



Positive and negative predictive values of a combination of celiac disease serology test as compared to intestinal histology damage

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ABSTRACT

Background: Currently, the gold standard for the diagnosis of celiac disease (CD) is an upper GI endoscopy (EGD) with an intestinal biopsy. During the past few years, several non-invasive serological screening tools for CD have been developed. To establish the true sensitivity and specificity of these serological tests, either alone or in combination, and to develop possible non-invasive CD diagnostic algorithms alternative to EGD, a study design in which an intestinal biopsy is the entry criterion is necessary. **Aims:** To establish the positive predicted value (PPV) and negative predicted value (NPV) of a combination of serological tests for CD using an intestinal biopsy as a gold standard. **Methods:** Sixty-eight consecutive patients (average age 38 yrs, range 18-80) referred by the Small Bowel disorders clinic to EGD and intestinal biopsy because of suspicion of intestinal disorders (chronic diarrhea, weight loss, abdominal distention, recurrent abdominal pain, and/or anemia) were enrolled between August 2004 and July 2005 (Group A). During the same period, a random sample of patients (n=98, average age 47 yrs, range 23-73) undergoing to an EGD for symptoms or disorders not related to CD was also enrolled (Group B). All duodenal biopsies were blindly scored using the modified Marsh criteria by pathologists (AC and ZK). At the time of the procedure, a serum sample was also obtained to check for serum anti-actin antibodies (AAA), anti-tissue transglutaminase antibodies (TTG), and zonulin levels. **Results:** Thirty-three of the 68 patients from group A (48%) and 1/98 (1%) from group B showed histological findings compatible with CD (Marsh IIIa-IIIc). Of the 34 CD patients identified, 28 tested positive to all three tests, 3 tested positive to TTG and zonulin, and 3 tested positive to zonulin alone. The combination of AAA, TTG, and zonulin tests showed a sensitivity of 79%, a PPV of 100%, and a NPV of 100%. **Conclusions:** In subject experiencing malabsorptive symptoms, the combination of positive AAA, TTG, and zonulin can be used to rule in CD without the necessity to perform an EGD. This approach would have allowed avoiding an invasive procedure in 40% of the cases of malabsorption enrolled in this study, an approach that could translate in cost saving and better patient's acceptance. The combination of negative AAA, TTG, and zonulin rules out CD without the necessity of any additional study. In these cases, an EGD could be still necessary to rule out other causes of GI symptoms.

BACKGROUND

- Currently, the gold standard for the diagnosis of Celiac disease (CD) is an upper GI endoscopy (EGD) with an intestinal biopsy
- During the past few years, several non-invasive serological screening tools for CD have been developed
- To establish the true sensitivity and specificity of these serological tests, either alone or in combination, and to develop possible non-invasive CD diagnostic algorithms alternative to EGD, a study design in which an intestinal biopsy is the entry criterion is necessary

AIM

- To establish the positive predicted value (PPV) and negative predicted value (NPV) of a combination of serological tests for CD, using the intestinal biopsy as a gold standard

MATERIALS

Demographic and clinical data of the overall population

Patients
166 patients referred by the Small Bowel disorders clinic for an EGD, as a standard practice of care

- Group A:** with suspicious symptoms or disorders related to CD (diarrhea, weight loss, malnutrition, chronic anemia)
 - N of patients: 68
 - Age median (range) yr.: 38 (18 - 80)
- Group B:** without symptoms or disorders related to CD
 - N of patients: 98
 - Age median (range) yr.: 47 (23 - 73)

METHODS

Diagnostic procedures

Upper gastrointestinal endoscopy (EGD) and Intestinal biopsy. All duodenal biopsies were blindly scored by two pathologist using the modified Marsh criteria:

- Type 0, I, II, IIIa, IIIb and IIIc
- IEL density (IEL/100 epithelial cell)

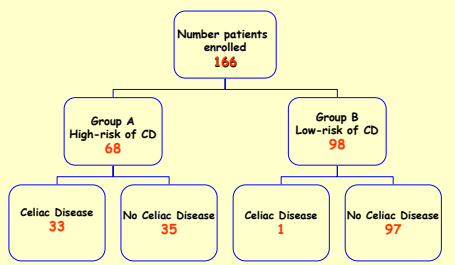
At the time of the EGD, a blood sample was drawn, to perform the assays below

Serum biochemical tests

- Anti-actin antibodies (AAA) (INOVA Diagnostics, Inc.CA, USA) Cut-off 25 AU/ml
- Anti-tissue transglutaminase antibodies (tTG-IgA) (INOVA Diagnostics, Inc.CA, USA) Cut-off 20 AU/ml
- Anti-endomysial antibodies (EMA-IgA) (Scimedx Corporation, NJ, USA)
- Zonulin levels (Center for Celiac Research, MD, USA)

RESULTS

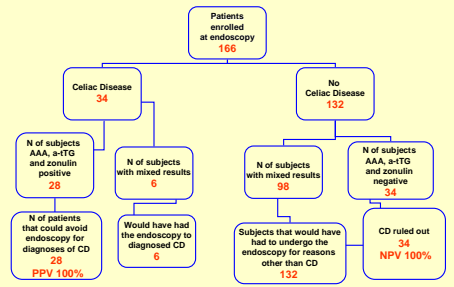
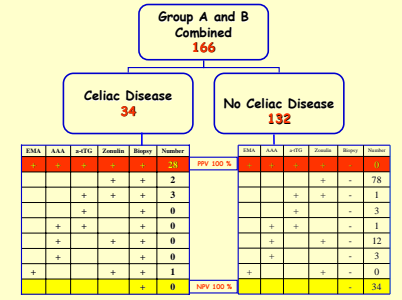
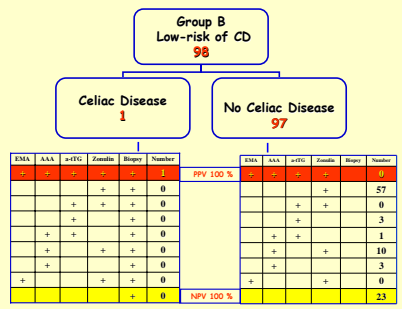
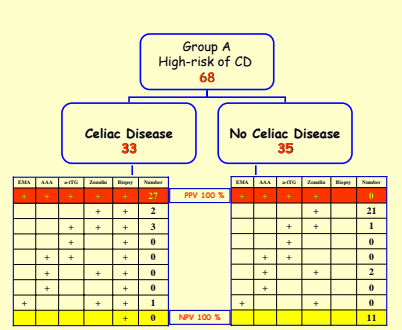
Celiac Disease Prevalence Among Enrolled Patients Based on Intestinal Biopsy Findings



Individual test or combinations	Sen %	Spe %	PPV %	NPV %	+LR	-LR	Acc %
a-tTG IgA	91.2	97.7	86.1	97.7	39.6	0.09	96.4
AAA IgA	82.3	97.7	63.6	95.1	35.8	0.18	94.5
Zonulin	100	31.1	27.2	100	1.45	0	45.2
A-tTG + zonulin	91.2	99.2	96.9	97.8	114	0.09	97.6
A-tTG + AAA	82.3	99.2	96.5	95.6	102.9	0.18	95.7
Zonulin + AAA	82.3	90.9	70	95.2	9.0	0.19	89.1
A-tTG + zonulin + AAA	82.3	100	100	100	INF	0.18	96.4
Ema	85.3	100	100	96.3	INF	0.15	97.0
Ema + zonulin	85.3	100	100	96.3	INF	0.15	97.0
Ema + a-tTG	82.3	100	100	96.3	INF	0.18	96.4
Ema + AAA + a-tTG + zonulin	82.3	100	100	85	INF	0.18	96.4

Statistical performance of individual tests or their combinations: Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio; Acc: diagnostic accuracy.

SUMMARY



- Thirty-three of the 68 patients from group A (48%) and 1/98 (1%) from group B showed histological findings compatible with CD (Marsh IIIa-IIIc)
- Of the 34 CD patients identified, 28 tested positive to all four tests, 3 tested positive to a-tTG and zonulin, 1 tested positive for EMA and zonulin, and 2 tested positive to zonulin alone
- The combination of EMA, AAA, a-tTG, and zonulin tests showed a sensitivity of 79%, a PPV of 100%, and a NPV of 100%
- Performing the Ema assay (a test that is time-consuming, expensive and operator-dependent) did not increase the PPV or NPV of the combination of the other three serological assays

CONCLUSIONS

- In subject experiencing symptoms suggesting a small bowel disorder, the combination of positive AAA, a-tTG, and zonulin can be used to rule in CD without the necessity to perform an EGD
- This approach would have allowed avoiding an invasive procedure in 40% (27/68) of the cases of high-risk enrolled in this study, an approach that could translate in cost saving and better patient's acceptance
- The combination of negative AAA, a-tTG, and zonulin rules out CD without the necessity of any additional study. In these cases, an EGD could be still necessary to rule out other causes of malabsorption