

## Endomysial antibodies predict celiac disease irrespective of the titers or clinical presentation

Kalle Kurppa, Tiia Räsänen, Pekka Collin, Sari Iltanen, Heini Huhtala, Merja Ashorn, Päivi Saavalainen, Katri Haimila, Jukka Partanen, Markku Mäki, Katri Kaukinen

Kalle Kurppa, Tiia Räsänen, Sari Iltanen, Merja Ashorn, Markku Mäki, Pediatric Research Centre, University of Tampere and Tampere University Hospital, Fin-33014, Tampere, Finland

Pekka Collin, Katri Kaukinen, Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital and School of Medicine, University of Tampere, Fin-33014, Tampere, Finland

Heini Huhtala, Tampere School of Public Health, University of Tampere, Fin-33014, Tampere, Finland

Päivi Saavalainen, Department of Medical Genetics and Research Program for Molecular Medicine, University of Helsinki, Fin-00014, Helsinki, Finland

Katri Haimila, Jukka Partanen, Research and Development, Finnish Red Cross Blood Service, Fin-00310, Helsinki, Finland  
Author contributions: Kurppa K, Räsänen T, Collin P, Iltanen S, Huhtala H, Ashorn M, Saavalainen P, Haimila K, Partanen J, Mäki M and Kaukinen K designed the research, contributed to the acquisition of the data and performed critical revision of the manuscript; Kurppa K, Huhtala H and Kaukinen K analyzed the data; Kurppa K and Kaukinen K wrote the paper.

Supported by The Academy of Finland Research Council for Health; the Competitive Research Funding of the Pirkanmaa Hospital District; the Sigrid Juselius Foundation; the Foundation for Paediatric Research; the National Graduate School of Clinical Investigation; the Ehrnrooth Foundation; the Finnish Gastroenterology Society; the Finnish Pediatric Society and the Finnish Celiac Society

Correspondence to: Katri Kaukinen, MD, PhD, Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital and School of Medicine, University of Tampere, Fin-33014, Tampere, Finland. [katri.kaukinen@uta.fi](mailto:katri.kaukinen@uta.fi)  
Telephone: +358-3-35518403 Fax: +358-3-35518402

Received: July 28, 2011 Revised: November 2, 2011

Accepted: March 10, 2012

Published online: May 28, 2012

### Abstract

**AIM:** To investigate the association between serum antibody levels and a subsequent celiac disease diagnosis

in a large series of children and adults.

**METHODS:** Besides subjects with classical gastrointestinal presentation of celiac disease, the study cohort included a substantial number of individuals with extraintestinal symptoms and those found by screening in at-risk groups. Altogether 405 patients underwent clinical, serological and histological evaluations. After collection of data, the antibody values were further graded as low [endomysial (EmA) 1:5-200, transglutaminase 2 antibodies (TG2-ab) 5.0-30.0 U/L] and high (EmA 1:  $\geq$  500, TG2-ab  $\geq$  30.0 U/L), and the serological results were compared with the small intestinal mucosal histology and clinical presentation.

**RESULTS:** In total, 79% of the subjects with low and 94% of those with high serum EmA titers showed small-bowel mucosal villous atrophy. Furthermore, 96% of the 47 EmA positive subjects who had normal mucosal villi and remained on follow-up either subsequently developed mucosal atrophy while on a gluten-containing diet, or responded positively to a gluten-free diet.

**CONCLUSION:** Irrespective of the initial serum titers or clinical presentation, EmA positivity as such is a very strong predictor of a subsequent celiac disease diagnosis.

© 2012 Baishideng. All rights reserved.

**Key words:** Celiac disease; Diagnosis; Endomysial antibodies; Transglutaminase 2 antibodies; Clinical presentations

**Peer reviewers:** Khaled Jadallah, MD, Assistant Professor of Medicine, Gastroenterologist and Hepatologist, Department of Internal Medicine, King Abdullah University Hospital, Jordan University of Science and Technology, Irbid 22110, Jordan; Alyssa M Krasinskas, MD, Assistant Professor, Department of Pathology, University of Pittsburgh Medical Center, Presbyterian

Hospital, A610, 200 Lothrop Street, Pittsburgh, PA 15213-2546, United States

Kurppa K, Räsänen T, Collin P, Iltanen S, Huhtala H, Ashorn M, Saavalainen P, Haimila K, Partanen J, Mäki M, Kaukinen K. Endomysial antibodies predict celiac disease irrespective of the titers or clinical presentation. *World J Gastroenterol* 2012; 18(20): 2511-2516 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i20/2511.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i20.2511>

## INTRODUCTION

Recent serological screening studies have revealed that up to 1%-2% of the Western population might be affected by celiac disease<sup>[1,2]</sup>. However, due to its heterogeneous clinical picture the disease remains markedly underdiagnosed. Sensitive serum endomysial (EmA) and transglutaminase 2 antibodies (TG2-ab) are widely used as a method to select subjects for further investigations, but the diagnosis is based on the presence of small-bowel mucosal villous atrophy and crypt hyperplasia<sup>[3,4]</sup>. Unfortunately, the histological definition of the disease involves several problems. First, invasive studies are needed to acquire the mucosal specimens. In addition, biopsy samples may be of poor quality or wrongly orientated, increasing the risk of false positive or negative results<sup>[5]</sup>. The mucosal damage may be patchy and missed even if several samples are taken<sup>[6,7]</sup>. Finally, the histological lesion develops gradually and interpretation of borderline cases can be challenging. Since particularly EmA and high values of TG2-ab seem to predict celiac disease with a high specificity, it has been advocated that in seropositive subjects endoscopic studies might not always be needed to establish the diagnosis<sup>[8-15]</sup>. However, most studies so far have been carried out in tertiary centers with high-risk patients, and the results might not be applicable in everyday clinical practice.

In our local health-care district active celiac disease case-finding has been carried out since the 1980s. As a result, a substantial part of the patients are detected because of atypical symptoms or by active risk-group screening, and currently about 0.7% of the population have a biopsy-proven diagnosis<sup>[16]</sup>. Hence, we now sought to establish whether the serum antibodies could predict subsequent celiac disease also in subjects with mild or atypical clinical presentation. Because of the high specificity, EmA has traditionally been considered the gold standard for celiac disease serology, and was thus chosen as the primary inclusion criterion<sup>[17,18]</sup>. In addition, the results were compared to the widely used serum TG2-ab.

## MATERIALS AND METHODS

The study cohort comprised consecutive EmA positive children and adults investigated at the Departments of Pediatrics and Gastroenterology and Alimentary Tract

Surgery, Tampere University Hospital. Primary care physicians were encouraged to refer individuals with celiac disease suspicion for further investigations applying a low index of suspicion. In addition, subjects who participated in population-based research studies were accepted. In the hospital demographic data, a family history of celiac disease and symptoms leading to the disease suspicion were recorded, and all subjects underwent extensive clinical, serological and histological evaluations. Thereafter, voluntary EmA positive children and adults continued in the trial. Participants who showed small-bowel mucosal villous atrophy and crypt hyperplasia (Marsh III) received a celiac disease diagnosis and were placed on a gluten-free diet. Subjects who had normal villi continued on a gluten-containing diet and were placed on regular serological and histological follow-up. In addition, the possibility to start an experimental trial with a gluten-free diet was offered to EmA positive individuals with normal villous structure (Marsh 0- II). Those who consented were re-evaluated after one year, and if a positive clinical, serological and histological response was observed, celiac disease diagnosis was established. Finally, serum TG2-ab were used for comparison in all from whom they were available.

Serum immunoglobulin A (IgA)-class EmA were measured by an indirect immunofluorescence method using human umbilical cord as antigen<sup>[19]</sup>. A dilution of 1:5 was considered positive, and positive sera were further diluted 1:50, 1:100, 1:200, 1:500, 1:1000, 1:2000 and 1:4000. The antibody titers were further graded as low (1:5-1:200) and high (1:500-1:4000). Serum IgA-class TG2-ab were measured by enzyme-linked immunosorbent assay (ELISA) (Celikey, Phadia GmbH, Freiburg, Germany) according to the manufacturers' instructions. Serum TG2-ab values  $\geq 5.0$  U were considered positive, and the values were further graded as low (5.0-29.9 U/L) and high ( $\geq 30$  U/L)<sup>[13]</sup>. Total IgA values were tested in all subjects negative to the IgA class serological tests. In case of IgA deficiency the corresponding antibodies were measured in immunoglobulin G (IgG) class.

Upon upper gastrointestinal endoscopy a minimum of three forceps specimens were taken from the distal duodenum, and small-bowel mucosal morphology was determined from several well-oriented biopsy sections as previously described<sup>[17]</sup>. The degree of mucosal damage was further graded according to the Marsh-Oberhuber classification, where Marsh 0 represents normal mucosa, Marsh I - II represents increased intraepithelial lymphocytosis without (I) or with (II) hyperplastic crypts and Marsh III partial (a), subtotal (b) or total (c) villous atrophy<sup>[20,21]</sup>. A patchy mucosal lesion was graded according to the most severe histological damage.

Genotyping of the participants for celiac disease-associated human leukocyte antigen (HLA)-DQB1\*02 and DQB1\*0302 alleles (DQ2 and DQ8) was performed using the DELFIA<sup>®</sup> Celiac Disease Hybridization Assay (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) or the SSP<sup>™</sup> DQB1 low resolution kit (Olerup SSP AB, Saltsjöbaden, Sweden) according to the

**Table 1** Demographic data on the study participants and primary reason for celiac disease suspicion *n* (%)

Female	265 (67)
Age below 18 yr	92 (23)
Age (yr), median (range)	40 (1-79)
Main reason for disease suspicion	
Gastrointestinal symptoms <sup>1</sup>	166 (43)
Anemia or malabsorption	38 (10)
Extraintestinal symptoms <sup>2</sup>	50 (13)
Screening in at-risk groups <sup>3</sup>	97 (24)
Screening in the population <sup>4</sup>	39 (10)
Unknown	5 (1)

<sup>1</sup>Diarrhea, abdominal pain, flatulence, constipation, dyspepsia, and heartburn; <sup>2</sup>Osteoporosis, infertility, aphthous stomatitis, short stature, delayed puberty, arthralgia, ataxia, epilepsy, fatigue, and alopecia; <sup>3</sup>Family history of celiac disease, type 1 diabetes, thyroid disorders, Sjögren's syndrome, and immunoglobulin A nephropathy; <sup>4</sup>Population-based research studies that included serological screening.

**Table 2** Serum endomysial and transglutaminase 2 antibody values, divided according to the clinical presentation

	EmA, titer		TG2-ab, U/L	
	Low 1:5-200	High 1:≥ 500	Low 5.0-29.9	High ≥ 30
	<i>n</i> = 224, %	<i>n</i> = 154, %	<i>n</i> = 116, %	<i>n</i> = 166, %
Abdominal symptoms	45	40	45	45
Anemia or malabsorption	8	12	5	13
Extraintestinal symptoms	9	16	5	13
Screen-detected subjects	38	31	45	28
	<i>P</i> = 0.061		<i>P</i> = 0.002	

EmA: Endomysial; TG2-ab: Transglutaminase 2 antibody.

manufacturer's instructions.

$\chi^2$  with cross-tabulation was used for statistical analysis. A *P* value less than 0.05 was considered statistically significant.

The study protocol was approved by the Ethics Committee of Tampere University Hospital. All subjects or their parents gave written informed consent.

## RESULTS

In total, 405 EmA positive children and adults participated in the study. In 10 subjects the quality of the small-bowel biopsies was insufficient, in 14 EmA was determined as positive (1:5) without further dilution and in three subjects the clinical data were ambiguous. These cases were excluded from further statistical analyses. One patient had selective IgA deficiency and the corresponding antibodies were measured in the IgG class. Gastrointestinal symptoms remained the primary reason for celiac disease suspicion, but almost half of the patients were detected on the basis of extraintestinal symptoms or by screening of at-risk groups and the population (Table 1).

By definition, all participants were positive for EmA.

**Table 3** Association between high and low serum endomysial and transglutaminase 2 antibody values and small-bowel mucosal morphology

	EmA (L)		TG2-ab(U/L)	
	Low 1:5-200	High 1:≥ 500	Low 5.0-29.9	High ≥ 30
	<i>n</i> = 227, %	<i>n</i> = 156, %	<i>n</i> = 146, %	<i>n</i> = 169, %
Marsh 0	5	1	4	1
Marsh I - II	16	5	16	5
Marsh IIIa	22	13	24	12
Marsh IIIb	28	29	31	28
Marsh IIIc	29	52	25	53
	<i>P</i> < 0.001		<i>P</i> < 0.001	

EmA: Endomysial; TG2-ab: Transglutaminase 2 antibody.

**Table 4** Association between endomysial antibody titers and small-bowel mucosal damage

EmA titer	Subjects	Marsh 0-II, <i>n</i> (%)	Marsh III, <i>n</i> (%)
1: ≥ 5	372	57 (15)	315 (85)
1: ≥ 50	323	39 (12)	284 (88)
1: ≥ 100	282	26 (9)	256 (91)
1: ≥ 200	243	22 (9)	221 (91)
1: ≥ 500	155	9 (6)	146 (94)
1: ≥ 1000	96	3 (3)	93 (97)
1: ≥ 2000	48	2 (4)	46 (96)
1:4000	20	0 (0)	20 (100)

EmA: Endomysial.

Serum TG2-ab were measured in 316 EmA positive subjects and proved positive in 286 (91%) of them. Altogether 41% of the participants had high EmA and 54% high TG2-ab value defined at baseline. There was a significant association between serum TG2-ab level and clinical presentation, low antibody values being more common in the screen- than symptom-detected subjects (Table 2). A similar trend was observed with EmA, but the results were not statistically significant (*P* = 0.061).

Small-bowel mucosal villous atrophy and crypt hyperplasia (Marsh III) were found in altogether 85% of the EmA-positive subjects. There was a significant association between high antibody values and more severe small-bowel mucosal deterioration; in total 94% of those with high EmA titer evinced villous atrophy (Table 3). There was in this respect no significant difference between children and adults. The percentage of subjects evincing severe small-bowel mucosal damage increased progressively with higher EmA titers, but only the highest titer 1:4000 was 100% predictive of subsequent villous atrophy and crypt hyperplasia (Table 4).

In total, 40 patients had low and 17 high serum antibody values without simultaneous villous atrophy (Table 5). Irrespective of the baseline titers, 45 (79%) of these subjects (96% of those who remained on follow-up) either subsequently developed villous atrophy while on a gluten-containing diet, or experienced a positive clinical and serological response and disappearance of early mucosal changes on a gluten-free diet (Table 5). The pres-

**Table 5** Baseline and follow-up data on subjects with positive endomysial antibodies but normal small-bowel mucosal villous structure

	Low <sup>1</sup> EmA and TG2-ab, n = 40	High EmA or TG2-ab, n = 17
Baseline		
Age, median (range), yr	39 (5-68)	39 (6-70)
Females, n (%)	30 (75)	11 (65)
Age below 18 yr	7 (18)	7 (41)
Gastrointestinal symptoms	28 (70)	12 (71)
Extraintestinal symptoms	2 (5)	4 (23)
Screen-detected subjects	10 (25)	1 (6)
EmA, median (range), titer	1:50 (1:5-1:200)	1:500 (1:5-1:2000)
TG2-ab, median (range), U/L	6.3 (0-24.8)	45.5 (13.9->100)
HLA DQ2 or DQ8, n (%)	33/33 (100)	16/16 (100)
Marsh 0	9 (23)	3 (18)
Marsh I - II	31 (77)	14 (82)
Follow-up		
Celiac disease diagnosis	29 (73)	16 (94)
Villous atrophy later <sup>2</sup>	12 (30)	8 (47)
Positive response to GFD	17 (43)	8 (47)
Gluten, no villous atrophy	2 (5)	0
Lost to follow-up	9 (22)	1 (6)

<sup>1</sup>EmA titer 1: < 500, TG2-ab value < 30.0 U/L; <sup>2</sup>Up to 10 yr of follow-up. EmA: Endomysial; TG2-ab: Transglutaminase 2 antibody; HLA: Human leukocyte antigen; GFD: Gluten-free diet.

ence of the celiac disease-associated HLA-DQ2 or DQ8 genotype was assessed in 299 EmA positive subjects and was found in all of them.

## DISCUSSION

In our large series consisting of both children and adults, approximately half of the participants evinced high serum EmA levels, which was indicative of subsequent small-bowel mucosal villous damage in up to 94% of them. The results showed a high antibody titer to be an excellent predictor of villous atrophy and celiac disease also in high disease prevalence areas and in subjects with subtle or atypical symptoms. In the past few decades it has been observed that besides the classical gastrointestinal presentation, celiac disease patients may have a wide range of different extraintestinal symptoms. The patients may suffer for example from arthralgia or arthritis, osteoporosis, infertility and different neurological symptoms. In addition, screen-detected celiac patients may show only minor laboratory abnormalities or have no symptoms at all<sup>[6]</sup>. It was essential to investigate the performance of the celiac autoantibodies also in these atypical patients, as they are frequently seen in clinical practice, and may in fact represent the most common clinical presentation of celiac disease<sup>[6]</sup>.

In patients with classical gastrointestinal celiac disease, Valdimarsson *et al*<sup>[8]</sup> observed a 100% positive predictive value of EmA for celiac disease in 19 adults, and suggested that histological confirmation might not be necessary in all such seropositive patients. Recently, similar results have been obtained with high values of TG2-ab. In a study by Barker *et al*<sup>[10]</sup>, 48 out of 49 children having

TG2-ab more than five times the upper limit of normal (ULN) had diagnostic small bowel mucosal damage. Likewise, Donaldson *et al*<sup>[11]</sup> observed a 100% positive predictive value for celiac disease by using the same cut-off level. In adults, Hill *et al*<sup>[13]</sup> suggested that TG2-ab levels more than ten times ULN would be exclusively indicative for celiac disease, and some other authors have presented comparable results<sup>[12]</sup>.

Our findings thus largely accord with those in earlier studies carried out in specialized centers with high-risk patients having classical gastrointestinal presentation of celiac disease. Nevertheless, in the present study there was still a subpopulation of individuals in whom the current histological criteria were not fulfilled. Approximately 6 % of the participants with high and up to 21% of those with low antibody values had normal small-bowel mucosal villous structure, and in total this was seen in 15% of the EmA-positive subjects. It could thus be argued that EmA are not sufficiently specific for a definite diagnosis of celiac disease as such. Interestingly, however, there is an increasing body of data showing that EmA positivity is a very strong predictor of forthcoming celiac disease also in subjects with initially normal villi<sup>[17,22-26]</sup>. In line with this conception, almost all of our EmA positive patients who had no structural villous damage either evinced a positive serological, clinical and histological response to a gluten-free diet, or subsequently developed villous atrophy while on a normal diet. The existence of a celiac-type disorder in these individuals was further supported by the presence of the relevant HLA type in all in whom it was measured. There is thus strong evidence that, irrespective of the initially normal villous morphology, these EmA positive subjects are truly suffering from celiac disease.

Our study is subject to some limitations. First, although a high percentage of the participants had mild or atypical clinical presentation, the number of those found by population-based serological screening was rather low. Consequently, the results cannot be generalized to this patient group, and further studies are needed<sup>[27]</sup>. Secondly, the mucosal biopsies were taken from the distal duodenum as previously recommended<sup>[28]</sup>. Judging from recent evidence, however, villous atrophy can occasionally be detected only in the bulb area of the small intestine, and in theory celiac disease might in such cases already have been confirmed at the time of the first biopsy<sup>[7]</sup>. Nevertheless, interpretation of bulb specimens may be biased on Brunner glands or peptic inflammation, and their role in the diagnostics remains controversial. In addition, a patchy small-bowel mucosal lesion is always possible in celiac disease, which further highlights the importance of serology in the diagnosis.

Although EmA shows excellent specificity for an untreated celiac disease, it has certain limitations. The immunofluorescence method is laborious, time-consuming and always somewhat subjective. Since TG2-abs can be easily measured using a practical ELISA method, it would be tempting to use it instead of EmA. Neverthe-

less, TG2-ab are measured by commercial tests which use different epitopes of TG2 as antigen, and thus the specificity figures for the method have been somewhat inconsistent. Consequently, the positive predictive value of TG2-ab has sometimes been rather low, particularly in low-risk populations<sup>[29]</sup>. TG2-ab can also be positive in some conditions such as in liver diseases<sup>[30]</sup>. For these reasons, we decided to use the more laborious and time-consuming but celiac disease-specific EmA as the primary inclusion criterion in our series. As a consequence, the results should not be applied to TG2-ab positive EmA negative subjects. Finally, since antibody-negative subjects were not included in our study, the overall sensitivity of the serological tests could not be obtained.

To conclude, EmA positivity as such is a very strong predictor of a subsequent celiac disease diagnosis also in patients with low serum antibody titers and subtle or atypical clinical presentation. Judging from the findings here, invasive endoscopic studies might not be obligatory in all such seropositive patients.

## COMMENTS

### Background

The diagnosis of celiac disease is based on the presence of small-bowel mucosal villous atrophy and crypt hyperplasia, but this histological definition involves several problems. Since particularly endomysial (EmA) and high values of transglutaminase 2 antibodies (TG2-ab) seem to predict celiac disease with high specificity, it has been advocated that in seropositive subjects with gastrointestinal symptoms endoscopic studies might not be obligatory to establish the diagnosis.

### Research frontiers

New diagnostic criteria of celiac disease based to serological tests might make the burdensome and invasive endoscopic investigations unnecessary. The authors aimed to investigate the association between serum antibody levels and a subsequent celiac disease diagnosis in children and adults with a heterogeneous clinical presentation.

### Innovations and breakthroughs

The results showed that high positive values of serological tests are excellent predictors of subsequent villous atrophy and celiac disease also in subjects with atypical or subtle clinical presentation. In addition, positivity of EmA is a very strong indicator of celiac disease diagnosis irrespective of the baseline titers.

### Applications

These results indicate that gastrointestinal endoscopy might be omitted and celiac disease diagnosis established without further histological confirmation in children and adults with positive EmA.

### Terminology

Celiac disease is a chronic autoimmune-based triggered by ingested gluten in genetically susceptible individuals. EmA and TG2-ab are serological test with high accuracy for an untreated celiac disease.

### Peer review

This is a nice study that highlights the significance of positive EmA results in a large series of children and adults. The paper is well-written and adds pertinent information to the literature.

## REFERENCES

- 1 **Fasano A**, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003; **163**: 286-292
- 2 **Lohi S**, Mustalahti K, Kaukinen K, Laurila K, Collin P, Ris-

- sanen H, Lohi O, Bravi E, Gasparin M, Reunanen A, Mäki M. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther* 2007; **26**: 1217-1225
- 3 **Green PH**, Cellier C. Celiac disease. *N Engl J Med* 2007; **357**: 1731-1743
- 4 Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990; **65**: 909-911
- 5 **Collin P**, Kaukinen K, Vogelsang H, Korponay-Szabó I, Sommer R, Schreier E, Volta U, Granito A, Veronesi L, Mascart F, Ocmant A, Ivarsson A, Lagerqvist C, Bürgin-Wolff A, Hadziselimovic F, Furlano RI, Sidler MA, Mulder CJ, Goerres MS, Mearin ML, Ninaber MK, Gudmand-Høyer E, Fabiani E, Catassi C, Tidlund H, Alaintalo L, Mäki M. Antiendomysial and antihuman recombinant tissue transglutaminase antibodies in the diagnosis of coeliac disease: a biopsy-proven European multicentre study. *Eur J Gastroenterol Hepatol* 2005; **17**: 85-91
- 6 **Scott BB**, Losowsky MS. Patchiness and duodenal-jejunal variation of the mucosal abnormality in coeliac disease and dermatitis herpetiformis. *Gut* 1976; **17**: 984-992
- 7 **Gonzalez S**, Gupta A, Cheng J, Tennyson C, Lewis SK, Bhagat G, Green PH. Prospective study of the role of duodenal bulb biopsies in the diagnosis of celiac disease. *Gastrointest Endosc* 2010; **72**: 758-765
- 8 **Valdimarsson T**, Franzen L, Grodzinsky E, Skogh T, Ström M. Is small bowel biopsy necessary in adults with suspected celiac disease and IgA anti-endomysium antibodies? 100% positive predictive value for celiac disease in adults. *Dig Dis Sci* 1996; **41**: 83-87
- 9 **Scoglio R**, Di Pasquale G, Pagano G, Lucanto MC, Magazzù G, Sferlazzas C. Is intestinal biopsy always needed for diagnosis of celiac disease? *Am J Gastroenterol* 2003; **98**: 1325-1331
- 10 **Barker CC**, Mitton C, Jevon G, Mock T. Can tissue transglutaminase antibody titers replace small-bowel biopsy to diagnose celiac disease in select pediatric populations? *Pediatrics* 2005; **115**: 1341-1346
- 11 **Donaldson MR**, Firth SD, Wimpee H, Leiferman KM, Zone JJ, Horsley W, O'Gorman MA, Jackson WD, Neuhausen SL, Hull CM, Book LS. Correlation of duodenal histology with tissue transglutaminase and endomysial antibody levels in pediatric celiac disease. *Clin Gastroenterol Hepatol* 2007; **5**: 567-573
- 12 **Donaldson MR**, Book LS, Leiferman KM, Zone JJ, Neuhausen SL. Strongly positive tissue transglutaminase antibodies are associated with Marsh 3 histopathology in adult and pediatric celiac disease. *J Clin Gastroenterol* 2008; **42**: 256-260
- 13 **Hill PG**, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. *Aliment Pharmacol Ther* 2008; **27**: 572-577
- 14 **Vivas S**, Ruiz de Morales JG, Riestra S, Arias L, Fuentes D, Alvarez N, Calleja S, Hernando M, Herrero B, Casqueiro J, Rodrigo L. Duodenal biopsy may be avoided when high transglutaminase antibody titers are present. *World J Gastroenterol* 2009; **15**: 4775-4780
- 15 **Sugai E**, Moreno ML, Hwang HJ, Cabanne A, Crivelli A, Nachman F, Vázquez H, Niveloni S, Argonz J, Mazure R, La Motta G, Caniggia ME, Smecuol E, Chopita N, Gómez JC, Muriño E, Bai JC. Celiac disease serology in patients with different pretest probabilities: is biopsy avoidable? *World J Gastroenterol* 2010; **16**: 3144-3152
- 16 **Collin P**, Huhtala H, Virta L, Kekkonen L, Reunala T. Diagnosis of celiac disease in clinical practice: physician's alertness to the condition essential. *J Clin Gastroenterol* 2007; **41**: 152-156
- 17 **Kurppa K**, Collin P, Viljamaa M, Haimila K, Saavalainen P, Partanen J, Laurila K, Huhtala H, Paasikivi K, Mäki M, Kaukinen K. Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. *Gastroenterology* 2009; **136**: 816-823

- 18 **Tosco A**, Salvati VM, Auricchio R, Maglio M, Borrelli M, Coruzzo A, Paparo F, Boffardi M, Esposito A, D'Adamo G, Malamisura B, Greco L, Troncone R. Natural history of potential celiac disease in children. *Clin Gastroenterol Hepatol* 2011; **9**: 320-335; quiz e336
- 19 **Ladinsler B**, Rossipal E, Pittschieler K. Endomysium antibodies in celiac disease: an improved method. *Gut* 1994; **35**: 776-778
- 20 **Marsh MN**. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ("celiac sprue"). *Gastroenterology* 1992; **102**: 330-354
- 21 **Oberhuber G**, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999; **11**: 1185-1194
- 22 **Mäki M**, Holm K, Koskimies S, Hällström O, Visakorpi JK. Normal small bowel biopsy followed by coeliac disease. *Arch Dis Child* 1990; **65**: 1137-1141
- 23 **Troncone R**. Latent coeliac disease in Italy. The SIGEP Working Group on Latent Coeliac Disease. Italian Society for Paediatric Gastroenterology and Hepatology. *Acta Paediatr* 1995; **84**: 1252-1257
- 24 **Kaukinen K**, Mäki M, Partanen J, Sievänen H, Collin P. Celiac disease without villous atrophy: revision of criteria called for. *Dig Dis Sci* 2001; **46**: 879-887
- 25 **Paparo F**, Petrone E, Tosco A, Maglio M, Borrelli M, Salvati VM, Miele E, Greco L, Auricchio S, Troncone R. Clinical, HLA, and small bowel immunohistochemical features of children with positive serum antiendomysium antibodies and architecturally normal small intestinal mucosa. *Am J Gastroenterol* 2005; **100**: 2294-2298
- 26 **Kurppa K**, Ashorn M, Iltanen S, Koskinen LL, Saavalainen P, Koskinen O, Mäki M, Kaukinen K. Celiac disease without villous atrophy in children: a prospective study. *J Pediatr* 2010; **157**: 373-380, 380.e1
- 27 **van Koppen EJ**, Schweizer JJ, Csizmadia CG, Krom Y, Hylkema HB, van Geel AM, Koopman HM, Verloove-Vanhorick SP, Mearin ML. Long-term health and quality-of-life consequences of mass screening for childhood celiac disease: a 10-year follow-up study. *Pediatrics* 2009; **123**: e582-e588
- 28 **Hill ID**, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivov M, Seidman EG. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005; **40**: 1-19
- 29 **Hopper AD**, Cross SS, Hurlstone DP, McAlindon ME, Lobo AJ, Hadjivassiliou M, Sloan ME, Dixon S, Sanders DS. Preendoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. *BMJ* 2007; **334**: 729
- 30 **Villalta D**, Crovatto M, Stella S, Tonutti E, Tozzoli R, Biz-zaro N. False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. *Clin Chim Acta* 2005; **356**: 102-109

S- Editor Shi ZF L- Editor A E- Editor Li JY