“Diagnóstico actual de las Patologías Asociadas al Gluten. Enfermedad Celíaca - Sensibilidad al Gluten No Celíaco”

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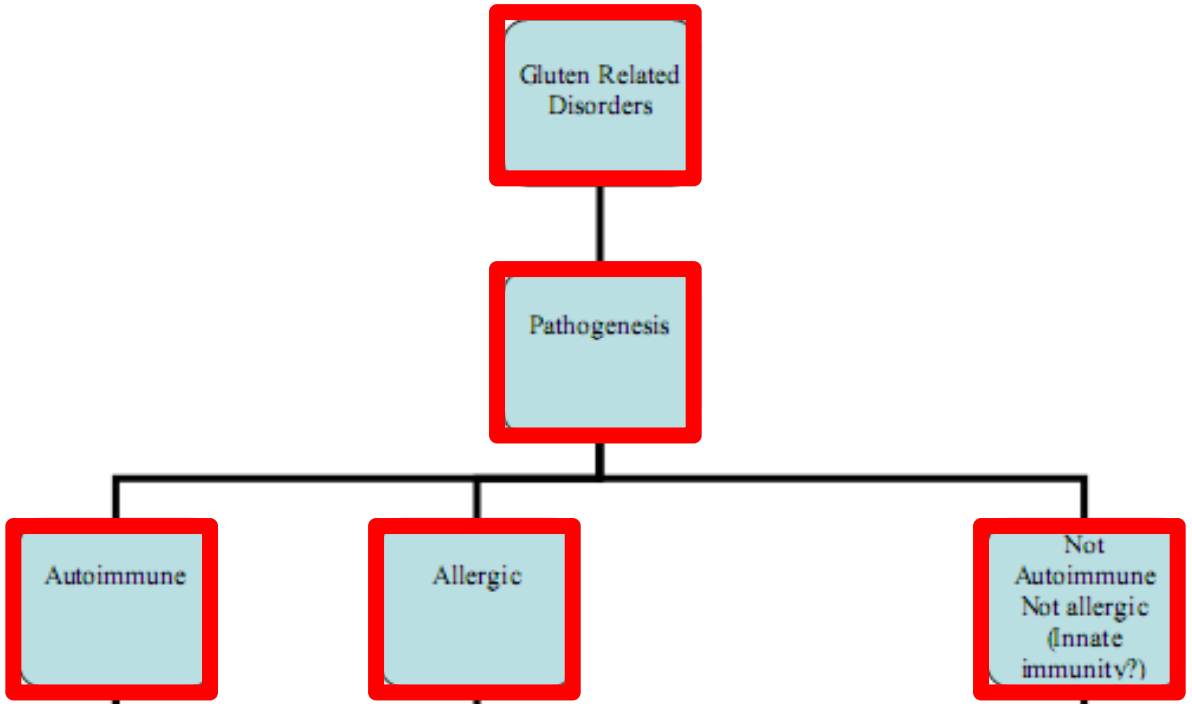
El gluten es el disparador de un heterogéneo set de condiciones clínicas que incluyen, la alergia al trigo, la sensibilidad al gluten y la enfermedad celíaca que en su conjunto afectan a cerca del 10% de la población general



Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

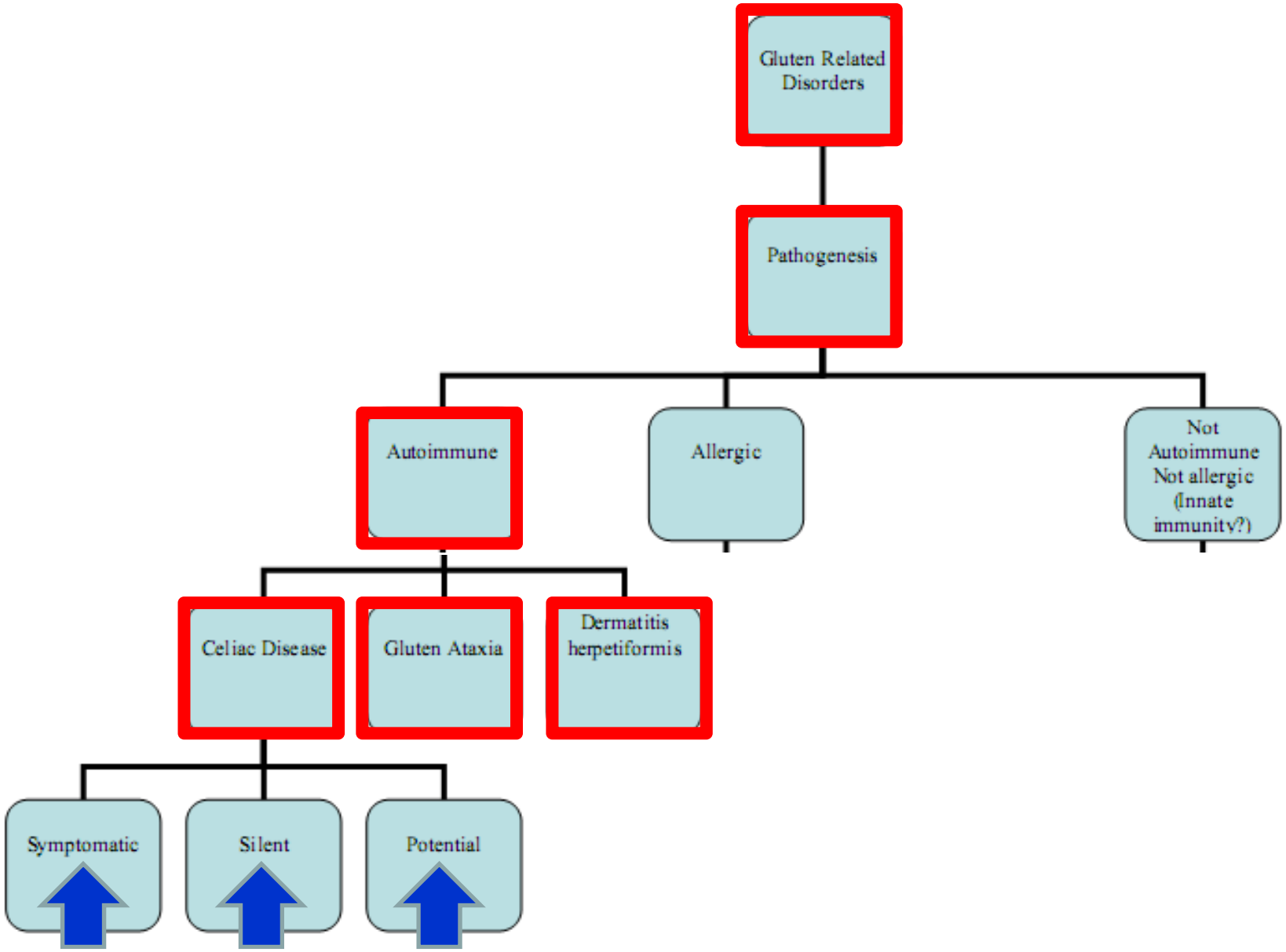


Figure 1 Proposed new nomenclature and classification of gluten-

Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

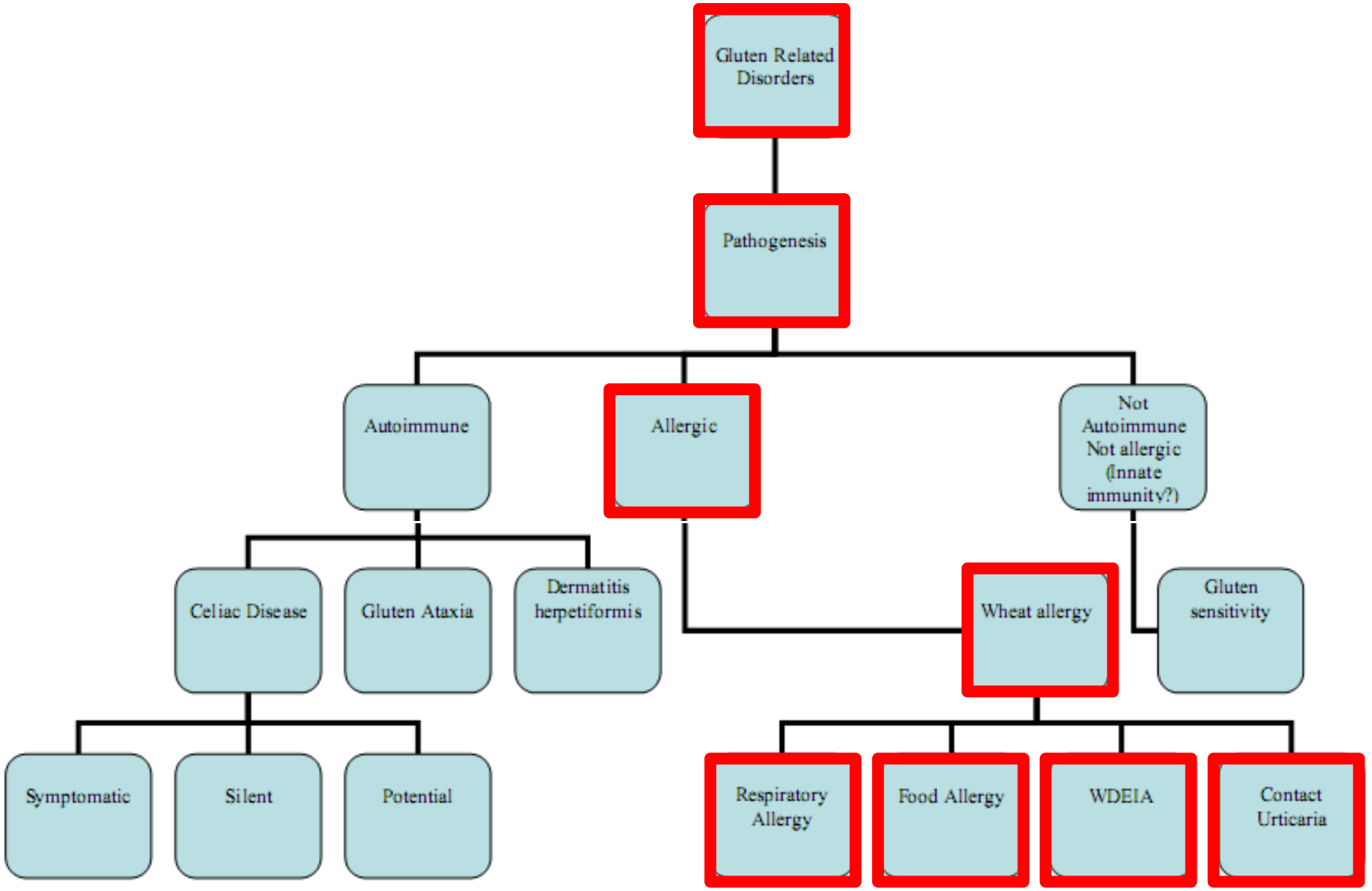


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

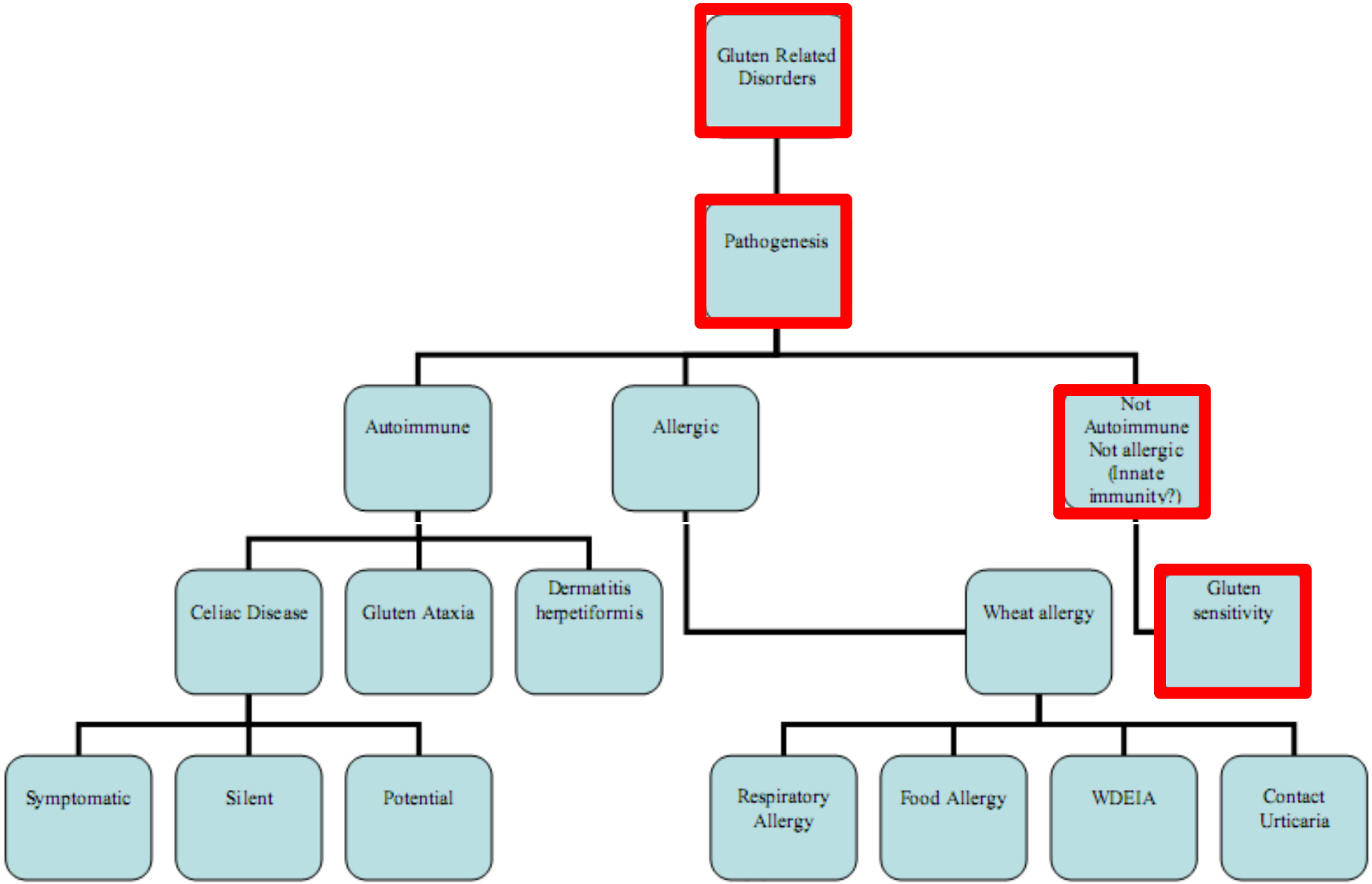


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

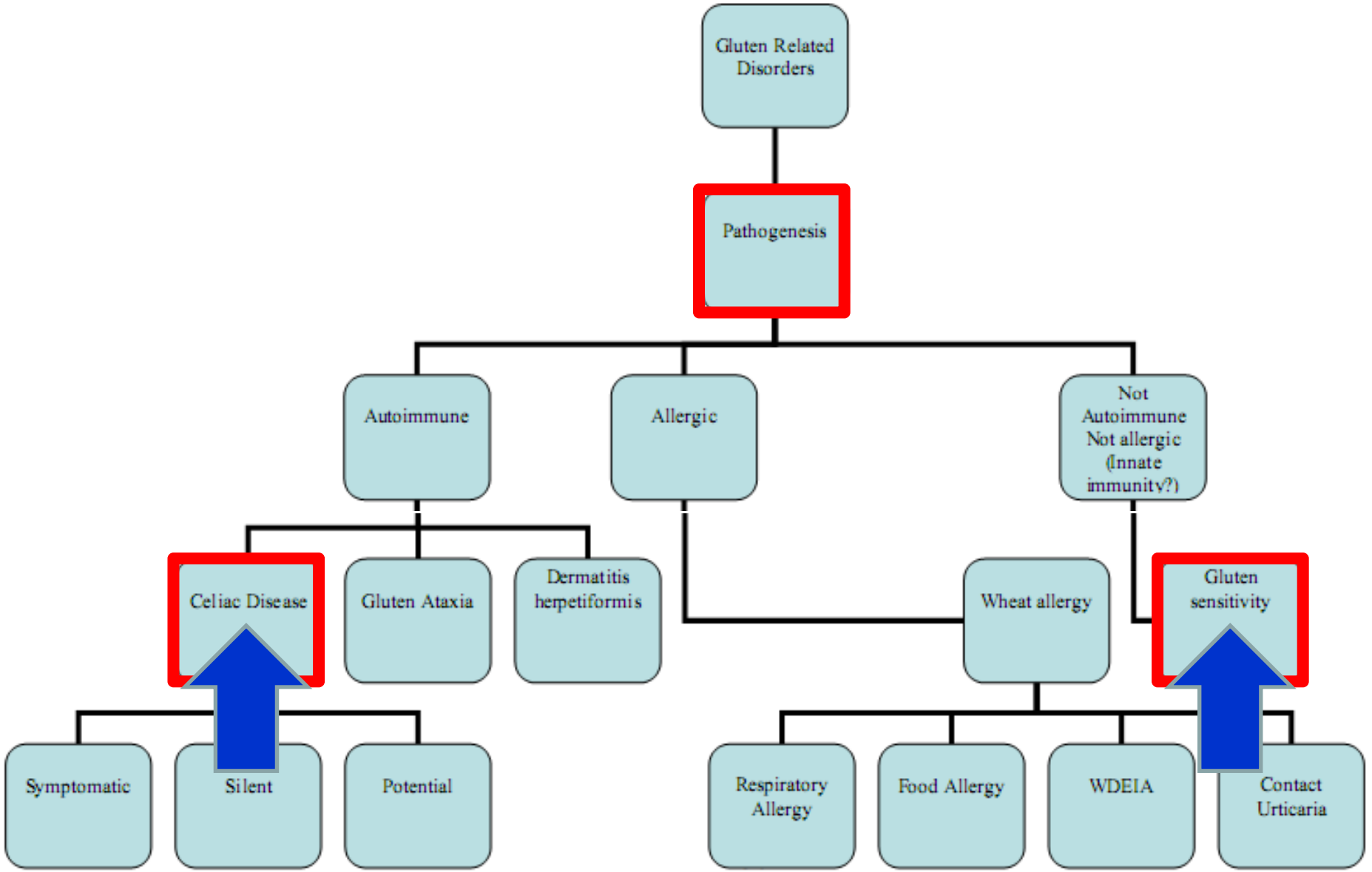


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

Enfermedad celíaca

Es una enfermedad sistémica autoinmune producida por la intolerancia permanente a una secuencia determinada de aminoácidos (gluten), mediada por células T en individuos genéticamente predispuestos

Sensibilidad al gluten

"La SG es una entidad recientemente descripta caracterizada por síntomas intestinales y extraintestinales relacionados con la ingesta de alimentos que contienen gluten, en individuos no celíacos [anticuerpos específicos negativos (a-tTG y EmA) sin enteropatía ni alérgicos al gluten"

Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

Annals of Internal Medicine | IDEAS AND OPINIONS

Nonceliac Gluten Sensitivity: Sense or Sensibility?

Antonio Di Sabatino, MD, and Gino Roberto Corazza, MD

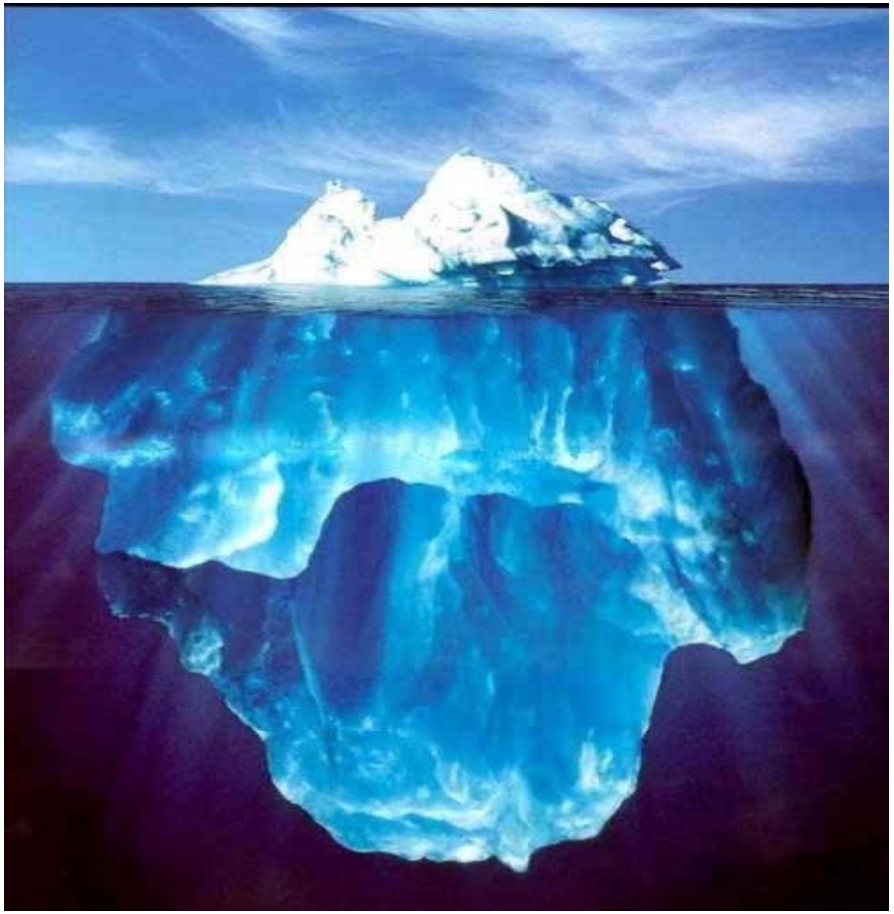
Table 1. **Main Characteristics Distinguishing Celiac Disease From Nonceliac Gluten Sensitivity**

Characteristic	Celiac Disease	Nonceliac Gluten Sensitivity
Synonyms	Celiac sprue, gluten-sensitive enteropathy	Nonceliac gluten intolerance, nonceliac wheat intolerance, gluten sensitivity, gluten hypersensitivity
Prevalence	About 1% of the general population	Unknown, but suspected to be higher than that of celiac disease
Genetics	Related to *HLA-DQ2* or *HLA-DQ8*	Unrelated to a specific HLA haplotype
Mechanisms	Predominant adaptive immune reaction to gluten peptides restricted by *HLA-DQ2* or *HLA-DQ8*	Unknown but multiple mechanisms are suspected, including innate immune reaction to gluten; IgE-mediated wheat allergy; starch carbohydrate malabsorption; opioid-like activity of gluten; gluten-induced, low-grade inflammation; and nocebo effect of gluten-containing food
Serum antibodies	Positive results on TTA, EMA, or AGA testing	Negative results on TTA and anti-EMA testing, sometimes positive results on IgG AGA testing
Villous flattening	Present	Absent
Symptoms	Intestinal and extraintestinal	Intestinal and extraintestinal
Morbidity	Increased	No data
Mortality	Increased	No data

AGA = antigliadin antibodies; EMA = endomysial antibodies; TTA = antitransglutaminase antibodies.

Ann Intern Med. 2012;156:309-311.

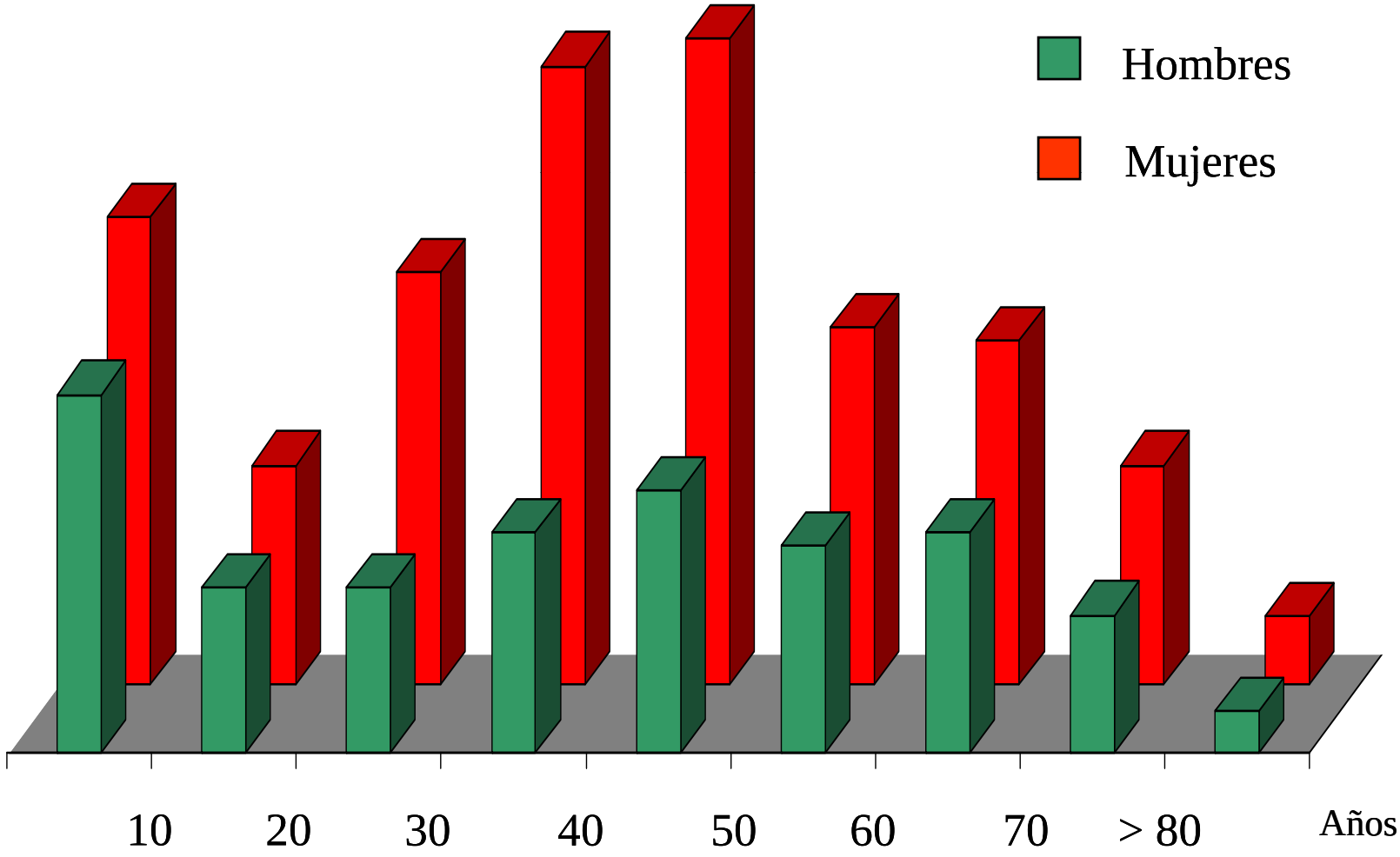
Epidemiología de la Enfermedad Celíaca Pasado?



Epidemiología de la Enfermedad Celíaca
Presente

EC: GENERO Y EDAD

Nro ptes x año



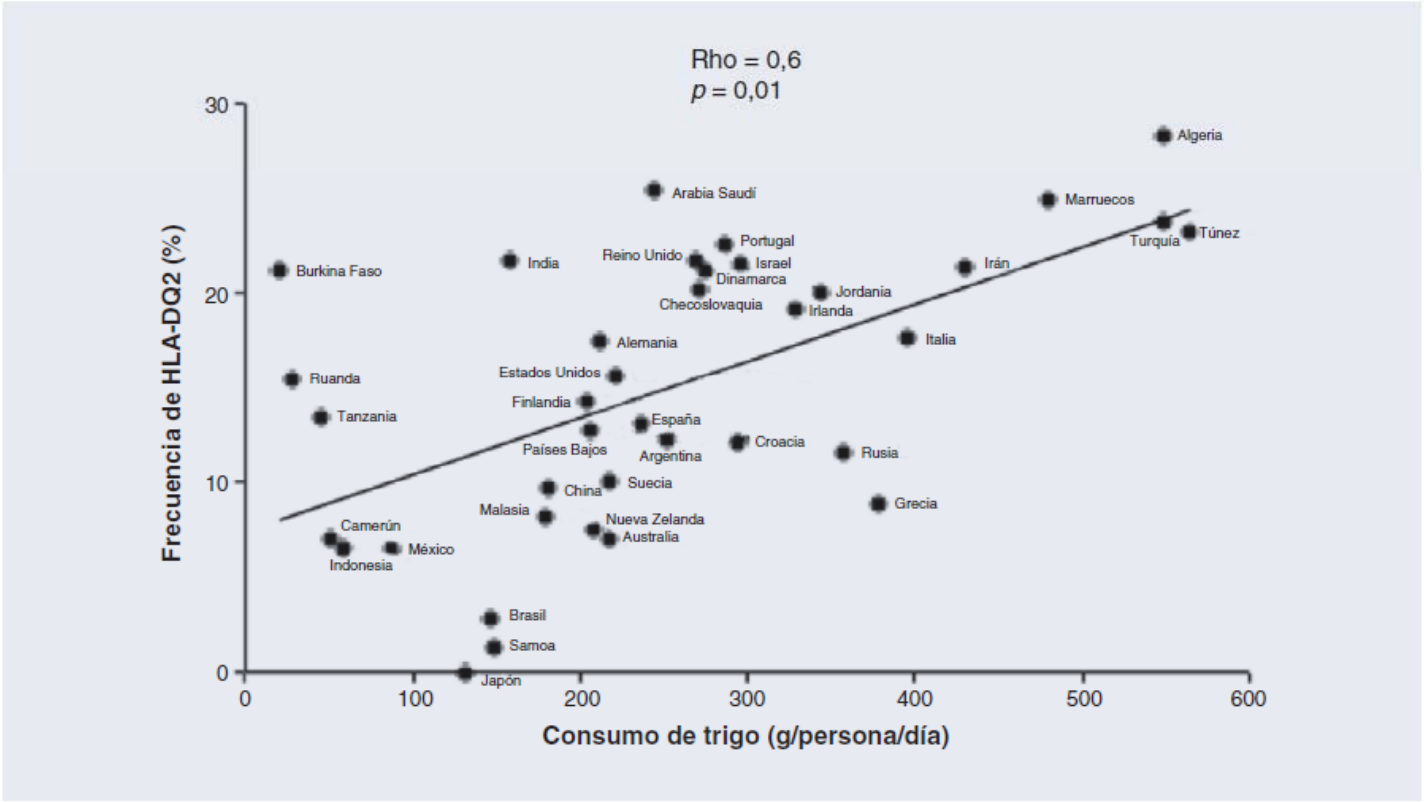


FIGURA 1-4. Correlación entre el nivel de consumo de trigo y la frecuencia de HLA-DQ2. *(Modificado de Lionetti E, Catassi C. Co-localization of gluten consumption and HLA-DQ2 and -DQ8 genotypes, a clue to the history of celiac disease. Dig Liver Dis 2014;46(12):1057-63.)*

FIGURA 1-2. distribución geográfica de la prevalencia de enfermedad celíaca (%) en el mundo. *(Tomado de Lionetti E, Catassi C. Co-localization of gluten consumption and HLA-DQ2 and -DQ8 genotypes, a clue to the history of celiac disease. Dig Liver Dis 2014;46(12):1057-63.)*

Enfermedad celíaca

Patogénesis

. Predisposición genética
. Falla en la tolerancia al gluten
. Alteración de la permeabilidad?
. Fenómenos inmunológicos
- Inmunidad innata
- linfocitos T gluten reactivos específicos
- Inmunización activa contra el gluten
- Desarrollo de autoinmunidad

Enfermedad celíaca

Patogénesis

Fenómenos inmunológicos

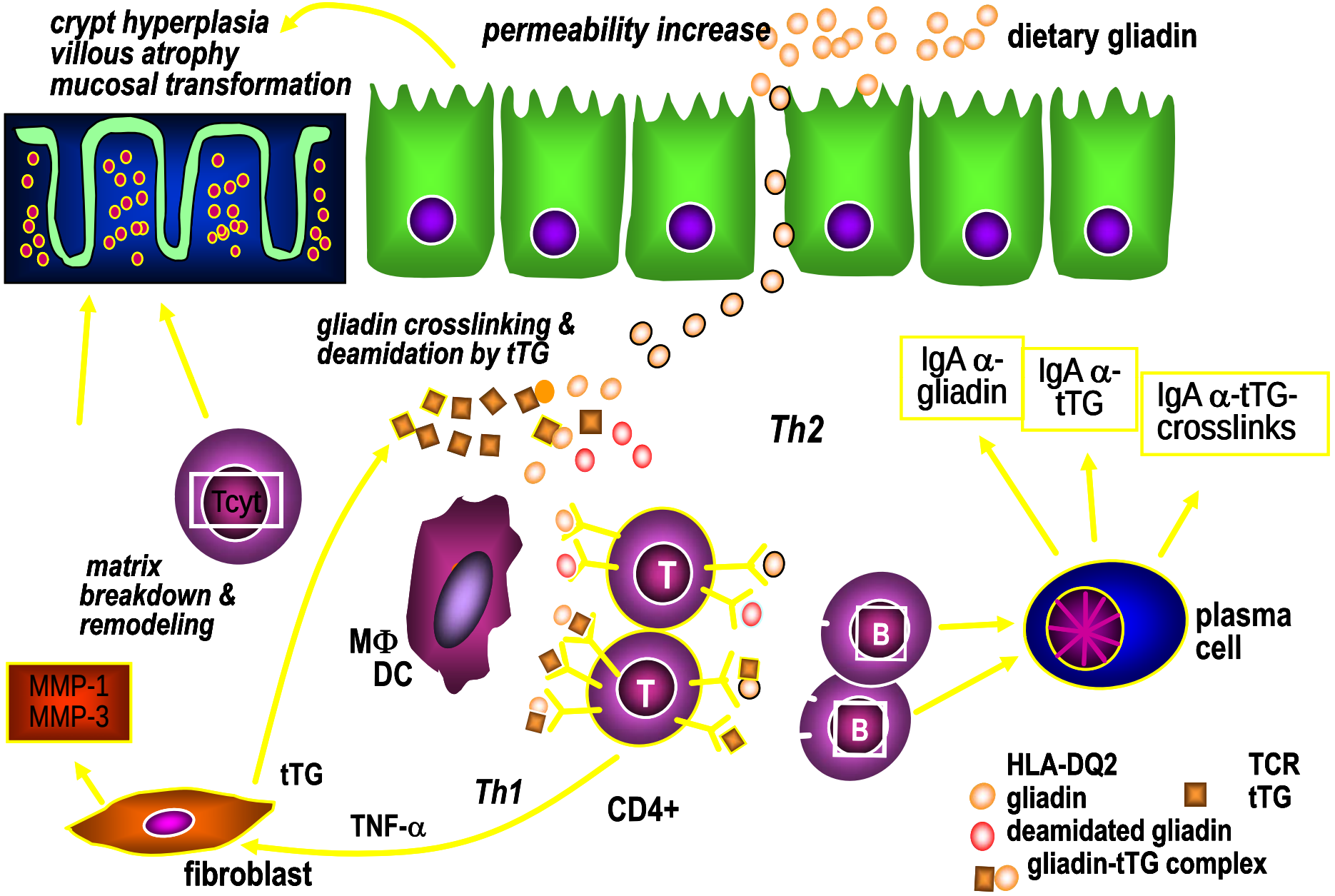
- Inmunidad adaptativa
- Inmunidad innata

ESTRUCTURA BASICA DEL GLUTEN

- ✓ **LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPQPF**
- ✓ **La identificación de una región de la gliadina que llamaremos péptido 33-mer**
- ✓ **Mientras otras fracciones relativamente estables fueron fragmentadas en pequeños segmentos cuando los tiempos de exposición se prolongaban, el péptido 33 - mer permaneció estable (vida media de 20 Hs vs 6 de péptidos controles)**

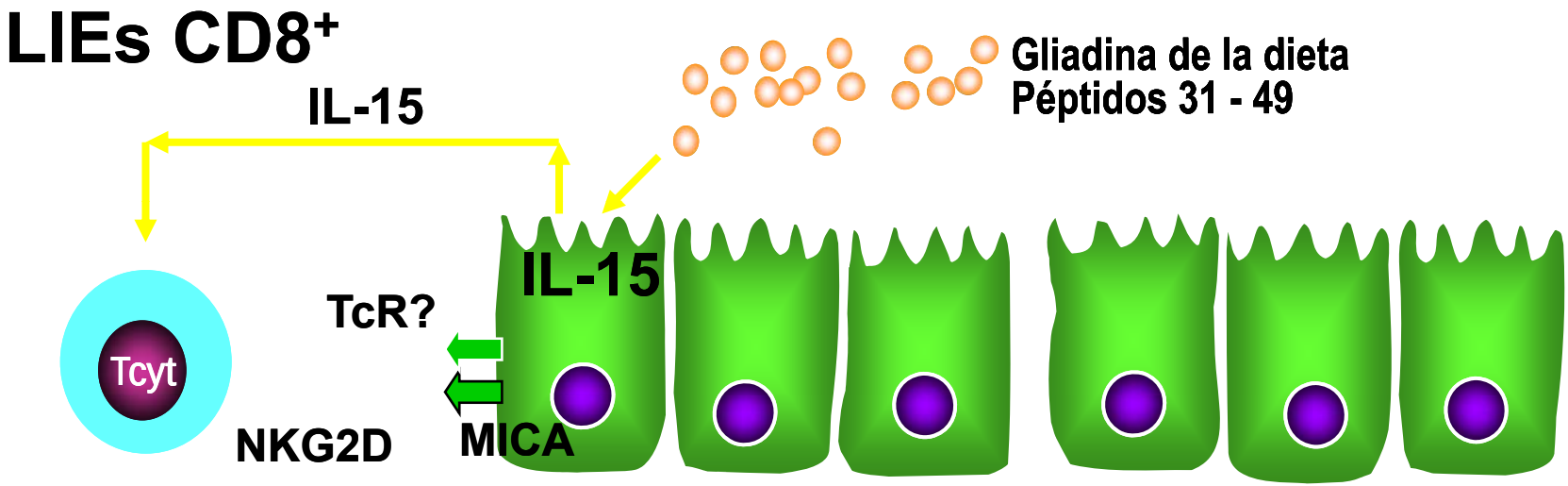
Secuencia de aminoácidos de péptidos de gluten con estimulación inmunológica

- ✓ **Alpha Gliadina** **PQPQLPYQ Y**
  PFPQPQLPY
- ✓ **Gamma Gliadina** **FPQQPQQPF Y**
  PQQSFPQQQ
- ✓ **LMW-Gluteninas** **FSQQQQSPF**
- ✓ **HMW-Gluteninas** **QGYYPTSPQ**



D. Schuppan; Science 2002

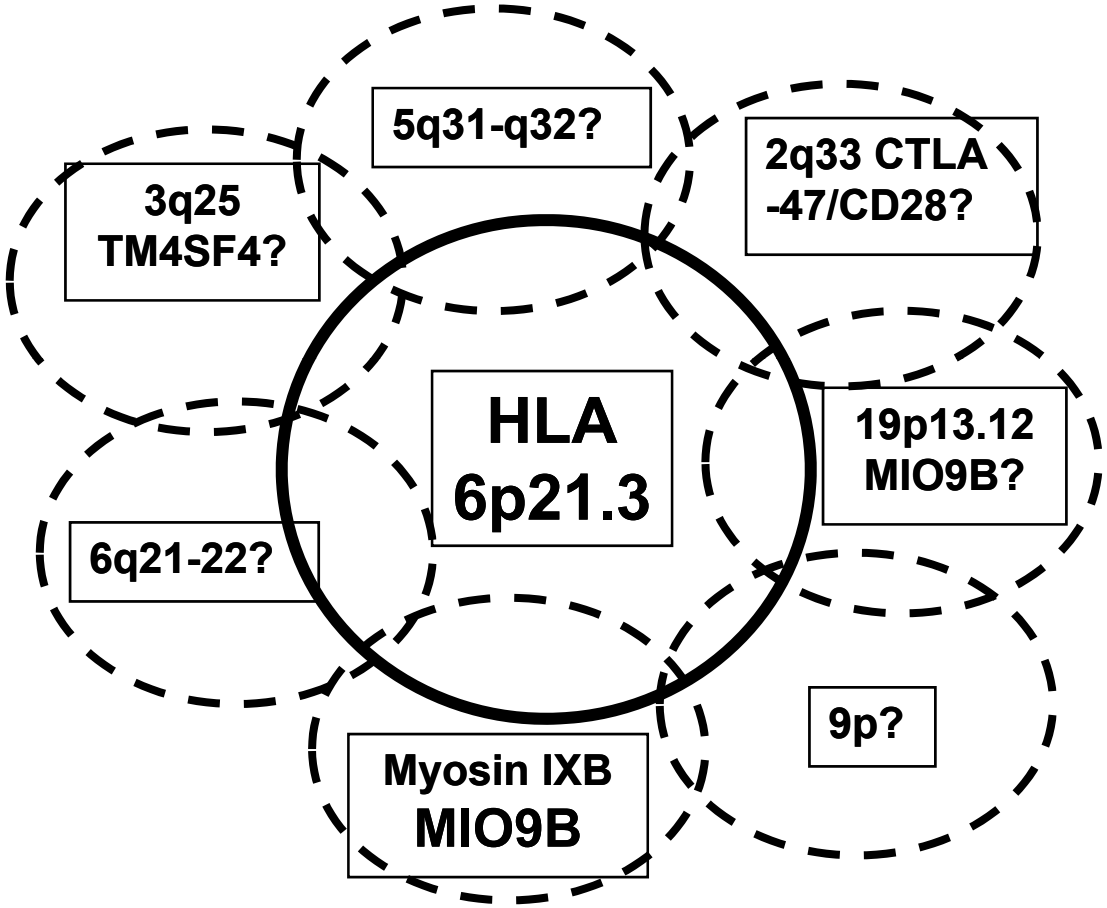
Inmunidad innata



Citotoxicidad INF-γ

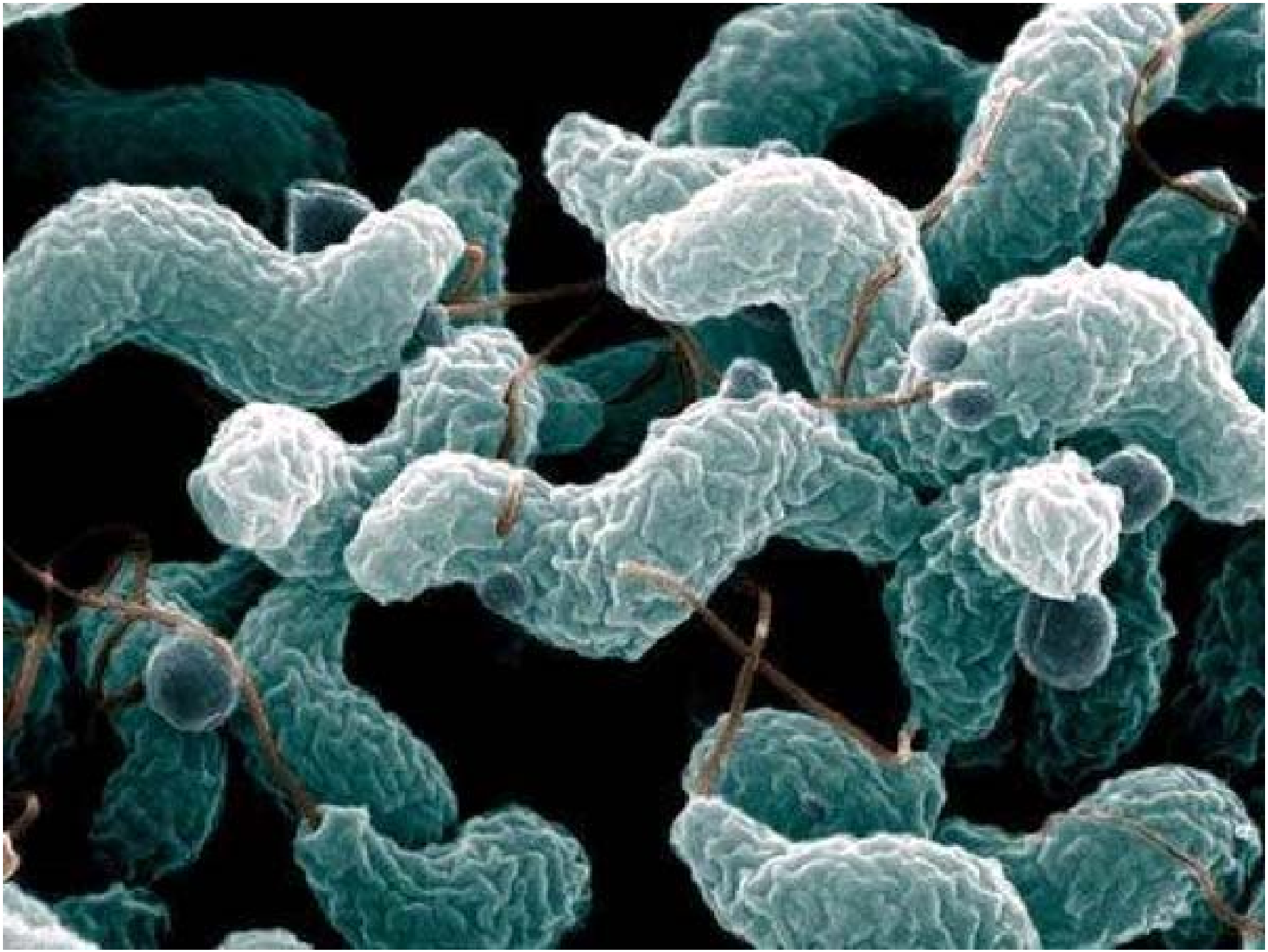
Schuppan et al. Lancet 2003
Koning et al. BPR 2006

Genética



Heterogeneidad clínica e histológica??

EC Refractaria Tipo II y Linfoma



The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease.

Wacklin P1, Kaukinen K, Tuovinen E, Collin P, Lindfors K, Partanen J, Mäki M, Mättö J.

Celiac disease is classically manifested in the gastrointestinal (GI) tract but extraintestinal symptoms, such as dermatitis herpetiformis (DH), are also common. Besides several well-known shared genetic risk factors and an environmental trigger, gliadin, factors determining the clinical outcome of the disease are not known. In this study, the role of duodenal microbiota in the celiac disease outcome was studied by analyzing mucosa-associated microbiota in celiac disease patients with a variety of intestinal and extraintestinal symptoms.

METHODS

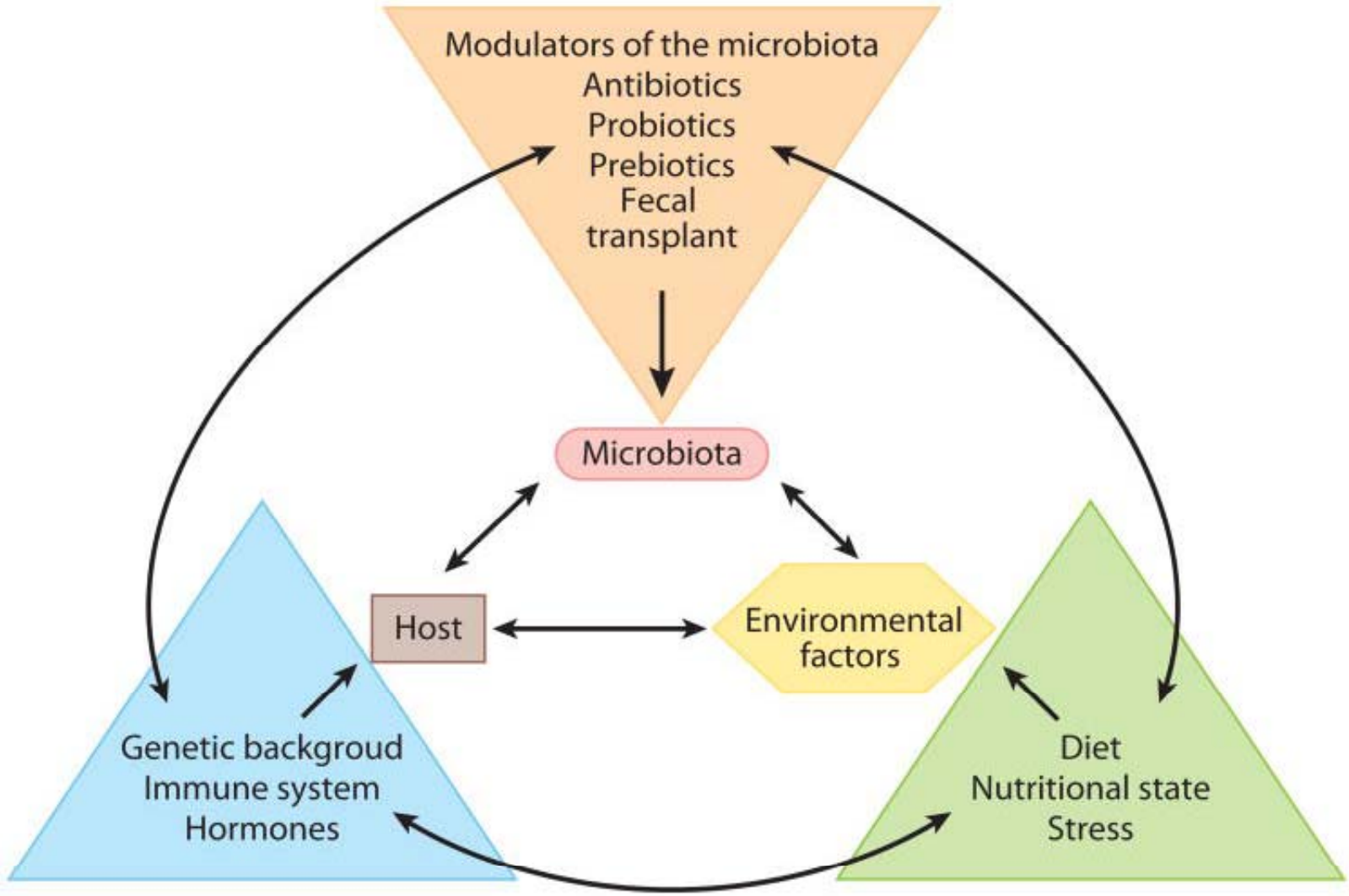
Microbiota in duodenal biopsy samples obtained from 33 patients with celiac disease with GI, DH, anemia, or mixed symptoms, as well as screen-detected asymptomatic celiac disease and 18 control subjects were analyzed using PCR denaturing gradient gel electrophoresis and a subset of samples additionally by the 16S ribosomal RNA gene sequencing.

RESULTS:

The composition and diversity of mucosal microbiota was associated with the manifestation of celiac disease when analyzed using PCR denaturing gradient gel electrophoresis and the 16S ribosomal RNA gene sequencing. The patients with celiac disease with GI symptoms or anemia had lower microbial diversity than those with DH. Moreover, the patients with GI symptoms had different intestinal microbiota composition and structure, dominated by Proteobacteria, in comparison to those with DH or control subjects (patients with dyspepsia). The relatively similar intestinal microbiota composition in the control subjects and those with DH was characterized by the high abundance of Firmicutes.

CONCLUSIONS

The two common outcomes of celiac disease, classical GI and extraintestinal manifestations, had marked differences on the diversity and composition of intestinal microbiota. This association suggested that intestinal microbiota may have a role in the manifestation of the disease.


Modulators of the microbiota
Antibiotics
Probiotics
Prebiotics
Fecal
transplant
Microbiota
Host
Environmental
factors
Genetic backgroud
Immune system
Hormones
Diet
Nutritional state
Stress

Hindawi Publishing Corporation
Journal of Immunology Research
Volume 2015, Article ID 123653, 10 pages
http://dx.doi.org/10.1155/2015/123653

Review Article

The Interaction among Microbiota, Immunity, and Genetic and Dietary Factors Is the *Condicio Sine Qua Non* Celiac Disease Can Develop

D. Pagliari,[1] R. Urgesi,[2] S. Frosali,[1] M. E. Riccioni,[3] E. E. Newton,[4] R. Landolfi,[1] F. Pandolfi,[1] and R. Cianci[1]

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[2] *Gastroenterology and Digestive Endoscopy Unit, Belcolle Hospital, 01100 Viterbo, Italy*
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RESEARCH ARTICLE

CELIAC DISEASE

Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease

Romain Bouziat,[1,2]* Reinhard Hinterleitner,[1,2]* Judy J. Brown,[3,4]* Jennifer E. Stencel-Baerenwald,[3,4] Mine Ikizler,[4,5] Toufic Mayassi,[1,2] Marlies Meisel,[1,2] Sangman M. Kim,[1,2] Valentina Discepolo,[1,6] Andrea J. Pruijssers,[4,5] Jordan D. Ernest,[1,2] Jason A. Iskarpatyoti,[4,5] Léa M. M. Costes,[1,7] Ian Lawrence,[1,2] Brad A. Palanski,[8] Mukund Varma,[9,10] Matthew A. Zurenski,[1,2] Solomiia Khomandiak,[4,5] Nicole McAllister,[3,4] Pavithra Aravamudhan,[4,5] Karl W. Boehme,[4,5] Fengling Hu,[1] Janneke N. Samsom,[7] Hans-Christian Reinecker,[9] Sonia S. Kupfer,[1,11] Stefano Guandalini,[11,12] Carol E. Semrad,[1,11] Valérie Abadie,[13] Chaitan Khosla,[8,14,15] Luis B. Barreiro,[16] Ramnik J. Xavier,[9,10,17] Aylwin Ng,[9,10] Terence S. Dermody,[3,4,5,18,19]† Bana Jabri[1,2,11,12,20]†

Viral infections have been proposed to elicit pathological processes leading to the initiation of T helper 1 (T_H1) immunity against dietary gluten and celiac disease (CeD). To test this hypothesis and gain insights into mechanisms underlying virus-induced loss of tolerance to dietary antigens, we developed a viral infection model that makes use of two reovirus strains that infect the intestine but differ in their immunopathological outcomes. Reovirus is an avirulent pathogen that elicits protective immunity, but we discovered that it can nonetheless disrupt intestinal immune homeostasis at inductive and effector sites of oral tolerance by suppressing peripheral regulatory T cell (pT_{reg}) conversion and promoting T_H1 immunity to dietary antigen. Initiation of T_H1 immunity to dietary antigen was dependent on interferon regulatory factor 1 and dissociated from suppression of pT_{reg} conversion, which was mediated by type-1 interferon. Last, our study in humans supports a role for infection with reovirus, a seemingly innocuous virus, in triggering the development of CeD.

Clínica de la Enfermedad Celíaca 2016

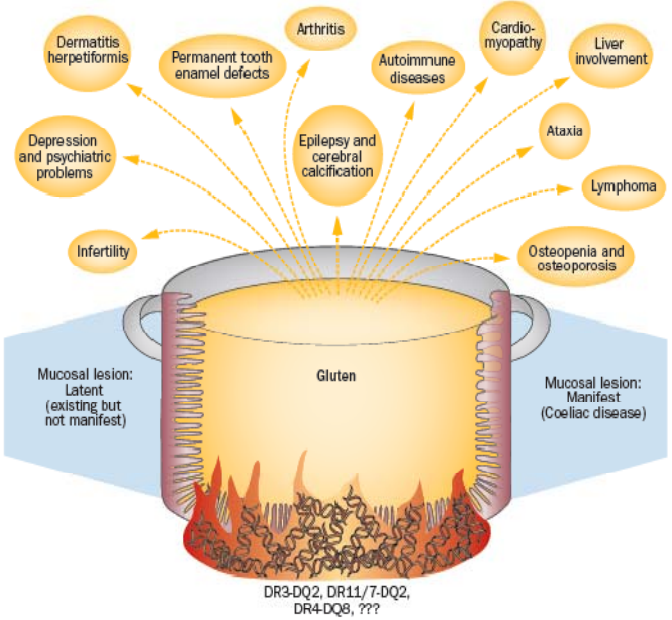

Figure 1 | Coeliac gluten sensitivity. A spectrum of gluten-induced diseases is depicted splashing out of a cooking pot for patients with the correct autoimmune extended HLA haplotypes and ingesting normal gluten-containing food on a daily basis. At endoscopy, the small intestinal mucosal lining may be architecturally normal (latent mucosal lesion) or showing a flat lesion, which means there is villous atrophy and crypt hyperplasia (manifest mucosal lesion). Dermatitis herpetiformis is a classic example of an extraintestinal disease manifesting in patients who have both normal and abnormal small intestinal mucosal architecture. The fire fuelling the cooking pot is the contribution of genetics, including unknown susceptibility genes. Adapted with permission from BMJ Publishing Group Ltd. © Kaukinen, K. *et al. Gut* **56**, 1339–1340 (2007).

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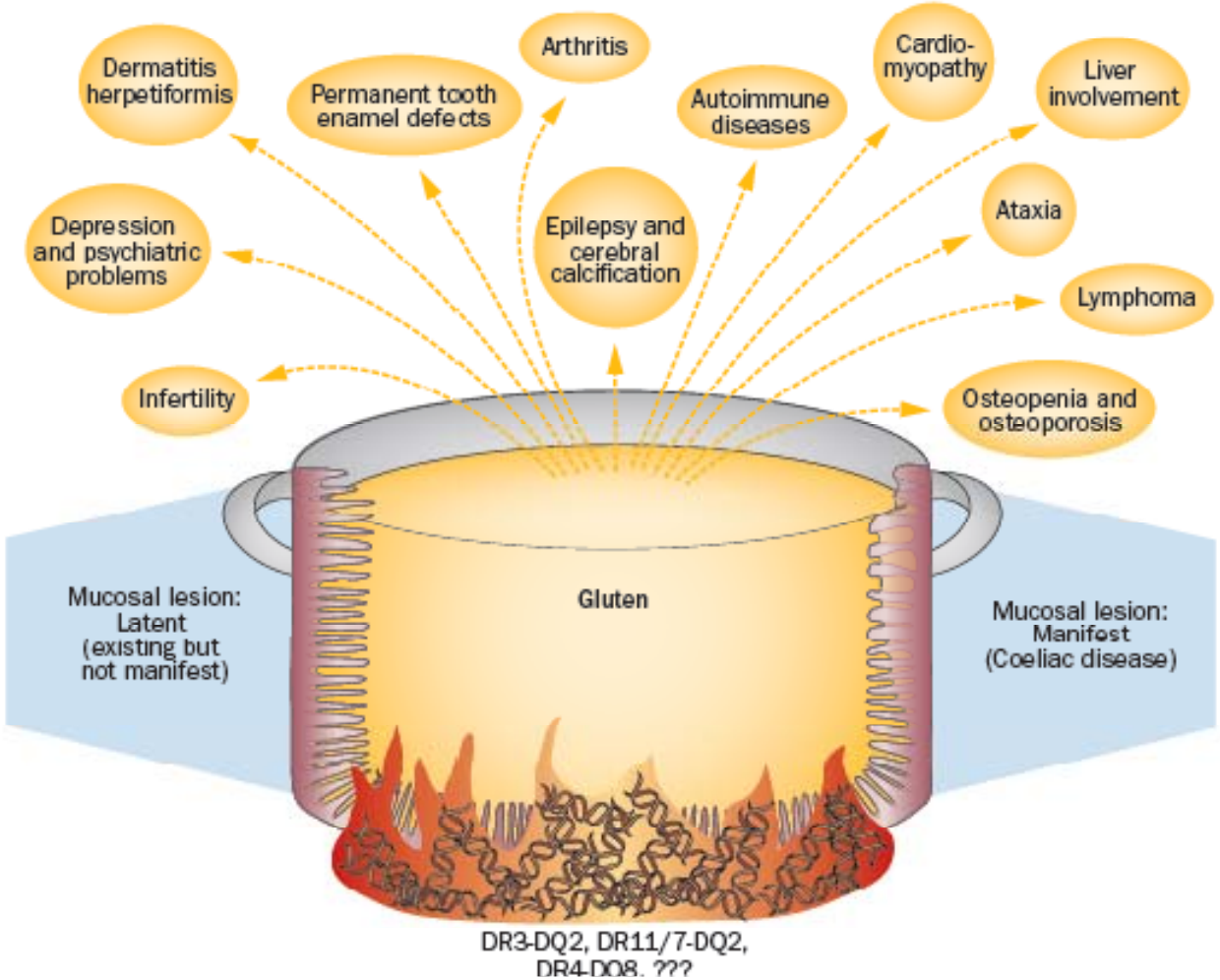

Dermatitis herpetiformis
Permanent tooth enamel defects
Arthritis
Autoimmune diseases
Cardio-myopathy
Liver involvement
Depression and psychiatric problems
Epilepsy and cerebral calcification
Ataxia
Lymphoma
Infertility
Osteopenia and osteoporosis
Mucosal lesion: Latent (existing but not manifest)
Gluten
Mucosal lesion: Manifest (Coeliac disease)
DR3-DQ2, DR11/7-DQ2,
DR4-DQ8, ???

AP&T Alimentary Pharmacology and Therapeutics

Body mass index and the risk of obesity in coeliac disease treated with the gluten-free diet

T. A. Kabbani[1], A. Goldberg[1], C. P. Kelly, K. Pallav, S. Tariq, A. Peer, J. Hansen, M. Dennis & D. A. Leffler

Background

Coeliac disease is increasingly diagnosed and weight changes are common after adoption of a gluten-free diet (GFD), however data on body mass index (BMI) changes are limited.

Aim

To assess changes in BMI after diagnosis in a large coeliac population.

Methods

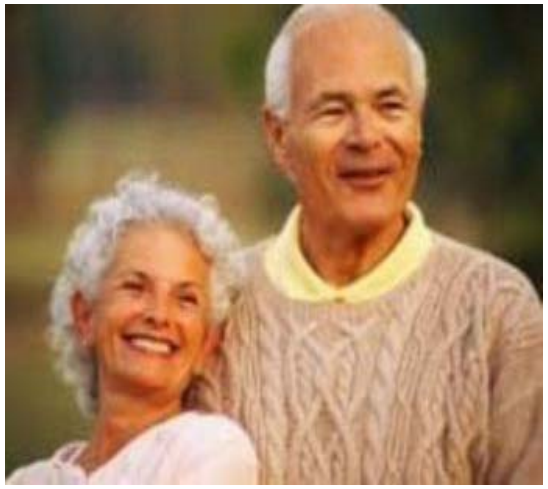
A total of 1018 patients with biopsy confirmed coeliac disease seen at our centre were studied retrospectively. Initial and follow-up BMIs were recorded, as was GFD adherence as assessed by an expert dietitian.

Results

A total of 679 patients with at least two recorded BMIs and GFD adherence data were included in the study. Mean follow-up was 39.5 months. Compared to regional population data, the coeliac cohort was significantly less likely to be overweight or obese (32% vs. 59%, $P < 0.0001$). Mean BMI increased significantly after GFD initiation (24.0 to 24.6; $P < 0.001$). 21.8% of patients with normal or high BMI at study entry increased their BMI by more than two points.

Conclusions

Individuals with coeliac disease have lower BMI than the regional population at diagnosis. BMI increases on the GFD, especially in those that adhere closely to the GFD. On the GFD, 15.8% of patients move from a normal or low BMI class into an overweight BMI class, and 22% of patients overweight at diagnosis gain weight. These results indicate that weight maintenance counselling should be an integral part of coeliac dietary education.



Estudios publicados en 1960 los nuevos pacientes diagnosticados después de los 60 años era de solo el 4% ,

Estudios recientes(2008) sugieren que esa cifra trepo al 20–34%

Por lo tanto hoy se estima que la prevalencia de la ese grupo etáreo (por histología – serología) hoy es del 2.13 a 2.45%


MEDICO
ARQUITECTO
DENTISTA
ABOGADO
PSICOLOGO

AP&T Alimentary Pharmacology and Therapeutics

The quality of sleep in patients with coeliac disease

F. Zingone*, M. Siniscalchi*, P. Capone*, R. Tortora*, P. Andreozzi*, E. Capone† & C. Ciacci*

Conclusions
Sleep disorders are common in coeliac disease not only at diagnosis but also during treatment with a gluten-free diet. Sleep disorders are related to depression, anxiety and fatigue, and inversely related to quality of life scale scores.

Aliment Pharmacol Ther 2010; 32: 1031–1036

Social phobia in coeliac disease

GIOVANNI ADDOLORATO[1], ANTONIO MIRIJELLO[1], CRISTINA D'ANGELO[1], LORENZO LEGGIO[1], ANNA FERRULLI[1], LUISA VONGHIA[1], SILVIA CARDONE[1], VERUSCKA LESO[1], ANTONIO MICELI[2] & GIOVANNI GASBARRINI[1]

[1]*Institute of Internal Medicine, Catholic University of Rome, Rome, Italy, and* [2]*Department of Cardiac Surgery, St Andrea Hospital, University "La Sapienza", Rome, Italy*

Abstract

Objective. A high prevalence of anxiety and depression has been reported in coeliac disease (CD). Although social phobia is included among the anxiety disorders, its presence in CD has never been investigated. The aim of the present study was to evaluate social phobia in CD patients. ***Material and methods.*** A total of 40 CD patients were consecutively enrolled in the study. Fifty healthy subjects were studied as controls. Social phobia was assessed by the Liebowitz Social Anxiety Scale (LSAS) and current depression by the modified version of the Zung Self-rating Depression Scale (M-SDS). ***Results.*** The percentage of subjects with social phobia was significantly higher in CD patients than in controls (70% versus 16%; $p < 0.0001$), and also when the more severe generalized form was considered (15.0% versus 0%; $p = 0.006$). The percentage of subjects with social phobia was not statistically different between newly diagnosed subjects and patients on a gluten free diet (73.3% versus 68%; *p*: NS), nor considering its generalized form (7.0% versus 20%; *p*: NS). Current depression was present in a significantly higher percentage of CD patients in comparison with controls (52.5% versus 8%; $p < 0.0001$). A direct correlation between social phobia and current depression was found in CD patients ($r = 0.582$; $p < 0.0001$). ***Conclusions.*** Despite the limited number of cases evaluated, the present study showed a significantly higher prevalence of social phobia in CD patients compared with in healthy subjects. Future studies are needed to clarify the possible social phobia-induced risks such as school and/or work failure in CD patients.

Markers of Gluten Sensitivity and Celiac Disease in Recent-Onset Psychosis and Multi-Episode Schizophrenia

Faith Dickerson, Cassie Stallings, Andrea Origoni, Crystal Vaughan, Sunil Khushalani, Flora Leister, Shuojia Yang, Bogdana Krivogorsky, Armin Alaedini, and Robert Yolken

Background: Increased immune sensitivity to gluten has been reported in schizophrenia. However, studies are inconsistent about this association.

Methods: The sample of 471 individuals included 129 with recent-onset psychosis, 191 with multi-episode schizophrenia, and 151 controls. Immunoglobulin (Ig)G and IgA antibodies to gliadin and to tissue transglutaminase, and IgG antibodies to deamidated gliadin were measured. Quantitative levels of antibodies in the psychiatric groups were compared with controls. All participants were categorized as to whether their levels of antibodies met standardized cutoffs for celiac disease. HLA DQ2 and HLA DQ8 alleles were detected by real-time polymerase chain reaction.

Results: Individuals with recent-onset psychosis had increased levels of IgG (odds ratio [OR] 5.50; 95% confidence interval [CI] 2.65–11.42) and IgA (OR 2.75; 95% CI 1.31–5.75) antibodies to gliadin compared with control subjects. Individuals with multi-episode schizophrenia also had significantly increased levels of IgG antibodies to gliadin (OR 6.19; 95% CI 2.70–14.16). IgG antibodies to deamidated gliadin and IgA antibodies to tissue transglutaminase were not elevated in either psychiatric group, and fewer than 1% of individuals in each of the groups had levels of these antibodies predictive of celiac disease. There were no significant differences in the distribution of the HLA DQ2/8 alleles among the groups.

Conclusions: Individuals with recent-onset psychosis and with multi-episode schizophrenia who have increased antibodies to gliadin may share some immunologic features of celiac disease, but their immune response to gliadin differs from that of celiac disease.

Markers of gluten sensitivity and celiac disease in bipolar disorder

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Alaedini A, Yolken R. Markers of gluten sensitivity and celiac disease in bipolar disorder.
Bipolar Disord 2011: 13: 52–58.

Objectives: Increased immune sensitivity to dietary gluten proteins has been reported in schizophrenia but has not been studied in bipolar disorder. In this study, we examine the levels of antibody reactivity to gliadin, deamidated gliadin, and tissue transglutaminase (tTG) in individuals with bipolar disorder and compare these levels to those in individuals who do not have any history of psychiatric disorder.

Methods: The sample of 275 individuals included 102 with bipolar disorder and 173 controls without a psychiatric disorder. Immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to gliadin and tTG and IgG antibodies to deamidated gliadin were measured by enzyme immunoassay. Participants' levels of antibodies to deamidated gliadin and tTG were classified based on the cutoffs for positivity that are predictive of celiac disease. Quantitative levels of antibodies were compared between groups employing regression models which were controlled for demographic variables.

Results: Individuals with bipolar disorder had increased levels of IgG antibodies to gliadin compared with controls in multivariate analyses. We also found evidence of increased levels of antibodies to deamidated gliadin in the bipolar disorder population. The levels of IgA class antigliadin antibodies and antibodies to tTG did not differ significantly between groups. There was also not a significant difference between groups in the number of persons who were classified as having levels of antibodies to deamidated gliadin or tTG that are predictive of celiac disease.

Conclusions: Individuals with bipolar disorder have increased levels of IgG antibodies to gliadin. However, such antibody increase is not accompanied by an elevation in IgA antibodies to gliadin or the celiac disease-associated antibodies against deamidated gliadin and tTG. These results warrant further detailed examination of the molecular specificity and pattern of reactivity of the antibody response to gluten antigens in bipolar disorder.

Faith Dickerson[a], Cassie Stallings[a], Andrea Origoni[a], Crystal Vaughan[a], Sunil Khushalani[a], Armin Alaedini[b] and Robert Yolken[c]

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doi: 10.1111/j.1399-5618.2011.00894.x

Key words: bipolar disorder – celiac disease – gliadin antibody – gluten sensitivity

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E-mail: fdickerson@sheppardpratt.org

Markers of Celiac Disease and Gluten Sensitivity in Children with Autism

Nga M. Lau1,2, Peter H. R. Green1,2, Annette K. Taylor3, Dan Hellberg4,Mary Ajamian1,2, Caroline Z. Tan1,2, Barry E. Kosofsky5,6, Joseph J. Higgins6, Anjali M. Rajadhyaksha5,6, Armin Alaedini1,2,

- ✓ **Serología**
- ✓ **Visión Endoscópica**
- ✓ **Histología**

RESULTADOS

Grupo de alto riesgo

SEROLOGIA	S	E	VPP	VPN	RP+	RP-	Area curva ROC
a-tTG	95.2	97.9	96.8	96.9	46.7	0.05	0.997
AAA	87.3	94.9	91.9	91.8	17.1	0.1	0.968
Ig A a-DGP	98.4	92.7	89.9	98.9	13.8	0.02	0.995
Ig G a-DGP	95.2	100	100	97	NC	0.05	0.989
a-DGP Dual	96.8	99	98.4	97.9	95	0.03	0.995
DGP/tTG screen	100	92.8	90.3	100	14	0	0.999
a-tTG+IgG a-DGP	90.5	100	100	94.0	NC	0.10	0.952
a-tTG+IgA a-DGP	93.6	99.0	98.4	95.9	91.8	0.06	0.963
a-tTG+ a-DGP Dual	92.0	100	100	95.0	NC	0.08	0.960
a-tTG+DGP/tTG screen	95.2	100	100	96.9	NC	0.05	0.976

RESULTADOS

Grupo de bajo riesgo

SEROLOGIA	S	E	VPP	VPN	RP+	RP-	Area curva ROC
a-tTG	72.2	97.8	54.2	99	32.8	0.28	0.888
AAA	50	91.8	18	98.1	6.1	0.54	0.800
Ig A a-DGP	77.8	96.2	42.4	99.2	20	0.23	0.888
Ig G a-DGP	66.7	99	70.6	98.8	66.5	0.34	0.894
a-DGP Dual	72.2	98.4	61.9	99	45	0.28	0.924
DGP/tTG screen	77.8	93.8	31.1	99.1	12.5	0.24	0.933
a-tTG+IgG a-DGP	66.7	100	100	98.8	NC	0.33	0.833
a-tTG+IgA a-DGP	72.2	99.8	92.9	99.0	360.4	0.28	0.860
a-tTG+ a-DGP Dual	72.2	99.8	92.8	99.0	361.0	0.28	0.861
a-tTG+DGP/tTG screen	72.2	98.8	68.4	99.0	60.2	0.28	0.855

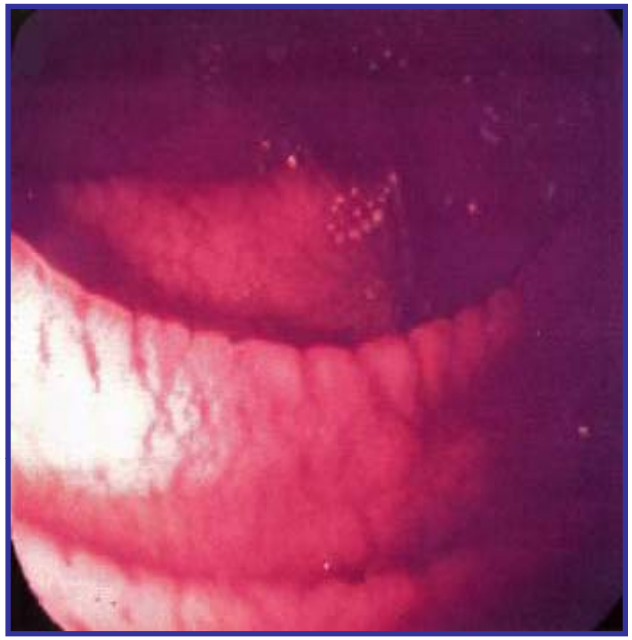
✓ Visión endoscópica

Signos de atrofia en segunda porción distal

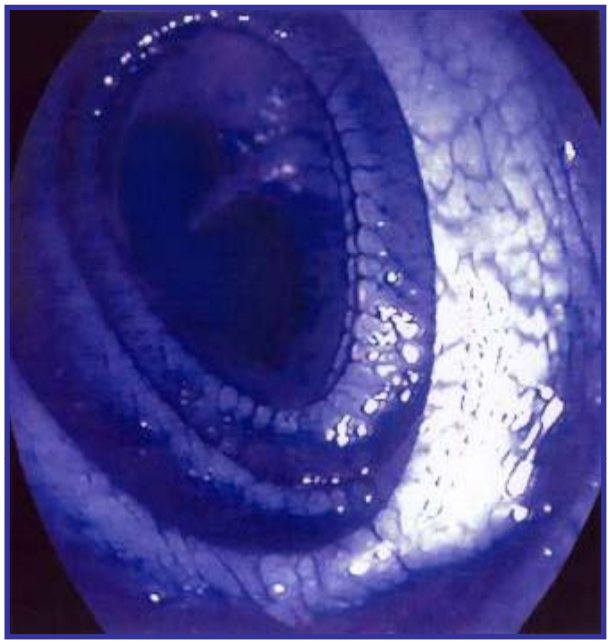
- ✓ **PEINADO**
- ✓ **AUSENCIA O DISMINUCION DE PLIEGUES**
- ✓ **MOSAICO**
- ✓ **VASOS POR TRANSPARENCIA**

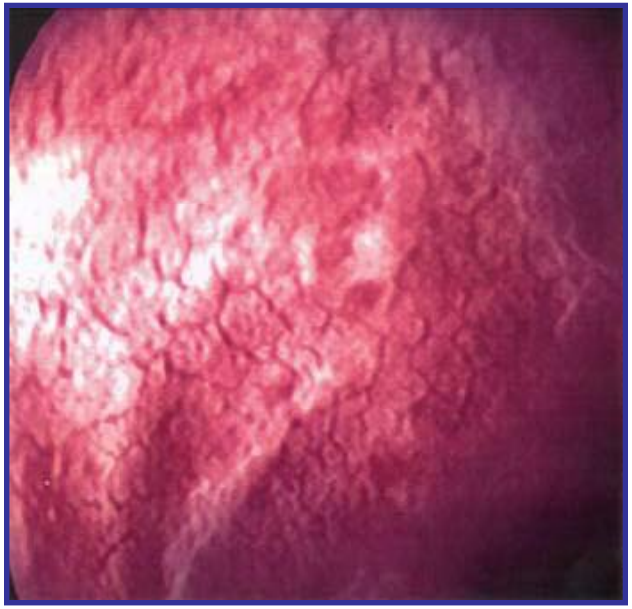
✓**Jabbari et al.** ✓**Corazza et al.** ✓**Mauriño et al.**

Visión endoscópica

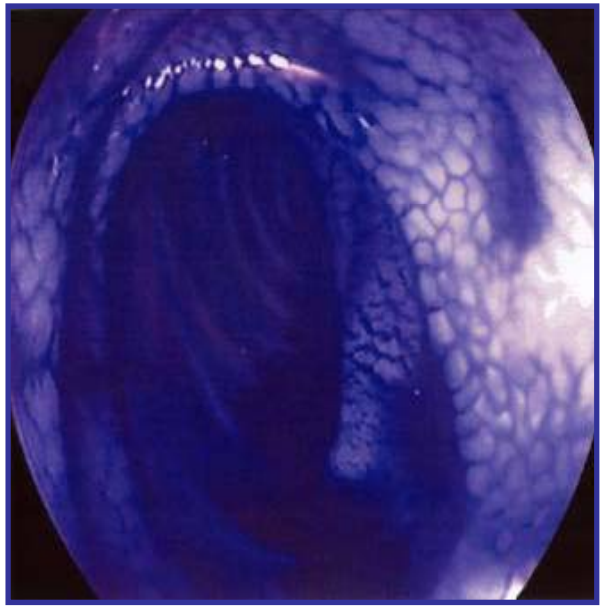


Peinado





Mosaico

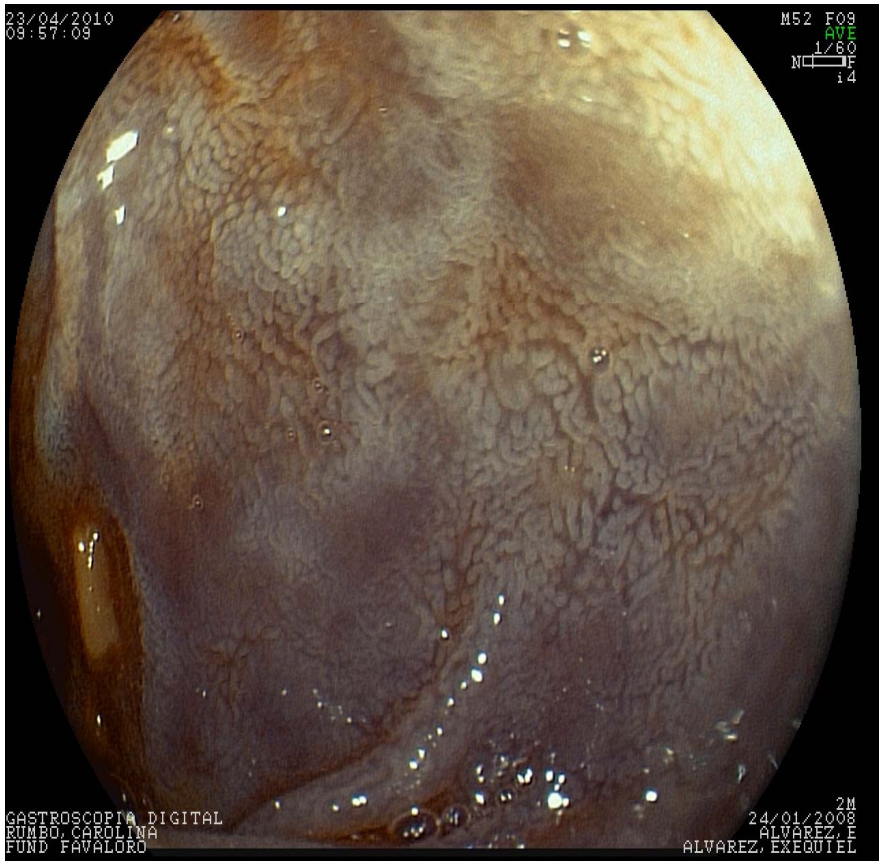


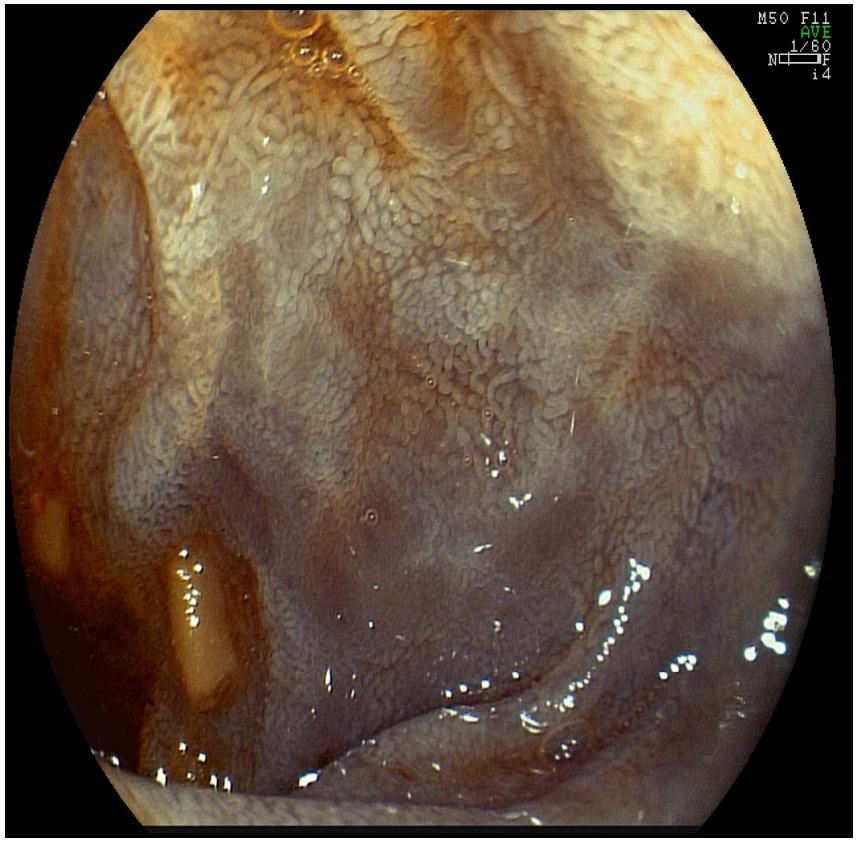
Sensibilidad y Especificidad

	Markers	sensitivity	specificity
Brocchi *et al*	Loss of Folds	88 %	83 %
Mauriño *et al*	Loss of Folds	75 %	98 %
Mc Intyre *et al*	Loss of Folds	73 %	97 %
Shah *et al*	Scalloping	44 %	99 %
Smith *et al*	Scalloping	29 %	94 %
Magazzu *et al*	Mosaic or LF	100 %	99 %
Mauriño *et al*	All markers	94 %	92 %
Dikey *et al*	All markers	88 %	100 %
Oxentenko *et al*	All markers	59 %	92 %

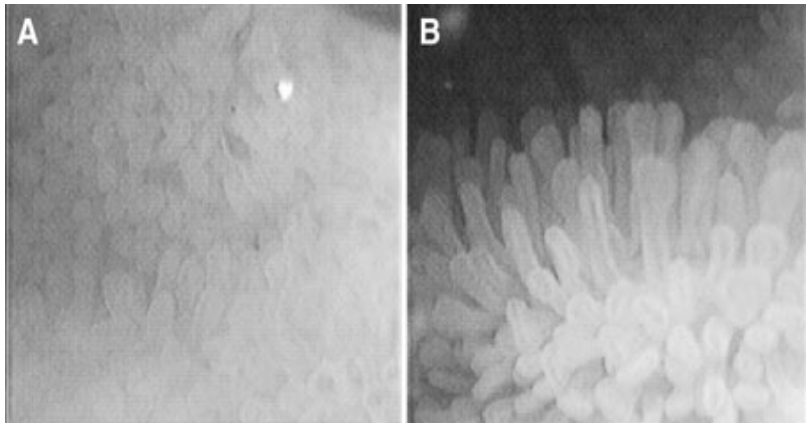
American j Gastroenterol 2002. Mayo clinic

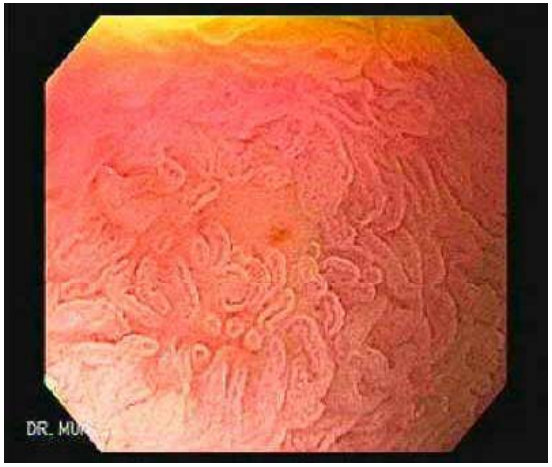
ATROFIA PARCELAR

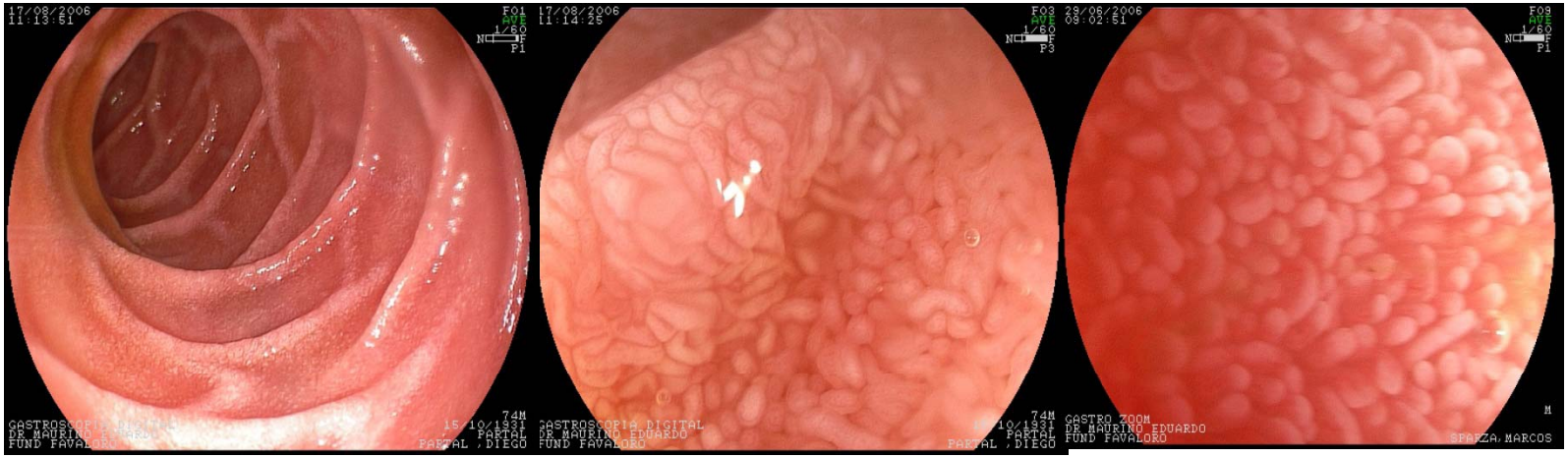




MAGNIFICACIÓN

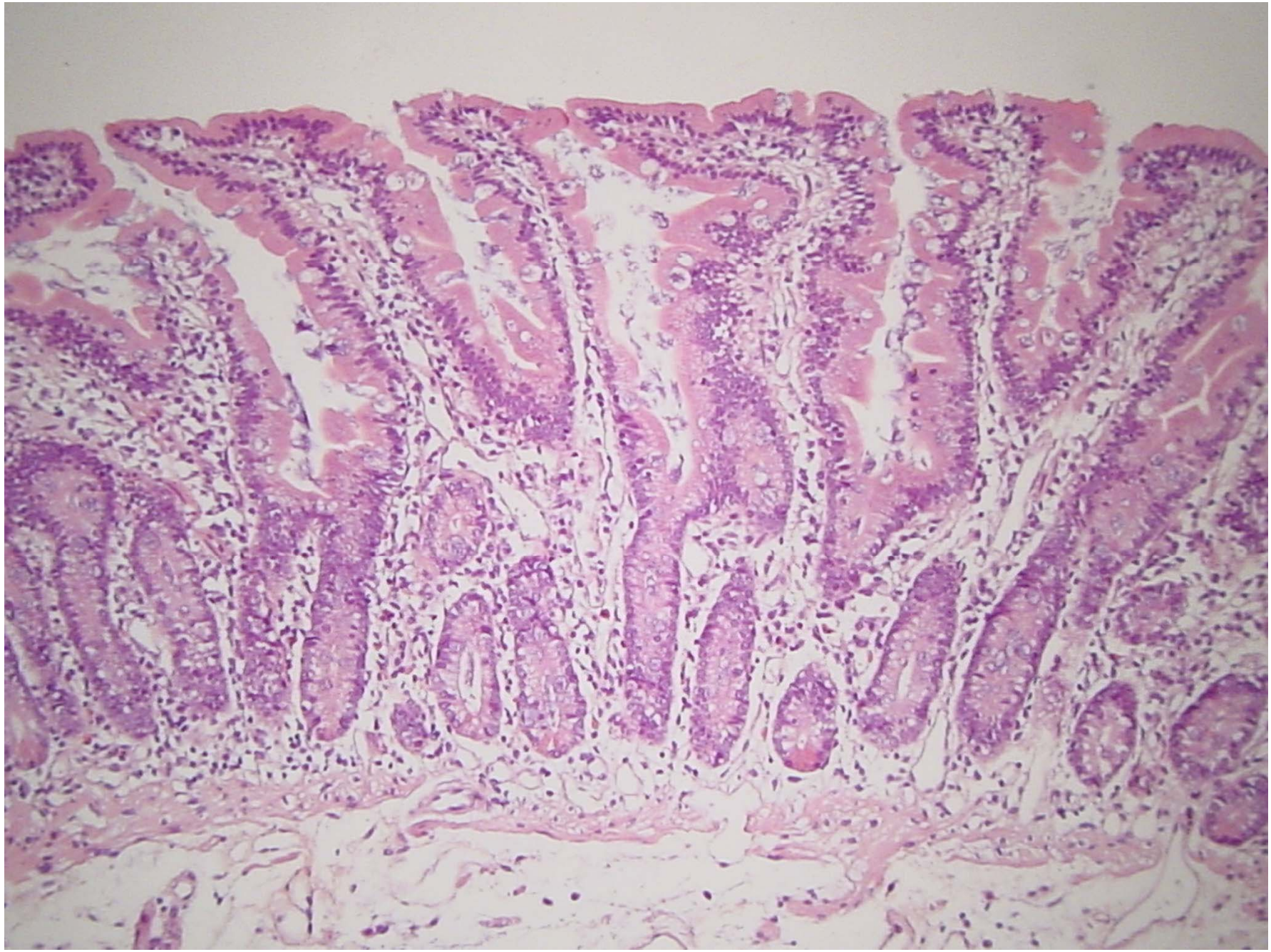


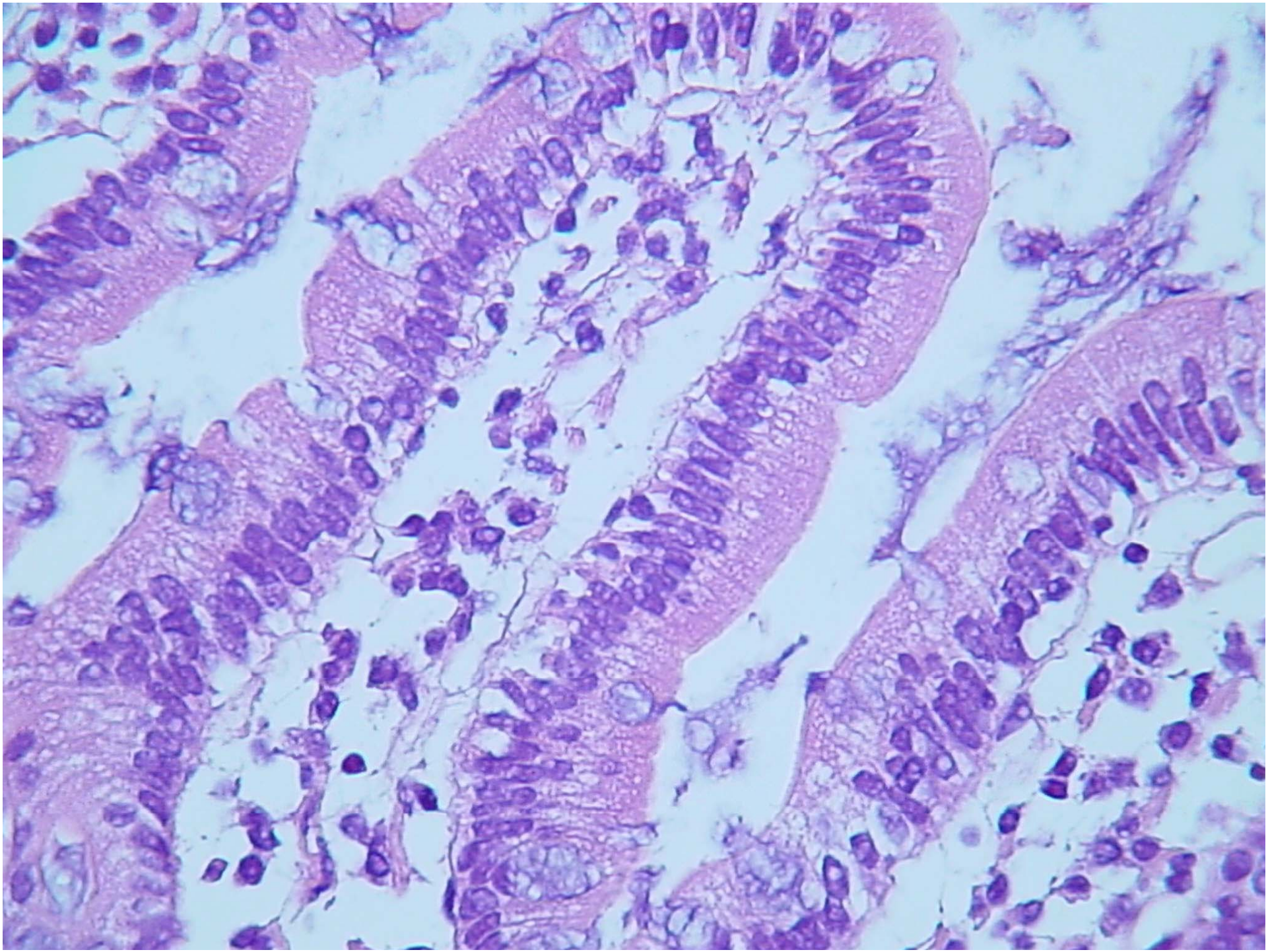


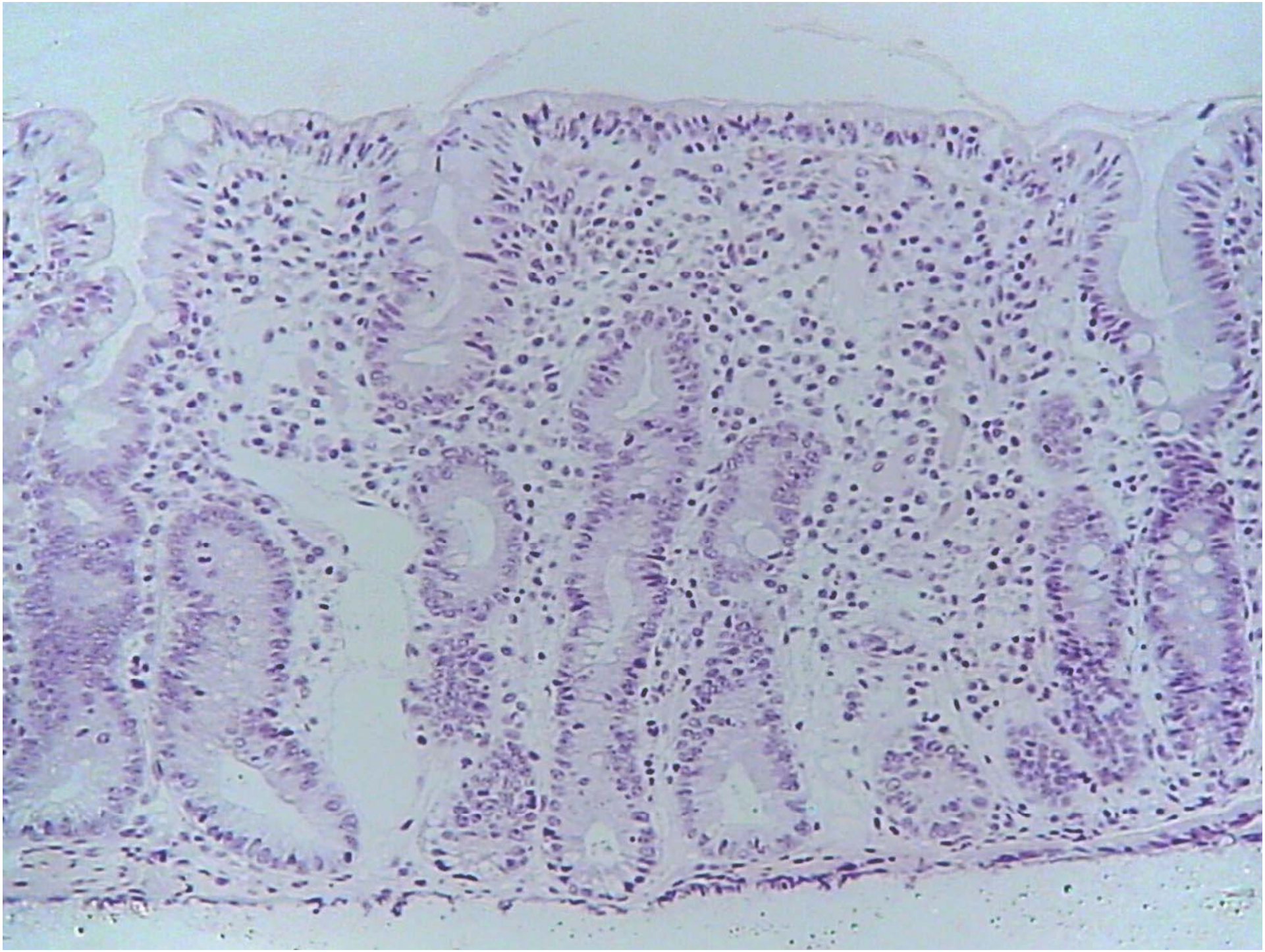


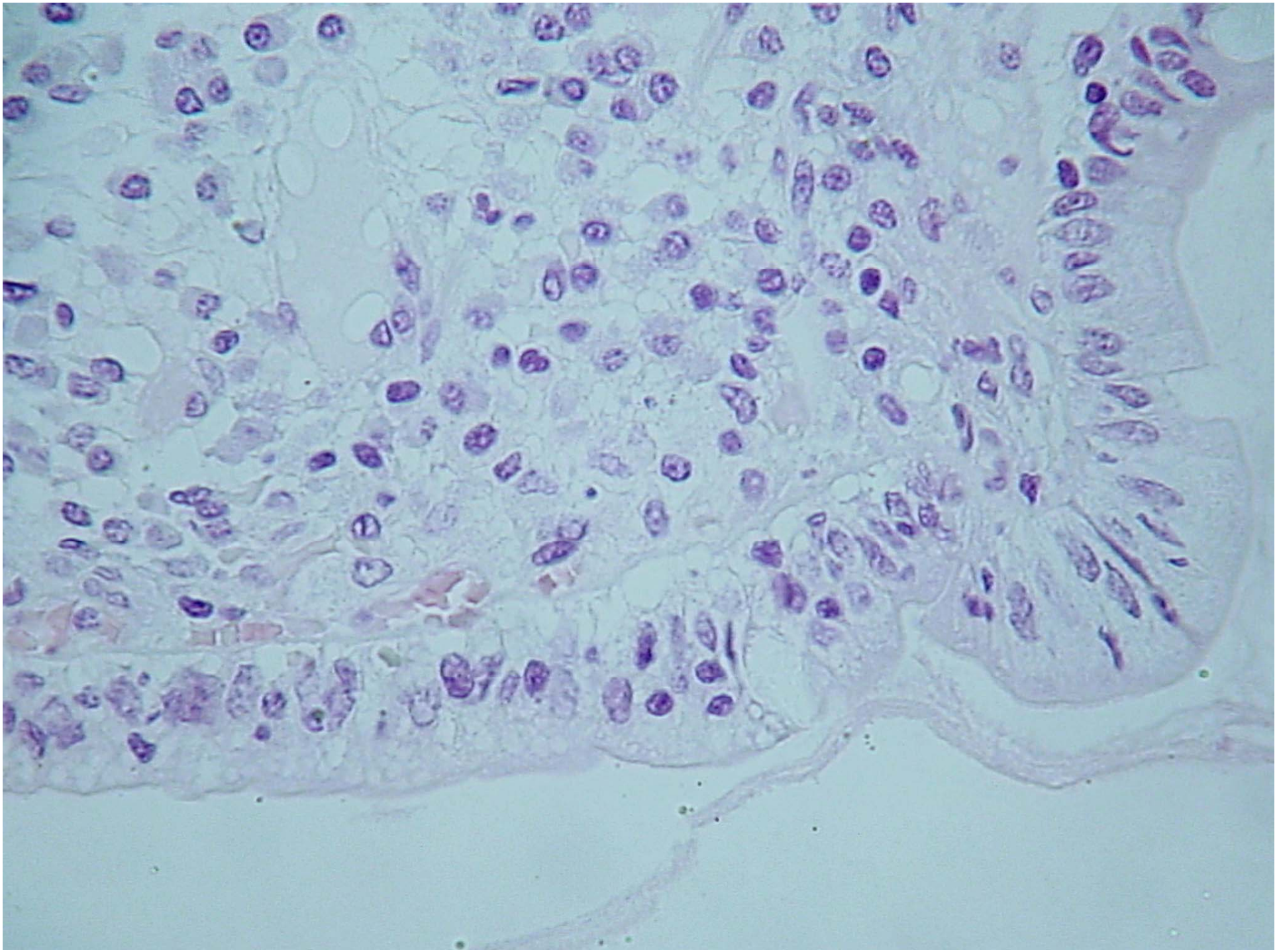
HISTOLOGÍA

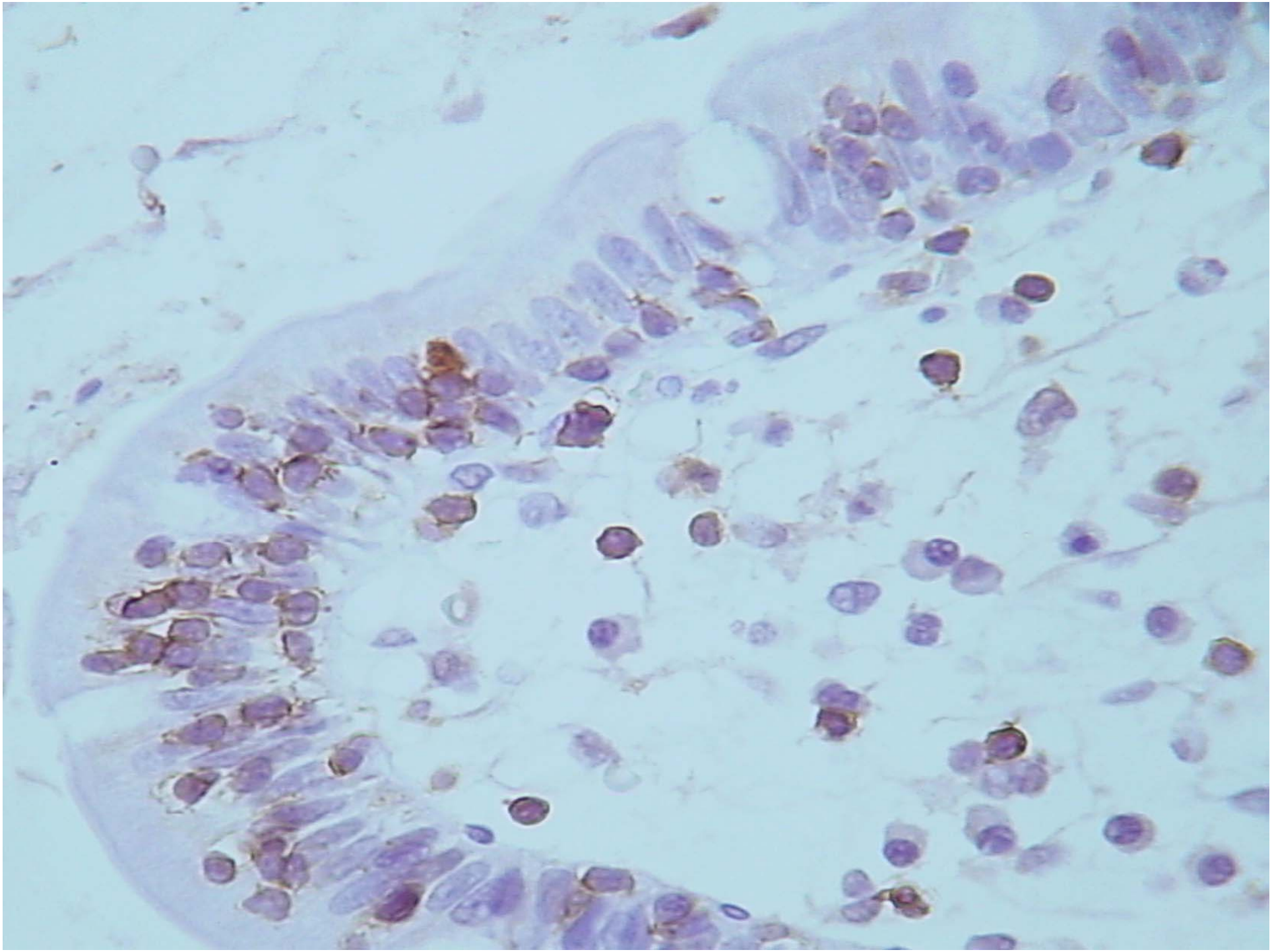
- ✓ **Linfocitos intraepiteliales**
- ✓ **Relación cripta/vellosidad**







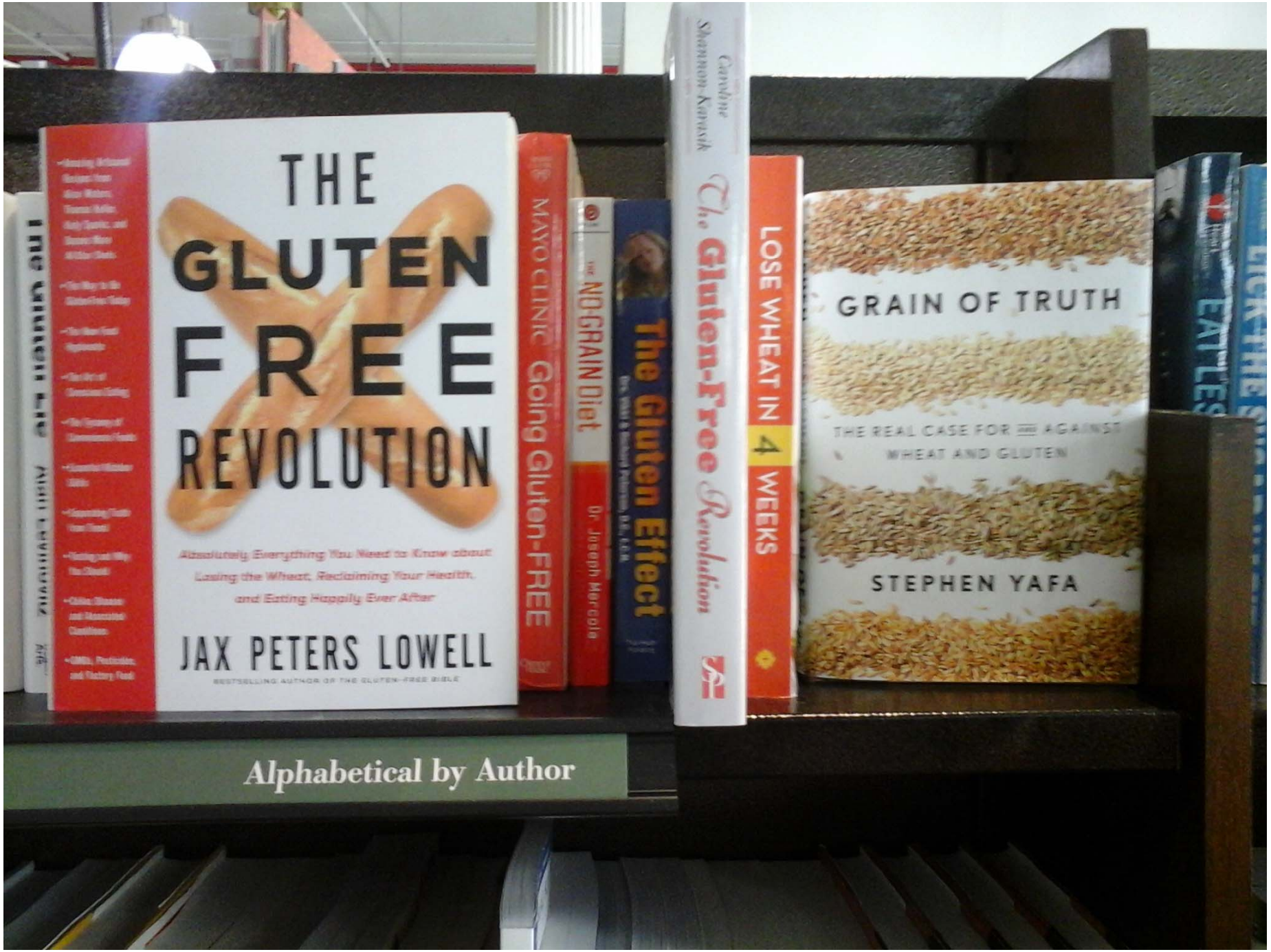




Sensibilidad al gluten

"La SG es una entidad recientemente descripta caracterizada por síntomas intestinales y extraintestinales relacionados con la ingesta de alimentos que contienen gluten, en individuos no celíacos [anticuerpos específicos negativos (a-tTG y EmA) sin enteropatía ni alérgicos al gluten"

Spectrum of gluten-related disorders: consensus on new nomenclature and classification. Anna Sapone et al. BMC Medicine 2012; 7: 10-13

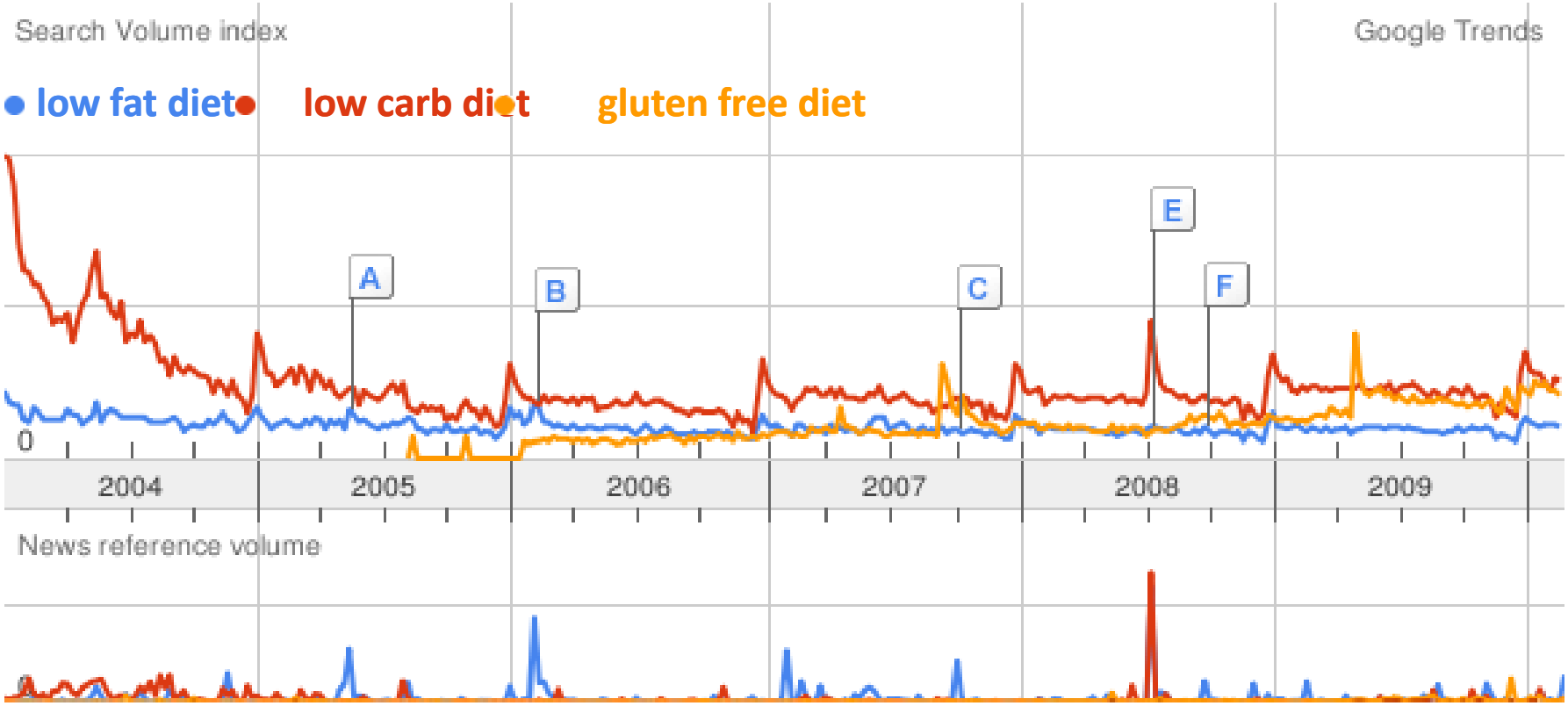

THE GLUTEN FREE REVOLUTION
Absolutely Everything You Need to Know about Losing the Wheat, Reclaiming Your Health, and Eating Happily Ever After
JAX PETERS LOWELL
MAYO CLINIC Going Gluten-FREE
THE NO-GRAIN Diet
Dr. Joseph Mercola
The Gluten Effect
Caroline Shannon-Kovach
The Gluten-Free Revolution
LOSE WHEAT IN 4 WEEKS
GRAIN OF TRUTH
THE REAL CASE FOR AND AGAINST WHEAT AND GLUTEN
STEPHEN YAFA
Alphabetical by Author

Sustento Económico

Mercado “Libre de Gluten”

USA. A. Fasano 2011

Mercado “Libre de Gluten”



Indicaciones médicas y no médicas

- ✓ ~ 3.000.000 de pacientes con EC
- ✓ Otros trastornos asociados al gluten:
  Alergia y sensibilidad al gluten
- ✓ SII, autismo, moda saludable

USA. A. Fasano 2011

THE JOURNAL OF PEDIATRICS • www.jpeds.com

MEDICAL PROGRESS

Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

Stefano Guandalini, MD[1], and Isabel Polanco, MD[2]

THE JOURNAL OF PEDIATRICS • www.jpeds.com Vol. 166, No. 4

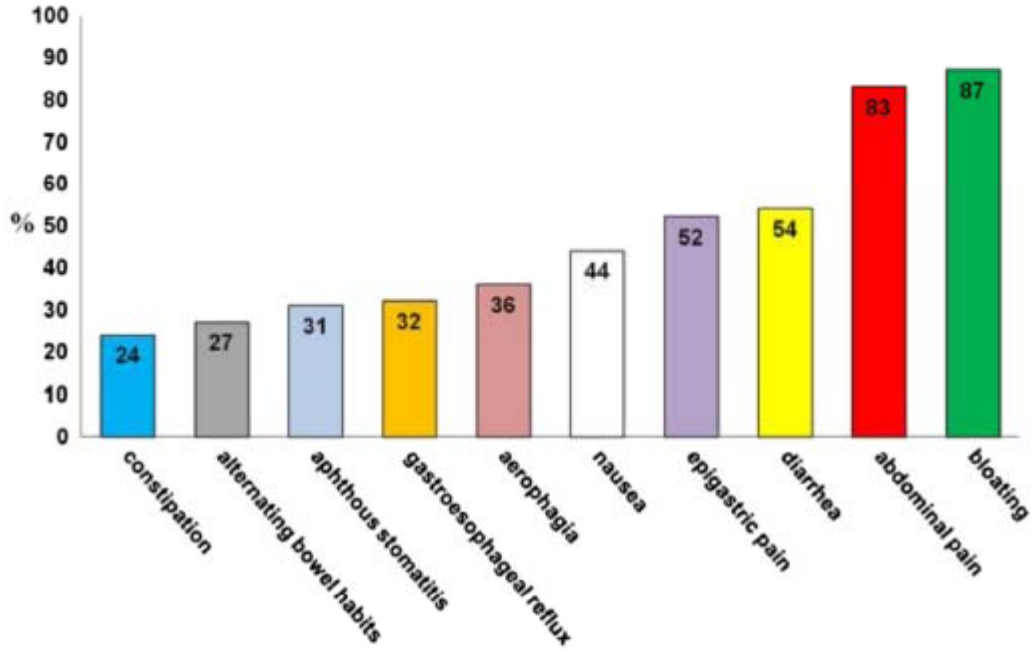


Figure 1. Gastrointestinal manifestations of NCGS (from reference[11]).

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Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

Stefano Guandalini, MD[1], and Isabel Polanco, MD[2]

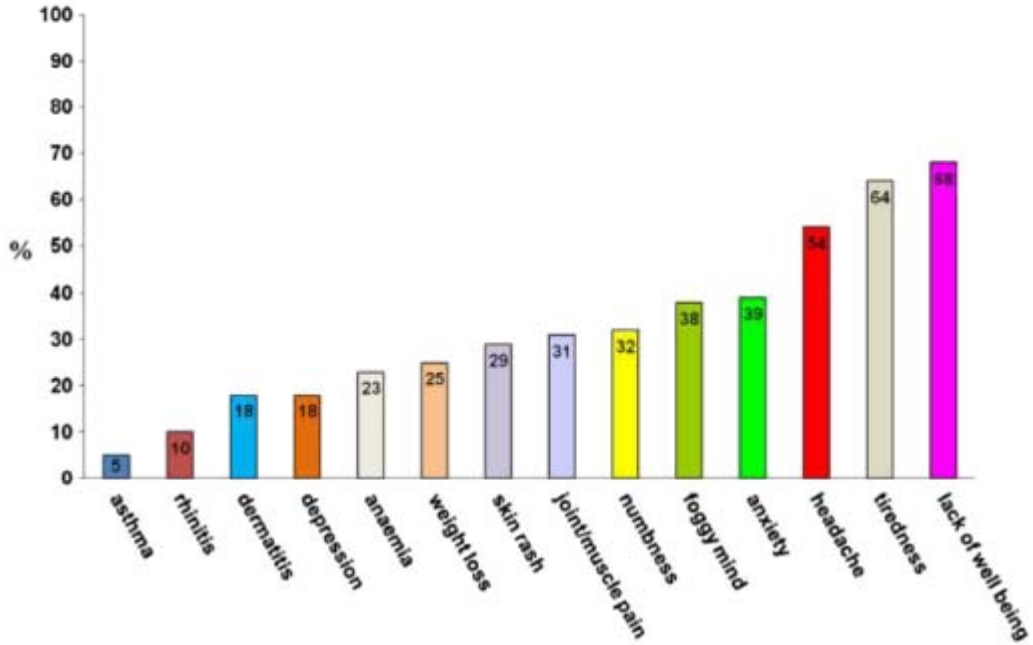

Figure 2. Extra intestinal manifestations of NCGS (from reference[11]).

Best Practice & Research Clinical Gastroenterology 29 (2015) 477–491

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

10

Non-celiac gluten sensitivity: A work-in-progress entity in the spectrum of wheat-related disorders

Umberto Volta, M.D., Professor [a, *], Giacomo Caio, M.D. [a, 1], Roberto De Giorgio, M.D., PhD., AGAF, Associate Professor [a, 2], Christine Henriksen, PhD., RD, Associate Professor [b, 3], Gry Skodje, RD [c, 4], Knut E. Lundin, M.D., Associate Professor [c, d, 5]

[a] Department of Medical and Surgical Sciences, St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
[b] Department of Nutrition, University of Oslo, Oslo, Norway
[c] Department of Gastroenterology, Oslo University Hospital Rikshospitalet, Oslo, Norway
[d] Centre for immune Regulation, University of Oslo, Oslo, Norway

- Sensibilidad al gluten no celíaca es un síndrome definido con manifestaciones gastrointestinales y extra-intestinales provocadas por el gluten en pacientes sin enfermedad celíaca y sin alergia al trigo.

- La patogénesis implica mecanismos inmunes que requieren más investigación. Los síntomas desaparecen en pocas horas o días después de la retirada del gluten y se repiten rápidamente después de la ingestión de gluten.

- Además de gluten, otras proteínas de trigo, así como fermentables oligo-, di-, monosacáridos y polioles (FODMAPs) pueden contribuir a este síndrome.

- Este síndrome se presenta principalmente en mujeres jóvenes, siendo poco frecuente en niños.

- Su prevalencia oscila entre el 0,6% y el 6%, en base a estimaciones centro de atención primaria o terciarios

- No tiene ningún biomarcador disponible patognomónico, pero la mitad de los pacientes pueden presentar pruebas positivas para anticuerpos anti-gliadina IgG que desaparecen rápidamente después de la dieta libre de gluten, junto con los síntomas.

- Además, los marcadores genéticos son todavía indefinido.

- Aunque actualmente limitado a un contexto de investigación, se recomienda la estrategia de ensayo cruzado controlado doble ciego con placebo para confirmar el diagnóstico.

- El tratamiento se basa en la restricción dietética con especial cuidado a la ingesta de nutrientes

AP&T Alimentary Pharmacology and Therapeutics

Systematic review: noncoeliac gluten sensitivity

J. Molina-Infante*, S. Santolaria†, D. S. Sanders‡ & F. Fernández-Bañares§,¶

*Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres, Spain.
†Department of Gastroenterology, Hospital San Jorge, Huesca, Spain.
‡Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, UK.
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Correspondence to:
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E-mail: xavi_molina@hotmail.com

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EV Pub Online 6 March 2015

This uncommissioned review article was subject to full peer-review.

SUMMARY

Background
Noncoeliac gluten sensitivity (NCGS) is a controversial emerging disorder. Despite reported symptoms related to the ingestion of gluten, NCGS remains a diagnosis based on the exclusion of coeliac disease, given the absence of reliable biomarkers.

Aim
To evaluate the prevalence, diagnostic exclusion of coeliac disease and the efficacy of a gluten-free diet (GFD) for NCGS patients.

Methods
A PubMed search was performed up to December 2014. According to consensus diagnostic criteria, NCGS was defined as self-reported gluten intolerance, negative coeliac serology and absence of villous atrophy. Studies evaluating the impact of a GFD on patients with irritable bowel syndrome (IBS) were also included.

Results
Prevalence rates of NCGS (0.5–13%) differed widely. Seventeen studies, including 1561 patients (26 children), met the inclusion criteria for NCGS. HLA haplotypes could not be linked to histology [normal or lymphocytic enteritis (LE)] in 1123 NCGS patients. HLADQ2/DQ8 haplotypes were present in 44% of NCGS patients. After advanced diagnostic techniques in 189 NCGS patients combining LE and HLADQ2/DQ8 haplotypes, 39 (20%) were reclassified as coeliac disease. There was a higher than expected family history of coeliac disease and autoimmune disorders in NCGS patients. A GFD resulted in variable results for variable, but significantly improved stool frequency in HLADQ2 positive diarrhoea-predominant IBS patients.

Conclusions
Prevalence rates for NCGS are extremely variable. A subset of NCGS patients might belong in the so-called 'coeliac-lite' disease. The benefit of a GFD for NCGS patients is currently controversial. HLADQ2 positive diarrhoea-type IBS patients might gain symptom improvement from a GFD.

AP&T Alimentary Pharmacology and Therapeutics

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Table 1 | Prevalence figures for non-coeliac gluten sensitivity (NCGS)

First author, year of publication	Country	Target population	NCGS prevalence
Tanpowpong, 2012[8]	New Zealand	916 children general population	5% GFD (1% CoD)
Sapone, 2012[5]	USA	5896 referred patients	6%
DiGiacomo, 2013[25]	USA	7762 general population free of CoD	0.55%
Aziz, 2014[26]	UK	1002 general population	13% (GFD 3.7%, 0.8% CoD)
Volta, 2014[27]	Italy	12,255 referred patients	3.2%

CoD, coeliac-disease; GFD, gluten-free diet.

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Table 3 | Family history of coeliac disease, malabsorption signs, autoimmune disorders and extraintestinal manifestations in patients with NCGS

Author, year publication	*n*	Family history of coeliac disease	Autoimmune disorders	Malabsorption signs/symptoms (%)	Extraintestinal manifestations (%)
Cooper, 1980[3]	8	None	None	Diarrhoea/weight loss (66.6%) Folate deficiency (33.3%)	Oral apthous ulcers (33.3%)
Massari, 2011[32]	77	N.S.	N.S.	Diarrhoea/weight loss (N.S.) Anaemia (19.4%) Iron deficiency (11.6%) Folate deficiency (7.8%)	N.S.
Carroccio, 2012[34*]	70	10 (14%)	N.S.	Anaemia (70%) Weight loss (45%)	N.S.
Volta, 2012[35]	78	N.S.	N.S.	Anaemia (15%)	'Foggy mind' (42%) Tiredness (36%) Eczema/skin rash (33%) Headache (32%) Joint/muscle pain (28%) Limb numbness (17%) Depression (15%)

Aziz, 2014[26]	186	23 (12.4%)	18 (9.7%)	Anaemia (3.3%) Low ferritin (16.2%) Folate deficiency (7.2%) Vitamin B12 deficiency (3.2%) Hypoalbuminaemia (2.8%)	Tiredness (23%) Headache (22%) Joint pains (8%) Confusion (5%) Leg numbness (6%) Rash (6%)
Isasi, 2014[40]†	20	N.S.	9 (45%)	Iron deficiency anaemia (15%)	Tiredness (40%) Migraine (45%) Arthritis (30%) Osteoporosis (10%) Depression (40%) Hypothyroidism (15%) Oral apthous ulcers (10%)
Kabbani, 2014[41]	125	16 (12.8%)	15 (12%)	Diarrhoea/weight loss (24.8%) Iron deficiency anaemia (2.4%) Vitamin D deficiency (16%) Vitamin B12 deficiency (0.8%)	N.S.
Volta, 2014[27]	486	87 (18%)	68 (14%)	Diarrhoea/weight loss (25%) Anaemia (23%) Low ferritin (23%) Vitamin D deficiency (11%) Folate deficiency (11%)	Lack of well being (68%) Tiredness (64%) Headache (54%) Anxiety (39%) 'Foggy mind' (38%) Numbness (32%) Joint/muscle pain (31%) Skin rash (29%) Depression (18%) Dermatitis (18%) Rhinitis (10%)

AP&T Alimentary Pharmacology and Therapeutics

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Table 5 | Effect of a gluten-free diet evaluated in patients with diarrhoea-predominant irritable bowel syndrome (IBS-D)

First author, year of publication	Patients	Measurements	Results	Effect of a GFD
Wahnschaffe, 2001[42]	102 IBS-D; negative CoD serology	• IgA and CoD-antibodies (anti-gliadin and anti-tTG in duodenal aspirate) Intraepithelial lymphocytes (IEL) • HLA-DQ2	• 35% DQ2+ • 23% IEL >40% • 30% CoD-antibodies in duodenal aspirate	Six months GFD ($n = 26$) Significant decrease in stool frequency and IgA levels in duodenal aspirate ($P < 0.05$) in DQ2+ patients with CoD-antibodies in duodenal aspirate
Wahnschaffe, 2007[43]	145 IBS-D	• CoD-serology • Stool frequency • GI symptom scores	• 39% DQ2+ • 37% IgG-CoD-antibodies • 11/41 (26%) IEL >40%	6 months GFD ($n = 45$) Normalisation of stool frequency and GI symptoms in 60% DQ2+ *plus* CoD-IgG-antibodies+ patients (vs. 12% in DQ2- patients; $P < 0.05$)

Vazquez-Roque, 2012[44]	45 IBS-D	• Mucosal permeability • Biopsy samples small bowel and rectosigmoid for pathology and tight junction proteins. • GI & colonic transit time • HLA-DQ2/8	• Small bowel permeability increased • DQ2/8+ patients had a decrease in ZO-1 protein in rectosigmoid (vs. DQ2/8- patients)	–
Vazquez-Roque, 2013[45]	45 IBS-D; negative CoD serology GFD vs. GCD	• DQ2/8 • Stool frequency • Small bowel & colon transit • Mucosal permeability • *Ex vivo* cytokine production • Tight junction proteins • Small bowel histology (n = 28)	• Increase in intestinal permeability in DQ2/8+ patients on a GCD. • Increase in IL-10, TNFalpha, GM-CSF (but not IFN-gamma) in GCD patients. • No patient had villous atrophy.	4 weeks GFD Significant decrease in stool frequency GCD vs. GFD, P 0.04 DQ2/8+ vs. DQ2/8- P 0.019 No impact on daily stool form, ease of passage and gastrointestinal or colonic transit

CoD, coeliac-disease; GCD, gluten-containing diet; GFD, gluten-free diet; IBS, irritable bowel syndrome; IBS-D, diarrhoea-predominant IBS.

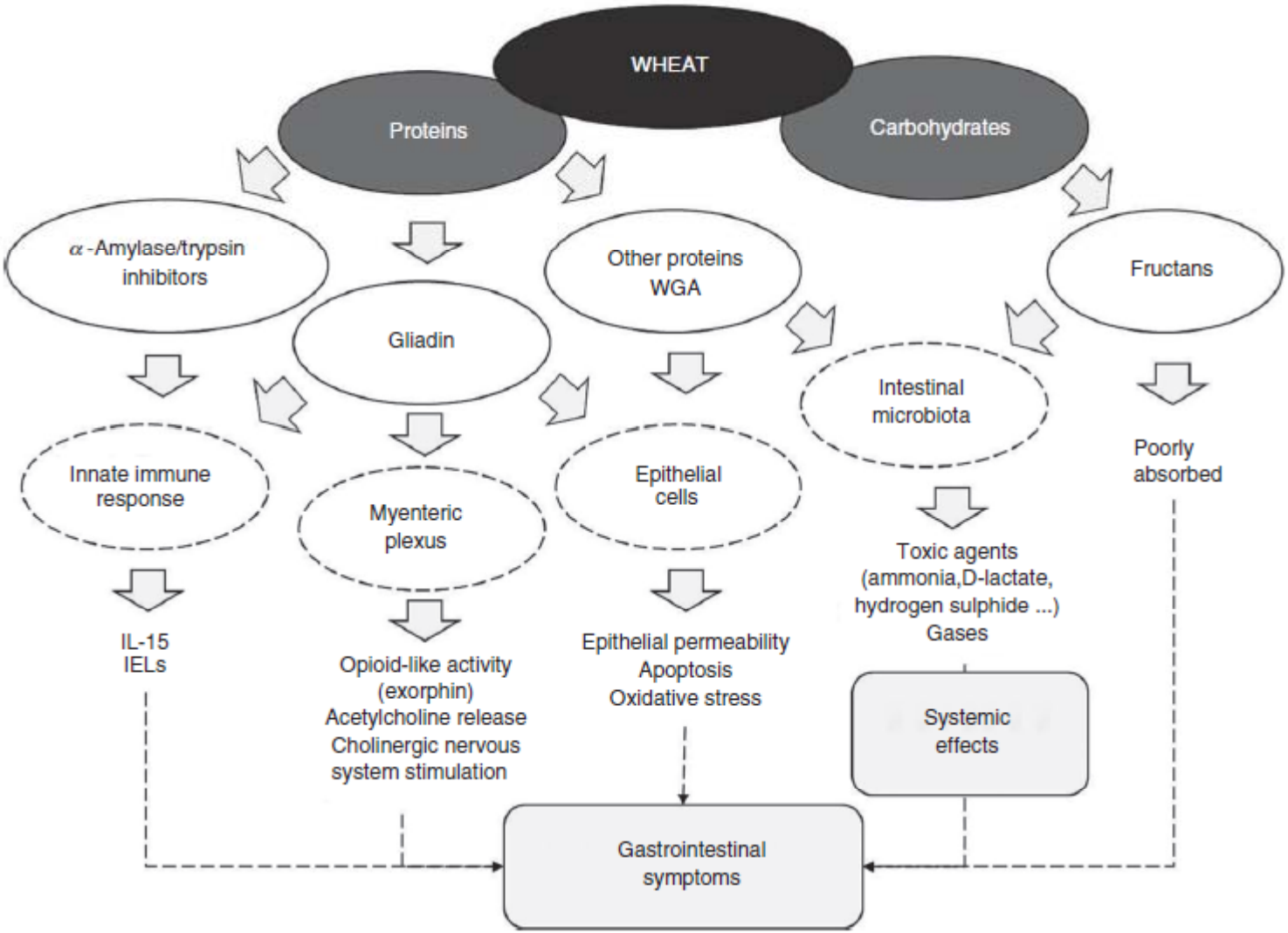

Figure 3 | Potential culprits in wheat and pathogenic pathways for the development of gastrointestinal and extraintestinal symptoms in NCGS. WGA, wheat germ agglutinin; IELs, intraepithelial lymphocytes.

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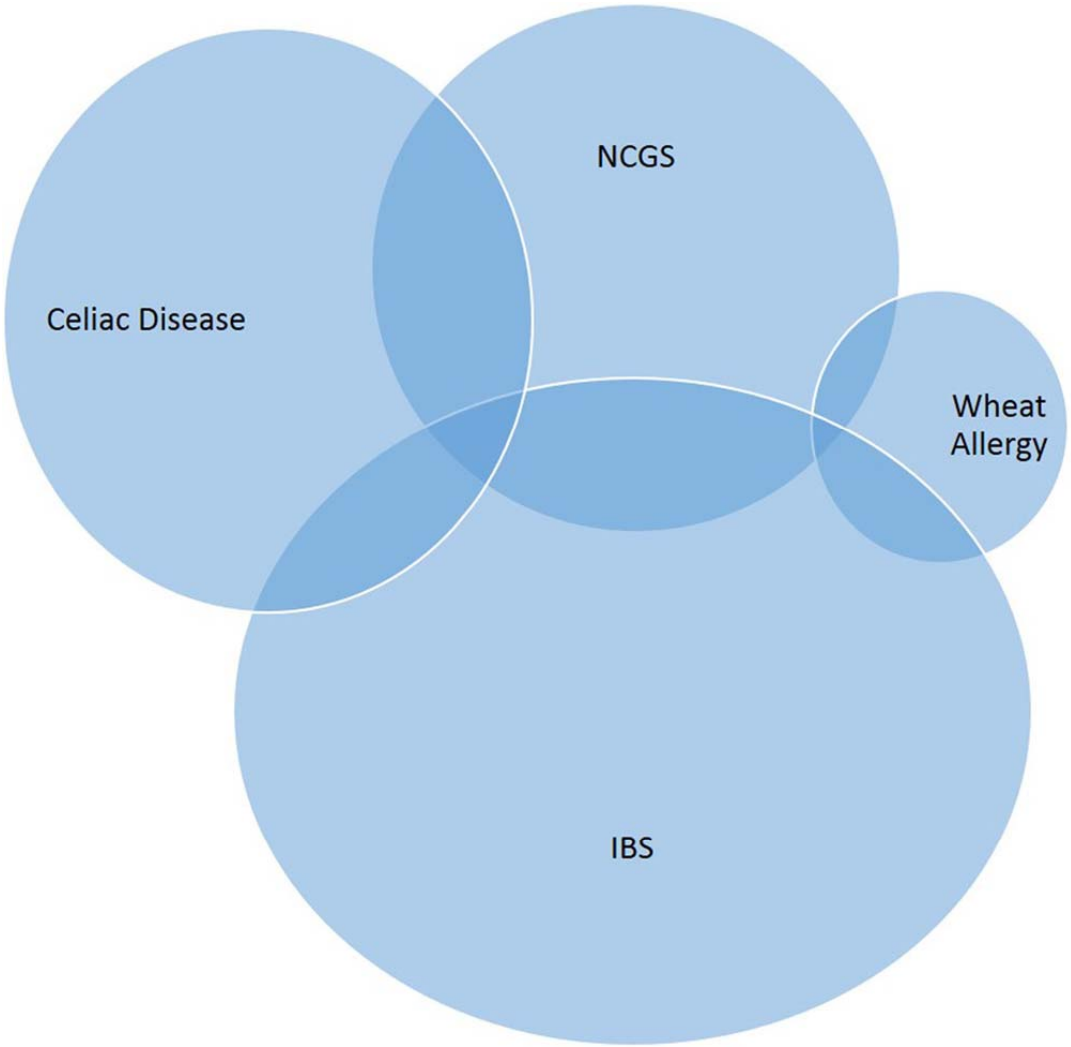
Conclusions

Prevalence rates for NCGS are extremely variable. A subset of NCGS patients might belong in the so-called ‘coeliac-lite’ disease. The benefit of a GFD for NCGS patients is currently controversial. HLADQ2 positive diarrhoea- type IBS patients might gain symptom improvement from a GFD.

¿Quiénes son los individuos sujetos a investigación por trastornos asociados al consumo de gluten?



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Review

Gluten free diet and nutrient deficiencies: A review

Giorgia Vici [a, b], Luca Belli [b], Massimiliano Biondi [b], Valeria Polzonetti [b, *]

[a] School of Advanced Studies, University of Camerino, Italy
[b] School of Biosciences and Veterinary Medicine, University of Camerino, Italy

ARTICLE INFO

Article history:
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Accepted 2 May 2016

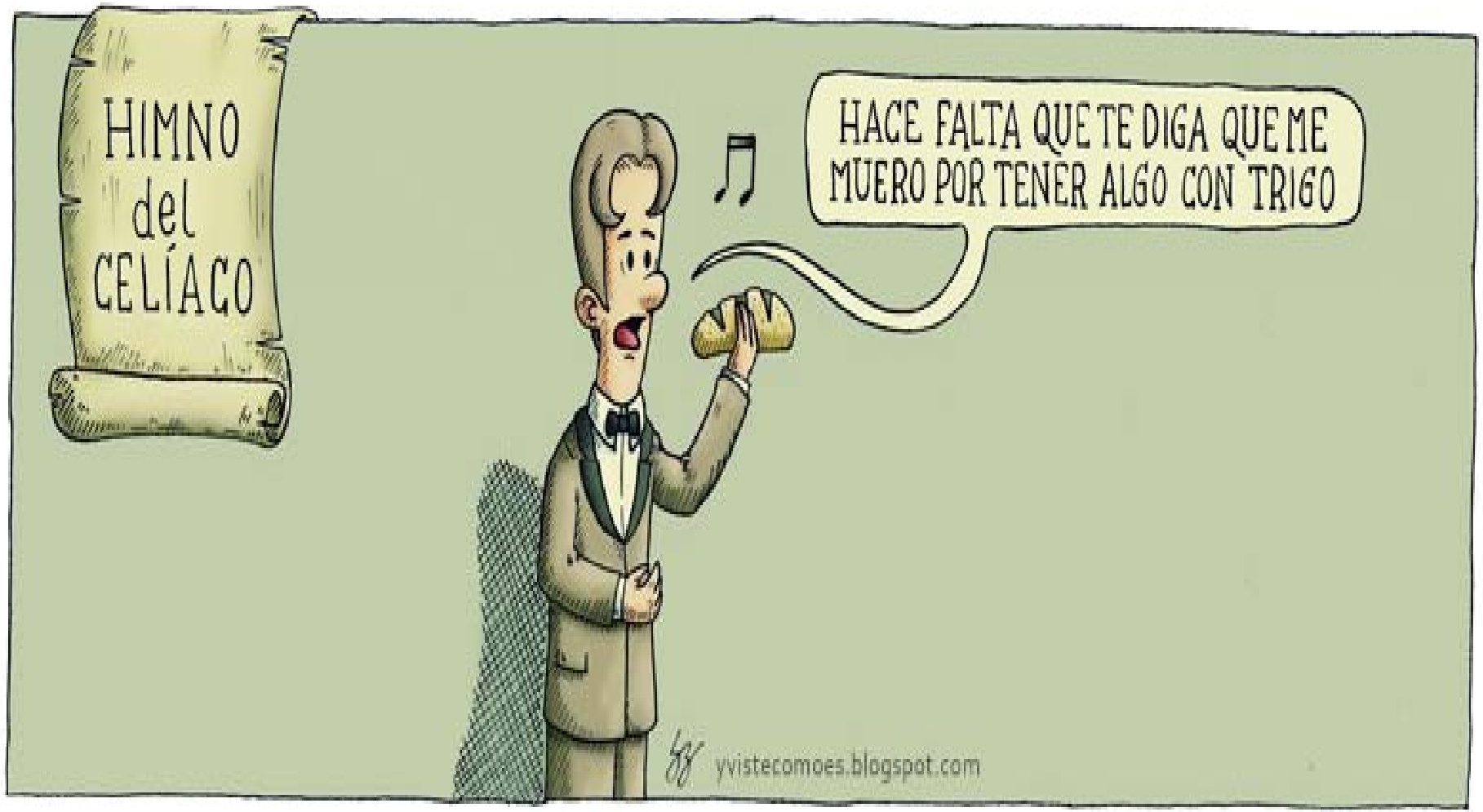
Keywords:
Celiac disease
Gluten free diet
Quality of diet
Nutrients deficiency

SUMMARY

Background & aims: The only available treatment for celiac disease (CD) is lifelong adherence to gluten free (GF)-diet. However, GF-diet may lead to possible nutrient unbalance resulting in improper nutritional quality of diet. The aim of this study is to evaluate the nutritional quality of GF-diet.
Methods: MEDLINE®/PubMed and Cochrane Library were electronically searched for articles published between 1990/01/01 and 2015/09/01.
Results: GF-diet was found to be poor in alimentary fiber due in particular to the necessary avoidance of several kinds of foods naturally rich in fiber (i.e. grain) and the low content of fiber of GF product that are usually made with starches and/or refined flours. Micronutrients are also found to be poor, in particular Vit. D, Vit. B12 and folate, in addition to some minerals such as iron, zinc, magnesium and calcium. Moreover, an inadequate macronutrient intake was reported related above all to the focus on the avoidance of gluten that often leaving back the importance of nutritional quality of the choice. In particular, it was found a higher content of both saturated and hydrogenated fatty acids and an increase in the glycemic index and glycemic load of the meal.
Conclusions: Despite the GF-diet is necessary in celiac disease treatment and the attention is on gluten avoidance, the evaluation of nutritional quality of the diet must be considered. Moreover, educational strategies based on the relationship between nutrients and food and human health could be developed to optimize the therapeutic approach in celiac patients.

Table 1
Nutritional deficiencies and excess of GF-diet.

	Country and year	Design	Study population	GF-diet nutritional evaluation method	Deficiencies	Excesses
Caruso et al. [1]	Italy, 2013	Review	–	–	Folate, Vit. B12, Vit. D	–
Saturni et al. [6]	Italy, 2010	Review	–	–	Dietary fiber, folate, niacin, Vit. B12	Total fat, saturated fat, energy intake
Zuccotti et al. [8]	Italy, 2013	Cross-sectional age-matched study	18 CD patients (mean age 7,6)	Food frequency questionnaire + 24-h dietary recall	Fat	Carbohydrate, energy intake
Penagini et al. [9]	Italy, 2013	Review	–	–	Vit. B, iron, folate, fiber, calcium, magnesium	Saturated fat, sugar, complex carbohydrates (high glycemic index)
Kupper et al. [10]	USA, 2010	Review	–	–	Vit. B, calcium, Vit. D, iron, zinc, magnesium, fiber	Lipids
Wild et al. [11]	UK, 2010	Observational study	139 CD patients	Validated 5-day food diary	Magnesium, iron, zinc, manganese, selenium, folate	Sugar
Martin et al. [12]	Germany, 2013	Observational Study	88 CD patients aged 45-80	7-day food diary + food questionnaire	Fiber, Vit.B, Folic Acid, Magnesium, Iron	Lipids
Mariani et al. [13]	Italy, 1998	Case–control study	47 CD adolescent patients	3-Day alimentary record	Calcium, fiber, iron, carbohydrates	Proteins, lipids
Samasca et al. [15]	Romania, 2014	Review	–	–	Dietary fiber, Vit. D, magnesium	Sucrose, saturated fat, energy intake
Hallert et al. [16]	Sweden, 2009	Double blind placebo controlled multicenter trial	65 CD patients aged 45–64	Randomized daily dose of 0.8 mg of folic scid, 0.5 mg Cyanocobalamin, 3 mg Pyridoxine or Placebo for 6 months	Vitamins status, Vit. B	–
Hallert et al. [19]	Sweden 2002	Observational study	30 CD patients (mean age 55, range 45–64)	Measure of total plasma homocysteine level + 4-day food record	Vitamins, Vit. B12	–
Grace-Farfaglia [21]	USA, 2015	Systematic review	–	–	Iron, Folate, Vit. B12, Vit. D, Vit. K, calcium, magnesium	–
Shepherd et al. [27]	Australia, 2013	Observational study	55 CD patients on GFD from more than 2 years + 50 newly diagnosed CD patients	7-Day food intake questionnaire	Dietary fiber, thiamine, folate, Vit. A, magnesium, calcium, iron, zinc	–
Öhlund et al. [28]	Sweden, 2010	Observational study	30 children aged 4–17 with CD on GFD	5-Day food record	Fiber, Vit. D, magnesium, selenium	Sucrose, saturated fat
Theethira et al. [29]	USA, 2014	Review	–	–	Dietary fiber, iron, Vit. B	Fats
Thompson et al. [31]	USA, 2005	Observational study	47 CD patients	3-Day self-reported food records	Iron, calcium, fiber	–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NONCELIAC GLUTEN AND WHEAT SENSITIVITY

Nonceliac Gluten Sensitivity




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During the past decade there has been an impressive increase in popularity of the gluten-free diet (GFD)—now the most trendy alimentary habit in the United States and other countries. According to recent surveys, as many as 100 million Americans will consume gluten-free products within a year. Operating under the concept that the GFD benefits only individuals with celiac disease, health care professionals have struggled to separate the wheat from the chaff; there are claims that eliminating gluten from the diet increases health and helps with weight loss, or even that gluten can be harmful to every human being. However, apart from unfounded trends, a disorder related to ingestion of gluten or gluten-containing cereals, namely nonceliac gluten sensitivity (NCGS), has resurfaced in the literature, fueling a debate on the appropriateness of the GFD for people without celiac disease. Although there is clearly a fad component to the popularity of the GFD, there is also undisputable and increasing evidence for NCGS. However, we require a better understanding of the clinical presentation of NCGS, as well as its pathogenesis, epidemiology, management, and role in conditions such as irritable bowel syndrome, chronic fatigue, and autoimmunity. Before we can begin to identify and manage NCGS, there must be agreement on the nomenclature and definition of the disorder based on proper peer-reviewed scientific information. We review the most recent findings on NCGS and outline directions to dissipate some of the confusion related to this disorder.

Keywords: Allergy; Celiac Disease; FODMAP; Food; Gluten; IBS; Sensitivity; Wheat.

organoleptic characteristics, and palatability. It can be processed into many foods, such as breads, pasta, pizza, bulgur, couscous, and drinks such as beer. Furthermore, the functional properties of gluten proteins have led to their addition to many foods and cosmetics.

The same characteristics that make gluten so unique and desirable for human consumption also lead to diseases: the best known, wheat allergy and celiac disease, are mediated by the adaptive immune system (Figure 1). Each disorder is characterized by activation of T cells in the intestinal mucosa against gluten. In wheat allergy, immunoglobulin E (IgE) is cross-linked by repeat sequences in gluten peptides (eg, Ser-Gln-Gln-Gln-[Gln-]Pro-Pro-Phe), and nongluten proteins induce the release of immune mediators such as histamine from basophils and mast cells.[1] In contrast, celiac disease, which affects approximately 1% of most populations, has characteristics of an autoimmune disorder. It can be identified based on serologic markers such as serum antibodies against tissue transglutaminase-2 (TG2), followed by intestinal biopsy confirmation,[2,3] and its link to autoimmune comorbidities.[4,5]

In addition to celiac disease and wheat allergy, there have been cases of reactions to gluten-containing grains that involved neither allergic nor autoimmune mechanisms. These generally are termed nonceliac gluten sensitivity (NCGS) or simply gluten sensitivity (Figure 1).[6–8] Individuals who experience distress when eating gluten-containing products and then improve on a gluten-free diet (GFD) might have NCGS instead of celiac disease. Patients with NCGS develop adverse reactions when eating

Table 3. Main Food Sources of ATIs and Gluten

	ATIs		Gluten	
Food sources	Structural class	Bioactivity	Main molecules	Level
Wheat, rye, barley	Cereal type	High	Gliadins, hordeins, secalins, HMW and LMW glutenins	High
Soy beans, buckwheat, peas	Legume lectin and cereal type	Medium (2%–10% of gluten-containing staples)	Prolamines	Low
Amaranth, rice, maize, potato	Knottin, Kunitz, and Thaumatin type	Low (<2% of gluten-containing staples)	Prolamines	Low

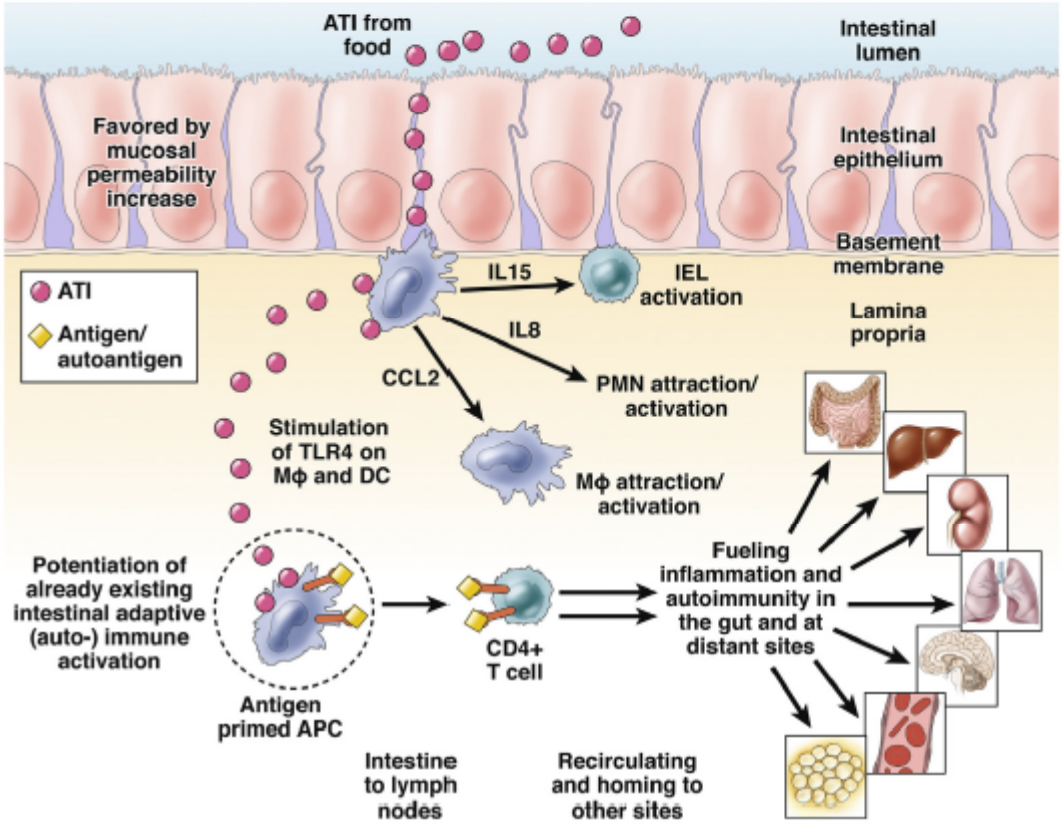

Figure 3. ATIs induce intestinal and extraintestinal adaptive immunity. The mechanisms by which ATIs from gluten-containing cereals are sensed: via TLR4, by lamina propria monocytes, macrophages, and dendritic cells. TLR4 signaling leads to the release of inflammatory cytokines and chemokines. ATIs also are adjuvants for adaptive immune reactions in the intestine and possibly nearby lymph nodes, where they also might promote extraintestinal T-cell responses. This could cause adaptive inflammation in remote organs (see the article by Junker et al[49]). APC, antigen presenting cell; CCS2, chemokine C-C motif ligand; DC, dendritic cell; IEL, intraepithelial lymphocyte.

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Non-celiac wheat sensitivity: differential diagnosis, triggers and implications.

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Abstract

Non allergy-non-celiac wheat sensitivity (NCWS) has become a common and often overrated diagnosis. Skepticism mainly relates to patients with prominent intestinal symptoms in the absence of general or intestinal signs of inflammation. There is consensus that the major wheat sensitivities, celiac disease and wheat allergy, have to be ruled out which may be difficult for wheat allergy. The non-inflammatory intolerances to carbohydrates, mainly lactose and FODMAPs (fermentable oligi-, di-, monosaccharides and polyols), which cause bloating or diarrhoea, can usually be excluded clinically or by simple tests. Recent studies and experimental data strongly indicate that NCWS exists in a substantial proportion of the population, that it is an innate immune reaction to wheatand that patients often present with extraintestinal symptoms, such as worsening of an underlying inflammatory disease in clear association with wheat consumption. Wheat amylase-trypsin inhibitors (ATIs) have been identified as the most likely triggers of NCWS. They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa. Non-gluten containing cereals or staples display no or little TLR4 stimulating activity. Wheat ATIs are a family of up to 17 similar proteins of molecular weights around 15 kD and represent 2-4% of the wheat protein. With oral ingestion they costimulate antigen presenting cells and promote T cell activation in celiac disease, but also in other immune-mediated diseases within and outside the GI tract