Received: 3 November 2023 | Accepted: 9 May 2024

DOI: 10.1002/jpn3.12251

JPGN

ORIGINAL ARTICLE

Gastroenterology: Celiac Disease

Outcome in pediatric celiac disease is independent of the diagnostic approach in patients with high antibody levels

Simon Klöti[1] | **Joachim Schaad**[1,2] | **Johannes Spalinger**[1,2] | **Susanne Schibli**[2] | **Lara Hart**[3] | **Christiane Sokollik**[2] | **Franziska Righini-Grunder**[1]

[1]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Children's Hospital of Central Switzerland, Lucerne, Switzerland

[2]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[3]Division of Pediatric Gastroenterology, Hepatology and Nutrition, McMaster University, Hamilton, Ontario, Canada

Correspondence

Simon Klöti, Children's hospital of Central Switzerland, Spitalstrasse 16, 6000 Luzern, Switzerland.
Email: simon.kloeti@uzh.ch

Abstract

Objectives: European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines enable the diagnosis of celiac disease (CD) without biopsies in patients with immunoglobulin A (IgA)-antibodies against tissue transglutaminase (TGA-IgA) ≥ 10× the upper limit of normal (ULN) and positivity of endomysial antibodies in a second blood sample. Limited data exist comparing the biopsy versus the nonbiopsy diagnostic approach regarding long-term outcomes in CD patients. Our study aimed to investigate the influence of the diagnostic approach on adherence to gluten-free diet (GFD), serological remission (defined as normalization of TGA-IgA during follow-up (FU)) and clinical remission in CD patients with TGA-IgA ≥ 10× ULN.

Methods: Retrospective multicenter study. Patients with CD and TGA-IgA ≥ 10× ULN at diagnosis were included in the study. Patients with confirmed diagnosis by biopsy were compared to patients diagnosed by nonbiopsy approach using univariate analysis, Kaplan–Meier survival curve, and logistic regression models.

Results: A total of 282 CD patients (192 [68.1%] in the biopsy group; 90 [31.9%] in the nonbiopsy group) were analyzed. The median time to normalization of TGA-IgA was 16.5 months [interquartile range, IQR: 13, 28] in the biopsy and 15 months [IQR: 12, 26] in the nonbiopsy group; $p = 0.14$). Rates of normalized TGA-IgA at first to third-year FU were comparable between both groups. Adherence to GFD did not seem to be influenced by the diagnostic approach.

Conclusions: The nonbiopsy approach is not inferior to the biopsy approach in terms of adherence to GFD and serological remission in patients with CD.

KEYWORDS

adherence to gluten-free diet, children, IgA-antibodies against tissue transglutaminase, nonbiopsy, serological remission

1 | INTRODUCTION

Confirmation of celiac disease (CD) in pediatric patients has traditionally been based on histological presence of villous atrophy and intraepithelial lymphocytic infiltrate. However, CD-specific antibody tests have improved significantly over the last decade, with high sensitivity and specificity of immunoglobulin A-antibodies against tissue transglutaminase (TGA-IgA) and endomysial antibodies (EMA-IgA).[1–3] In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published new guidelines, supporting a new, nonbiopsy approach to confirm diagnosis of CD.[4] Recently,

Simon Klöti and Joachim Schaad contributed equally to this study.

prospective trials have demonstrated reliability of antibody tests in diagnosing CD in children and adolescents.[5–7] In an international multicenter study, the positive predictive value for CD was greater than 99% in symptomatic patients with TGA-IgA ≥ 10× the upper limit of normal (ULN) and a positive EMA-IgA in a second blood sample.[8] Since 2020, the nonbiopsy approach is applicable even without consideration of clinical symptoms and genetic HLA-testing, if TGA-IgA is ≥10× ULN and confirmed by a positive EMA-IgA in an independent blood sample.[9]

One concern with the nonbiopsy approach may be the poor acceptance of the diagnosis by patients and families and the risk of nonadherence to a lifelong gluten-free diet (GFD), particularly in asymptomatic patients. From the patients and family perspective, a biopsy could provide more credibility and objectivity to the diagnosis. However, there is limited data available comparing the biopsy and nonbiopsy diagnostic approaches and their long-term outcomes. We hypothesized that the diagnostic approach does not have an impact on the adherence to GFD of patients with CD.

What is Known

- Latest guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition of 2020 recommend the nonbiopsy approach for all patients with immunoglobulin A (IgA)-antibodies against tissue transglutaminase (TGA-IgA) ≥ 10× the upper limit of normal (ULN) and positive endomysial antibodies in a second independent blood sample.
- Prospective trials have shown the reliability of antibody tests in diagnosing celiac disease (CD) in pediatrics.

What is New

- Outcome of patients during follow-up is independent of the diagnostic approach in CD patients with TGA-IgA ≥ 10× ULN.
- The nonbiopsy approach is not inferior to the biopsy approach in terms of adherence to gluten-free diet and serological remission.

2 | METHODS

2.1 | Study design and population

This is a retrospective cohort study of patients with CD who were followed in the outpatient clinics of two tertiary care centers for pediatric gastroenterology in Switzerland, Europe. Pediatric patients who presented either for new diagnosis of CD or for follow-up (FU) visit between January 1, 2017 and December 31, 2019 were eligible for this study. Patients who were selected based on an FU visit were analyzed retrospectively from the time of diagnosis (the earliest year of diagnosis of CD was 2002). Only patients with TGA-IgA ≥ 10× ULN at diagnosis were included in the study. Available FU data until June 2021 was included. We excluded patients older than 18 years, patients without TGA-IgA measurement within the inclusion period, patients with IgA-deficiency or patients without FU.

All patients with confirmed CD, TGA-IgA ≥ 10× ULN at diagnosis and with FU available were identified and separated into two groups: (a) patients diagnosed by biopsy (histologically confirmed CD) and (b) patients diagnosed by the nonbiopsy approach (CD exclusively confirmed by serology).

2.2 | Outcome measurements

Outcomes of patients in both diagnostic groups were compared. The primary endpoint was the rate of TGA-IgA normalization depending on adherence to GFD at each FU. Secondary endpoints included time to normalization of TGA-IgA over time, adherence to GFD, rate of clinical remission, and anthropometric data (*z* scores of weight and height) during FU.

To control for the different time periods within the FU, we grouped all clinical visits according to the time after diagnosis (first, second, and third year with a range of ±0.25 years). Clinical visits completed outside of that time were not included in the analysis.

Enzyme-linked immunosorbent assay (ELISA) (Thermo Fisher Scientific [Phadia] or Inova) or chemiluminescence (Bioflash, Inova Diagnostics, Werfen-Group) was used to analyze serum TGA-IgA. Normal values were determined based on the laboratory technique.

Symptoms were classified as either gastrointestinal or extra-intestinal, in accordance with recent ESPGHAN guidelines.[9] Anthropometric data was presented as *z* scores for weight and height at the time of diagnosis and FU's. To calculate *z* scores for weight and height, we used growth reference centile data from the working group of the University Children's Hospital Zurich,[10] following the LMS method of Cole and Green.[11] Biopsies were interpreted using the Marsh–Oberhuber classification[12]; histologically confirmed CD was defined as Marsh–Oberhuber classification type 2 or higher. Adherence to GFD was evaluated during every outpatient visit in a semistructured manner by either a pediatric gastroenterologist or a pediatric dietician. Adherence was categorized into three groups "good," "moderate," and "poor" (good was defined as having no accidental gluten exposures,

moderate as having less than five accidental gluten exposures per year, poor as having five or more accidental gluten exposures per year). Clinical remission was defined as complete resolution of all initial symptoms related to the diagnosis of CD, with a symptom-free period of at least 3 months before the FU visit. The description of symptoms was collected from the medical chart, as reported by the treating physician.

2.3 | Statistical analysis

Data is presented as median [Q1, Q3] for continuous variables and as frequency (%) for qualitative variables. Univariate analysis is performed by Wilcoxon rank sum test, Fisher's exact, or χ^2 test. Kaplan–Meier (KM) survival curve is used to study the probability of normalization of TGA-IgA values over time. Time to event was considered as the time between date of diagnosis of CD and the date of normalization of TGA-IgA. Only first events were represented in the KM curve. A subanalysis was conducted to ensure that baseline TGA-IgA levels were equal in both diagnostic groups at the time of diagnosis. The association between the type of diagnostic approach and TGA-IgA normalization at each FU was estimated using multiple regression. An adjusted model was used with controlling for potentially associated factors (GFD adherence, clinical remission, age at diagnosis and duration of FU). The limitation of 1 variable per 10 included subjects was respected. Akaike information criterion value was used to choose the model with the best fit. All analyses were performed using SAS software, version 9.3 (SAS Institute); all statistical tests were two-sided. $p < 0.05$ were considered statistically significant for all analyses.

3 | RESULTS

A total of 451 patients with confirmed CD were identified, of which 12 patients (2.7%) had an IgA-deficiency. At diagnosis, 286 patients had a level of TGA-IgA ≥ 10× ULN. Four patients were lost to FU, the remaining 282 patients were included for further analysis. The study flowchart is depicted in Figure 1. Dates of CD diagnosis ranged from 2002 to 2019. From 2012 to 2019, 237 patients (83%) received a diagnosis (147 patients by biopsy and 90 by nonbiopsy), while 49 patients (17%) were diagnosed before 2012 (45 patients by biopsy and 4 by nonbiopsy).

3.1 | Analysis at the time of diagnosis

CD patients with TGA-IgA ≥ 10× ULN at diagnosis were further analyzed. A total of 194 patients diagnosed by biopsy were compared to 92 patients in the nonbiopsy group (Table 1). At diagnosis, there was no significant difference in the following factors: gender, age, height, weight, presence of co-morbidities, family history of CD, and iron intake or vitamin D supplementation. The biopsy approach was the more frequent method of diagnosis for asymptomatic patients or patients with exclusively extraintestinal symptoms compared to the nonbiopsy

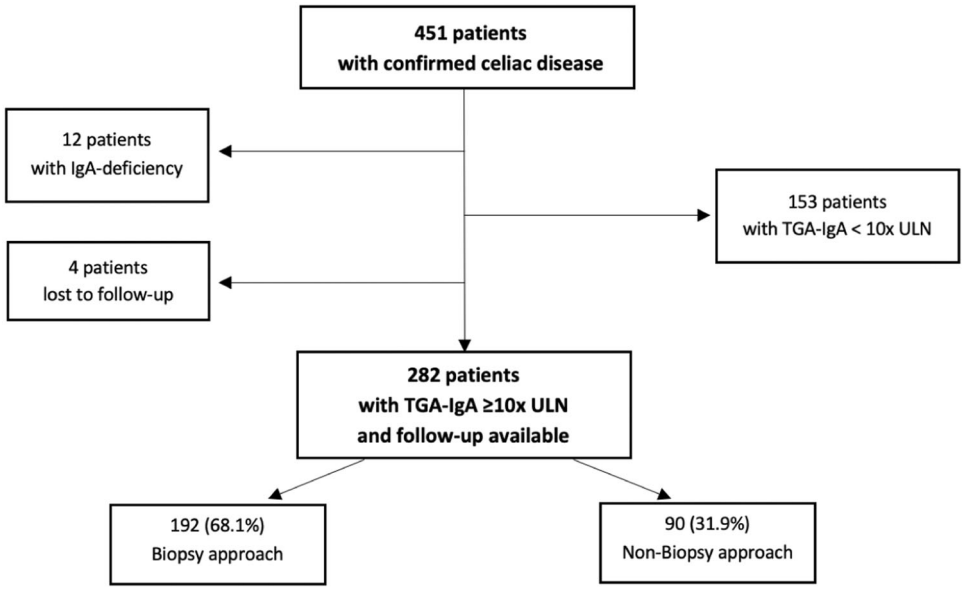

FIGURE 1 Flowchart of selected study population. TGA-IgA, immunoglobulin A-antibodies against tissue transglutaminase; ULN, upper limit of normal.

TABLE 1 CD patients with TGA-IgA ≥ 10× ULN at diagnosis; comparison of the biopsy and nonbiopsy groups.

	Biopsy group, *n* = 194	Nonbiopsy group, *n* = 92	OR [95% CI]	*p* Value
Gender				
Males	68 (35%)	35 (38%)	0.9 [0.5, 1.5]	0.62
Females	126 (65%)	57 (62%)		
Age at diagnosis, years	6.3 [3.4, 9.8]	5.3 [3.4, 9.7]	–	0.50
Associated co-morbidities				
No	174 (90%)	85 (92%)	1.4 [0.6, 3.4]	0.46
Yes[a]	20 (10%)	7 (8%)		
Family history				
No	153 (79%)	67 (73%)	–	0.56
Yes, first degree relative	31 (16%)	21 (23%)		
Yes, second degree relative	10 (5%)	4 (4%)		
Symptoms at diagnosis, *n*	193	91		
Exclusively gastrointestinal symptoms	32 (17%)	20 (22%)	–	0.0011
Exclusively extraintestinal symptoms	44 (23%)	5 (5%)		
Gastro- and extraintestinal symptoms	103 (53%)	63 (69%)		
No symptoms	14 (7%)	3 (3%)		
Weight, *z* score	−0.3 [−1.0, 0.3]	−0.5 [−0.9, 0.3]	–	0.61
Height, *z* score	−0.3 [−1.0, 0.4]	−0.4 [−1.1, 0.4]	–	0.80
Medication intake				
Iron supplementation	34 (18%)	15 (16%)	1.1 [0.6, 2.2]	0.76
Vitamin D supplementation	6 (3%)	4 (4%)	0.7 [0.2, 2.6]	0.61
Serological workup, *n*	52	92		
EMA-IgA positivity	52 (100%)	92 (100%)	–	1.0[b]
Laboratory workup				
Hb (g/L)	124 [112, 133]	119 [112, 131]	–	0.14
n	178	79		
MCV (fL)	77 [73, 80]	77 [71, 81]	–	0.82
n	172	78		
MCH (pg)	26 [24, 28]	26 [23, 28]	–	0.40
n	171	77		
Ferritine (µg/L)	14 [5,32]	10 [4, 25]	–	0.33
n	88	39		
Tc (G/L)	327 [281, 410]	361 [281, 450]	–	0.31

TABLE 1 (Continued)

	Biopsy group, $n = 194$	Nonbiopsy group, $n = 92$	OR [95% CI]	p Value
n	174	77		
Lc (G/L)	7.3 [6.0, 8.6]	6.9 [5.5, 8.3]	–	0.12
n	175	78		

Note: Data represented as frequency (%) for qualitative variables and as median (interquartile Q1, Q3) for continuous variables.

Abbreviations: CI, confidence interval; EMA-IgA, endomysial antibodies; Hb, hemoglobin; Lc, leukocytes; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; OR, odds ratio; Tc, thrombocytes; TGA-IgA, immunoglobulin A-antibodies against tissue transglutaminase; ULN, upper limit of normal.

[a]Diabetes mellitus type 1, Down syndrome, autoimmune thyroid disease, Autoimmune polyglandular syndrome type 2, Williams–Beuren syndrome.

[b]Use of Fisher's exact test.

approach ($p = 0.0011$). The main laboratory findings (hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, ferritin) at the time of diagnosis were comparable between the groups.

3.2 | FU analysis

A total of 282 patients underwent at least one FU. Median duration of total FU was 3.4 years [2.1, 7.3; maximum 16.3] in the biopsy and 2.1 years [1.1, 3.4; maximum 10.8] in the nonbiopsy group ($p < 0.0001$). Univariate analysis showed that time to normalization of TGA-IgA was comparable in both groups (16.5 months [13, 28] in the biopsy group and 15 months [12, 26] in the nonbiopsy group; $p = 0.14$). The KM curve illustrates the probability of TGA-IgA normalization over time (Supporting Information S1: Figure 1).

Table 2 shows the comparison of yearly FU results between the biopsy and the nonbiopsy groups. Rates of normalized TGA-IgA at yearly FU were similar. A significant difference in terms of complete clinical remission on a GFD was observed at the first-year FU, with 77% of patients in the biopsy group achieving remission to 62% in the nonbiopsy group, $p = 0.03$). However, no difference was seen at the second- and third-year FU. Regarding adherence to GFD, we found no significant difference during FU.

On multivariable logistic regression analysis, older age proved to be associated with a lower rate of normalized TGA-IgA values at the first-year FU (odds ratio: 0.91 [0.85, 0.98]; $p = 0.01$). The rates of TGA-IgA normalization were not significantly influenced by the diagnostic approach (biopsy vs. nonbiopsy group), adherence to GFD, or clinical response on a GFD. Results on the second- and third-year FU did not differ from those of the first FU.

4 | DISCUSSION

Our study compared 192 CD patients diagnosed by biopsy to 90 patients diagnosed by the nonbiopsy approach with TGA-IgA values ≥ 10× ULN at diagnosis. The results indicate that the diagnostic approach does not significantly influence the adherence to GFD of patients with CD. Specifically, the rate of TGA-IgA normalization at each FU was comparable in both diagnostic groups.

Our primary endpoint was the rate of TGA-IgA normalization depending on adherence to GFD during FU. We found only one study published with similar primary endpoints. This prospective cohort study with 143 pediatric patients, followed over a 3 years period, found no differences between the biopsy and the nonbiopsy group in terms of clinical remission, adherence to GFD, and serological remission.[13] Our study supports these findings, as we did not observe any differences between the biopsy and nonbiopsy groups during FU considering the investigated primary endpoint. With 80% of patients with normalized TGA-IgA after 1 year on a GFD, this study had even a higher remission rate compared to our study with 41%. One possible explanation for this difference might be our study design, including only children with very high TGA-IgA values, taking naturally longer to become negative. Additionally, the prospective study design of Benelli et al. with strictly scheduled visits and shorter control intervals may have contributed to better control of diet adherence.

In other pediatric studies, rates of TGA-IgA normalization were comparable to our study after 1 year on GFD (45%–55%).[14,15] Including only patients with TGA-IgA values ≥ 10× ULN at diagnosis, we state that our study provides a more precise depiction of the rates of TGA-IgA normalization during FU in this particular population of CD patients. Based on our findings, it is likely that the normalization rate in CD patients with TGA-IgA ≥ 10× ULN after 1 year on GFD is lower than in some previously published studies.[16,17]

There are existing studies which have shown that TGA-IgA values ≥ 10× ULN at diagnosis are associated with a significantly longer time to TGA-IgA normalization compared to TGA-IgA values < 10× ULN.[14,16,18,19]

Regarding the influence of adherence to GFD on TGA-IgA normalization, we found studies which identified poor adherence to GFD as a significant factor for

TABLE 2 CD patients with TGA-IgA ≥ 10× ULN and yearly follow-up available; comparison of the biopsy and the nonbiopsy groups.

	Biopsy group	Nonbiopsy group	OR [95% CI]	*p* Value
First-year follow-up	154 patients	70 patients		
Age, years	7.5 [4.6, 11.3]	6.3 [4.5, 10.7]	–	0.35
Time from diagnosis to follow-up, years	1.1 [1.0, 1.2]	1.1 [1.0, 1.1]	–	0.23
Clinical response, *n*	151	69		
Clinical remission	116 (77%)	43 (62%)	–	0.03[a]
Gluten-free diet adherence, *n*	151	69		
Good (no accidental gluten exposures)	82 (54%)	47 (68%)	–	0.10[a]
Moderate (<5 accidental gluten exposures per year)	39 (26%)	17 (25%)	–	
Poor (≥5 accidental gluten exposures per year)	30 (20%)	5 (7%)	–	
Weight, *z* score	0.0 [−0.8, 0.8]	0.1 [−0.7, 0.6]	–	0.99
Height, *z* score	0.0 [−0.8, 0.5]	−0.3 [−0.9, 0.4]	–	0.48
Laboratory results, *n*	154	70		
Normalization of TGA-IgA	65 (42%)	27 (39%)	1.2 [0.7, 2.1]	0.61
Elevated TGA-IgA	89 (58%)	43 (61%)		
Second -year follow-up	78 patients	29 patients		
Age, years	7.8 [4.9, 11.5]	7.0 [5.1, 12.5]	–	0.97
Time from diagnosis to follow-up, years	2.1 [2.0, 2.2]	2.1 [1.9, 2.1]	–	0.17
Clinical response, *n*	78	29		
Clinical remission	63 (81%)	23 (79%)	–	0.84[a]
Gluten-free diet adherence, *n*	78	29		
Good (no accidental gluten exposures)	47 (60%)	23 (79%)	–	0.27[a]
Moderate (<5 accidental gluten exposures per year)	19 (24%)	5 (17%)	–	
Poor (≥5 accidental gluten exposures per year)	12 (15%)	1 (3%)	–	
Weight, *z* score	0.0 [−0.6, 0.7]	0.0 [−0.8, 0.5]	–	0.43
Height, *z* score	0.0 [−0.9, 0.6]	−0.3 [−0.8, 0.3]	–	0.70
Laboratory results, *n*	78	29		
Normalization of TGA-IgA	49 (63%)	17 (59%)	1.2 [0.5, 2.8]	0.69
Elevated TGA-IgA	29 (37%)	12 (41%)		
Third-year follow-up	71 patients	24 patients		
Age, years	9.2 [6.8, 12.8]	8.3 [6.6, 12.8]	–	0.78
Time from diagnosis to follow-up, years	3.1 [3.0, 3.2]	3.1 [3.0, 3.1]	–	0.27

TABLE 2 (Continued)

	Biopsy group	Nonbiopsy group	OR [95% CI]	*p* Value
Clinical response, *n*	71	24		
Clinical remission	60 (85%)	20 (83%)	–	1.0[a]
Gluten-free diet adherence, *n*	71	24		
Good (no accidental gluten exposures)	39 (55%)	17 (71%)	–	0.51[a]
Moderate (<5 accidental gluten exposures per year)	12 (17%)	4 (17%)	–	
Poor (≥5 accidental gluten exposures per year)	20 (28%)	3 (13%)	–	
Weight, *z* score	−0.1 [−0.6, 0.9]	−0.2 [−0.9, 0.7]	–	0.58
Height, *z* score	−0.1 [−0.5, 0.7]	−0.1 [−0.9, 0.9]	–	0.98
Laboratory results, *n*	71	24		
Normalization of TGA-IgA	52 (73%)	17 (71%)	1.1 [0.4, 3.1]	0.82
Elevated TGA-IgA	19 (27%)	7 (29%)		

Note: Data represented as frequency (%) for qualitative variables and as median (interquartiles Q1, Q3) for continuous variables. All clinical visits were grouped by time after diagnosis (first, second, and third year with a range of ±0.25 years). Clinical visits completed outside of that time were not included in the analysis.

Abbreviations: CD, celiac disease; CI, confidence interval; OR, odds ratio; TGA-IgA, immunoglobulin A-antibodies against tissue transglutaminase; ULN, upper limit of normal.

[a]Use of Fisher's exact test.

longer time to normalization.[16,19] In a prospective study by Pedoto et al., questionnaires adapted to pediatric population were used for assessment of adherence to GFD.[20] The biopsy group demonstrated better adherence to GFD than the nonbiopsy group ($p = 0.036$). However, only one-sixth of all patients were diagnosed using the nonbiopsy approach, which makes an interpretation of those results difficult. In our study adherence to GFD did not differ between the groups and did not appear to significantly influence the rate of TGA-IgA normalization. It should be noted that a gold standard method for assessing dietary compliance is still lacking and verifying adherence to GFD during FU remains a challenge.[21]

Previously studies have identified older age at diagnosis as an independent predictor for a longer time to normalization of TGA-IgA.[14,17] This finding may be explained by a decrease in adherence to GFD during puberty.[20] Our study confirms that older age at diagnosis is associated with a longer time to TGA-IgA normalization, which was observed in both diagnostic groups. This indirectly supports our finding that both approaches lead to comparable outcomes.

In terms of clinical remission rate, our study did not show a significant association between clinical remission rate and higher rates of TGA-IgA normalization, using logistic regression analysis. Similar to our study, Benelli et al. found no difference in regard to clinical remission rates during FU between the biopsy and nonbiopsy groups.[13] They reported a clinical remission rate of more than 90% after 1 year on GFD in both groups. Comparison of the different studies concerning the remission rate of clinical symptoms during FU is difficult because a standardized definition of clinical remission is missing.

Our study has some limitations. The study groups were of different sizes with more patients diagnosed by the biopsy approach. This may be due to a delay in adopting the revised ESPGHAN guidelines in the clinical setting. This was not surprising, especially when a paradigm is changed dramatically.

The two diagnostic groups also had different FU durations and we therefore compared both groups at each yearly FU. Additionally, logistic regression analysis was performed for each FU to control for this potential bias. Analysis was stopped after the third FU due to the loss of patients and subsequent reduction in statistical power.

As this study was retrospective, standardized and validated questionnaires could not be used to assess GFD adherence in our patients. Questionnaires are recommended to evaluate patients' adherence to GFD in addition to dietary interview in daily clinical practice, as stated in the ESPGHAN position paper.[22]

In conclusion, our study indicates that the type of diagnostic approach does not affect the outcome of CD patients. In particular, we provide more evidence that the resolution of symptoms, adherence to GFD, and

normalization of TGA-IgA are not influenced by the type of diagnostic approach. Our findings support the use of the nonbiopsy approach in clinical practice, in accordance with the ESPGHAN guidelines. The possibility of omitting a biopsy for diagnosing CD might lower the burden of endoscopy, save healthcare costs, and allow an earlier start on GFD.

ACKNOWLEDGMENTS

The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Ethical approval was obtained (project-ID 2021-00014; use of health-related personal data for research without consent pursuant to Article 34 HRA).

REFERENCES

1. Rostom A, Dubé C, Cranney A, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. *Gastroenterology*. 2005;128:S38-S46.
2. Sheppard AL, Elwenspoek MMC, Scott LJ, et al. Systematic review with meta-analysis: the accuracy of serological tests to support the diagnosis of coeliac disease. *Aliment Pharmacol Ther*. 2022;55:514-527.
3. Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology*. 2005;128:S25-S32.
4. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr*. 2012;54:136-160.
5. Wolf J, Petroff D, Richter T, et al. Validation of antibody-based strategies for diagnosis of pediatric celiac disease without biopsy. *Gastroenterology*. 2017;153:410-419.
6. Vivas S, Morales JGR, Riestra S, et al. Duodenal biopsy may be avoided when high transglutaminase antibody titers are present. *World J Gastroenterol*. 2009;15:4775-4780.
7. Mubarak A. Tissue transglutaminase levels above 100 U/mL and celiac disease: a prospective study. *World J Gastroenterol*. 2012;18:4399-4403.
8. Werkstetter KJ, Korponay-Szabó IR, Popp A, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. *Gastroenterology*. 2017;153:924-935.
9. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70:141-156.
10. Braegger C, Jenni O, Konrad D, et al. Neue Wachstumskurven für die Schweiz. *Paediatrica*. 2011;22:9-11.
11. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med*. 1992;11:1305-1319.
12. 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.
13. Benelli E, Carrato V, Martelossi S, Ronfani L, Not T, Ventura A. Coeliac disease in the ERA of the new ESPGHAN and BSPGHAN guidelines: a prospective cohort study. *Arch Dis Child*. 2016;101:172-176.
14. Sansotta N, Alessio MG, Norsa L, et al. Trend of antitissue transglutaminase antibody normalization in children with celiac disease started on gluten-free diet: a comparative study between chemiluminescence and ELISA serum assays. *J Pediatr Gastroenterol Nutr*. 2020;70:37-41.
15. Esch CEH, Wolters VM, Gerritsen SAM, et al. Specific celiac disease antibodies in children on a gluten-free diet. *Pediatrics*. 2011;128:547-552.
16. Sbravati F, Cosentino A, Lenzi J, et al. Antitissue transglutaminase antibodies' normalization after starting a gluten-free diet in a large population of celiac children-a real-life experience. *Dig Liver Dis*. 2022;54:336-342.
17. Kori M, Goldstein S, Hofi L, Topf-Olivestone C. Adherence to gluten-free diet and follow-up of pediatric celiac disease patients, during childhood and after transition to adult care. *Eur J Pediatr*. 2021;180:1817-1823.
18. Gidrewicz D, Trevenen CL, Lyon M, Butzner JD. Normalization time of celiac serology in children on a gluten-free diet. *J Pediatr Gastroenterol Nutr*. 2017;64:362-367.
19. Isaac DM, Rajani S, Yaskina M, Huynh HQ, Turner JM. Antitissue transglutaminase normalization postdiagnosis in children with celiac disease. *J Pediatr Gastroenterol Nutr*. 2017;65:195-199.
20. Pedoto D, Troncone R, Massitti M, Greco L, Auricchio R. Adherence to gluten-free diet in coeliac paediatric patients assessed through a questionnaire positively influences growth and quality of life. *Nutrients*. 2020;12:3802.
21. Wieser H, Ruiz-Carnicer Á, Segura V, Comino I, Sousa C. Challenges of monitoring the gluten-free diet adherence in the management and follow-up of patients with celiac disease. *Nutrients*. 2021;13:2274.
22. Mearin ML, Agardh D, Antunes H, et al. ESPGHAN position paper on management and follow-up of children and adolescents with celiac disease. *J Pediatr Gastroenterol Nutr*. 2022;75:369-386.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Klöti S, Schaad J, Spalinger J, et al. Outcome in pediatric celiac disease is independent of the diagnostic approach in patients with high antibody levels. *J Pediatr Gastroenterol Nutr*. 2024;1-8. https://doi:10.1002/jpn3.12251