Antibodies Against Deamidated Gliadin Peptides and Tissue Transglutaminase for Diagnosis of Pediatric Celiac Disease

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ABSTRACT

Objectives: The aim of the present study was to evaluate diagnostic performance and actual costs in clinical practice of immumoglobulin (Ig)G/IgA deamidated gliadin peptide antibodies (DGP) as a complement to IgA antibodies against tissue transglutaminase (tTG) for the diagnosis of pediatric celiac disease (CD).

Methods: All of the consecutive patients younger than 18 years tested for tTG and/or DGP, who underwent duodenal biopsy because of suspected CD in Stockholm and Gothenburg, Sweden, from 2008 to 2010, were included. Medical records were reviewed.

Results: Of 537 children who underwent duodenal biopsy, 278 (52%) had CD. A total of 71 (13%) were younger than 2 years and 16 (4%) had IgA deficiency. Sensitivity and specificity for tTG were 94% and 86%, respectively. Corresponding values for DGP were 91% and 26%. Positive predictive values (PPV) were 88% for tTG and 51% for DGP. There were 148 children who were tTG-negative and DGP-positive, of which only 5% (8/148) had villous atrophy. Among children younger than 2 years with normal IgA, PPV was 96% (25/26) for tTG and 48% (24/50) for DGP. In 16 IgA-deficient children, 11 were DGP positive, of which 5 had CD (PPV 45%). Eight of 278 cases of CD would possibly have been missed without DGP. The cost of adding DGP and consequently more biopsies to be able to detect 8 extra cases of CD was €399,520 or €49,940 per case.

Conclusions: For diagnosing CD, tTG is superior to DGP, even in children younger than 2 years. Combining tTG and DGP does not provide a better tradeoff between number of missed cases of CD, number of unnecessary duodenal biopsies, and cost than tTG alone.

Key Words: celiac disease, child, diagnosis, positive predictive value

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Celiac disease (CD) is a common chronic autoimmune disorder with a prevalence around 1% in Europe (1) and as much as 3% in a recent Swedish screening study (2). The diagnosis is based on a combination of serology tests and pathological mucosa from intestinal biopsies (3,4). Immunoglobulin A (IgA) tissue transglutaminase (tTG) is considered the best test with sensitivity and specificity of >95% but performs less well in children younger than 2 years and IgA-deficient individuals (5). The combined IgG/IgA deamidated gliadin antibody test (IgG/IgA-deamidated gliadin peptide antibodies [DGP]) or the IgG-DGP also performs well with both high sensitivity and specificity (5–7). DGP has replaced antibodies against native gliadin (8) because of much better test characteristics. DGP has been proposed to be a good complement to tTG (9–11), especially in case of IgA deficiency (12).

Despite excellent test characteristics for DGP in research laboratories, evaluations in everyday clinical practice of the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), as well as the cost of introducing the test, are lacking. In 2008, analyses against DGP were introduced into routine medical care at the immunological laboratories in Stockholm (IgG-DGP) and Gothenburg (IgG/IgA-DGP), the 2 largest cities in Sweden, as a complement to IgA-tTG.

We conducted a population-based chart review of test characteristics, as used in clinical practice, to establish whether DGP test kits had improved the workup for CD in children and to what cost.

METHODS

Inclusion

"All of the consecutive patients younger than 18 years who were tested for tTG and/or DGP and underwent duodenal biopsy because of suspected CD in Stockholm and Gothenburg (roughly one-third of Sweden's population according to Statistics Sweden; *www.scb.se*) between September 1, 2008, and March 31, 2010, were included (n = 630, Fig. 1). Medical records were reviewed for clinical presentation and duodenal biopsy pathology report. Serology data were obtained from the laboratory report databases at the departments of clinical immunology of the participating hospitals.

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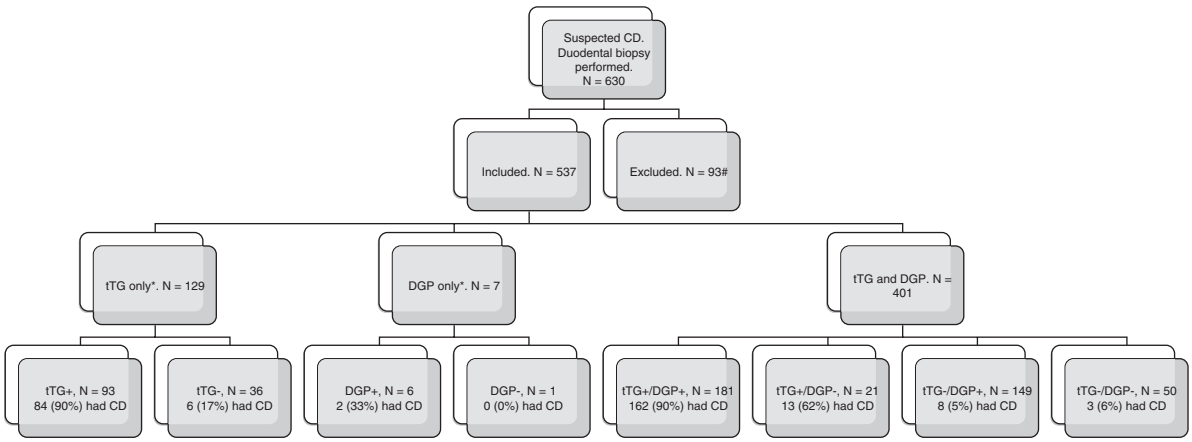

FIGURE 1. All of the study participants, exclusions, and proportion of celiac disease (CD) among different combinations of test results. *In 136 individuals, only tTG or DGP was analyzed. #Ninety-three individuals were excluded because the serology analyses had not been carried out at the participating immunology departments. Fifty-five of 93 individuals had CD, 5 of 93 had intraepithelial lymphocytosis and 33 of 93 had normal duodenal mucosa.

Exclusion

Children were excluded if the CD serology preceding the duodenal biopsy had not been performed in one of the departments of clinical immunology of the participating hospitals (n = 93 [15%], Fig. 1). If CD serology had been performed in other laboratories, it would have been difficult to confirm test values and type of test kit used.

Definition of CD

All of the participants had been referred to a pediatric gastroenterology unit because of suspected CD and underwent duodenal biopsy under general anesthesia. It was mandatory in all of the participating centers to take 4 biopsies from the distal duodenum and 2 biopsies from the duodenal bulb. CD was defined as Marsh 3 (total villous atrophy, subtotal villous atrophy, or partial villous atrophy) (13). Two individuals had crypt hyperplasia (Marsh 2) and were also regarded as having CD. They both had gastrointestinal symptoms and positive serology titers. Pathology reports of Marsh 1 (intraepithelial lymphocytosis) were not regarded specific enough to represent CD, irrespective of serology results (13). Individuals with Marsh 0 (normal mucosa) were regarded as not having CD (13).

Serology Tests Used

The serology test kits and cutoff values used (cutoff values as suggested by the manufacturers were used) are summarized in the online-only Supplemental Digital Content 1 (*http://links.lww.com/MPG/A149*). In Stockholm, the tests GAFx3 enzyme linked immunosorbent assay (ELISA) (Euroimmun Medizinische Labordiagnostika AG, Lübeck, Germany) and Celikey, ELISA (Phadia AB, Uppsala, Sweden) were used. In Gothenburg QUANTA Lite Celiac DGP Screen ELISA (INOVA Diagnostics Inc, San Diego, CA), and Celikey, ImmunoCAP (Phadia AB, Uppsala, Sweden) were used.

Cost Data

Direct medical costs for serology analyses were based on figures provided by the economy units of the participating immunology departments. The mean cost (or charge) that health care providers had actually paid for the serology analyses during the study period and the total number of analyses performed in children during the study period were provided.

Direct medical costs of duodenal biopsies in general anesthesia were based on figures provided by the economy units of the participating gastroenterology and anesthesiology departments. Direct costs included physician costs, pathologist costs, facilities, and/or hospitalization costs for anesthetic and endoscopic procedures. We did not include indirect patient costs (time lost from parents' work or transportation costs) in the model.

Statistics

Sensitivity, specificity, PPV, and NPV for IgA-tTG and IgG-DGP used alone or in combination were calculated for children undergoing duodenal biopsy. The number of gastroscopies owing to false-positive serologies was also calculated. Receiver operating characteristics (ROC) curves were plotted. The number of CD cases that would likely have been missed if DGP had not been included in the CD workup was calculated assuming that a negative tTG would not have led to a duodenal biopsy in the absolute majority of tested children.

Cost per diagnosed case of CD was calculated in 2 scenarios:

1. Costs for all of the pediatric analyses of tTG and DGP performed in the participating hospitals during the study period and costs for all of the gastroscopies performed in the study population were divided by all of the new cases of CD.
2. In an alternative scenario, the number of cases that would have been missed without the use of DGP was subtracted from the total number of CD cases in the study. We excluded all of the costs for DGP in the population (approximation based on costs for DGP in Stockholm) and all of the costs of gastroscopies of children with a positive DGP and a negative tTG. Total cost for serologies and endoscopies in this scenario was divided with cases that would have been detected even without use of DGP.

RESULTS

Five hundred thirty-seven children underwent duodenal biopsy and fulfilled criteria for participation, of which 278 (52%) had CD (Fig. 1). Age ranged from 12 months to 18 years (mean 7.6 years); 71 (13%) were younger than 2 years and 308 (57%) were girls (Table 1). Specific IgA values were available in

TABLE 1. Participant characteristics

	Celiac disease	Not celiac disease	Total
N (%)	278 (52)	259 (48)	537
Girls (%)	180 (58)	128 (42)	308
Boys (%)	98 (43)	131 (57)	229
Age (%)			
Mean (SD)	8.1 (4.5)	7.1 (5.0)	7.6 (4.8)
Median (IQR)	8.0 (4–12)	6.0 (3–11)	7.0 (3–12)
Younger than 2 y (%)	26 (37)	45 (63)	71
IgA deficiency (%)	5 (31)	11 (69)	16
Symptoms preceding workup (%)			
GI complaints	182 (51)	176 (49)	358
Non-GI symptoms	58 (50)	59 (50)	117
Risk group screening*	38 (61)	24 (39)	62
Stockholm	166 (48)	179 (52)	345
Gothenburg	112 (58)	80 (42)	192

GI = gastrointestinal; IgA = immunogobulin A; IQR = interquartile range; SD = standard deviation.
* Risk groups screened: diabetes mellitus type I, Down syndrome, family member with celiac disease, and so on.

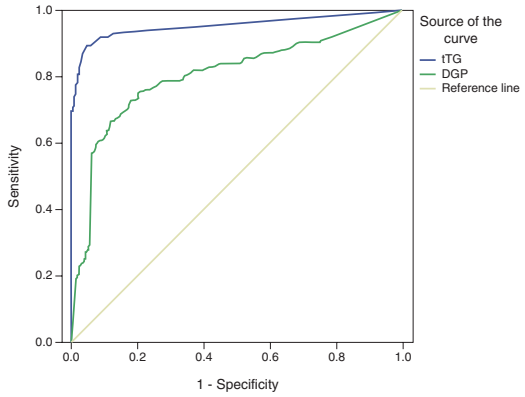

FIGURE 2. Receiver operating characteristics of tissue transglutaminase and deamidated gliadin peptides in all of the children in the study (age 0–17 years). Tissue transglutaminase (tTG): area under the curve = 0.95 (95% CI 0.93%–0.98%); deamidated gliadin peptides (DGP): area under the curve 0.81 (95% CI 0.76%–0.85%).

366 children, of whom 16 (4%) had IgA deficiency (Table 1). Symptoms preceding workup for suspected CD were gastrointestinal complaints (n = 358 [66%]), nongastrointestinal symptoms (n = 117 [22%]), and screening of risk groups (eg, heredity for CD, diabetes mellitus, or Down syndrome, and so on, n = 62 [12%]) (Table 1).

Diagnostic Characteristics of tTG and DGP in the Total Sample

tTG had been analyzed in 530 (99%) of children and DGP had been analyzed in 408 (76%) (Fig. 1). The ROC curve was significantly better for tTG compared with DGP (Fig. 2). The ROC curve restricted to children younger than 2 years was based on few individuals (n = 71) and should be interpreted with caution. DGP was not superior to tTG among children younger than 2 years (online-only Supplemental Digital Content 2, *http://links.lww.com/MPG/A150*). In post-hoc analyses, we also made ROC curves for children younger than 3, 4, 5, 6, and 7 years, all of which showed a tendency to tTG being better than DGP; however, ROC curves in all of the age groups had narrowly overlapping confidence intervals, and results should still be interpreted with caution (online-only Supplemental Digital Content 2, *http://links.lww.com/MPG/A150*). Among children undergoing duodenal biopsy for suspected CD, sensitivity, specificity, PPV, and NPV for tTG were 94%, 86%, 88%, and 93%, respectively (Table 2). Corresponding values for DGP were 91%, 26%, 51%, and 78% (Table 2). If intermediate values had been regarded as negative, the sensitivity, specificity, PPV, and NPV would have been 91%, 91%, 92%, and 90% for tTG

TABLE 2. Performance of immunoglobulin antibodies against deamidated gliadin peptides and tissue translutaminase in the whole study population

		Not celiac disease			
	Celiac disease	IEL	Normal mucosa	Row sum	
tTG* positive	251	12	10	273	PPV 88%†
tTG* borderline	8	6	8	22	
tTG* negative	17	12	206	235	
		30	224		
Column sum	276	254		530‡	
	Sensitivity 94%‡	Specificity 86%‡			
DGP‖ positive	165	15	110	290	PPV 51%†
DGP‖ borderline	7	5	34	46	
DGP‖ negative	16	3	53	72	
		23	197		
Column sum	188	218		408‡	
	Sensitivity 91%‡	Specificity 26%‡			

IEL = intraepithelial lymphocytosis; DGP = deamidated gliadin peptide antibodies; PPV = positive predictive values; tTG = tissue transglutaminase.
* Immunoglobulin A antibodies against tissue transglutaminase.
† If borderline values had been regarded as negative, PPV for tTG and DGP would have been 91% and 57%, respectively.
‡ Among the 537 individuals included in the study, 530 had been tested with tTG, 408 with DGP, and 401 with both.
‖ Immunoglobulin G or G/A antibodies against deamidated gliadin peptides.
§ If borderline values had been regarded as negative, then sensitivity and specificity for tTG would have been 91% and 91%. Corresponding results for DGP would have been 88% and 44%.

(Table 2) and 88%, 44%, 57%, and 81% for DGP (Table 2). If intraepithelial lymphocytosis had been regarded as CD, the sensitivity, specificity, PPV, and NPV would have been 86%, 92%, 94%, and 88% for tTG (Table 2) and 90%, 26%, 57%, and 74% for DGP (Table 2). tTG performed better than DGP, regardless of test kits used (online-only Supplemental Digital Content 3, *http://links.lww.com/MPG/A151*; and online-only Supplemental Digital Content 4, *http://links.lww.com/MPG/A152*) or cutoff levels chosen (Fig. 2 and online-only Supplemental Digital Content 2–4, *http://links.lww.com/MPG/A150*, *http://links.lww.com/MPG/A151*, *http://links.lww.com/MPG/A152*).

There were 149 children who were tTG negative and DGP positive (ie, children who would likely not have undergone duodenal biopsy if DGP had not been used; Fig. 1). In this subgroup, only 8 of 149 had villous atrophy, corresponding to a PPV of 5%, or 20 negative duodenal biopsies per new case of CD. In case intermediate values would have been regarded as negative, PPV for a positive DGP together with a negative tTG would have been 6% (7/115). All of the children undergoing duodenal biopsy in spite of negative serologies (tTG or DGP alone or both combined) had gastrointestinal symptoms suggestive of CD. The 3 children in this group who had villous atrophy improved on a gluten-free diet and had a normal mucosa on control biopsy. Patient characteristics of children who were only tested for either tTG (n = 129) or DGP (n = 7) did not differ markedly from the total sample, except for the fact that only 6 of 136 children were younger than 2 years in this group (data not shown).

No false-positives were found among the 143 (53%) CD cases who had a tTG value >80 U/mL (ie, 10 times the cutoff for a clearly positive value stated by the manufacturer). False-positive values of DGP ranged from intermediate values to >200 U/mL (data not shown).

Diagnostic Characteristics of Children Younger Than 2 Years and of IgA-deficient Children

Among the 71 children younger than 2 years with normal IgA, the proportion of positive serologies representing CD (ie, PPV) were 96% (25/26) for tTG and 48% (24/50) for DGP (Table 3). No patient with CD younger than 2 years would have been missed if DGP had not been used in this sample (1 child younger than 2 years had a negative tTG, but also a negative DGP and had been biopsied because of extensive symptoms). In 16 IgA-deficient children, 11 were DGP-positive, of which 5 had CD, corresponding to a PPV of 45%.

Costs

During the study period, 26,180 unique children underwent serologic testing (tTG and/or DGP) for suspected CD in the participating study centers. Cost of all serologic testings for CD in children of all ages during the study period, when tests for both tTG and DGP were available, was €51 per test kit. If DGP would not have been available, the price would have been €42 per test kit.

The mean cost of endoscopy in general anesthesia during the study period was €1100. The total cost for CD work-up in the study population was €1,925,840, or €6878 per new case of CD (total cost of all serologies and all duodenal biopsies divided by all new cases of CD). If DGP would not have been available, the total workup cost would have been lower, but resulted in more missed cases of CD. In a scenario without DGP, 8 cases of CD could have been missed (for patient characteristics, see Fig. 1). In this setting, the cost of using DGP to find these 8 cases of CD, that would possibly otherwise have been missed, amounts to €399,520 or €49,940 per extra CD case.

We also compared different test strategies among the 401 children who had been tested for both tTG and DGP. The consequences of different testing strategies with regard to number of CD cases missed, number of unnecessary duodenal biopsies, and cost per detected CD case are summarized in Table 4. A test strategy requiring both a positive tTG and a positive DGP rendered the best specificity and the lowest cost (Table 4). A strategy requiring either a positive tTG or a positive DGP rendered the highest sensitivity and the highest cost (Table 4). The use of tTG alone was the best tradeoff between sensitivity, specificity, and cost (Table 4).

TABLE 3. Performance of immunoglobulin antibodies against deamidated gliadin peptides and tissue transglutaminase in 71 pediatric patients younger than 2 years

		Not celiac disease			
	Celiac disease	IEL	Normal mucosa	Row sum	
tTG* positive	24	0	0	24	PPV 96%†
tTG* borderline	1	0	1	2	
tTG* negative	1‡	2	38	41	
		2	39		
Column sum	26		41	67§	
	Sensitivity 96%‖		Specificity 98%‖		
DGP¶ positive	24	2	24	50	PPV 44%†
DGP¶ borderline	0	0	5	5	
DGP¶ negative	0	0	14	14	
		2	43		
Column sum	24		45	69§	
	Sensitivity 100%‖		Specificity 31%‖		

IEL = intraepithelial lymphocytosis; DGP = deamidated gliadin peptide antibodies; PPV = positive predictive values; tTG = tissue transglutaminase.
* Immunoglobulin A antibodies against tissue transglutaminase.
† If borderline values had been regarded as negative, then PPV for tTG and DGP would have been 100% and 48%, respectively.
‡ This patient had not been tested for DGP, but underwent duodenal biopsy because of strong clinical suspicion.
§ Among the 71 children younger than 2 years included in the study, 67 had been tested with tTG, 69 with DGP, and 65 with both.
‖ If borderline values had been regarded as negative, then sensitivity and specificity for tTG would have been 92% and 100%. Corresponding values for DGP would have been 100% and 42%.
¶ Immunoglobulin G or G/A antibodies against deamidated gliadin peptides.

TABLE 4. Costs, number of celiac disease cases missed, and number of unnecessary duodenal biopsies performed when evaluating different testing strategies in 401 children tested for both tissue transglutaminase and deamidated gliadin peptides

Test results required to perform biopsy	1 tTG+ and DGP+*	2 tTG+ only	3 DGP+ only	4 tTG+ or DGP+	5 tTG+ or DGP+ or grave symptoms
No. biopsies†	181	202	330	351	401
No. positive tests	181	202	330	351	401
No. negative tests	220	199	71	50	0
PPV‡	162/181 (90%)	175/202 (87%)	183/351 (52%)	170/330 (52%)	186/401 (46%)
NPV‡	194/220 (88%)	186/199 (93%)	53/71 (75%)	45/50 (90%)	—
Sensitivity‡	162/188 (86%)	175/188 (93%)	170/188 (90%)	183/188 (97%)	—
Specificity‡	194/213 (91%)	186/213 (87%)	160/213 (25%)	45/213 (21%)	—
CD cases found	162	162 + 13 = 175	162 + 8 = 170	162 + 13 + 8 = 183	162 + 13 + 8 + 3 = 186
Costs of					
Serologies	€51 × 401 = €20,451	€4 × 401 = €16,842	€3 × 401 = €14,035	€5 × 401 = €20,451	€5 × 401 = €20,451
Biopsies	18 × €1100 = €199,100	20 × €1100 = €222,200	33 × €1,100 = €363,000	35 × €1100 = €386,100	40 × €1100 = €441,100
Summary					
Total cost	€219,551	€239,042	€377,035	€406,551	€461,551
CD found (true-positives)	162 (87%)	175 (94%)	170 (91%)	183 (98%)	186 (100%)
CD missed (false-negatives)	26 (14%)	13 (7%)	18 (10%)	5 (3%)	—
Unnecessary biopsies	19	27	160	168	215
Cost per case CD found	€1355	€1366	€2135	€2221	€2481

CD = celiac disease; DGP = deamidated gliadin peptide antibodies; tTG = tissue transglutaminase.
* Positive result (+) of IgA antibodies against tTG and IgG (or IgG + IgA) antibodies against DGP.
† Number of children undergoing duodenal biopsy for suspected CD.
‡ Note that the true sensitivity, specificity, and negative predictive values are not possible to calculate because the majority of children tested for tTG or DGP did not undergo duodenal biopsy.

If duodenal biopsies would not have been performed in the 143 children with tTG >80 U/mL, total cost of workup for CD during the study period would have decreased by €157,300 (8%).

DISCUSSION

We reviewed performance of tTG and DGP as used when diagnosing consecutive cases of CD in clinical practice. Of 278 cases, 8 could possibly have been missed if only tTG but not DGP had been available. The cost of detecting the extra 8 cases by introducing DGP was considerable in terms of number of unnecessary duodenal biopsies and money. DGP was not superior to tTG in children younger than 2 years, and was of questionable value in IgA-deficient children.

To our knowledge, this is the first evaluation of the performance and cost of DGP as prospectively tested in clinical practice in an unselected population seeking medical care. We were able to include all of the consecutive patients who underwent duodenal biopsy during the CD workup in the 2 largest Swedish cities, resulting in a large cohort for study. We had access to all medical chart data including original laboratory results and biopsy reports for all of the study participants as well as cost data for serology analyses and gastroscopies. Our findings of good test performance for tTG and poor test performance for DGP were consistent, regardless of analysis method used and regardless of which of the 2 independent and officially certified clinical laboratories that had carried out the analyses (online-only Supplemental Digital Content 3, *http://links.lww.com/MPG/A151*; and online-only Supplemental Digital Content 4, *http://links.lww.com/MPG/A152*).

Our study also has limitations. The absolute majority of children with negative serologies in primary care was naturally not referred for further workup and hence did not undergo duodenal biopsies. Therefore, we were able to evaluate the diagnostic performance in clinical practice post primary care screening, whereas diagnostic performance at the primary care level could not be calculated. Despite the relatively large size of the present study, the subanalyses of DGP performance in children younger than 2 years and in IgA-deficient children are based on small numbers, and those results should be interpreted with caution. Misclassification of CD status based on histological samples is possible (14), but because duodenal biopsies were reviewed by experienced pathologists in routine medical care, with no knowledge of the present study or its hypothesis, any misclassification of CD status is most likely nondifferential.

In a few earlier studies of tTG and DGP, consecutive patients with villous atrophy have been compared with patients with normal duodenal biopsies (6–10) and/or to healthy, unbiopsied controls (6,15). In all of the listed studies, serology analyses have been performed retrospectively in research laboratories, and performance of IgA-tTG and IgG-DGP has been excellent with mostly both high sensitivity (60%–99%) and specificity (80%–100%) regardless of test kit, but dependent on cutoff limits used. Most studies, including ours, used cutoff values as suggested by the manufacturers.

Our findings that performance of tTG is extremely good, but that sensitivity can be increased if tTG and DGP are combined (positive tTG or DGP required) are in concordance with earlier studies (7,9,11,15); however, the relatively poor test performance of DGP found in our study, with a large proportion of false-positives has only been described once before in a study of 116 children with high risk for CD (16). In that study, as well as in ours, serology samples were analyzed prospectively in standard medical care as opposed to all of the earlier studies, which may be part of the explanation for the dramatic difference in results regarding DGP specificity.

Earlier studies have concluded that DGP does not outperform tTG (not even in children younger than 2 years) (8,17), but that the combination of tTG and DGP has higher sensitivity than tTG alone (15), which is also in concordance with our findings. Some studies have suggested that DGP should be included as a complement to tTG in future diagnostic algorithms for CD (9–11), but monetary costs and unnecessary duodenal biopsies have hitherto not been investigated. Given the considerable costs and the high proportion (42%) of unnecessary biopsies when including DGP in the diagnostic algorithm, as we have shown in the present study, we support the recommendation that IgG-DGP is used only in children with IgA deficiency (5).

Our findings that there were no false-positive tTG values >80 U/mL and that it is potentially possible to safely exclude the biopsy in a subset of patients with suspected CD are in line with revised guidelines regarding CD (4).

CONCLUSIONS

In conclusion, tTG was superior to DGP, even in children younger than 2 years. IgG-DGP was of questionable value even in IgA-deficient children. The introduction of DGP as a complement to tTG for the workup of suspected CD in children rendered few extra cases of CD and generated considerable costs and many unnecessary gastroscopies performed under general anesthesia.

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