Follow-up of adult celiac patients: which noninvasive test reflects mucosal status most reliably?[1]

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Background and study aims: The best mode of follow-up in celiac disease has not yet been established. The intention of this study was to clarify which noninvasive follow-up investigation – serological tests or intestinal permeability test (IPT) – correlates best with histology and whether the interval between diagnosis and follow-up affects the accuracy of these tests.

Patients and methods: Data from adult patients with celiac disease (diagnosed between December 1989 and July 2006) followed up with biopsy, IPT, and serological tests [IgG anti-gliadin antibodies (AGA-IgG), AGA-IgA, and endomysial antibodies (EMA)] were retrieved from a computerized database. Results of noninvasive tests were compared with the persistence of villous atrophy on biopsy. Patients were divided into groups A, which comprised patients followed up within 2 years after diagnosis, and B, comprising patients followed up later than 2 years.

Results: Forty-seven patients were evaluable. The lactulose/mannitol (L/M) ratio had a sensitivity of 85 % and a specificity of 46.2 % for mucosal atrophy, whereas saccharose excretion showed a sensitivity of 60 % and a specificity of 52.6 %. The sensitivities of AGA-IgA and AGA-IgG were 15 % and 20 %, respectively, while specificity was 100 % for both. Validity of AGA was limited due to low number of positive results. EMA assay was 50 % sensitive and 77.8 % specific. In group A (n = 23) L/M ratio performed best in terms of sensitivity (88.9 %), whereas EMA achieved a higher specificity (71.4 %). In group B, the sensitivity of the L/M ratio decreased to 85.7 %, while the specificity of EMA increased to 91.7 %.

Conclusions: In this study, none of the noninvasive tests was an accurate substitute for follow-up biopsy in detecting severe mucosal damage.

Introduction

Celiac disease is an autoimmune disorder requiring a gluten-free diet (GFD) for life if acute and chronic complications are to be avoided [1]. Achieving patient adherence to a GFD is difficult in some cases, because drastic changes in eating habits are required.

Serological tests have become important screening tools for celiac disease in the past 20 years. However, diagnosis is still based on histological criteria [1]. The use of anti-gliadin antibodies (AGA) is problematic due to the extremely low specificity of AGA-IgG and low sensitivity of AGA-IgA. For this reason AGA are no longer important in the diagnosis of celiac disease [2], but they could be useful in patients already established as having celiac disease, to monitor their adherence to a GFD, since these antibodies are prone to reappear even after slight dietary transgressions [3]. In these situations, anti-endomysial antibodies (EMA) are less sensitive [4]. Regarding the use of IgA anti-tissue-transglutaminase antibodies (anti-tTG), various studies have given contradictory results. Hansson et al. found that anti-tTG are reliable indicators of even brief dietary transgressions [5], whilst Vahedi et al. challenged their usefulness in monitoring GFD adherence [6].

Among other noninvasive tests, the intestinal permeability test (IPT) using orally administered inert sugars such as lactulose and mannitol turned out to be an unreliable screening tool in children at diagnosis of celiac disease [7] because

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of its low specificity for discriminating between healthy subjects and those with celiac disease. However, for follow-up in adults IPT recently was proven superior to AGA-IgA in detecting persistent mucosal alterations during a GFD [8]. Furthermore, intestinal permeability normalizes in the majority of individuals with celiac disease who are on a strict GFD. Gluten ingestion as measured by a 3-day food record correlates with changes in the IPT [9]. Nevertheless, biopsy remains the gold standard for monitoring the effect of a GFD. The value of noninvasive tests for follow-up of celiac disease after gluten withdrawal can only be assessed by comparison with simultaneously conducted biopsies [10].

Therefore, the aim of this study was to investigate which noninvasive test best reflects the mucosal status by comparing the results of serology and IPT with histology on follow-up. In addition, we addressed the question: Does the performance of various noninvasive tests vary with the length of the interval between diagnosis and follow-up?

Patients and methods

Subjects

Data regarding all patients diagnosed with celiac disease at the Department of Gastroenterology, Medical University of Vienna, between December 1989 and July 2006, and followed by dietary history, clinical examination, and blood tests including celiac serology and IPT were retrieved from a computerized database. Serology and permeability testing was performed in all patients regularly on a yearly basis, whereas re-biopsies were not part of their routine follow-up. Only in the case of persistent EMA positivity (> 1 year), suspected noncompliance, dietary resistance, or silent celiac disease at diagnosis, or else at their own request, did patients undergo repeat endoscopy at irregular intervals [11]. For final analysis, only patients with biopsy-proven celiac disease followed by biopsy and simultaneous noninvasive tests were included.

Patients were divided into two groups (A, B) according to follow-up time. Patients allocated to group A were followed for up to 2 years after diagnosis, patients from group B for longer. Subgroups were defined in respect of normal villous architecture (groups A1 and B1) and persistent mucosal damage (groups A2 and B2) on follow-up histology.

Dietary assessment

Adherence to a GFD was assessed by a physician at follow-up. Patients were classified as either keeping a strict GFD or admitting dietary transgressions at least once a month.

Biopsy

Upper gastrointestinal endoscopy was performed using an Olympus gastroscope with an Endoflex KF225B (Endoflex, Voerde, Germany) and Olympus FB24K-1 Forceps (Olympus Austria, Vienna, Austria) with an open-cup diameter of 7 mm. Four biopsies were taken from the second part of the duodenum and two from the bulb, the latter having shown equal or superior diagnostic value to more distal biopsies [12].

The intestinal biopsy specimens were fixed in 4% phosphate-buffered formalin (pH 7.4) for histological analysis. Celiac disease was diagnosed according to modified ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology, and Nutrition) criteria [13]. Morphological characteristics of the crypts and villi and the number of intraepithelial lymphocytes (IEL) were included in the report. The stages of histological changes were classified using a modified Marsh classification [14].

Serology

EMA-IgA levels were determined by an immunofluorescence assay using monkey esophagus sections (Biosystems, Barcelona, Spain) according to the manufacturer's instructions. Sera were tested starting with a screening dilution of 1 : 10. Results were rated as positive if an apple-green luminescent fluorescence pattern of the intermyofibril substance of the smooth muscle was observed. All slides were assessed by the same experienced observer.

AGA-IgA levels were measured by enzyme-linked immunosorbent assay (ELISA) (1989 – 2003: Gluten IgA EIA, Pharmacia GmbH Diagnostics, Freiburg, Germany; 2003 – 2005: Pharmacia CAP System, Uppsala, Sweden; since 2005: QUANTA Lite Gliadin IgA, Inova Diagnostics, Inc., San Diego, USA). Cut-offs were 25 U/ml, 2.5 U/ml, and 30 U/ml, respectively for the three different assays.

AGA-IgG levels were assessed by ELISA (materials sourced as for AGA-AgA). Cut-offs were 25 U/ml, 25 U/ml, and 30 U/ml, respectively.

Intestinal permeability test

A sugar test solution containing 20 g saccharose, 10 g lactulose, and 5 g mannitol dissolved in 100 ml water was administered to the patients. Lactulose and mannitol concentrations in a 5-hour urine collection were measured by high-performance liquid chromatography as previously described [15]. An L/M ratio above 0.03 was considered a positive test result indicating increased intestinal permeability. For gastroduodenal permeability, the urinary concentration of saccharose was determined by UV spectrometry (Sucrose/D-Glucose/D-Fructose UV Test Assay, Boehringer Mannheim, Mannheim, Germany) [16]. Values above 43 mg were indicative of increased gastroduodenal permeability.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows 15.0. The x^2 test was used for comparison of frequencies (positivity of various tests, gender) between groups A and B. The results of noninvasive tests were evaluated by calculating specificity, sensitivity, PPV, and NPV for the detection of villous atrophy with binomial 95 % exact confidence intervals (CI). For comparison of permeability parameters, the Mann–Whitney *U* test was performed. A *P*-value less than 0.05 was considered statistically significant.

Results

Study population

Between December 1989 and July 2006, 305 patients were diagnosed with celiac disease (80 men and 225 women, mean age at diagnosis 38.9 ± 16.6 years, median age 36 years, age range 16 – 84 years). Of these 305 patients, 250 attended for at least one follow-up in our clinic. Out of the 250, 47 (16 men and 31 women, mean age 44.1 ± 14.7 years, median age 45 years, age range 16 – 74 years) with follow-up biopsies and simultaneously performed IPT were eligible for final analysis. None of these had IgA deficiency. On histological examination, 57.5 % showed complete villous recovery.

Table 1 Results of histological analysis and noninvasive tests at diagnosis and at follow-up in relation to adherence to gluten-free diet and positivity of noninvasive results regarding persistence of villous atrophy in group A (follow-up within 2 years).

	At diagnosis		At follow up				*P*-value
			Group A1 *		Group A2†		
	n	%	n	%	n	%	
Strict GFD[1] upon inquiry	0 / 23	0	12 / 14	85.7	7 / 9	77.8	0.624
Histology *(Marsh ≥ 3)*	23 / 23	100	0 / 14	0	9 / 9	100	nd
EMA[1]	19 / 23	82.6	4 / 14	28.6	6 / 9	66.7	0.072
AGA-IgG[1]	1 / 20	5	0 / 13	0	3 / 9	33.3	0.025
AGA-IgA[1]	1 / 20	5	0 / 13	0	2 / 9	22.2	0.075
L/M ratio[1]	20 / 21	95.2	8 / 14	57.1	8 / 9	88.9	0.106
Saccharose	9 / 10	90	3 / 7	42.9	2 / 3	66.7	0.490

[1]GFD, gluten-free diet; EMA, endomysial antibodies; AGA, antigliadin antibodies; L/M, lactulose/mannitol ratio.
*Normal villous architecture.
† Persistent villous atrophy.

Table 2 Results of histological analysis and noninvasive tests at diagnosis and at follow-up in relation to adherence to gluten-free diet and positivity of noninvasive results regarding persistence of villous atrophy in group B (follow-up after 2 years).

	At diagnosis		At follow up				*P*-value
			Group B1 *		Group B2†		
	n	%	n	%	n	%	
Strict GFD[1] upon inquiry	0 / 27	0	10 / 13	76.9	7 / 14	50	0.075
Histology *(Marsh ≥ 3)*	27 / 27	100	0 / 13	0	14 / 14	100	nd
EMA[1]	23 / 27	85.2	1 / 12	8.3	8 / 14	57.1	0.009
AGA-IgG[1]	4 / 23	17.4	0 / 11	0	3 / 13	23.1	0.089
AGA-IgA[1]	3 / 23	13	0 / 11	0	3 / 13	23.1	0.089
L/M ratio[1]	22 / 25	88	10 / 13	76.9	12/14	85.7	0.557
Saccharose	13 / 15	86.7	7 / 11	63.6	7 / 12	58.3	0.795

[1]GFD, gluten-free diet; EMA, endomysial antibodies; AGA, antigliadin antibodies; L/M, lactulose/mannitol ratio.
*Normal villous architecture.
† Persistent villous atrophy.

Patients were further subdivided into two groups according to the interval between diagnosis and follow-up. Three patients had two or more follow-up biopsies and were allocated to both groups. The results of the first follow-up within each follow-up period were evaluated.

Group A (interval from diagnosis to follow-up ≤ 2 years, median 15 months, range 1 – 24 months) consisted of 23 patients (7 men and 16 women, mean age 38.5 ± 18.0 years, median age 40 years, age range 16 – 74 years). Group B (interval from diagnosis to follow-up > 2 years, median 40 months, age range 26 – 91 months) consisted of 27 patients (12 men and 15 women, mean age 44.52 ± 16.1 years, median age 47 years, age range 17 – 74 years). Fourteen group A patients (60.9 %) had normal or mildly altered mucosa (group A1); the remaining 9 exhibited persistent villous atrophy (group A2). Group B1 consisted of 13 patients (48.6 %) with Marsh stage 0 – 2 disease while group B2 comprised 14 individuals. No difference in persistence of villous atrophy was found between group A and group B ($P = 0.407$). A strict GFD was not adhered to by 17.4 % of group A and 34.6 % of group B ($P = 0.173$). Similarly, no differences of adherence to GFD were found in subgroup analysis (group A1 vs. A2 and B1 vs. B2; $P = 0.624$ and 0.075, respectively) (**Table 1** and **2**).

Results of noninvasive tests at diagnosis and follow-up

At diagnosis, L/M ratio, saccharose, and EMA proved to be most sensitive (91.3 %, 88 % and 84 %, respectively) for detecting mucosal atrophy (Marsh ≥ 3).

On follow-up, L/M ratio and saccharose values were lower than the pre-GFD values (median 0.053 vs. 0.177, $P = < 0.001$; and median 43 vs. 88 mg, $P = 0.038$, respectively).

In addition, patients with normal villous architecture had a lower L/M ratio than those with persistent villous atrophy, whereas saccharose showed no difference (**Tables 1** and **3**). However, there was no difference between these patients in the rate of positivity for both IPT parameters. Regarding late follow-up, only EMA reliably discriminated between villous atrophy and normal villous architecture (group B1 vs. B2, $P = 0.009$) (**Table 2**).

Test characteristics of noninvasive tests on follow-up

The sensitivity of the L/M ratio decreased from 88.9 % at early to 85.7 % at late follow-up, whereas the specificity of EMA increased from 71.4 % to 91.7 % (**Table 4**).

Table 3 Comparison of results of intestinal permeability test with respect to persistence of villous atrophy in all patients with follow-up biopsies, in group A (follow-up within 2 years), and group B (follow-up after 2 years).

	Marsh stage ≤ 2		Marsh stage ≥ 3		*P*-value
	Median	IR	Median	IR	
All patients with follow-up biopsies					
L/M	0.032	0.043	0.115	0.145	0.001
Saccharose, mg	40.5	51	56	42	0.279
Group A					
L/M	0.033	0.048	0.110	0.090	0.004
Saccharose, mg	37	90	43	49	0.909
Group B					
L/M	0.066	0.188	0.146	0.145	0.593
Saccharose, mg	68	78	44.5	41	0.902

IR, interquartile range, L/M, lactulose/mannitol ratio.

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value with 95 % confidence intervals of noninvasive follow-up procedures in all patients with follow-up biopsies, in group A (follow-up within 2 years) and group B (follow-up after 2 years).

	Sensitivity		Specificity %		NPV %		PPV %	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
Total study population								
EMA	50	27.2 – 72.8	77.8	57.7 – 91.4	67.7	48.6 – 83.3	62.5	35.4 – 84.8
AGA-IgG	20	5.7 – 43.7	100	86.6 – 100	61.9	45.6 – 76.4	100	39.8 – 100
AGA-IgA	15	3.2 – 37.9	100	86.6 – 100	60.5	44.4 – 75.0	100	29.2 – 100
L/M	85	62.1 – 96.8	46.2	26.6 – 66.6	80	51.9 – 95.7	54.84	36.0 – 72.7
Saccharose	60	32.3 – 83.7	52.6	28.9 – 75.6	62.5	35.4 – 84.8	50	26.0 – 74.0
Group A								
EMA	66.6	29.2 – 92.5	71.4	41.9 – 91.6	76.9	46.2 – 95.0	60	26.2 – 87.8
AGA-IgG	33.3	7.5 – 70.1	100	75.3 – 100	68.4	43.5 – 87.4	100	29.2 – 100
AGA-IgA	22.2	2.8 – 60	100	75.3 – 100	65	40.8 – 84.6	100	15.8 – 100
L/M ratio	88.9	51.8 – 99.7	42.9	17.7 – 71.1	85.7	42.1 – 99.6	50	24.7 – 75.4
Saccharose	66.7	9.4 – 99.2	57.1	10.9 – 69.2	80	28.4 – 99.5	40	5.3 – 85.3
Group B								
EMA	57.1	28.9 – 82.3	91.7	61.5 – 99 – 8	64.7	38.3 – 85.8	88.9	51.8 – 99.7
AGA-IgG	23.1	5.0 – 53.8	100	71.5 – 100	52.4	29.8 – 74.3	100	29.2 – 100
AGA-IgA	23.1	5.0 – 53.8	100	71.5 – 100	52.4	29.8 – 74.3	100	29.2 – 100
L/M ratio	85.7	57.2 – 98.2	23.1	5 – 53.8	60	14.4 – 94.7	45.5	32.2 – 75.6
Saccharose	58.3	27.7 – 84.8	36.4	10.9 – 69.2	44.4	13.7 – 78.8	50	23.0 – 77.0

NPV, negative predictive value; PPV, positive predictive value; EMA, endomysial antibodies; AGA, antigliadin antibodies; L/M, lactulose/mannitol.

Influence of age on follow-up histology and permeability tests

No difference was found between older and younger patients (> 45 years, n = 26 vs. < 45 years, n = 21) with respect either to follow-up histology or to L/M ratio (*P* = 0.137 and 0.204, respectively).

Discussion

In this study we investigated which noninvasive test is best suited to reflect mucosal status and therefore might be used as a substitute for small-bowel biopsy for follow-up of patients with celiac disease. We observed that IPT – in particular the L/M ratio – performed best in terms of sensitivity, especially if follow-up was early, but had low specificity. A normal L/M ratio excluded villous atrophy in 80 % of cases. EMA achieved the highest specificity, exceeding even 90 % in patients with late follow-up.

Only one-sixth of the patients diagnosed in our clinic were completely lost to follow-up, which is lower than numbers given in the literature [17]. Only one-fifth of the patients underwent small-bowel biopsy for assessment of the recovery of the duodenal mucosa, especially those with suspected noncompliance, dietary resistance, or silent celiac disease at diagnosis. Thus, the results from our study might be subject to a selection bias because they particularly reflect the status of a difficult patient group. However, this selection bias, however, should not have any influence on the correlation of invasive with noninvasive test results. In addition, this patient group is particularly in need of easy follow-up procedures such as establishing reliable noninvasive methods as an alternative to intestinal biopsy.

Slightly more than half of these patients showed no mucosal atrophy on follow-up biopsy. No difference in the proportion of patients with normalized mucosal architecture was found between those followed up early as compared to those with late follow-up. Persistent villous atrophy in celiac disease, even in the absence of symptoms, carries a risk of subsequent severe complications [18]. For this reason a few centers recommend at least one follow-up biopsy to study the response to a GFD [18]. Wahab et al. reported histological remission in 65.0 % of patients

within 2 years, in 85.3% within 5 years, and in 89.9% after 5 years of follow-up [10]. Our results did not show this improvement over the years, but were still superior to those found by Lee et al., who observed no villous atrophy in only 21% of patients with celiac disease patients who adhered to a GFD for an average of 8.5 years [19]. The tendency to deterioration on long-term follow-up in our study population might be due to the selection of patients with whose compliance was doubtful, as previously mentioned. Furthermore, the longer the interval between diagnosis and follow-up visits, the higher the expected proportion of patients not who do not adhere to a strict GFD. One-third of our patients in the long-term follow-up group admitted not keeping a strict GFD – a proportion also reported in other follow-up studies [20,21].

Regarding the IPT as a follow-up tool, only the L/M ratio achieved acceptable sensitivity, which slightly weakened over the years. There is a clear relation between the extent of mucosal alteration and the results of the IPT at the diagnosis of celiac disease [22,23]. Changes in the IPT after the introduction of a GFD have been reported, e.g., by comparison with the duration and extent of a GFD [9] or with serological tests [8]. Duerksen et al. demonstrated that the IPT normalizes after adherence to a GFD for more than 1 year and correlated well with ingestion of trace amounts of gluten [9]. Comparing the IPT with serological tests during a GFD, Vilela et al. found a lower L/M ratio in AGA-negative patients but results remained above cutoff [8]. Among follow-up studies using intestinal biopsy as the gold standard, Uil et al. demonstrated a higher L/M ratio in villous atrophy than in normalized mucosa [24]. This finding is in accordance with our results (**Table 3**). However, only in the early follow-up period (< 2 years after diagnosis) a higher L/M ratio was observed in patients with villous atrophy. Regarding the second parameter of the IPT, Vogelsang et al. showed a significant correlation of the urinary recovery of saccharose and the presence of lymphocytic gastritis in untreated celiac disease [16]. Furthermore, it was demonstrated that saccharose permeation occurs mainly through the gastric mucosa in celiac disease [16]. As can be expected from these data, the saccharose test was not suitable for assessment of the status of the intestinal mucosa in our patients and showed low sensitivity and specificity, possibly due to rapid restoration of gastric mucosa.

Our findings confirmed the lack of reliability of EMA for use in monitoring either compliance or histological response to treatment, as reported elsewhere [4,25]. Dickey et al. demonstrated absence of EMA in 87% of patients after 12 months on a GFD [26]. Only 40% of these seronegative patients had complete villous recovery after 12 months, and in only 33% with villous atrophy did EMA remain positive. No patient who had recovered normalized villous structure showed persistent EMA positivity. In our study, a smaller percentage (63.2%) of compliant patients who had been followed up early became EMA-negative. Normalized villous architecture was found in 76.9% of our EMA-negative patients, and two-thirds of our patients with persistent Marsh stage 3 lesions had positive results for EMA. Four out of 14 patients with Marsh lesions of stage 2 or less still were positive for EMA, indicating faster mucosal recovery than EMA seroconversion. Indeed, all four developed EMA negativity on further follow-up within the next 3 months. Paradoxically, Dickey et al. [26], who took a titer of ≥ 1 : 5 as showing positivity, had a higher rate of false negative EMA results in their patients after 12 months on a GFD than we had with the higher cutoff of 1 : 10. This might be due to variations between the performance of different EMA test kits in detecting low autoantibody titers, and might also be related to very early histological restaging in some patients. However, the performance of EMA testing changed in our study in relation to the follow-up interval. Beyond 2 years after diagnosis, significantly more positive results were found in patients with persistent villous atrophy, possibly due to persistent dietary transgressions, and the specificity of EMA for detecting villous atrophy exceeded 90%. However, it can take more than 2 years for EMA to disappear following commencement of a GFD, especially if titers were very high to begin with [27]. This might explain the single false positive EMA result in our group of patients who had their follow-up later than 2 years after diagnosis.

Wauters et al. showed excellent sensitivity of AGA-IgA in 17 children after a gluten challenge, based on jejunal biopsies [3]. In contrast to these findings, AGA showed the lowest sensitivity of all noninvasive tests used in our adult patients. Its high specificity may be explained by the extremely low rate of positive titers. However, the changing the AGA testing kit twice during the study period limits the validity of these findings.

Regarding newer serological tests in the assessment of mucosal recovery, Vahedi et al. demonstrated that anti-tTG are poor predictors of dietary transgressions in adult celiac disease patients on a GFD [6]. Unfortunately, we were not able to correlate these antibodies with histological changes since anti-tTG results were available for only a few patients.

In conclusion, our results indicate that serology and IPT is far less sensitive and specific for follow-up of patients with celiac disease than for screening purposes. The L/M ratio had an acceptable sensitivity in patients followed up within 2 years after diagnosis, whereas EMA showed good specificity in those investigated later than that. However, there is no replacement for intestinal biopsy for the accurate detection of persistent mucosal atrophy in celiac patients on a GFD.

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Competing interests: None

References

1 AGA Institute Medical Position Statement on the Diagnosis and Management of Celiac Disease. Gastroenterology 2006; 131: 1977 – 1980
2 *Reeves GE, Squance ML, Duggan AE et al.* Diagnostic accuracy of coeliac serological tests: a prospective study. Eur J Gastroenterol Hepatol 2006; 18: 493 – 501
3 *Wauters EA, Jansen J, Houwen RH et al.* Serum IgG and IgA anti-gliadin antibodies as markers of mucosal damage in children with suspected celiac disease upon gluten challenge. J Pediatr Gastroenterol Nutr 1991; 13: 192 – 196
4 *Troncone R, Mayer M, Spagnuolo F et al.* Endomysial antibodies as unreliable markers for slight dietary transgressions in adolescents with celiac disease. J Pediatr Gastroenterol Nutr 1995; 21: 69 – 72
5 *Hansson T, Dahlbom I, Rogberg S et al.* Recombinant human tissue transglutaminase for diagnosis and follow-up of childhood coeliac disease. Pediatr Res 2002; 51: 700 – 705
6 *Vahedi K, Mascart F, Mary JY et al.* Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. Am J Gastroenterol 2003; 98: 1079 – 1087
7 *Catassi C, Fabiani E, Ratsch IM et al.* Is the sugar intestinal permeability test a reliable investigation for coeliac disease screening? Gut 1997; 40: 215 – 217

8 *Vilela EG, de Abreu Ferrari Mde L, de Gama Torres HO et al.* Intestinal permeability and antigliadin antibody test for monitoring adult patients with celiac disease. Dig Dis Sci 2007; 52: 1304 – 1309
9 *Duerksen DR, Wilhelm-Boyles C, Parry DM.* Intestinal permeability in long-term follow-up of patients with celiac disease on a gluten-free diet. Dig Dis Sci 2005; 50: 785 – 790
10 *Wahab PJ, Meijer JW, Mulder CJ.* Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery. Am J Clin Pathol 2002; 118: 459 – 463
11 *Vogelsang H, Propst A, Dragosics B, Granditsch G.* [Diagnosis and therapy of celiac disease in adolescence and adulthood]. Z Gastroenterol 2002; 40: I – VII
12 *Vogelsang H, Hanel S, Steiner B, Oberhuber G.* Diagnostic duodenal bulb biopsy in celiac disease. Endoscopy 2001; 33: 336 – 340
13 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
14 *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
15 *Wyatt J, Vogelsang H, Hubl W et al.* Intestinal permeability and the prediction of relapse in Crohn's disease. Lancet 1993; 341: 1437 – 1439
16 *Vogelsang H, Oberhuber G, Wyatt J.* Lymphocytic gastritis and gastric permeability in patients with celiac disease. Gastroenterology 1996; 111: 73 – 77
17 *Richter JC, Netzer P, Cottagnoud P, Stucki A.* Testing strategies and follow-up for coeliac disease in a general internal medicine outpatient department from 2000 to 2005. Swiss Med Wkly 2006; 136: 732 – 738
18 *Kaukinen K, Peraaho M, Lindfors K et al.* Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease. Aliment Pharmacol Ther 2007; 25: 1237 – 1245
19 *Lee SK, Lo W, Memeo L et al.* Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. Gastrointest Endosc 2003; 57: 187 – 191
20 *Leffler DA, Edwards-George J, Dennis M et al.* Factors that influence adherence to a gluten-free diet in adults with celiac disease. Dig Dis Sci 2008; 53: 1573 – 1581
21 *Mayer M, Greco L, Troncone R et al.* Compliance of adolescents with coeliac disease with a gluten free diet. Gut 1991; 32: 881 – 885
22 *Juby LD, Dixon MF, Axon AT.* Abnormal intestinal permeability and jejunal morphometry. J Clin Pathol 1987; 40: 714 – 718
23 *Vogelsang H, Schwarzenhofer M, Oberhuber G.* Changes in gastrointestinal permeability in celiac disease. Dig Dis 1998; 16: 333 – 336
24 *Uil JJ, van Elburg RM, van Overbeek FM et al.* Follow-up of treated coeliac patients: sugar absorption test and intestinal biopsies compared. Eur J Gastroenterol Hepatol 1996; 8: 219 – 223
25 *Valentini RA, Andreani ML, Corazza GR, Gasbarrini G.* IgA endomysium antibody: a valuable tool in the screening of coeliac disease but not its follow-up. Ital J Gastroenterol 1994; 26: 279 – 282
26 *Dickey W, Hughes DF, McMillan SA.* Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery. Am J Gastroenterol 2000; 95: 712 – 714
27 *Sategna-Guidetti C, Pulitano R, Grosso S, Ferfoglia G.* Serum IgA antiendomysium antibody titers as a marker of intestinal involvement and diet compliance in adult celiac sprue. J Clin Gastroenterol 1993; 17: 123 – 127