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OPINION REVIEW

Serologic diagnosis of celiac disease: May it be suitable for adults?

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Abstract

The diagnosis of coeliac disease (CD) in adult patients requires the simultaneous assessment of clinical presentation, serology, and typical histological picture of villous atrophy. However, several years ago, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines approved new criteria for the diagnosis in children: Biopsy could be avoided when anti-transglutaminase antibody (TGA) values exceed the cut-off of × 10 upper limit of normal (ULN) and anti-endomysium antibodies are positive, independently from value. This "no biopsy" approach is a decisive need for pediatric population, allowing to avoid stressful endoscopic procedures in children, if unnecessary. This approach relies on the correlation existing in children between TGA levels and assessment of mucosal atrophy according to Marsh's classification. Several lines of evidence have shown that patients with villous atrophy have markedly elevated TGA levels. Therefore, we aim to perform a narrative review on the topic in adults. Despite that some studies confirmed that the × 10 ULN threshold value has a very good diagnostic performance, several lines of evidence in adults suggest that TGA cut off should be different from that of pediatric population for reaching a good correlation with histological picture. In conclusion, the heterogeneity of study reports as well as some conditions, which may hamper the serological diagnosis of CD (such as seronegative CD and non-celiac villous atrophy) and are much more common in adults than in children, could represent a limitation for the "no biopsy" approach to CD diagnosis in patients outside the pediatric age.

Key Words: Celiac disease; Villous atrophy; Serology; Biopsy; Anti-transglutaminase antibody

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Core Tip: A "no biopsy" approach to celiac disease diagnosis, based only on anti-transglutaminase antibody titer, is a well-established strategy in children and an appealing matter of debate in adults. Indeed, the same strategy is recommended by pediatric guidelines, since it allows to avoid about one third of upper endoscopy procedures. In adults, literature on the topic is flourishing even if the topic is still under-investigated, results are heterogeneous, and some conditions may be relevant limiting factors.

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INTRODUCTION

Celiac disease (CD) is the most common immune-mediated enteropathy. It affects subjects with a genetic predisposition based on the presence of a human leukocyte antigen (HLA) DQ2/DQ8 haplotype and polymorphisms of several other inflammatory genes. The same genes are frequently involved in several other autoimmune conditions, and this explains why a high rate of coeliac patients suffer from at least another immune-mediated disease[1,2].

CD is the only autoimmune disease certainly triggered by an exogenous factor, *i.e.*, the ingestion of gluten. Gluten is a complex of alcohol soluble proteins such as gliadins, avenins, and secalins. These rich-in-proline and glutamine peptides are difficultly hydrolyzed by humans for the absence of an enzyme called prolyl-endopeptidase on the brush border of enterocytes[3].

The global prevalence of CD is about 1%[4]. However, considerable differences exist among various countries. Additionally, it is more frequent in females (2:1-3:1), like other autoimmune diseases. Diagnosis may occur in every moment of life. In the past, CD was considered a disease of the childhood[4], but nowadays the trend is changing because the 50% of new diagnoses occur in people over 50 years old. The most important difference between pediatric and adult patients concerns symptoms at onset: In children the intestinal signs are more frequent, while in adults the extra-intestinal manifestations are more typical[5].

Clinical manifestations may include both intestinal and extra-intestinal symptoms. Intestinal manifestations are diarrhea, dyspepsia, bloating, and abdominal pain. Extraintestinal findings are weight loss, iron deficiency anemia, microcytic or megaloblastic anemia, and osteopenia[6].

Malabsorption is the consequence of the mucosal injury caused by humoral and cell-mediated autoimmunity. In fact, tissue transglutaminase 2 (TTG2), an intestinal enzyme, makes gluten peptides toxic by reactions of transamidation and deamidation [7]. Plasma cells release IgA antibodies against both self-components of the mucosal layer and deamidated gluten peptides. IgA molecules pass into the bloodstream as antibodies against transglutaminase 2 (TGA), endomysium (EMA), and deamidated gliadin peptides (DGPs) and their detection is useful for the diagnosis of CD[4,8].

On the other side, an immune response mediated by CD3+ T cells takes place. These CD3+ T lymphocytes are called intraepithelial lymphocytes (IELs). IELs infiltrate the mucosal layer, thus damaging enterocytes. In CD, IELs are usually more than 25/100 enterocytes and lose their normal pattern of distribution in the villous area, which is called base-tip pattern and is characterized by a few number of IELs located at the base of the villi. Conversely, in CD, IELs are abnormally distributed in the whole surface of the villi[9].

The number of IELs is one of the two main histological criteria used for assessment of mucosal damage according to Marsh classification; the other one is the reduction of the villous-crypt ratio. In the normal duodenum, the villi are 3-fold longer than Lieberkhun crypt depth; in CD, the flattening of villi causes an inversion of the normal ratio from 3:1 to 1:1 until to 1:3.

Table 1 Sensitivity and specificity of serologic tests

Antibody	Sensitivity (range)	Specificity (range)
IgA TGA	98% (78%-100%)	98% (90%-100%)
EMA	95% (86%-100%)	99% (97%-100%)
IgA DGP	88% (74%-100%)	95% (90%-99%)
IgG TGA	70% (45%-95%)	95% (94%-100%)
IgG DGP	80% (63%-95%)	98% (90%-99%)

DGP: Deamidated gliadin antibodies; EMA: Anti-endomysium antibodies; TGA: Anti-transglutaminase antibodies.

These histological findings are assessed on biopsy samples taken from the duodenum. At least two samples from the bulb and four from the second part of the duodenum should be taken in order to obtain an adequate sample[10,11].

DIAGNOSIS

Currently, a combination of clinical presentation, serology, and histology is required to diagnose CD in adults.

A patient with suggestive intestinal or extraintestinal symptoms/signs should undergo a serological analysis to assess the IgA levels: IgA-class TGA are the most sensitive and specific antibodies for CD even if they do not allow to diagnose CD alone. The IgA-class TGA test is performed by enzyme-linked immunosorbent assay. It is reliable and inexpensive, and represents the most sensitive test for CD (98%), with a very low percentage of false positive when the titer is more than 5-fold the upper limit of normal value[12]. The hypothesis of CD should be confirmed by IgA-class EMA positivity. Indeed, IgA-class EMA measurement is the most specific test (near to 100%) but the test is immunofluorescence–based, so it is operator dependent for its difficult interpretation[13].

In patients with an IgA deficiency (a frequent condition in celiac patients), IgG levels should be assessed[3]. A summary of diagnostic performance of serologic tests in CD is reported in Table 1[14].

Antibodies against DPGs are not very useful in diagnosis, except if the patient is less than 2 years old; they could be considered in the follow-up, because their variations are very rapid after the starting of a gluten free diet (GFD)[15,16].

In adult population, endoscopy with duodenal biopsy samples is considered the gold standard for CD diagnosis. Several endoscopic findings may suggest CD with a high sensitivity and specificity. However, more than 33% of CD patients have a normal endoscopic appearance, so biopsy samples should be collected in all patients with suspected CD irrespectively of endoscopic appearance. During upper GI endoscopy, at least 4-6 specimens should be collected, including samples from the duodenal bulb, in order to increase the diagnostic yield[17]. In each pass of biopsy forceps, the endoscopist should take only a single biopsy specimen[18]. However, at least 10% of specimens may not have an acceptable quality, due to insufficient size or lack of orientation and, sometimes, endoscopy should be repeated. Moreover, endoscopy is an invasive procedure with risk of complications and expensive, and the sedation is often required due to the duration of the procedure.

A level 3 in Marsh assessment corresponds to a complete villous atrophy and is required to diagnose CD.

However, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines in these last years stated that a different diagnostic algorithm could be used for children.

Then, guidelines stated that, if clinical features are present, TGA level overcomes the threshold of 10 × UNL, and EMAs are positive, histology and genetics could not be carried out. This conclusion relies on the strong association between TGA and Marsh's grade of atrophy[19].

This approach, despite being not applicable to all children, has changed the clinical practice since, at least in children, upper endoscopy is not easily performed. It has been estimated that the cited cut-off may avoid endoscopy in 18% of celiac children, with a sensitivity of 96.3 and specificity of 98.6%[20]. In another study, 29% of children

could have avoided biopsy *as per* the 2020 ESPGHAN guidelines, and levels of TGA ≥ 60 U/mL or DGP ≥ 28 U/mL had a 100% specificity and 100% positive predictive value (PPV) for CD. HLA typing and EMA did not improve the PPV in patients with a TGA level ≥ 60 U/mL, but addition of DGP ≥ 28 U/mL improved the diagnostic sensitivity albeit maintaining the 100% specificity[21].

The promising data found in pediatric literature have, therefore, pushed researchers to investigate whether a pure serologic approach could be used in adults with suspicion of CD. Therefore, we aimed to perform a narrative review on the topic in adults.

A NO-BIOPSY, SEROLOGY-BASED APPROACH IN ADULTS: CURRENT EVIDENCE

Several studies supported the "no-biopsy strategy" in adult population. Sugai *et al*[22], in a prospective study, evaluated the diagnostic accuracy of duodenal biopsy and serology for CD diagnosis (TGA and DGP), in two cohorts of subjects with different pre-test probabilities. In the high-risk group (161 enrolled patients), the prevalence of CD was 39.1%, while in the low-risk group (518 enrolled patients), the CD prevalence was 3.3%. Using assay combinations, it would be possible to confirm or rule out a diagnosis of CD without biopsy in 92% of cases in both pre-test populations. Salmi *et al*[23] compared histological examination to serum and intestinal celiac autoantibodies in untreated CD. They corroborated a high sensitivity and specificity of autoantibodies TGAs for detection of CD with villous atrophy. In 2008, Hill *et al*[24] found that an IgA-class TGA level of × 10 ULN could be used as a diagnostic cut-off with a positive predictive value of 100% for CD in adults. A similar cut-off of TGA antibody level (× 10) was suggested by Beltran *et al*[25] for CD diagnosis, with a 100% specificity. However, the authors emphasized the necessity of local validation for the cut-off value. The study of Penny *et al*[26] confirmed that an IgA-class TGA titer of × 10 ULN had a 100% specificity as a cut-off value for detection of Marsh type 3 lesions.

Other cut-off values of TGA levels have also been suggested. In a retrospective study, Holmes *et al*[27] enrolled 270 CD adults with IgA-TGA levels measured and small bowel biopsy samples. The authors found that a cut-off greater than 45 U/mL (> × 8 ULN + 2SDs) had a PPV of 100% for CD. The same value was suggested by Tortora *et al*[28]. In their study, a cut-off value of TGA of 45 U/mL had a sensitivity of 70% and specificity of 100% for predicting Marsh ≥ 2 lesions. Moreover, the authors found that the best cut-off for predicting villous atrophy was 62.4 U/mL (sensitivity 69%, specificity 100%). A lower cut-off value of TGA was found in the retrospective study of Zanini *et al*[29]: They demonstrated a 100% specificity for duodenal atrophy with a cut-off value of five times higher than the ULN. The application of this diagnostic approach could avoid upper GI endoscopy in one out of three patients. In a multicenter retrospective analysis enrolling both pediatric and adult patients who underwent small-bowel biopsy for suspicion of CD and positivity for both TGA and EMA, Alessio *et al*[30] demonstrated that a TGA level ≥ × 7 ULN was able to diagnose CD with a specificity and PPV close to 100%. On the other hand, Di Tola *et al*[31] determined that the best TGA serum level/cut-off ratio was > 3.6 with a sensitivity of 76.8 % and PPV of 97.2 %. The use of threshold value for CD diagnosis could avoid endoscopy with biopsy in 75% of the patients. The authors also found a strong correlation between TGA serum levels/cut-off ratio and the degree of duodenal lesions.

The combination of serology for IgA-TGA and IgA-EMA for CD diagnosis was retrospectively evaluated by Wakim-Fleming *et al*[32]. In their cohort, a value of serum IgA-class TGA greater than 118 U had only a 2% false-positive rate. While, if the value of serum IgA TGA was between 21 and 118, the value of EMA at least 1:60 had a PPV of 83% for CD. IgA-class TGA level less than 20 U, in combination with an EMA dilution titer less than 1:10, had a negative predictive value of 92% for CD.

Oyaert *et al*[33] evaluated the use of IgA-class TGA value associated with IgG-DGP antibody for CD diagnosis, in both pediatric and adult populations. Patients with double positivity and high antibody levels (> 3 times and > 10 times ULN) had a high probability of having CD (likelihood ratio ≥ 649 for > 3 times ULN and ∞ for > 10 times ULN). However, the sensitivity was significantly higher for all test combinations in the group aged younger than 16 years compared to the adult group.

The study by Efthymakis *et al*[34] found that the optimal cut-off anti-TGA value was ≥ × 16 ULN. In this study, 11 different assays were used for TGA titer determination. Analyzing the two more prevalent, the authors found different optimal cut-off values

(14.3 × ULN *vs* 3.7 × ULN), even after standardization (-0.14 *vs* -1.2).

SEROLOGY AND PERSISTENT ATROPHY IN FOLLOW-UP

Key endpoints in the follow-up of CD patients are the absence of symptoms and the achievement of mucosal healing, *i.e.*, regression of atrophy. After 6-12 mo of adhering to a GFD, serology becomes negative in 80% of the patients and in 90% after 5 years.

Unfortunately, a normal TGA level at follow-up does not predict recovery of villous atrophy. Really, the lack of declining values and/or persistently positive serology 1 year after starting a GFD strongly suggest gluten contamination. Indeed, a recent meta-analysis demonstrated that IgA-class TGA and IgA-class EMA detected persistent villous atrophy with a high specificity (83%) but low sensitivity (50%).

Of interest, this study emphasized a presumable different CD diagnostic tool pattern between pediatric and adult ages. Indeed, the area under the curve for villous atrophy prediction was higher for children than for adults (0.879 *vs* 0.781)[16].

CONCLUSION

Biopsy-free strategy is a promising approach for the diagnosis of CD in adult population, with a sensitivity and specificity close to 100%. However, it should be highlighted that in adults the diagnosis of CD may be more challenging than in children, since villous atrophy and increased IELs might be related not only to CD, but even to other pathologic conditions, including drug damage, infections, or functional gastrointestinal disorders[35-41].

On the other hand, seronegative CD is a rare condition that may be found in adults. It should be always kept into account when clinical symptoms are highly suggestive of the disorder despite the absence of serological markers and, in this case, histological examination is the mandatory diagnostic tool[42,43].

Moreover, the possibility of false positivity of TGA has been described, especially after viral respiratory infections[44].

In conclusion, despite that the results show that biopsy-free strategy may be promising in adults, some cautions should be taken into account before performing a fully serologic diagnosis of CD. Indeed, the topic is still under-investigated, the results of the studies are heterogeneous, and some conditions, such as seronegative CD or intestinal damage due to causes other than gluten, may be relevant limiting factors. Furthermore, since most of studies are retrospective, the real possibility of avoiding endoscopic examination for diagnosing CD in adults is still a matter of debate and requires further research. Therefore, further studies with a standardized approach are still required to evaluate this strategy and determine the best cut-off.

REFERENCES

1 **Gutierrez-Achury J**, Coutinho de Almeida R, Wijmenga C. Shared genetics in coeliac disease and other immune-mediated diseases. *J Intern Med* 2011; **269**: 591-603 [PMID: 21401738 DOI: 10.1111/j.1365-2796.2011.02375.x]

2 **Kaukinen K**, Lindfors K, Collin P, Koskinen O, Mäki M. Coeliac disease--a diagnostic and therapeutic challenge. *Clin Chem Lab Med* 2010; **48**: 1205-1216 [PMID: 20578966 DOI: 10.1515/CCLM.2010.241]

3 **Biesiekierski JR**. What is gluten? *J Gastroenterol Hepatol* 2017; **32** Suppl 1: 78-81 [PMID: 28244676 DOI: 10.1111/jgh.13703]

4 **Rubin JE**, Crowe SE. Celiac Disease. *Ann Intern Med* 2020; **172**: ITC1-ITC16 [PMID: 31905394 DOI: 10.7326/AITC202001070]

5 **Singh P**, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, Kelly CP, Ahuja V, Makharia GK. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 823-836.e2 [PMID: 29551598 DOI: 10.1016/j.cgh.2017.06.037]

6 **Hujoel IA**, Reilly NR, Rubio-Tapia A. Celiac Disease: Clinical Features and Diagnosis. *Gastroenterol Clin North Am* 2019; **48**: 19-37 [PMID: 30711209 DOI: 10.1016/j.gtc.2018.09.001]

7 **Di Sabatino A**, Vanoli A, Giuffrida P, Luinetti O, Solcia E, Corazza GR. The function of tissue transglutaminase in celiac disease. *Autoimmun Rev* 2012; **11**: 746-753 [PMID: 22326684 DOI: 10.1016/j.autrev.2012.01.007]

8 **Tye-Din J**. Interpreting tests for coeliac disease: Tips, pitfalls and updates. *Aust J Gen Pract* 2018; **47**: 28-33 [PMID: 29429314 DOI: 10.31128/AFP-10-17-4357]

9 **Ensari A**. Gluten-sensitive enteropathy (celiac disease): controversies in diagnosis and classification. *Arch Pathol Lab Med* 2010; **134**: 826-836 [PMID: 20524861 DOI: 10.5858/134.6.826]

10 **Lagana SM**, Bhagat G. Biopsy Diagnosis of Celiac Disease: The Pathologist's Perspective in Light of Recent Advances. *Gastroenterol Clin North Am* 2019; **48**: 39-51 [PMID: 30711210 DOI: 10.1016/j.gtc.2018.09.003]

11 **Lebwohl B**, Kapel RC, Neugut AI, Green PH, Genta RM. Adherence to biopsy guidelines increases celiac disease diagnosis. *GastrointestEndosc* 2011; **74**: 103-109 [PMID: 21601201 DOI: 10.1016/j.gie.2011.03.1236]

12 **Li M**, Yu L, Tiberti C, Bonamico M, Taki I, Miao D, Murray JA, Rewers MJ, Hoffenberg EJ, Agardh D, Mueller P, Stern M, Bonifacio E, Liu E. A report on the International Transglutaminase Autoantibody Workshop for Celiac Disease. *Am J Gastroenterol* 2009; **104**: 154-163 [PMID: 19098864 DOI: 10.1038/ajg.2008.8]

13 **Lebwohl B**, Rubio-Tapia A, Assiri A, Newland C, Guandalini S. Diagnosis of celiac disease. *GastrointestEndosc Clin N Am* 2012; **22**: 661-677 [PMID: 23083985 DOI: 10.1016/j.giec.2012.07.004]

14 **Leffler DA**, Schuppan D. Update on serologic testing in celiac disease. *Am J Gastroenterol* 2010; **105**: 2520-2524 [PMID: 21131921 DOI: 10.1038/ajg.2010.276]

15 **Husby S**, Murray JA, Katzka DA. AGA Clinical Practice Update on Diagnosis and Monitoring of Celiac Disease-Changing Utility of Serology and Histologic Measures: Expert Review. *Gastroenterology* 2019; **156**: 885-889 [PMID: 30578783 DOI: 10.1053/j.gastro.2018.12.010]

16 **Silvester JA**, Kurada S, Szwajcer A, Kelly CP, Leffler DA, Duerksen DR. Tests for Serum Transglutaminase and Endomysial Antibodies Do Not Detect Most Patients With Celiac Disease and Persistent Villous Atrophy on Gluten-free Diets: a Meta-analysis. *Gastroenterology* 2017; **153**: 689-701.e1 [PMID: 28545781 DOI: 10.1053/j.gastro.2017.05.015]

17 **McCarty TR**, O'Brien CR, Gremida A, Ling C, Rustagi T. Efficacy of duodenal bulb biopsy for diagnosis of celiac disease: a systematic review and meta-analysis. *Endosc Int Open* 2018; **6**: E1369-E1378 [PMID: 30410959 DOI: 10.1055/a-0732-5060]

18 **Latorre M**, Lagana SM, Freedberg DE, Lewis SK, Lebwohl B, Bhagat G, Green PH. Endoscopic biopsy technique in the diagnosis of celiac disease: one bite or two? *GastrointestEndosc* 2015; **81**: 1228-1233 [PMID: 25638509 DOI: 10.1016/j.gie.2014.10.024]

19 **Husby S**, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, Shamir R, Troncone R, Auricchio R, Castillejo G, Christensen R, Dolinsek J, Gillett P, Hróbjartsson A, Koltai T, Maki M, Nielsen SM, Popp A, Størdal K, Werkstetter K, Wessels M. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr* 2020; **70**: 141-156 [PMID: 31568151 DOI: 10.1097/MPG.0000000000002497]

20 **Ho SS**, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. *J Paediatr Child Health* 2020; **56**: 1906-1911 [PMID: 32946186 DOI: 10.1111/jpc.15076]

21 **Thompson G**, Grover Z, Loh R, Mews C, Ravikumara M, Jevon G, D'Orsogna L, McLean-Tooke A. Assessment of European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines in an Australian paediatric population. *Pathology* 2020; **52**: 568-575 [PMID: 32586687 DOI: 10.1016/j.pathol.2020.05.002]

22 **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, Mauriño E, Bai JC. Celiac disease serology in patients with different pretest probabilities: is biopsy avoidable? *World J Gastroenterol* 2010; **16**: 3144-3152 [PMID: 20593499 DOI: 10.3748/wjg.v16.i25.3144]

23 **Salmi TT**, Collin P, Reunala T, Mäki M, Kaukinen K. Diagnostic methods beyond conventional histology in coeliac disease diagnosis. *Dig Liver Dis* 2010; **42**: 28-32 [PMID: 19473894 DOI: 10.1016/j.dld.2009.04.004]

24 **Hill PG**, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. *Aliment PharmacolTher* 2008; **27**: 572-577 [PMID: 18194500 DOI: 10.1111/j.1365-2036.2008.03609.x]

25 **Beltran L**, Koenig M, Egner W, Howard M, Butt A, Austin MR, Patel D, Sanderson RR, Goubet S, Saleh F, Lavender J, Stainer E, Tarzi MD. High-titre circulating tissue transglutaminase-2 antibodies predict small bowel villous atrophy, but decision cut-off limits must be locally validated. *Clin Exp Immunol* 2014; **176**: 190-198 [PMID: 24325651 DOI: 10.1111/cei.12249]

26 **Penny HA**, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, Bassotti G, Bontkes HJ, Carroccio A, Danciu M, Derakhshan MH, Ensari A, Ganji A, Green PHR, Johnson MW, Ishaq S, Lebwohl B, Levene A, Maxim R, MohagheghShalmani H, Rostami-Nejad M, Rowlands D, Spiridon IA, Srivastava A, Volta U, Villanacci V, Wild G, Cross SS, Rostami K, Sanders DS. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. *Gut* 2021; **70**: 876-883 [PMID: 33139268 DOI: 10.1136/gutjnl-2020-320913]

27 **Holmes GKT**, Forsyth JM, Knowles S, Seddon H, Hill PG, Austin AS. Coeliac disease: further evidence that biopsy is not always necessary for diagnosis. *Eur J Gastroenterol Hepatol* 2017; **29**: 640-645 [PMID: 28441689 DOI: 10.1097/MEG.0000000000000841]

28 **Tortora R**, Imperatore N, Capone P, De Palma GD, De Stefano G, Gerbino N, Caporaso N, Rispo A. The presence of anti-endomysial antibodies and the level of anti-tissue transglutaminases can be used to diagnose adult coeliac disease without duodenal biopsy. *Aliment PharmacolTher* 2014; **40**: 1223-1229 [PMID: 25263177 DOI: 10.1111/apt.12970]

29 **Zanini B**, Magni A, Caselani F, Lanzarotto F, Carabellese N, Villanacci V, Ricci C, Lanzini A. High tissue-transglutaminase antibody level predicts small intestinal villous atrophy in adult patients at high risk of celiac disease. *Dig Liver Dis* 2012; **44**: 280-285 [PMID: 22119616 DOI: 10.1016/j.dld.2011.10.013]

30 **Alessio MG**, Tonutti E, Brusca I, Radice A, Licini L, Sonzogni A, Florena A, Schiaffino E, Marus W, Sulfaro S, Villalta D; Study Group on Autoimmune Diseases of Italian Society of Laboratory Medicine. Correlation between IgA tissue transglutaminase antibody ratio and histological finding in celiac disease. *J Pediatr Gastroenterol Nutr* 2012; **55**: 44-49 [PMID: 22197946 DOI: 10.1097/MPG.0b013e3182470249]

31 **Di Tola M**, Marino M, Goetze S, Casale R, Di Nardi S, Borghini R, Donato G, Tiberti A, Picarelli A. Identification of a serum transglutaminase threshold value for the noninvasive diagnosis of symptomatic adult celiac disease patients: a retrospective study. *J Gastroenterol* 2016; **51**: 1031-1039 [PMID: 26928588 DOI: 10.1007/s00535-016-1188-y]

32 **Wakim-Fleming J**, Pagadala MR, Lemyre MS, Lopez R, Kumaravel A, Carey WD, Zein NN. Diagnosis of celiac disease in adults based on serology test results, without small-bowel biopsy. *Clin Gastroenterol Hepatol* 2013; **11**: 511-516 [PMID: 23305824 DOI: 10.1016/j.cgh.2012.12.015]

33 **Oyaert M**, Vermeersch P, De Hertogh G, Hiele M, Vandeputte N, Hoffman I, Bossuyt X. Combining antibody tests and taking into account antibody levels improves serologic diagnosis of celiac disease. *Clin Chem Lab Med* 2015; **53**: 1537-1546 [PMID: 25719330 DOI: 10.1515/cclm-2013-1099]

34 **Efthymakis K**, Serio M, Milano A, Laterza F, Bonitatibus A, Di Nicola M, Neri M. Application of the Biopsy-Sparing ESPGHAN Guidelines for Celiac Disease Diagnosis in Adults: A Real-Life Study. *Dig Dis Sci* 2017; **62**: 2433-2439 [PMID: 28717844 DOI: 10.1007/s10620-017-4672-1]

35 **Lauwers GY**, Fasano A, Brown IS. Duodenal lymphocytosis with no or minimal enteropathy: much ado about nothing? *Mod Pathol* 2015; **28** Suppl 1: S22-S29 [PMID: 25560597 DOI: 10.1038/modpathol.2014.135]

36 **Losurdo G**, Giorgio F, Piscitelli D, Montenegro L, Covelli C, Fiore MG, Giangaspero A, Iannone A, Principi M, Amoruso A, Barone M, Di Leo A, Ierardi E. May the assessment of baseline mucosal molecular pattern predict the development of gluten related disorders among microscopic enteritis? *World J Gastroenterol* 2016; **22**: 8017-8025 [PMID: 27672296 DOI: 10.3748/wjg.v22.i35.8017]

37 **Ierardi E**, Losurdo G, Iannone A, Piscitelli D, Amoruso A, Barone M, Principi M, Pisani A, Di Leo A. Lymphocytic duodenitis or microscopic enteritis and gluten-related conditions: what needs to be explored? *Ann Gastroenterol* 2017; **30**: 380-392 [PMID: 28655974 DOI: 10.20524/aog.2017.0165]

38 **Malamut G**, Cerf-Bensussan N, Cellier C. Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-celiac villous atrophy. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 719-721 [PMID: 25990839 DOI: 10.1586/17474124.2015.1039990]

39 **Burbure N**, Lebwohl B, Arguelles-Grande C, Green PH, Bhagat G, Lagana S. Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology. *Hum Pathol* 2016; **50**: 127-134 [PMID: 26997446 DOI: 10.1016/j.humpath.2015.12.001]

40 **Losurdo G**, Piscitelli D, Ierardi E, Di Leo A. Intraepithelial lymphocytes: bystanders or causative factors in functional gastrointestinal disorders? *Cell Mol Immunol* 2021; **18**: 1620-1621 [PMID: 33479415 DOI: 10.1038/s41423-020-00614-3]

41 **Losurdo G**, Piscitelli D, Giangaspero A, Principi M, Buffelli F, Giorgio F, Montenegro L, Sorrentino C, Amoruso A, Ierardi E, Di Leo A. Evolution of nonspecific duodenal lymphocytosis over 2 years of follow-up. *World J Gastroenterol* 2015; **21**: 7545-7552 [PMID: 26140001 DOI: 10.3748/wjg.v21.i24.7545]

42 **Ierardi E**, Losurdo G, Piscitelli D, Giorgio F, Sorrentino C, Principi M, Montenegro L, Amoruso A, Di Leo A. Seronegative celiac disease: where is the specific setting? *Gastroenterol Hepatol Bed Bench* 2015; **8**: 110-116 [PMID: 25926935]

43 **Schiepatti A**, Sanders DS, Zuffada M, Luinetti O, Iraqi A, Biagi F. Overview in the clinical management of patients with seronegative villous atrophy. *Eur J Gastroenterol Hepatol* 2019; **31**: 409-417 [PMID: 30557227 DOI: 10.1097/MEG.0000000000001340]

44 **De Leo L**, Quaglia S, Ziberna F, Vatta S, Martelossi S, Maschio M, Not T. Serum anti-tissue transglutaminase antibodies detected during febrile illness may not be produced by the intestinal mucosa. *J Pediatr* 2015; **166**: 761-763 [PMID: 25722272 DOI: 10.1016/j.jpeds.2014.12.005]

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