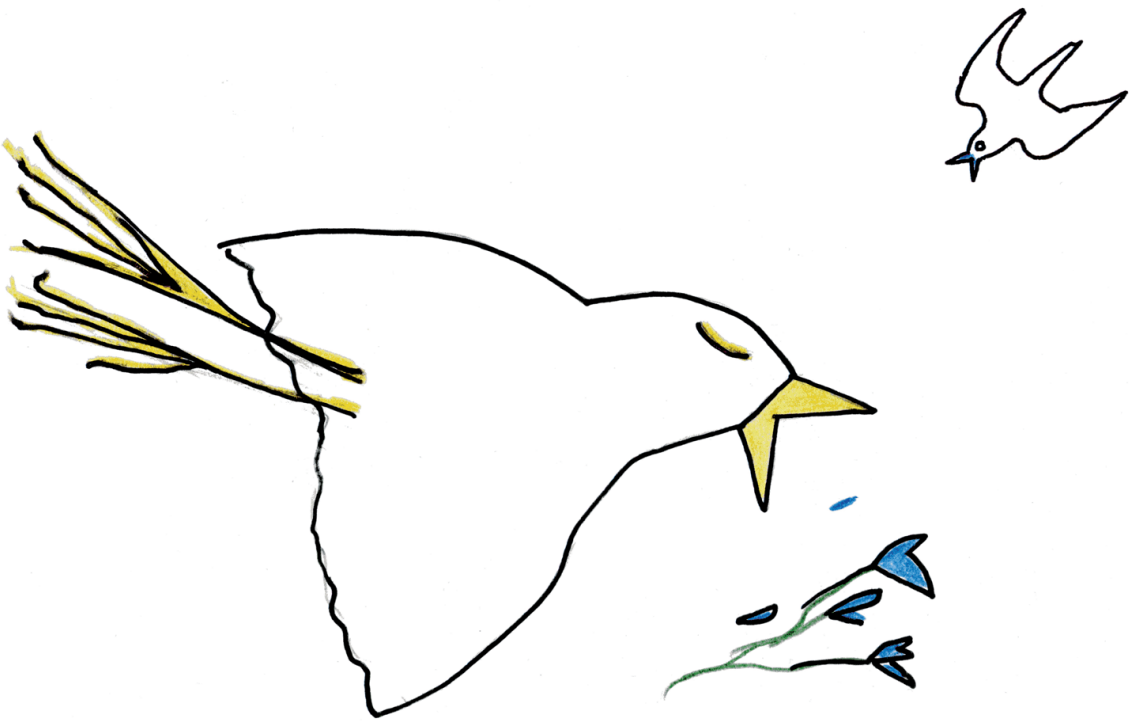

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ACCURACY OF THREE COMMERCIALLY AVAILABLE POINT-OF-CARE TESTS IN MONITORING COELIAC DISEASE

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Submitted

ABSTRACT

Objective

To evaluate and compare three different, commercially available point-of-care (POC) tests for anti-tissue transglutaminase (TG2A) in children with treated coeliac disease (CD) against results of conventional TG2A at the laboratory using ELISA.

Design

Cross-sectional study, evaluating three different POC tests (X, Y and Z) on 142 blood samples from IgA-competent CD patients aged ≤18 years, attending the paediatric gastroenterology outpatient clinic of Leiden University Medical Center, the Netherlands. Results were evaluated while blinded to the outcome of conventional TG2A assessment (EliA™ Celikey™ IgA test) at 10 and 30 minutes, and 1 day after performing the test (T10, T30 and T1d respectively). We calculated the sensitivity and specificity at 95% confidence intervals (CI) and the negative and positive predictive values. A test was considered acceptable if its sensitivity was ≥90%.

Results

Serum TG2A was positive in 47/142 samples. Test Y* had a greater sensitivity than the other 2 evaluated tests (89% [95% CI 0.81-0.98] versus test X: 34% [95% CI 0.20-0.48] and Z: 55% [95% CI 0.41-0.70], and its sensitivity was 96% [95% CI 0.90-1.0]) when results were read one day after the test was conducted. Prolonging the reading time from T10 to T30 significantly improved the performance of tests X and Z in case of positive serum TG2A (sensitivity test X 62% [95% CI 0.48-0.76], p<0.001; and test Z 70% [95% CI 0.57-0.83], p=0.016) but for test Z this was associated with a drop in specificity.

Conclusions

The studied POC tests have different sensitivities for the relatively low positive TG2A in treated CD patients. Prolonging the reading time may improve a test's performance. To implement POC tests in the follow-up of treated CD patients, we recommend the use of tests that have been validated in this specific group of patients.

* Celiac quick test for IgA, IgG and IgM TG2A (Biohit Oyj, Helsinki, Finland)

INTRODUCTION

Coeliac disease (CD) is a chronic disorder of the small intestine and other organs of genetically susceptible individuals, affecting 1-3% of the Western population.[1] The disease is characterized by the production of autoantibodies against a.o. transglutaminase type 2 (TG2A), among others, during a period of gluten ingestion, which usually disappear 9-12 months after a gluten free diet (GFD) is initiated.[2-5] Serum detection of TG2A is therefore not only useful to screen and diagnose CD but also to monitor a patient's remission *and* dietary adherence.[6-9] TG2A serum testing is part of standard care in the CD follow-up.[9-12] However, TG2A measurement requires specialized laboratories and the results are not immediately available. Readily available TG2A results during consultations with the physician would facilitate doctor-patient communication about dietary adherence. Self-testing can empower patients in the management of their disease (chapter 4). The call for point-of-care (POC) testing, defined as performing a diagnostic procedure outside the laboratory,[13] has resulted in the commercial availability of several POC tests for TG2A. These tests obviate the need for purified or recombinant transglutaminase type 2 (TG2) or for serum separation because TG2 is also found in red blood cells (RBCs). Therefore, the patient's own TG2 can be used in TG2A detection by haemolysing a whole blood sample and liberating the self-TG2 from the RBCs. Tests can be performed at home and results become available within 10 minutes, which may save costs and prove to be more convenient for the patients (Chapter 4).[14-17] Several studies have investigated the accuracy of POC tests based on TG2A for CD screening and diagnosing, and sensitivities and specificities similar to those of determination of TG2A in serum were reported (70.1- 97% and 76-100% respectively).[14, 16-23] There is, however, less consensus over the accuracy of POC testing to monitor CD once treatment has been initiated.[20] These patients usually have less TG2A titers than untreated patients.[24] Subsequently, the aim of this study was to compare the performance of three different, commercially available POC tests against the serum TG2A of CD-affected children treated with a GFD.

METHODS

Study design and patients

In this cross-sectional study, we performed 3 different POC tests on IgA-competent CD patients aged ≤18 years who attended the paediatric gastroenterology outpatient clinic of Leiden University Medical Center (LUMC). The study ran from March 28, 2014 to August 18, 2015. Patients were included if all inclusioncriteria were met: 1) CD diagnosed according to the guidelines of the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN); [9] 2) GFD initiated prior to POC testing; and 3) TG2A determined at the

hospital laboratory as part of standard care.[12] Information about a patient's sex, age and disease duration was obtained. All identifying details were encoded.

POC tests

POC testing was performed on-site by using 30uL (10uL per POC test) of fresh waste blood from a venous whole blood sample that remained in the needle system after venipuncture for conventional TG2A determination. The blood was not coagulated or dried. The three POC tests that were compared against the conventional TG2A results are henceforth referred to as tests X, Y and Z, respectively. Using a lateral flow immunochromatographic strip system, the diluted blood sample migrates through the test strip. The principles of the different tests vary. For test X, if TG2A are present in the blood sample, they form complexes with the liberated self TG2. These complexes bind to a solid surface protein coated with TG2-capturing proteins. A red/pink test line becomes visible with the help of labelled anti-human IgA solution. In tests Y and Z, TG2A (IgA, IgG for test Z and IgA, IgG and IgM for test Y) antibodies in a blood sample react with human recombinant TG2 labelled with latex particles. These latex particle-TG2-TG2A complexes reach the reaction zone through a chromatographic process, where immobilised human TG2 captures the complex, forming a red/pink line. In addition, an integrated control system checks proper function of the test by showing a control line. A positive test result shows two lines (test and control line), while only one line (the control line) appears if the test is negative. A test result with no control line is invalid and cannot be used.[25, 26] According to the manufacturers, the test results should be evaluated after 5-10 minutes. Three of this study's authors, after being trained to assess the POC tests, evaluated and photographed the test results on-site in a well-lit room to determine the test result after 10 minutes, but also after 30 minutes and 1 day to assess the stability of the test result. Another trained author who was blinded to the outcome of the on-site result interpretation and without having any clinical information, evaluated the pictures of the POC test results. For assessment of interobserver agreement, the interpretations of the on-site and photographed test results were compared.

Conventional serologic testing

The results of IgA TG2A serum testing at the hospital laboratory were used as the gold standard. Serum IgA-class TGA were determined with the ELISA technique, using EliA™ Celikey™ IgA test (Phadia GmbH, Freiburg, Germany) following the manufacturer's instructions. A value of <7 units per milliliter (U/ml) was considered negative while ≥7 U/ml was deemed positive. The test has a measuring range of 0.1 - ≥128 U/ml. Results were available after approximately 1 week.

Statistics

For the POC tests, a sensitivity of 90% or higher is considered acceptable. The power calculation is made based on the non-inferiority principle, using test Y. Assuming that the real sensitivity of the POC test equals 98% and assuming a required power of 80%, we needed to include a minimum of 45 patients who would test positive on the gold standard for TG2A determination. In our practice, approximately 35% of the treated CD patients have elevated TG2A yearly, including those in their first year after initiating the GFD. This means that the expected number of samples which we had to test was estimated to be 129 ((10/3.5)*45) Results of each POC test after 10 minutes, 30 minutes and 1 day were used to calculate the test's sensitivity and specificity (with 95% confidence intervals [95% CI]) using two different approaches: uninterpretable test results were considered "negative" in the case of a positive gold standard, and as "positive" in the case of a negative gold standard ("worst case" sensitivity and specificity); and when uninterpretable testresults are omitted ("conventional" sensitivity and specificity). In the samples with a positive gold standard, the McNemar test was used to compare the performance of each POC test when reading time was prolonged to 30 minutes or to 1 day, and to compare the performance of the different POC tests' with each other. Inter-observer agreement was evaluated using Cohen's Kappa (K). Analyses were performed with SPSS software (version 23.0).

Ethics

The study protocol was approved by the medical ethical committee of the LUMC. No informed consent was needed because residual blood was used and TG2A serum determination is standard care. This study is performed according to the Standards for the Reporting of Diagnostic Accuracy studies (STARD). The manufacturers of the POC tests used in this study provided the tests free of charge for the purpose of the study. They were neither directly or indirectly involved in the study design or conduct, nor in the analysis of the results or preparation of the manuscript.

RESULTS

There was a total of 144 blood samples obtained. In 2/144 samples, the amount of blood was insufficient to perform all three POC tests. Therefore, 142 blood samples from 122 different patients were analysed (testing on 1, 2 or 3 separate occasions during the study period in N=104, N=16 and N=2, respectively). Patient characteristics at time of blood withdrawal are presented in Table 1. Results of the gold standard for TG2A testing were positive in 47/142 samples (33%). These belonged to patients with significantly shorter disease duration than patients with a sample negative for TG2A (Table 1). The inter-observer agreement between interpretation of on-site and photographed POC test results was substantial (0.80, 0.70, and

Table 1 Characteristics of 122 individual patients with coeliac disease (CD) whose blood samples were withdrawn and tested for anti-transglutaminase type 2 antibodies (TG2A) with the conventional ELISA in the hospital laboratory on 142 occasions, split out for and compared between positive and negative TG2A results in serum (cut-off for normality ≥7 U/ml).

Patient characteristic	All samples (n=142)	Positive TG2A samples (n=47)	Negative TG2A samples (n=95)	*p*-value
Female gender – n (%)	91 (64.1)	30 (63.8)	61 (64.2)	0.97
Age in years – mean (± SD)	9.7 (4.3)	9.8 (4.6)	9.6 (4.1)	0.93
Duration of CD in years – mean (± SD)	4.4 (4.2)	1.9 (3.0)	5.7 (4.1)	<0.001
Serum TG2A titer in U/ml – mean (± SD)	12.5 (24.6)	34.8 (33.1)	1.47 (1.48)	<0.001

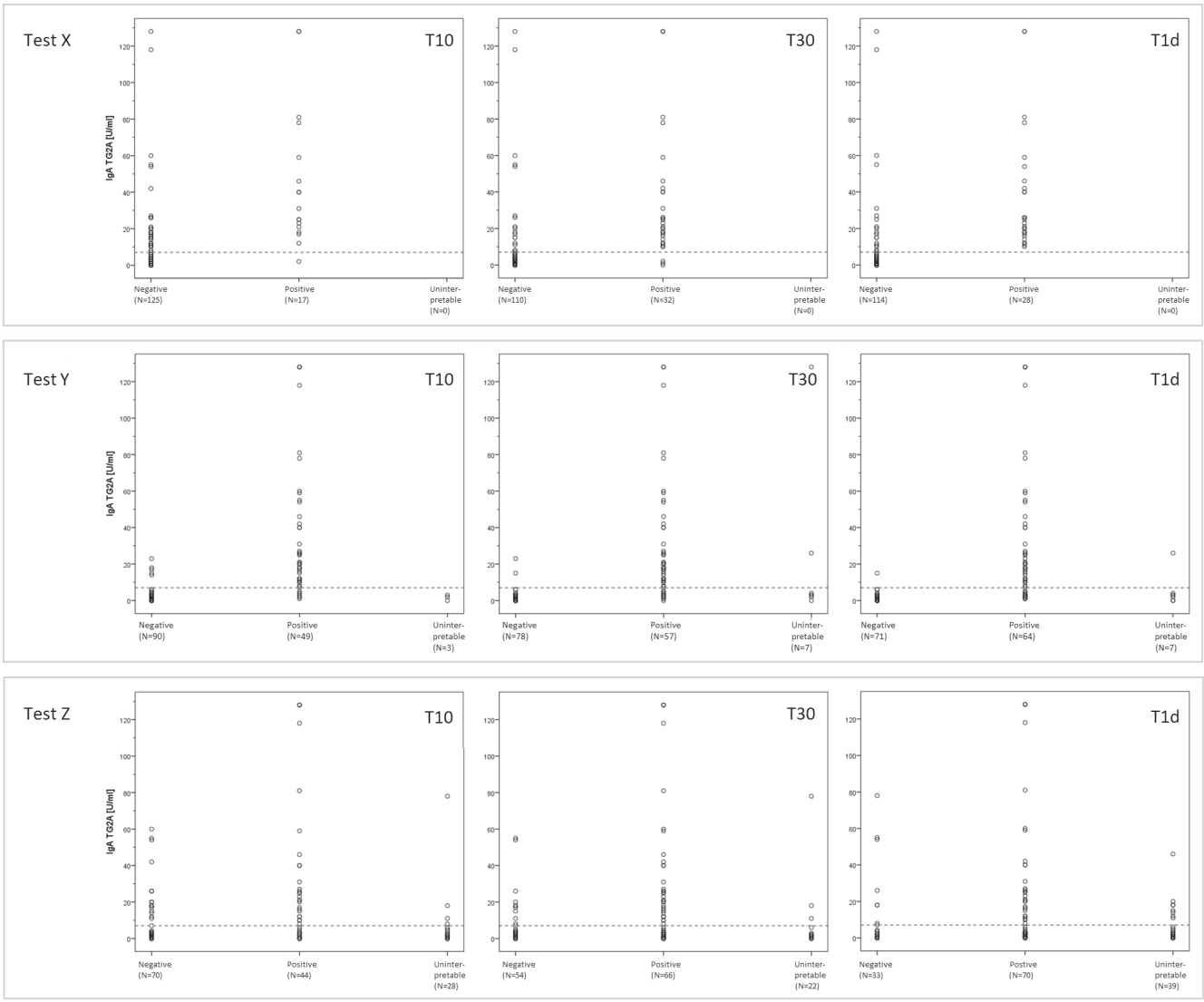

Figure 1 Correlation of the results of IgA anti-transglutaminase type 2 (TG2A) in U/ml measured in the laboratory (y-axis) and results of the point-of-care tests (x-axis) at 10 minutes (T10), 30 minutes (T30) and 1 day (T1d) after applying the blood sample. The horizontal dotted line represents the cut-off for normality of TG2A as measured in the laboratory (7 U/ml).

0.66 for tests X, Y and Z, respectively). The results of the POC tests after 10 minutes (T10), 30 minutes (T30) and 1 day (T1d) compared with the gold standard are presented in Figure 1 and in Table 2. Uninterpretable test results only occurred in tests Y and Z, and were due to the absence of a control line or appearance of a red haze in the test window.

When analysing the results at T10, as recommended by the manufacturer, test X was considered as false-negative in 31 samples, with serum TG2A titers ranging from 7-128 U/ml (mean 27.84 U/ml) (Figure 1). Test Y was false-negative in five tests, correlating with TG2A levels ranging from 14-23 U/ml (mean 17.40 U/ml) (Figure 1). The three uninterpretable tests Y concerned samples with negative serum TG2A (Figure 1). Test Z was false-negative in 17 tests, with serum TG2A ranging from 7-60 U/ml (mean 25.47 U/ml) and the 28 uninterpretable tests occurred in samples with serum TG2A titers ranging from 0-78 U/ml (mean 5.43 U/ml). The outcome of all three tests (false negative or true positive) was not influenced by time interval since CD diagnosis (p=0.572, 0.323, 0.125 for tests X, Y and Z, respectively) or the age of the participant (p=0.492, 0.569, 0.797 for tests X, Y and Z, respectively). In addition, the outcome of tests X and Z (false negative or true positive) was uninfluenced by the TG2A serum titer (p=0.962 and 0.461 respectively). This in contrast to test Y, where serum TG2A levels of tests with a false negative outcome were significantly lower than those of tests with a true positive outcome (17.40 U/ml versus 36.80 U/ml, p=0.027). When considering the "worst case" scenario (i.e. uninterpretable test results considered "negative" in the case of a positive gold standard and as "positive" in the case of a negative gold standard), the sensitivities of all 3 tests were less than 90% at T10, with the best outcome for test Y* (89% [95% CI 0.81-0.98]) and poorest outcome for test X (34.0% [95% CI 0.20-0.48]) (Table 2).

When confining to those samples with a positive gold standard (N=47), performance of test X and Z increased significantly when reading time was prolonged from T10 to T30 (positive tests X: N=16 to N=29, p<0.001; positive tests Z: N=26 to N=33, p=0.016) or from T10 to T1d (positive tests X: N=16 to N=28, p=0.004; positive tests Z: N=26 to N=31, p=0.031). However, their performance at T1d was not significantly improved when compared with T30 (test X p=1.000; test Z p=0.500). The improvement in the performance of test Y when reading time was prolonged to T30 or T1d, was not statistically significant (p=0.250 and p=0.125 respectively). Nevertheless, test Y is the only test whose sensitivity reached a value of over 90% (T30: 91% [95% CI 0.84-0.99] and T1d: 96% [95% CI 0.90-1.0]) (Table 2). Furthermore, test Y performed significantly better than X and Z at all evaluated time points in case of positive serum TG2A (T10: Y versus X p<0.001, Y versus Z p=0.002; T30: Y versus X p<0.001, Y versus Z p=0.021; T1d: Y versus X p<0.001, Y versus Z p=not applicable because all 39 interpretable results of test

* Test Y = Celiac quick test for IgA, IgG and IgM TG2A (Biohit Oyj, Helsinki, Finland)

Table 2 Comparison of 3 point-of-care (POC) tests for anti-transglutaminase type 2 antibodies (TG2A) with the TG2A result in conventional laboratory (gold standard). Sensitivity and specificity (95% confidence intervals [95% CI]) were calculated with or without taking the un-interpretable test results into account (worst case [A] and conventional [B] respectively). Results are given after an evaluation time of 10 minutes, 30 minutes and 1 day.

			TG2A in conventional laboratory						
			Positive (N=47)	Negative (N=95)	Total	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Test X	10 min	Positive	16	1	17	0.34 (0.20-0.48)	0.99 (0.97-1.0)	0.94 (0.83-1.00)	0.75 (0.68-0.83)
		Un-interpretable	0	0	0				
		Negative	31	94	125				
	30 min	Positive	29	3	32	0.62 (0.48-0.76)	0.97 (0.93-1.0)	0.91 (0.81-1.00)	0.84 (0.77-0.91)
		Un-interpretable	0	0	0				
		Negative	18	92	110				
	1 day	Positive	28	0	28	0.60 (0.46-0.74)	1.00	1.00	0.83 (0.76-0.90)
		Un-interpretable	0	0	0				
		Negative	19	95	114				
Test Y	10 min	Positive	42	7	49	A: 0.89 (0.81-0.98) B: 0.89 (0.81-0.98)	A: 0.92 (0.83-0.96) B: 0.92 (0.87-0.98)	0.86 (0.76-0.96)	0.94 (0.90-0.99)
		Un-interpretable	0	3	3				
		Negative	5	85	90				
	30 min	Positive	43	14	57	A: 0.91 (0.84-0.99) B: 0.96 (0.90-1.0)	A: 0.80 (0.72-0.88) B: 0.84 (0.77-0.91)	0.75 (0.64-0.87)	0.97 (0.94-1.00)
		Un-interpretable	2	5	7				
		Negative	2	76	78				
	1 day	Positive	45	19	64	A: 0.96 (0.90-1.0) B: 0.98 (0.94-1.0)	A: 0.74 (0.65-0.83) B: 0.79 (0.70-0.87)	0.70 (0.59-0.82)	0.99 (0.96-1.00)
		Un-interpretable	1	6	7				
		Negative	1	70	71				

Table 2 (continued)

			TG2A in conventional laboratory						
			Positive (N=47)	Negative (N=95)	Total	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Test Z	10 min	Positive	26	18	44	A: 0.55 (0.41-0.70) B: 0.60 (0.46-0.75)	A: 0.56 (0.46-0.66) B: 0.75 (0.65-0.85)	0.59 (0.44-0.74)	0.76 (0.66-0.86)
		Un-interpretable	4	24	28				
		Negative	17	53	70				
	30 min	Positive	33	33	66	A: 0.70 (0.57-0.83) B: 0.77 (0.64-0.89)	A: 0.45 (0.35-0.55) B: 0.57 (0.45-0.68)	0.50 (0.38-0.62)	0.80 (0.69-0.90)
		Un-interpretable	3	19	22				
		Negative	11	43	54				
	1 day	Positive	31	39	70	A: 0.66 (0.53-0.80) B: 0.79 (0.67-0.92)	A: 0.26 (0.17-0.35) B: 0.39 (0.27-0.51)	0.44 (0.33-0.56)	0.76 (0.61-0.90)
		Un-interpretable	8	31	39				
		Negative	8	25	33				

Z were positive with test Y). Test Z performed significantly better than test X at T10 (p=0.007), but both tests performed similarly at T30 and T1d (p=0.180 and 0.096, respectively).

DISCUSSION

This study evaluated and compared three different commercially available TG2A POC tests in children with treated CD against conventional serologic TG2A testing. Our results show that test Y had a greater sensitivity than the other 2 POC tests, and that its sensitivity was acceptable (95% CI excluded values <90%) if reading time was prolonged from 10 minutes to 1 day. Implementation of such a test in a clinical setting may reduce the frequency of venipuncture for conventional TG2A testing in children (and probably also in adults) with treated CD and could improve self-management of their disease. An important advantage of a POC test is its potential to be a more rapid alternative to conventional serologic testing. To accommodate the longer reading time of test Y, well instructed patients could do the test at home on the day prior to their outpatient clinic visit and bring the test for evaluation by their physician. This allows for an on-the-spot management decision in case of a positive result. This may include, for instance, conventional serologic testing, dietetic counselling on GFD adherence, and discussion with the physician on the harmful effects of gluten ingestion. Furthermore, the use of a POC test instead of the conventional TG2A testing may have health cost-saving implications, and a finger-prick is considered less invasive than a venipuncture, particularly for children (Chapter 4).[27]

Our cohort's prevalence of positive TG2A in serum (according to conventional serology) of 33% is slightly higher than what is reported in literature, with a reported prevalence that ranges from 12-32%.[18, 28-32] In contrast to most of these studies, however, we also included children diagnosed with CD less than 1 year and therefore with a high likelihood of having positive serum TG2A.[5]

A high sensitivity and negative predictive value (NPV) are crucial for monitoring CD activity, leading to fewer missed cases of uncontrolled CD. The specificity and positive predictive value (PPV) are considered to be less important in this situation, although they do influence the efficiency of a POC test. Tests X and Y had been validated in CD screening, with reported sensitivities compared to biopsy of 72.2-96.7% for test X,[17, 19, 22, 27] and 77.8% for test Y [27]. The lower sensitivities in our study could be explained by the fact that antibody titers in treated CD are typically lower than in untreated CD cases identified by screening or case-finding. However, in a study with 15 patients treated with a strict GFD for 1 year, test X was used and compared with the outcome of serum TG2A testing.[19] In 13/15 patients, test X was negative, as well as serum TG2A. In the remaining 2 positive tests, serum TG2A values

were considered borderline (4.2 and 4.6 U/mL).[19] In addition, in the same study 91 long-term treated coeliac disease patients (median duration of a strict gluten-free diet = 9 years, range 1–24 years) were tested for TG2A with test X and conventional laboratory: 88 (96.7%) were negative with test X and 90 (98.9%) with the conventional method.[19] As virtually all tests were negative for serum TG2A, this study does not provide enough information about the performance of this test in case of low positive serum TG2A. Another study with test X suggested that prolonging the reading time to 10-15 minutes increased the sensitivity as faint test-lines became clearer.[16] While we also observed this phenomenon in our study, it did not result in an acceptable sensitivity for test X. The results of two studies published in 2013, comparing conventional laboratory results with POC tests other than the ones used in our study, showed sensitivities of 63% and 84% in treated CD.[24, 33] The false-negative POC tests concerned samples with antibody levels near the cut-off of normality.[24, 33] While we also observed this in our study for test Y, tests X and Z yielded false-negative results in samples with serum TG2A up to 128 U/ml and 60 U/ml respectively. Based on these results, we may conclude that all three tests have different cut-offs of normality. Another explanation for their difference in performance may be attributed to the varying principles of each of them. Test X uses self-TG2 while tests Y and Z use recombinant human TG2. Self-TG2 is known to be a sensitive protein. If the protein is damaged, it may be unable to form immunocomplexes with the serum auto-antibodies.[17] It is recommended to avoid using blood that has been frozen and thawed multiple times, or blood that is coagulated or dried.[17] In our study, however, fresh blood was used on-site and directly from the needle system. As the blood was not coagulated or dried, it seemed unlikely that the self-TG2 was damaged. Furthermore, test X only detects IgA TG2A; while test Z also detects IgG TG2A and test Y detects IgA, IgG and IgM TG2A. However, the added value of IgG and IgM antibody measurements in our cohort is questionable since all our patients were IgA sufficient and all 47 patients with positive conventional ELISA had positive serum TG2A of the IgA class. Thus, IgA TG2A was present in all samples that yielded false-negative results.

In a previous study from our hands, evaluating the effectiveness of online consultations for follow-up of children and young adults with CD, we found that test X was not sensitive enough for home measurements of TG2A in the follow-up of children and young adults with treated CD. The results of our present study confirm our previous findings. To the best of our knowledge, we are the first to report that prolonging the reading time of test X improves its performance in case of positive serum TG2A. A possible explanation could be that the haemolysation process, releasing self-TG2 from the erythrocytes, is not completely finished after 10 minutes. However, at its peak performance (T30), test X still failed to recognize almost 40% of the positive samples, indicating that prolonging the reading time from 10 to 30 minutes or 1 day will not make the test suitable for utilization in patients with treated CD. For test Z, we do not recommend prolonging reading time to 30 minutes or 1 day due to

the associated significant drop in specificity. Furthermore, test Z showed a high number of uninterpretable test results (N=28 after 10 minutes) caused by the absence of a control line in 27 of them. As these tests' expiration dates have not yet passed and this event occurred in tests that were all from the same batch, this was almost certainly a manufacturing defect. Nevertheless, when these uninterpretable results were disregarded, the sensitivity of test Z at T10 was still unacceptable for follow-up of treated CD (conventional sensitivity 0.60; 95% CI 0.46-0.75).

The strengths of our study include a design wherein the same trained personnel carried out three different commercially available POC tests on the same blood sample and evaluated the outcome, blinded to the results of the conventional ELISA that was performed in the same laboratory throughout the study. Additionally, we used the widely implemented EliA™ Celikey™ IgA test (Phadia GmbH, Freiburg, Germany) as the gold standard to measure serum TG2A, thereby increasing the generalizability of our results. To the best of our knowledge, we are the first to report the results of three different commercially available POC tests in monitoring treated CD. One may argue that we should have included adherence to the GFD as a variable in our analysis. However, as an objective tool to assess dietary adherence is not available, serum TG2A and dietary adherence do not always agree.[24, 34] Furthermore, it may be argued that we assessed inter-observer variability by comparing the on-the-spot evaluation with the interpretation of a photograph of the result. While the agreement between these methods was acceptable for all three tests, the positive tests with a faint test line were difficult to capture on a photograph. However, our results suggest that photographs of POC test results have the potential to be used as an alternative for on the spot evaluation of the results. This could be useful in self-management programmes, wherein CD patients could send a photograph of the test result to their physician. Alternatively, a reader could be developed that will interpret the photographed test result, minimizing the risk of observer bias.

In conclusion, we found that out of the 3 studied POC tests for TG2A, the Celiac Quick Test for IgA, IgG and IgM TG2A (Biohit Oyj, Helsinki, Finland) had the highest sensitivity for TG2A in children with treated CD. We recommend reading this test's results a day after performing it and that further validation studies be carried out in patients with treated CD.

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