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Critically Appraised Topic

The serologic diagnosis of celiac disease in adults

Author: Dr. Pieter Vermeersch

Supervisor: Prof. Dr. Xavier Bossuyt

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CLINICAL BOTTOM LINE

IgA anti-tTG is considered the best serologic test for the diagnosis of celiac disease in non-IgA deficient patients with a sensitivity and specificity of >90-95%. This is supported by several systematic reviews. A retrospective analysis in our own hospital confirmed that the sensitivity and specificity of our current second generation IgA anti-tTG assay (Genesis, Cambridgeshire, United Kingdom) in routine diagnostic performance was good and comparable to previous studies. Specificity, however, was reduced when anti-tTG was 7-20 units/ml or when the IgA concentration was increased. Taking into account anti-tTG concentration and the IgA concentration will improve clinical interpretation of serologic testing for CD.

In IgA deficient patients, detection of antibodies directed against deamidated gliadin (DGP-AGA) peptides is a better alternative than detection of traditional antibodies directed against gliadin (AGA). A limited number of studies found that the detection of IgG DGP-AGA is both more sensitive and more specific than detection of IgG anti-gliadin antibodies. Further research is, however, needed to determine the routine diagnostic performance of IgG DGP-AGA.

CLINICAL/DIAGNOSTIC SCENARIO

Celiac disease is an autoimmune disorder characterized by a heightened immunological responsiveness to ingested gluten (from wheat, barley, or rye) in genetically susceptible individuals.¹ The disease is typically characterized by malabsorption that results from inflammatory injury of the mucosa of the small intestine. Originally considered a rare disorder in infants or children with severe malabsorption, celiac disease is now recognized as a common disorder diagnosed at all ages and affecting 0.5-1.0% of all adults.^{1, 2} In fact, most patients who are diagnosed with celiac disease present as adults, most commonly during their 40s.¹ Given the specific nature of diagnosing celiac disease in young children, particularly

children <2 years old (ESPGHAN guidelines 1990), we will focus on the serologic diagnosis of celiac disease in adults (≥ 16 years old).

The definitive diagnosis of celiac disease requires a small intestinal biopsy examination.³ The detection of auto-antibodies is often used as first-line test to identify individuals who require a duodenal biopsy. For many years, the serologic diagnosis of celiac disease has been based on the detection of anti-endomysial antibodies. The identification of tissue transglutaminase (tTG) as the target antigen of anti-endomysial antibodies in 1997⁴ resulted in the development of enzyme-linked immunosorbent assays for the detection of anti-tTG antibodies.

Detection of IgA antibodies directed against endomysium or tTG is preferred over detection of IgG antibodies or the detection of antibodies directed against gliadin because of the better sensitivity and specificity.⁵ This was confirmed in two systematic reviews.^{6, 7} The detection of IgA antibodies directed against endomysium by an indirect immunofluorescence assay is more time consuming and operator dependent than the tTGA. The “American Gastroenterological Association (AGA) Institute Technical Review on the Diagnosis and Management of Celiac Disease” (2006) and the “AGA Medical Position Statement on the Diagnosis and Management of Celiac Disease” recommends the use of IgA anti-tTG in the primary care setting as the most efficient serologic test for the diagnosis of celiac disease.^{8, 10} A systematic review from 2006 also concluded that a second generation IgA anti-tTG assay is the preferred test for excluding celiac disease in asymptomatic patients or patients with a relatively low pre-test probability (<25%).⁹ The AGA technical review also discourages the use of multiple serologic tests since this adds little to the sensitivity and will lead to a substantial economic cost due to the reduced specificity.¹⁰ For the moment, however, only detection of antibodies against anti-endomysium or gliadin are covered by the national health insurance system (RIZIV). It is, however, expected that reimbursement of IgA anti-tTG testing will be approved in the next months.

In the University Hospitals Leuven, we currently use a second generation ELISA (Genesis, Cambridgeshire, United Kingdom) for the detection of IgA anti-tTG antibodies. We perform approximately 450 tests/month (frequency 1x/week). Since the test is not covered by the RIZIV, the patient is charged 10€. The second generation assays, which use highly purified or recombinant human tTG antigen, are reported to have excellent sensitivities and specificities.^{6, 11} Several authors have, however, raised questions regarding the diagnostic performance of IgA anti-tTG testing in routine clinical practice.^{2, 12} The reported high sensitivities and specificities might be related to the use of pre-selected groups of celiac disease patients (e.g. severe histological changes of the small bowel) and/or controls. The sensitivity of IgA anti-tTG has been reported to be lower in patients with limited mucosal damage (e.g. Marsh 1 and Marsh 2).¹³ As a consequence, sensitivity decreases when more patients with a lesser degree of mucosal damage are included in the study. It has also been suggested, based on a limited number of observations, that specificity is reduced in patients with an increased IgA concentration.¹⁴ There are, however, no

studies that have systematically examined the potential interference by increased IgA on IgA anti-tTG testing and diagnostic accuracy in routine clinical practice.

Traditionally, a cut-off is used for the clinical interpretation of IgA anti-tTG results. All values above or below the cutoff are given the same interpretation (positive or negative, respectively). However, it is reasonable to assume that the likelihood for celiac disease increases with increasing IgA anti-tTG antibody concentration. Villalta et al., for example, reported that IgA anti-tTG values in patients with liver cirrhosis who tested false-positive for IgA anti-tTG were lower than IgA anti-tTG values in patients diagnosed with celiac disease.¹⁵ There are, however, no studies that have examined whether taking into account IgA anti-tTG titer would improve clinical interpretation of serologic testing.

When IgA antibodies are determined, it is important to rule out selective IgA deficiency since celiac disease occurs 10-15 times more often in these patients.^{10, 16} It is therefore required to measure serum IgA in all patients who have a IgA anti-tTG test.² Selective IgA deficiency is a primary immunodeficiency characterized by a selective deficiency of IgA in patients with normal serum levels of IgG and IgM in whom other causes of hypogammaglobulinemia have been excluded. Patients with selective IgA deficiency are often asymptomatic, but have an increased incidence of upper respiratory tract infections, allergies and auto-immune disorders.¹⁷ The frequency in Western Europe is estimated at 1/400-1/900. In the University Hospitals Leuven, serum IgA is measured in all patients who have a IgA anti-tTG test. When serum IgA is below the lower limit of the normal reference range (0.82-4.53 g/L in patients ≥ 16 years or older), IgG anti-gliadin is performed instead of IgA anti-tTG. We perform approximately 70 AGA assays/month (frequency 1x/2 weeks). The specificity and sensitivity of IgG anti-gliadin are, however, reported to be lower. The recently developed assays that recognize antibodies against deamidated gliadin could be a better alternative in patients who have a decreased serum IgA.

QUESTION(S)

- 1) What is the diagnostic performance of IgA anti-tTG in routine clinical practice?
- 2) Does taking into account IgA anti-tTG titer and IgA concentration improve clinical interpretation?
- 3) Is the detection of IgG antibodies against deamidated gliadin peptides (IgG DGP-AGA) a better alternative than IgG anti-gliadin antibodies (IgG AGA) in patients with a selective IgA deficiency?

SEARCH TERMS

- 1) *MeSH Database (PubMed)*

MeSH term: “celiac disease”, “Tissue type transglutaminase”, “gliadin”, “immunologic tests”

2) PubMed

- celiac disease AND immunologic tests
- celiac disease AND Tissue type transglutaminase
- deamidated gliadin AND celiac disease

3) SUMSearch (<http://sumsearch.uthscsa.edu/>),

4) National Guideline Clearinghouse (<http://www.ngc.org/>)

5) Cochrane (<http://www.update-software.com/cochrane>)

6) Guidelines:

- American Gastroenterological Association
(<http://www.gastro.org/wmspage.cfm?parm1=2>)
- World Gastroenterology Organisation
(www.worldgastroenterology.org)

7) UpToDate Online version 16.1 (January 2008)

RELEVANT EVIDENCE/REFERENCES

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1 What is the diagnostic performance of IgA anti-tTG in routine clinical practice?

1.1 Methods

After receiving approval from the Institutional Ethics Committee of the University Hospital of the University of Leuven, we retrospectively identified all patients aged 16 years or older attending the University Hospital of Leuven who had a serum IgA anti-tTG antibody test at the request of the treating physician between May 1st 2004 and October 31st 2007 (42 months). Only patients for whom biopsy results were available were included for further analysis. For evaluation of the diagnostic performance, only the first test result was included for each patient and all patients who were previously diagnosed with celiac disease or dermatitis herpetiformis, a severe skin manifestation of gluten sensitivity associated with celiac disease, or that were on a gluten-free diet were excluded.

Serum IgA was measured by immunonephelometry on an Immage nephelometer (Beckman Coulter) to exclude IgA deficiency (serum IgA <0.82 g/L). IgA anti-tTG antibody concentrations were determined using a commercially available ELISA (Genesis, Cambridgeshire, United Kingdom) with human recombinant tTG as antigen. The recombinant tTG antigen was expressed in an *E. coli* cell system. The ELISA was performed according to the manufacturer's instructions and was carried out on an automated ELISA instrument (PhD System, BioRad). Results were expressed as arbitrary units/ml. The recommended cut-off value by the manufacturer (7 units/ml) was used.

Intestinal biopsies were taken in the second or third part of the duodenum and graded according to a modified Marsh classification.¹⁸ The pathologist was unaware of the IgA anti-tTG result.

Medical records were checked of all patients. The diagnosis of celiac disease or dermatitis herpetiformis (CD) was considered confirmed (i) in patients with Marsh 3a to 3c lesions on intestinal biopsies or in patients with confirmation in skin biopsies of dermatitis herpetiformis, and (ii) in patients with Marsh 1 or 2 lesions on intestinal biopsies who responded to a gluten free diet serologically or on intestinal biopsy. The diagnosis of non-CD was considered confirmed when (i) intestinal biopsy showed a Marsh 0 at initial presentation or (ii) when intestinal biopsy showed Marsh 1 or Marsh 2 and the morphologic lesion could be explained by another disease such as *Helicobacter pylori* gastritis or giardiasis according to the physician.

Pre- and post-test probability were calculated as described by Moore and Weatherford.¹⁹ A Fisher's exact test was used to analyze 2x2 contingency tables and calculations were performed using GraphPad QuickCalcs (GraphPad Software).

1.2 Results

Of the 606 non-IgA deficient patients aged 16 years or older who had a IgA anti-tTG request during the 42-month study and for whom biopsy results were available, 48 patients diagnosed with CD and 558 patients as non- CD (see Table 1 for patient characteristics). Of the 48 patients diagnosed with CD, 46 had a IgA Anti-tTG result of ≥ 7 units/ml. There were also two patients with IgA anti-tTG < 7 units/ml who were diagnosed with celiac disease (based on clinical presentation and duodenal biopsy). These two patients had a Marsh 3 lesion on intestinal biopsy. The IgA anti-tTG results in these two patients were 1.8 and 0.8 units/ml. The distribution of IgA anti-tTG results in patients diagnosed as CD is shown in Figure 1.

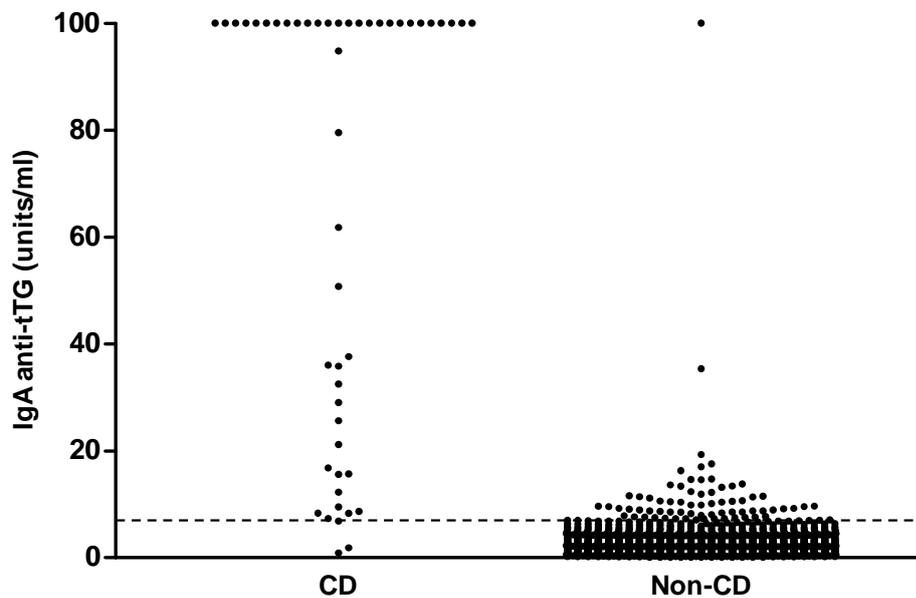


Figure 1: IgA anti-tTG concentration in patients diagnosed as celiac disease (CD) and non-celiac disease (non-CD). The dashed line indicates the cut-off of 7 units/ml.

Forty-five patients had a positive IgA anti-tTG result but were diagnosed as non-celiac disease by the treating physician. Forty-two patients were classified as Marsh 0, two patients as Marsh 1, and one patient as Marsh 2. One of the two patients classified as Marsh 1 was subsequently diagnosed with Crohn's disease, while the other patient, who had disturbed liver function tests at initial presentation, was Marsh 0 during follow-up. The patient with Marsh 2 had giardiasis. Three patients had a IgA anti-tTG result of > 20 units/ml. The first patient was diagnosed with auto-immune hepatitis (> 100 units/ml, Marsh 0), the second patient had iron deficiency of unknown origin (35.4 units/ml, Marsh 0), and the third patient had IgE-mediated hypersensitivity (23.4 units/ml, Marsh 0).

Table 1: Characteristics of the patients diagnosed with celiac disease or dermatitis herpetiformis (CD) and with non celiac disease (non-CD) at the time of diagnosis

	CD	Non-CD
Demographic data		
Number of patients	48	558
Male/Female, n	15/33	207/351
Mean age (years)		
Biopsy results		
Marsh 0	0	522
Marsh 1	7	35
Marsh 2	3	1 ¹
Marsh 3 (3a-3c)	34	0
Dermatitis Herpetiformis	4	0
IgA anti-tTG result¹		
<7 units/ml	2	513
7-20 units/ml	9	42
>20-100 units/ml	11	2
>100 units/ml	26	1
IgA concentration		
0.82-<2.00 g/L	14	233
2.00-4.53 g/L	25	300
>4.53 g/L	9	25

¹ This patient was diagnosed with giardiasis

Overall sensitivity and specificity of IgA anti-tTG for the diagnosis of CD was 95.8% and 91.9%, respectively, with a likelihood ratio (LR) of 11.9. The cut-off of 7 units/ml was confirmed as the optimum cut-off on the basis of the ROC curve (maximizing sensitivity and specificity). Given a prevalence of 7.9% in our study population, the positive predictive value was only 50.5%.

1.3 Conclusion

Sensitivity (95.8%) and specificity (91.9%) of the second generation IgA anti-tTG assay used in our hospital were good and comparable to previous studies.^{11, 20, 21} Given a prevalence of 7.9% in patients who had a IgA anti-tTG test and for whom biopsy results were available, however, the positive predictive value (PPV) of a positive IgA anti-tTG result was only 50.5%. When the 22 patients who clinically diagnosed as non-CD without the need of a duodenal biopsy were included, the PPV was only 40.7%.

1.3 To do

- Inform clinicians that the performance of the current IgA anti-tTG assay is good.

2 Does taking into account IgA anti-tTG titer and IgA concentration improve clinical interpretation?

2.1 Methods

Cfr. Section 1.1

2.2 Results

Most patients (76%) that were diagnosed with CD had a IgA anti-tTG result of >20, while 42 of the 45 patients who were considered false-positive had a IgA anti-tTG result between 7 and 20 units/ml, suggesting that taking into account IgA anti-tTG concentration could improve clinical interpretation. To examine this, we calculated the LR for different IgA anti-tTG test result intervals. The LRs were 0.05, 5.5, 64 and 302 for test result intervals of <7 units/ml, 7-20 units/ml, 20-100 and >100 units/ml, respectively (see Figure 2). These results clearly demonstrate that the LR depends on the anti-tTG concentration. IgA anti-tTG concentration should be taken into account when interpreting an IgA anti-tTG result.

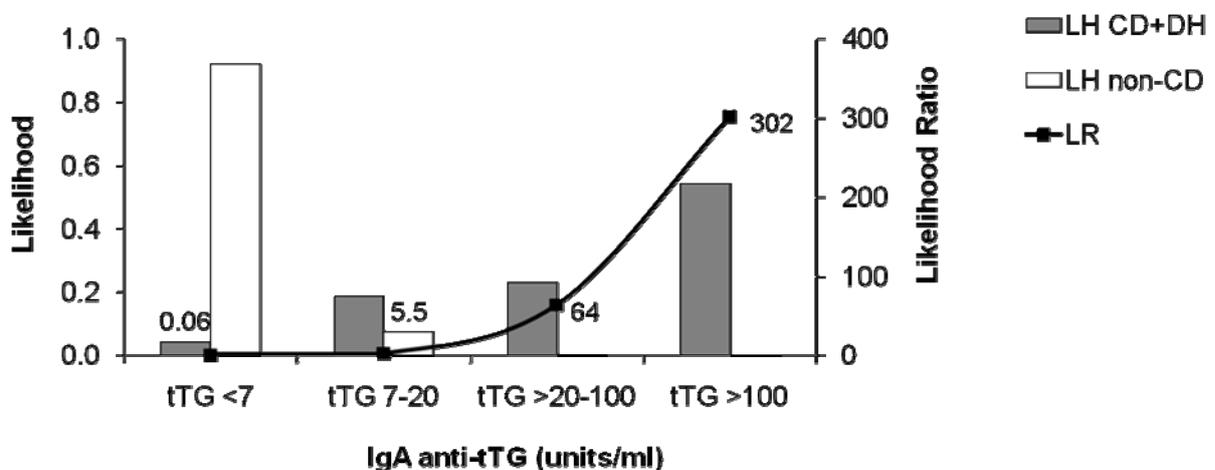


Figure 2: Likelihood ratio for different IgA anti-tTG concentration intervals.

The post-test probabilities for the different test result intervals as a function of pre-test probabilities were calculated through application of Bayes' Theorem. The results are shown in Figure 3. This graphical approach illustrates how the post-test probability of CD depends on the pre-test probability and the concentration of anti-tTG antibodies. The estimated post-test probability increases with both increasing pre-test probability and increasing antibody concentration. The pre-test probability for a random patient in our study population who underwent an intestinal biopsy was 8%. For a patient with Marsh 1, Marsh 2 or Marsh 3 on intestinal biopsy, in contrast, the

probability that the patient was diagnosed with CD was 17%, 75%, and 100%, respectively.

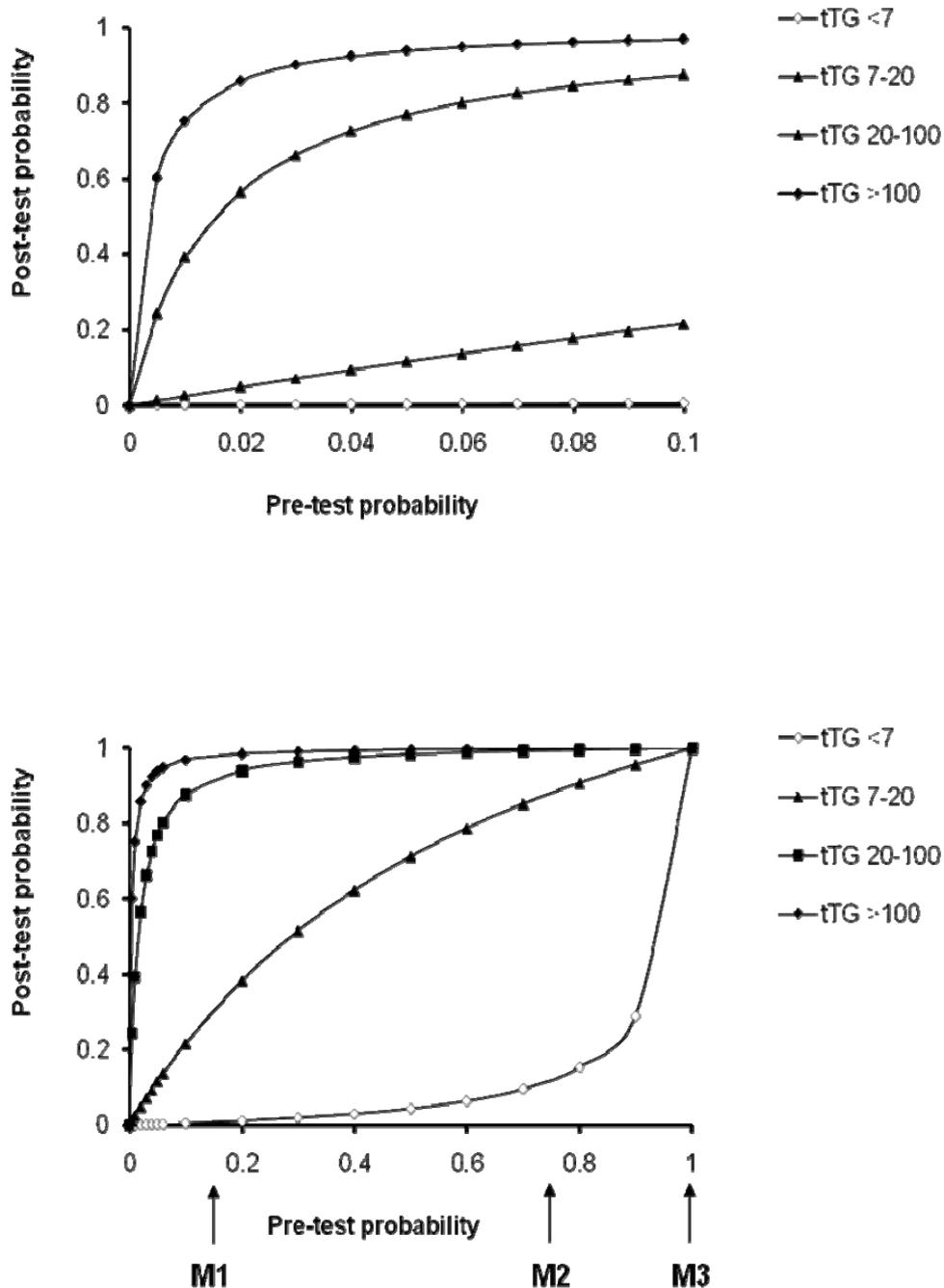


Figure 3: Post-test probability for celiac disease for different pre-test probabilities. The upper and lower panel represent pre-test probabilities between 0 and 0.1 and 0 and 1, respectively. The probability that a patient with Marsh 1, 2 or 3 was diagnosed with CD in our study is indicated in the lower panel.

To examine whether an increased IgA concentration affects the specificity of IgA anti-tTG testing, we determined the LR for different IgA concentration intervals. For a normal IgA concentration (0.82-4.53 g/L), specificity was 97.1% and the LR 32.2. When the IgA concentration exceeded 4.53 g/L, specificity decreased to 68.0% and

the LR was only 3.1. The reduced specificity in patients with an increased IgA concentration was associated with an increased percentage of false-positive results. 8 of the 25 non-CD patients with an increased IgA concentration tested false-positive for IgA anti-tTG compared to 37 of the 533 non-CD patients with a normal IgA concentration (32% vs. 7%, respectively, $p < 0.01$). The prevalence of CD, however, was also higher in patients with an increased IgA concentration compared to patients with a normal IgA concentration (26% versus 7%, respectively, $p < 0.01$).

To determine whether taking into account both IgA concentration and IgA anti-tTG concentration could improve diagnostic accuracy, we calculated the LR for different IgA and IgA anti-tTG test result intervals. The results are displayed in Figure 4. An IgA anti-tTG result of 7-20 units/ml was almost always false-positive, except in patients with a low normal IgA concentration (0.82-2.0 g/L) where the positive predictive value was 38%. A strong positive IgA anti-tTG result (>100 units/ml), in contrast, almost always indicated CD, irrespective of the IgA concentration. An intermediate IgA anti-tTG result of >20-100 units/ml was also usually associated with CD, except when the IgA concentration was increased.

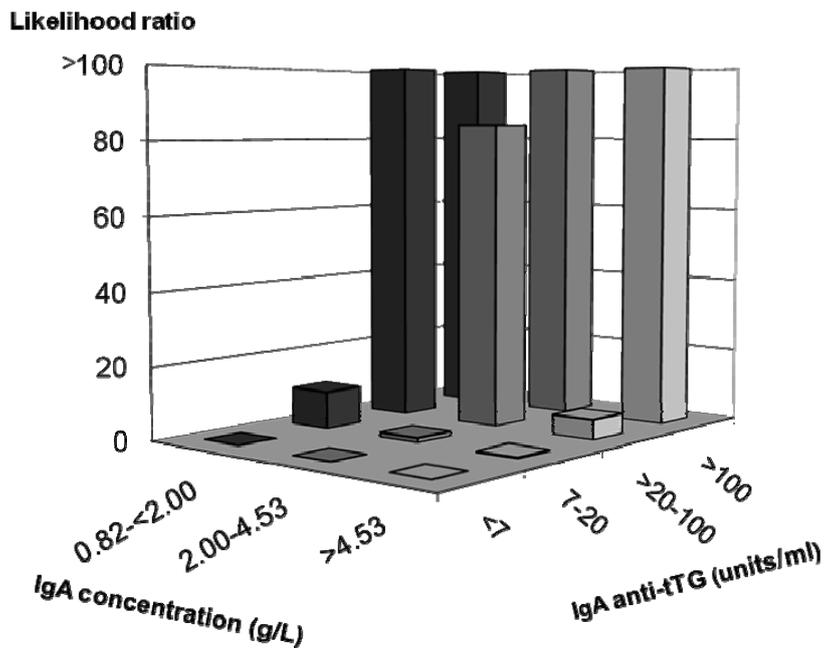


Figure 4: Likelihood ratios for different IgA concentration intervals and IgA anti-tTG concentration intervals.

2.3 Conclusion

Taking into account IgA anti-tTG concentration and serum IgA concentration improves clinical interpretation.

2.4 To Do's

- To report the likelihood ratio of the relevant interval to clinicians.

3) Is the detection of IgG antibodies against deamidated gliadin peptides (IgG DGP-AGA) a better alternative than IgG anti-gliadin antibodies (IgG AGA) in patients with a selective IgA deficiency?

3.1 Critical appraisal of the literature

Several authors have evaluated the usefulness of antibodies against deamidated gliadin peptides for the diagnosis of celiac disease (Table 2).²²⁻²⁵ There are currently two manufacturers of IgA and IgG DGP-AGA assays: Innova en Euroimmune. The price of these assays would be comparable to our current IgG AGA assay. One of these studies (Villalta et al., 2007) specifically investigated the performance in patients with a selective complete IgA deficiency (IgA <0.05 g/L). The studies by Volta et al.²⁴, Niveloni et al.²³ and Villalta et al.²⁵ show that detection of IgG DGP-AGA is both more sensitive and more specific than detection of IgG AGA. Based on the studies by Volta et al.²⁴, Niveloni et al.²³ and Ankelo et al.²², the sensitivity and specificity of IgG DGP-AGA does not seem to be superior to the much better characterized IgA anti-tTG.

While several authors have evaluated the performance in selected patients with CD and diseased controls or healthy volunteers, there is only one study which investigated the performance in consecutive patients (Niveloni et al., 2007).²³ The prevalence of CD in the study by Niveloni et al., however, was 42.5%. The results of this study with regard to positive and negative predictive value and the possible use of 2 screening tests are therefore not useful for our setting. The number of diseased control patients (n=81) in this study is also too low to allow a good estimate of the false-positive rate. Further research is needed to determine the diagnostic performance, especially the false-positive rate, of IgG DGP-AGA in routine clinical practice.

3.2 Conclusion

Studies have shown that the detection of IgG DGP-AGA is both more sensitive and more specific than detection of IgG AGA. In these studies, the sensitivity and specificity of IgG DGP-AGA was not superior to the much better characterized IgA anti-tTG. IgG DGP-AGA appears to be a better alternative than IgG AGA in patients with selective IgA deficiency, but cannot replace IgA anti-tTG as routine screening assay in non-IgA deficient patients. Further research is needed to determine the diagnostic performance, especially the false-positive rate, of IgG DGP-AGA in routine clinical practice.

3.2 To Do's

- Evaluate both IgG DGP-AGA assays on the consecutive non-IgA deficient patients described in 1.1.
- Replace IgG AGA with IgG DGP-AGA in patients with selective IgA deficiency

Table 1: Studies assessing performance of antibodies against deamidated gliadin peptides

	Patient selection	Consecutive patients	Prevalence	All Duodenal biopsy	Selection bias	Celiac disease	Diseased controls	Healthy individuals	Test	Method	Sensitivity	Specificity
Volta et al., 2008 ²⁴	Selected CD (M3) and DC patients	No	NA	Yes	Yes	128	134	None	IgA anti-tTG IgA DGP-AGA IgG AGA IgG DGP-AGA	Eurospital Inova Eurospital Inova	96.8% 83.6% 73.4% 84.4%	91.0% 90.3% 76.9% 98.5%
Villalta et al., 2007 ²⁵	Consecutive patients with a complete IgA deficiency and 113 controls	No	NA	Yes	Yes	20	63	50	IgG anti-tTG IgG AGA IgG DGP-AGA	Inova Radim Inova	95% 40% 80%	99% 87% 98%
Niveloni et al., 2007 ²³	Unselected consecutive patients attending small bowel clinic	Yes	43%	Yes	Yes	60	81	0	IgA anti-tTG IgA DGP-AGA IgG DGP-AGA	Inova Inova Inova	95.0% 98.3% 96.7%	97.5% 93.8% 100%
Ankelo et al., 2007 ²²	Selected CD patients and healthy controls	No	NA	Yes	Yes	87	0	81	IgA anti-tTG IgA DGP-AGA IgG AGA IgG DGP-AGA	Biofile In-house Biofile In-house	90% 92% 78% 75%	90% 90% 64% 98%

To do/ACTIONS

- 1) Inform clinicians that the performance of the current IgA anti-tTG assay is good.
- 2) To report the likelihood ratio of the relevant interval to clinicians
- 3) Evaluate both IgG DGP-AGA assays on the consecutive non-IgA deficient patients described in 1.1.
- 4) Replace IgG AGA with IgG DGP-AGA in patients with selective IgA deficiency

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