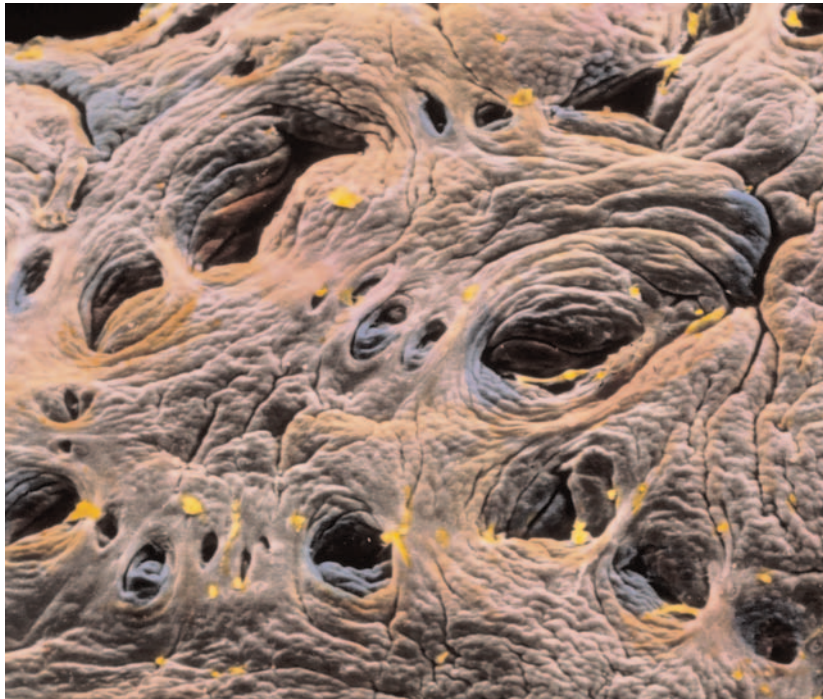


Fast Facts



Fast Facts: Celiac Disease

Geoffrey Holmes, Carlo Catassi, Alessio Fasano
Second edition





Fast Facts: Celiac Disease

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Geoffrey Holmes MD PhD FRCP

Consultant Physician and Gastroenterologist
Royal Derby Hospital
Derby, UK



Carlo Catassi MD

Associate Professor, Department of Pediatrics
Università Politecnica delle Marche, Ancona, Italy and
Co-Director, Center For Celiac Research
University of Maryland School of Medicine
Baltimore, MD, USA



Alessio Fasano MD

Professor of Pediatrics, Medicine and Physiology
Director, Mucosal Biology Research Center
University of Maryland School of Medicine
Baltimore, MD, USA

Declaration of Independence

This book is as balanced and as practical as we can make it.
Ideas for improvement are always welcome: feedback@fastfacts.com



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Cover image is a scanning electron micrograph of the wall of the small intestine in a patient with celiac disease. The mucosa appears flat and atrophied due to the loss of villi. Reproduced with permission from Professors PM Motta and FN Magliocca/ Science Photo Library.

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Geoffrey Holmes, Carlo Catassi, Alessio Fasano

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Glossary of abbreviations

AEA: anti-endomysial antibody

AGA: anti-gliadin antibody

Allele: one of the different forms of a gene

Anti-tTG: anti-tissue transglutaminase antibody

ARA: anti-reticulin antibody

CD: cluster of differentiation

CT: computed tomography

DEXA: dual-energy X-ray absorptiometry

DH: dermatitis herpetiformis

EATL: enteropathy-associated T-cell lymphoma

ELISA: enzyme-linked immunosorbent assay

Genotype: the two haplotypes on parental chromosomes

GFD: gluten-free diet

GH: growth hormone

Haplotype: combination of alleles at multiple loci that are transmitted together on the same chromosome

HLA: human leukocyte antigen

IEL: intraepithelial lymphocyte

IFN: interferon

Ig: immunoglobulin

IL: interleukin

Incidence: the number of new cases of a disease in a defined population during a specified period of time

LAD: linear IgA disease

MCV: mean corpuscular volume

MRI: magnetic resonance imaging

NHL: non-Hodgkin lymphoma

PET: positron emission tomography

ppm: parts per million

Prevalence: the total number of cases of a disease present in a defined population at a specified time

SD: standard deviation

TCR: T-cell receptor

TJ: tight junction

TNF: tumor necrosis factor

tTG: tissue transglutaminase

Introduction

The interest in celiac disease is now truly international: the corpus of knowledge about celiac disease is growing exponentially, with contributions from researchers around the world. Important advances have made a new edition of this book necessary. For example, new understandings of the mechanisms responsible for producing damage to the small-intestinal mucosa are leading to potential new treatments that may allow patients to consume gluten products without risk of ill health. There is even talk of preventing celiac disease. The age at which gluten is introduced in the diet in infancy, together with the gluten load and breastfeeding, are factors that determine the onset of the disorder; by manipulating these factors it is hoped to prevent celiac disease from arising.

It is easy to chart the landmarks in our increasing understanding of celiac disease. In 1888, Samuel Gee put celiac disease on the map with his delightful paper *On the celiac affection* in which he described the clinical features in children with remarkable accuracy. He predicted, with prophetic insight, that cure would come from manipulation of the diet. Idiopathic steatorrhea, or non-tropical sprue, was much later recognized to be celiac disease in adults.

The modern era was ushered in when Willem Dicke announced in 1950 that gluten damaged patients with celiac disease. This led to effective treatment with a gluten-free diet (GFD) and provided researchers with a protein to explore by means of newly emerging techniques in biochemistry and immunology. In the mid-1950s, it was possible for the first time to obtain peroral biopsies of the small intestine, so that celiac disease could be defined in morphologic terms. At the beginning of the 1970s, genetic markers of celiac disease were identified. In the 1980s, the ability to take intestinal biopsies using fiberoptic endoscopes and the development of serological tests for celiac disease greatly facilitated diagnosis. A decade later, the first screening studies showed celiac disease to be one of the commonest lifelong disorders in the Western world, causing considerable ill health and increases in mortality.

In the 1960s, an enteropathy was found in patients with dermatitis herpetiformis similar to that in celiac disease, with a rash that was gluten sensitive. Recently, some neurological disorders have also been identified as a manifestation of gluten sensitivity, so-called gluten neuropathy or gluten ataxia. Different forms of transglutaminase appear to determine which organs are affected by gluten. So the spectrum of gluten sensitivity is wider than first thought and may continue to expand.

Celiac disease can now be identified reliably thanks to the refinement of the serum anti-tissue transglutaminase antibody test. This has led to a reappraisal of the diagnostic criteria and has brought into question whether intestinal biopsy is always necessary. The genetic basis for celiac disease is proving difficult to establish, but progress is being made. Knowledge of the susceptibility genes carried by individuals should allow an accurate estimate of the risk they have of developing the condition.

Reassuringly for patients, several recent studies have shown that malignant complications are less common than previously thought. Once developed, however, lymphoma carries a very poor prognosis. One form of refractory celiac disease has been identified as a precursor to lymphoma, and attempts are under way to find a successful treatment that would reduce the malignant risk.

Finally, the effects of a GFD on the quality of life of those with celiac disease have been explored. Legislation regarding gluten-free products that should offer better guidance to patients has recently been enacted in both the USA and the EU.

Despite this remarkable progress the diagnosis of celiac disease is easily overlooked, resulting in a large number of undiagnosed patients who are unwell and exposed to various health risks in the community. The practical challenge for doctors and other healthcare workers is to identify these patients and offer them a GFD that will restore the majority to full health and may prevent the development of complications. This fully updated second edition of *Fast Facts: Celiac Disease* offers a concise account of the condition and explores all of the latest findings in relation to its diagnosis and management, with the hope that it will help to meet this challenge.

Celiac disease, or gluten-sensitive enteropathy, is characterized by immune-mediated damage to the jejunal mucosa that is triggered in genetically susceptible individuals by gluten, a protein complex in wheat, rye and barley cereals. Definitions of celiac disease have revolved around abnormalities found in the jejunal mucosa as well as responses to gluten withdrawal and challenge and the associated clinical reactions. The finding that certain antibodies are markedly associated with celiac disease has added an important dimension to the definition of the disease.

In practice, the diagnosis is usually straightforward and is based on:

- typical serology of positive anti-endomysial (AEA) and anti-tissue transglutaminase antibodies (anti-tTG)
- characteristic appearance of a small-bowel biopsy
- satisfactory response to a gluten-free diet (GFD).

Furthermore, celiac disease develops in the context of a positive HLA-DQ2 and/or -DQ8 haplotype.

For many years, the mucosal changes in celiac disease have been described as total, subtotal or partial villous atrophy; more recently, in an effort to standardize reporting, the modified Marsh classification has been widely adopted for clinical use (Table 1.1). In this classification, types 3a, 3b and 3c equate to partial, subtotal and total villous atrophy, respectively, and are characteristic of untreated celiac disease. It is clear, however, that the range of gluten sensitivity is wider than previously realized; several forms of celiac disease are now identified, and the modified Marsh classification recognizes a spectrum of mucosal change from a mild to a severe abnormality (Figure 1.1). Factors such as the amount of ingested gluten, gastrointestinal infection or the stress of a pregnancy or operation may influence the gradual shift from a minimal-change enteropathy to the typical flat lesion characteristic of celiac disease.

Typical celiac disease

Typical celiac disease is characterized by the classic features of malabsorption, such as weight loss, chronic diarrhea, steatorrhea and,

TABLE 1.1

Modified Marsh classification of mucosal lesions in celiac disease

Type	IELs/100 enterocytes	Crypts	Villi
0	< 25*	Normal	Normal
1	> 25	Normal	Normal
2	> 25	Hyperplastic	Normal
3a	> 25	Hyperplastic	Mild atrophy
3b	> 25	Hyperplastic	Marked atrophy
3c	> 25	Hyperplastic	Absent

Type 0	Normal mucosa; celiac disease very unlikely
Type 1	Infiltrative lesion; may indicate celiac disease and progress to a type 3 lesion
Type 2	Hyperplastic lesion; may indicate celiac disease
Type 3	Destructive lesion; spectrum of changes characteristic of untreated celiac disease. Patients may be symptomatic or asymptomatic

*The Marsh–Oberhuber classification indicated that 40 IELs/100 enterocytes should be the cut-off point. Based on recent data, the upper limit of the normal range has been reduced to 25 IELs/100 enterocytes. IEL, intraepithelial lymphocyte.

in infants, failure to thrive. Biopsies from the small intestine usually show types 3a to 3c mucosal lesions but occasionally damage can be less severe.

Atypical celiac disease

Atypical celiac disease is characterized by often isolated, usually extraintestinal, manifestations. These include chronic fatigue, anemia, short stature, pubertal delay, arthralgia and infertility. The degree of small-intestinal damage varies from a type 1 lesion to a fully expressed gluten-sensitive enteropathy (type 3c). Atypical forms are encountered more commonly than typical forms in clinical practice.

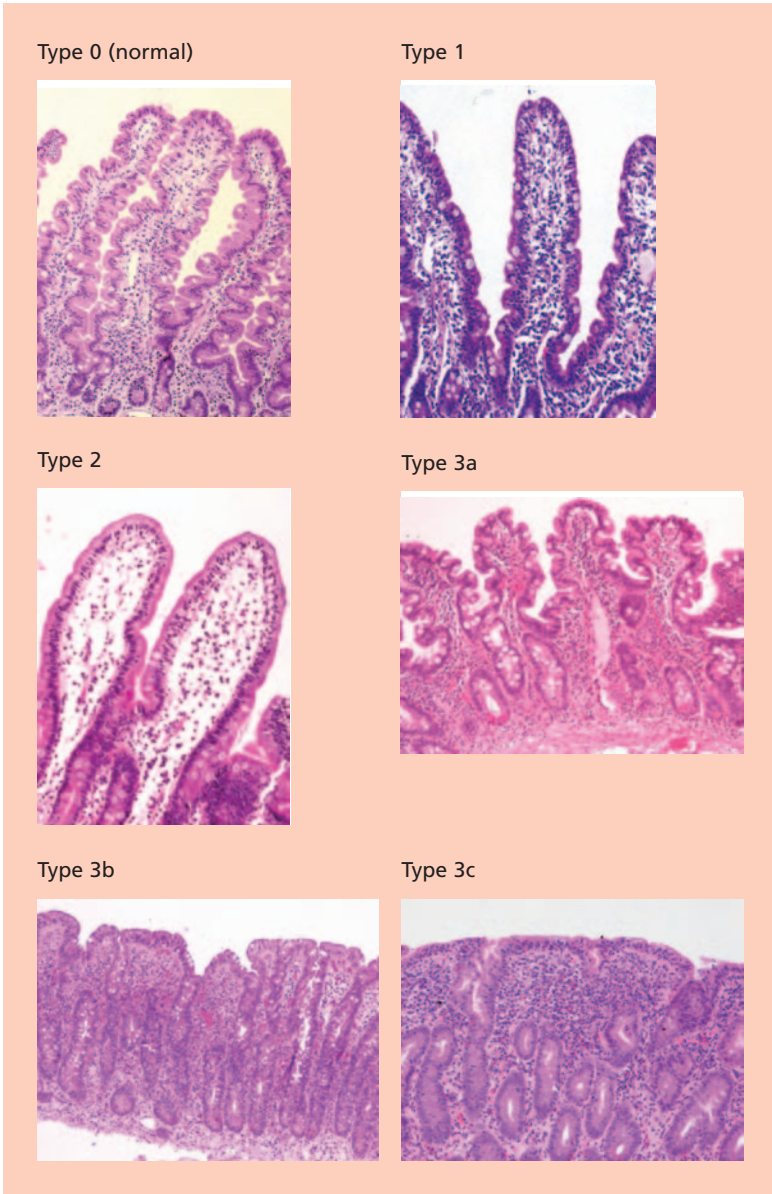


Figure 1.1 Histological appearances of small-bowel biopsies for types 0 to 3c according to the Marsh classification modified by Oberhuber. Reproduced courtesy of I. Bearzi, Department of Pathology, Università Politecnica delle Marche, Ancona, Italy.

3 Pathophysiology

Celiac disease is a multifactorial disorder that depends on both genetic and environmental factors for expression. The disease appears to be specific to humans, and the lack of an animal model has hampered research. Although the pathogenesis of celiac disease is not yet completely understood, there is evidence to indicate that it is an autoimmune disorder triggered and maintained by an external antigen, namely gluten, in the diet.

Gluten

The term gluten is generically applied to a family of storage proteins found in wheat, rye and barley (8–14% by weight) (Figure 3.1). All the

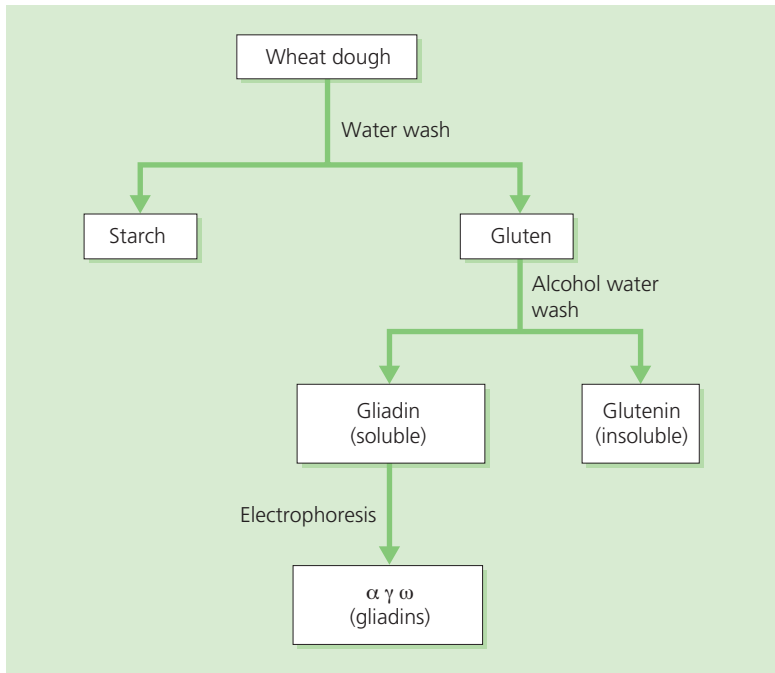


Figure 3.1 Fractionation of wheat showing derivation of gluten and gliadin.

proteins that are harmful to patients with celiac disease are rich in proline and glutamine, and are collectively called prolamins. The prolamins of the various cereals carry different names: gliadin (wheat), secalin (rye) and hordein (barley). The prolamins of oats (avenin) account for only 5–15% of the total seed protein, which could partly explain why celiac patients may tolerate oats in the diet.

The toxic protein fractions of gluten are not only gliadins (alcohol soluble) but also glutenins (alcohol insoluble), with gliadins containing monomeric proteins and glutenins containing aggregated proteins. The protein components and amino acid sequences of gliadins and glutenins are similar and repetitive. In a single wheat variety, there are approximately 45 different gliadins, which can be subdivided into α , γ , and ω subfractions according to their electrophoretic mobility. This complexity has made gluten a difficult substance to investigate within the context of celiac disease.

The sequence of A-gliadin, a protein made up of 266 amino acids, has been determined. The amino acid sequence(s) responsible for celiac disease have not been fully elucidated. Different parts of the gliadin molecules show different biological properties, all potentially involved in the pathogenesis of the disease (Figure 3.2). Several human leukocyte antigen (HLA)-DQ2-restricted T-cell epitopes have been found clustering in proline-rich regions of gliadin. A gliadin peptide of 33 residues, α 2-gliadin 57–89, has been identified. It is produced by normal gastrointestinal proteolysis and contains six partly overlapping copies of three T-cell epitopes. This 33-mer is an immunodominant peptide that is a remarkably potent T-cell stimulator after deamidation by intestinal tissue transglutaminase (tTG). Other sequences of A-gliadin (e.g. amino acids 31–43) have been shown to activate innate immunity mechanisms or interact with CD8+ cytotoxic T cells.

Other environmental factors

Some environmental factors may affect the risk or the timing of presentation of celiac disease. The risk is greater when gluten is introduced in large amounts in the diet during the first year of life. Conversely, breastfeeding has a consistently protective effect; in particular, the risk of celiac disease is reduced if children are still