severe giardiasis, infantile food sensitivities, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies, and other immune deficiencies and allograft rejection.

Serum tissue transglutaminase IgA antibody (anti-tTG-IgA) was measured for patients with histopathological findings suggestive to have CD (subtotal and total villous atrophy). It was measured using the ELiA Celikey IgA kit (Phadia AB, Uppsala, Sweden). As recommended by the manufacturer, levels greater than 10 U/mL were considered positive.

## Statistical analysis

The Statistical Package for Social Science (SPSS), version 20, was used for the statistical analysis. Simple statistics such as frequency, mean and standard deviation (SD) were used. Also, Chi-square, t-test was used for comparison. The results were considered statistically significant when the P values were <0.05.

## RESULTS

Only patients with functional dyspepsia according to Rome III criteria were enrolled in this study (228/400 patients). One hundred and seventy two (172) patients with endoscopic findings explaining their dyspeptic symptoms (gastritis or gastric ulcer etc.) were excluded. The included patients were 126 males and 102 females with age range of 14 to 50 years, mean age of  $33.46 \pm 10.47$  classified in four age groups; 1<sup>st</sup> from 14 to 20 years, 2<sup>nd</sup> from 21 to 30 years, 3<sup>rd</sup> from 31 to 40 years and 4<sup>th</sup> from 41 to 50 years.

Clinical bloating was the most common symptom (46.5%), normal villous pattern was found in 199 cases (87.3%). Twenty nine patients (14 females and 15 males) had villous atrophy either subtotal atrophy in 20 cases (8.8%) or total atrophy in 9 cases (3.9%). All these data are shown in Table 1.

Regarding the relation between villous pattern and age grouping, Table 2 showed that age grouping category of 14-20 years, 20/22 (90.9%) had villous atrophy with high statistically significant difference (P value =0.000), while no statistically significant difference was noticed between presence of villous atrophy and sex or residence. Table 2 shows also that bloating was the most frequent symptom between patient with total villous atrophy than abdominal pain and nausea with

**Table 1.** Demographic, clinical and pathological data of the patients.

Item			
Demographic data	Age	14-20 years	22 (9.6%)
		21-30 years	54 (23.6%)
		31-40 years	84 (36.8%)
		41-50 years	68 (29.8%)
	Sex	Male	126 (55.3%)
		Female	102 (44.7%)
Residence	Rural	91 (40%)	
	Urban	137 (60%)	
Clinical data	Bloating	106(46.5%)	
	Abdominal pain	94 (41.2%)	
	Nausea	62 (27.2%)	
Pathological findings	Normal villous pattern	199(87.3%)	
	Subtotal atrophy	20 (8.8%)	
	Total villous atrophy	9 (3.9%)	

**Table 2.** Relation between villous pattern and different parameters.

Item	No	Pathological findings		P value
		Normal villous pattern	Abnormal villous pattern	
Age	14-20 years	22 (9.6%)	2(9.1%)	0.0000*
	21-30 years	54 (23.6%)	50 (92.6%)	
	31-40 years	84 (36.8%)	80 (95.2%)	
	41-50 years	68 (29.8%)	67 (98.5%)	
Sex	Male	126 (55.3%)	111 (88.1%)	0.681
	Female	102 (44.7%)	88 (86.3%)	
Residence	Rural	91(40%)	78 (85.7%)	0.563
	Urban	137 (60%)	121 (88.3%)	
Complaint	Bloating	106(46.5%)	85(35.8%)	0.006*
	Abdominal pain	94 (41.2%)	(91.5%)86	
	Nausea	62(27.2%)	(95.2%)59	

**Table 3.** Pathology and Ttg-IgA results.

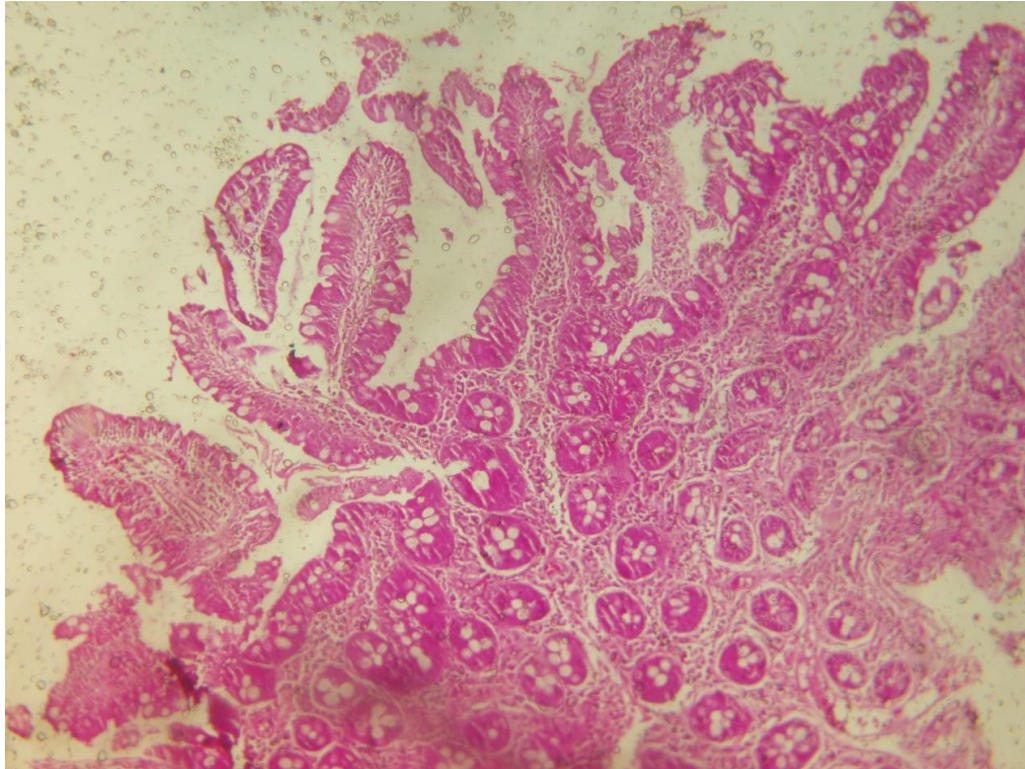
Clinical data	No.	Pathology		P value
		Subtotal v.atrophy	Total v.atrophy	
Serum TG	Negative	6	6(100%)	0.175
	Positive	23	14(61%)	

statistically significant difference (P value =0.006).

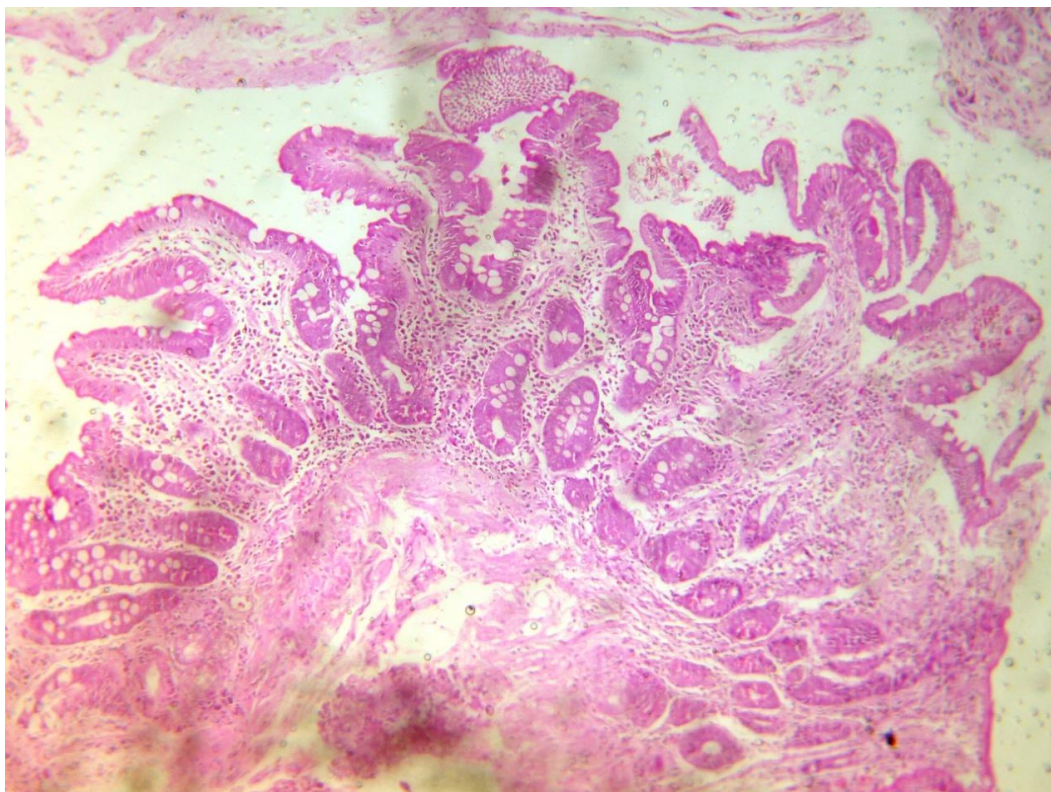
Nine patients are proved to have a celiac disease (total villous atrophy and positive anti-tTG-IgA) that could be diagnosed as occult celiac disease. There are 14 patients

with subtotal villous atrophy and positive anti-tTG-IgA. All patients with total atrophy had positive anti-tTG-IgA (Table 3). Finally, Figures 1, 2 and 3 show normal villous pattern, subtotal and total atrophy, respectively.

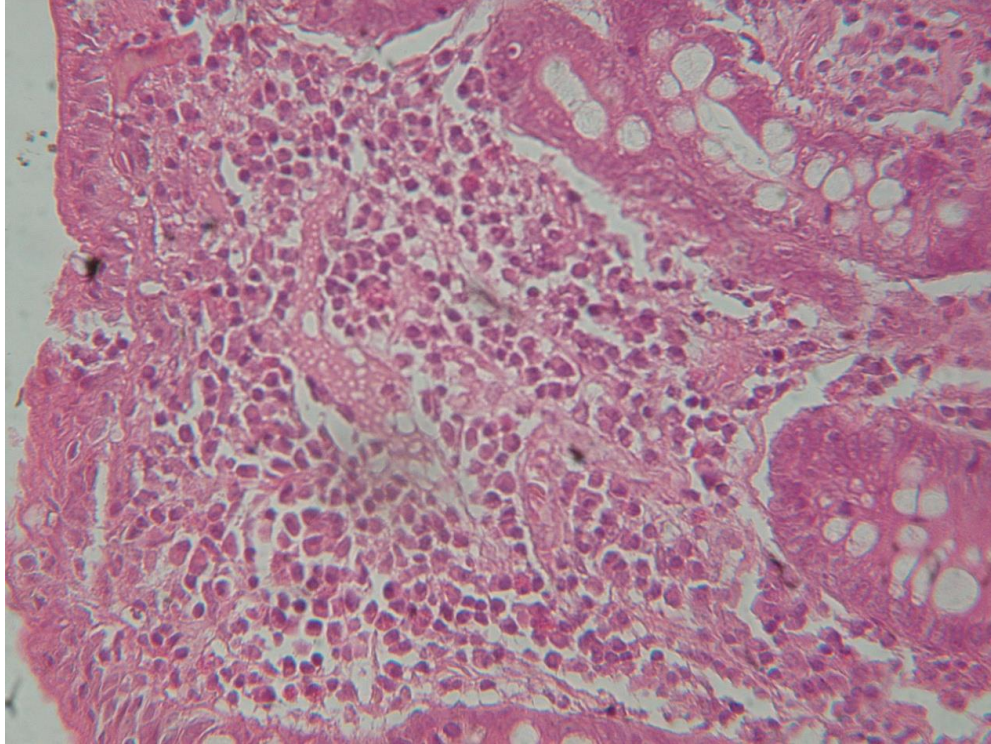




**Figure 1.** Normal villous pattern, with H&E (original magnification 100).



**Figure 2.** Subtotal villous atrophy, with H&E (original magnification 100).



**Figure 3.** Total villous atrophy, intense lymphocytic infiltration of the lamina propria and intraepithelial lymphocytes (with H&E, original magnification 400).

## DISCUSSION

The prevalence of clinically diagnosed disease is 0.05 to 0.27% in various studies. African and American population studies indicate that a large proportion of celiac disease remains undiagnosed; this is due to many clinicians being unfamiliar with the condition or the atypical presentation of the disease (Brar et al., 2006). As such, endoscopy with biopsy is still considered the gold standard in the diagnosis of celiac disease.

CD is reported to be associated with many functional GIT disorders, especially in its occult form; so many studies discussed the prevalence of CD in such functional disorders such as irritable bowel syndrome and functional dyspepsia. These studies recommended that screening for CD in patients suffering from functional GIT disorders should be done and confirmed by the data which revealed that the prevalence of celiac disease among patients with functional dyspeptic symptoms and patients with IBS ranges from 0.5 to 2% (Petrarca et al., 2014).

This study was done on 400 patients with dyspeptic symptoms. Upper GIT endoscopy was done to all patients and those with endoscopic findings explaining their dyspeptic symptoms (non-functional dyspepsia) were excluded from the study. 228 (57%) patients with dyspepsia showed macroscopically normal mucosa when performing upper gastrointestinal endoscopy. This was

similar to the study done by Petrarca et al. (2014) which revealed that 40 to 60% of the investigated patients with dyspepsia had normal endoscopic findings.

Those patients according to Rome criteria were diagnosed as functional dyspepsia and examined for villous atrophy by histopathological examination of the biopsies taken. Pathologically, the study revealed two categories, patients with normal villous pattern (199 patients) and patients with villous atrophy (29 patients) who were subclassified according to the degree of villous atrophy into two subgroups: group of patients with total villous atrophy (9 patients), and group of patients with subtotal villous atrophy (20 patients).

This study revealed that the age group, 14 to 20 years showed statistically significant relationship with abnormal villous pattern patients (90.9%) (P value=0.000), this in accordance with Emami et al. (2008), who found that 10% of patients with villous atrophy were under the age of 18 years, while Farahmand et al. (2012), revealed that 0.5% of patients under 18 years have occult celiac disease, this difference may be explained by the different sample types and different races.

As confirmed by most of the studies on occult celiac disease, the current study revealed no significant relationship between sex or residency and the presence of villous atrophy; however, Ganji et al. (2014) showed a significant relation between female sex and the presence of CD.

Bloating was the predominant complaint (64.2%) in both subtotal and total villous atrophy groups, similar results have been reported by Rahmati et al. (2014), who found that 65.4% patients with different degrees villous atrophy complained of bloating, also, Nejad and Zali (2012) showed that 16% of patients with bloating symptoms have high anti-tTG level; 60% of them had different degrees of villous atrophy. This is different from study of Emami et al. (2008) that about 1.3% of patients with non-specific gastrointestinal symptoms like bloating and abdominal pain have celiac disease and villous atrophy. The difference in these studies may be due to the different geographical areas.

In the present study, anti-tTG-IgA level was assessed in cases with villous atrophy and it was found that all patients with total villous atrophy have positive anti-tTG-IgA and they were confirmed to have celiac disease. Lima et al. (2005) found that out of 142 patients with dyspeptic symptoms, two were found to have total villous atrophy and positive tissue transglutaminase.

Although, many studies have confirmed the correlation between anti-tTG and the degree of duodenal damage and the high sensitivity and specificity of anti-tTG to diagnose CD, in this study, the authors emphasized on the detection of the occult CD by both histopathology and anti-tTG-IgA level.

This study revealed that, out of the 228 investigated patients with functional dyspepsia, 14 patients were diagnosed as occult celiac disease and had subtotal villous atrophy with positive anti-tTG-IgA with prevalence of about 6.1%. It is demonstrated that the prevalence of occult CD in patients with dyspepsia is higher than that of the general population in Egypt (Abu-Zekry et al., 2008). Another study from eastern country was conducted on 225 dyspeptic Iranian patients, revealing that about 6% of the selected patients with functional dyspepsia had occult celiac disease (Keshavarz et al., 2010). Also, Nakazawa et al. (2014) found that seven of the eleven patients with anti-tTG exhibited villous atrophy and partial infiltration of intraepithelial lymphocyte. On the other hand, Rostami et al. (1999) showed that 3 out of 1000 patients had partial villous atrophy with anti-tTG results and was defined as occult celiac disease.

In this study, comparison between the group of celiac disease (total villous atrophy with positive anti-tTG-IgA) and the group of occult celiac disease (subtotal villous atrophy and positive anti-tTG-IgA) as regard anti-tTG-IgA level using student t test revealed that, there was no statistically significant difference between the two groups as regard anti-tTG-IgA level which predicts the high probability of the patients with subtotal villous atrophy to develop overt celiac disease and total villous atrophy within time.

Therefore, celiac disease and occult CD should be kept in mind as a cause of functional dyspepsia during clinical activities. Routine serologic screening of CD among dyspeptic patients cannot be recommended based on

available literature. Based on this discussion, during endoscopic examination for dyspepsia if indicated, endoscopists should carefully inspect the duodenum for CD findings and should take biopsies, especially for patients with bloating and age group ranging from 14 to 20 years.

## Conclusion

In conclusion, based on the results obtained, it can be hypothesized that for patients who have been diagnosed as having functional dyspepsia with normal upper GIT endoscopic findings, endoscopic examination should be completed with duodenal biopsies and histopathological examination of the biopsies taken to exclude any degree of villous atrophy and the presence of occult celiac disease. Particular attention should be given to patients with high tissue transglutaminase level especially at the age group of 14 to 20 years and the presence of bloating as a predominant dyspeptic symptom. Such an approach could reveal another submerged part of the "Celiac iceberg" but it must be validated as regards the cost effectiveness, bearing in mind the variable prevalence of the disease in the different geographical areas.

A combination of clinical presentation, histology and serology would contribute to making a more accurate diagnosis.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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