

# **Celiac Disease**

**in the 21<sup>st</sup> Century**

**Anthony J. DiMarino Jr. M.D.**

**William Rorer Professor**

**Chief of Gastroenterology / Hepatology**

**Thomas Jefferson University Hospital**

**Pennsylvania Society of Gastroenterology**

**Gettysburg, Penna. September 20, 2008**

# CELIAC DISEASE

CELIAC DISEASE IS AN  
AUTOIMMUNE ENTEROPATHY  
TRIGGERED BY THE INGESTION  
OF GLUTEN CONTAINING  
GRAINS IN GENETICALLY  
SENSITIVE INDIVIDUALS

# Pathogenesis

- Wide spectrum of clinical manifestations ranging from asymptomatic to severe malabsorption

Intrinsic + Extrinsic factors = disease

# Pathogenesis Overview

## Infection

- ? Adenovirus 12

## Diet

- gluten

- ? Time of exposure

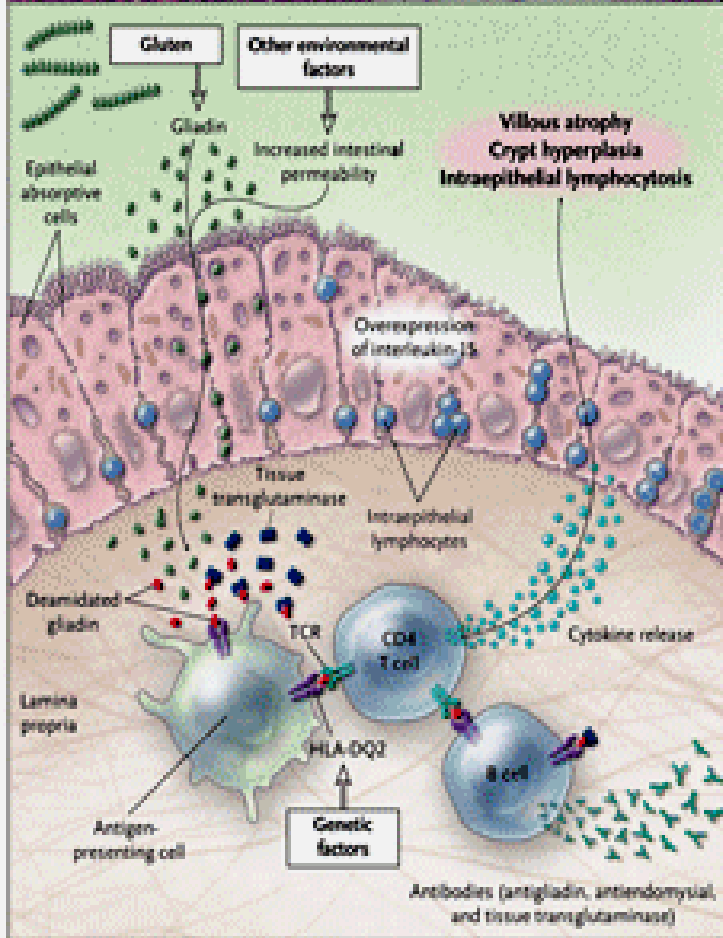
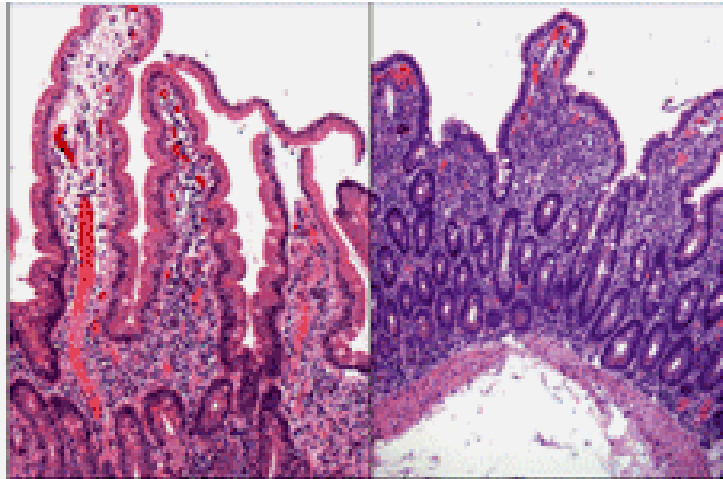
## Celiac Disease

## Autoimmunity

- ? tTG

## Genetics

- HLA-DQ<sub>2</sub>, DQ<sub>8</sub>



# CELIAC DISEASE EPIDEMIOLOGY IN USA

- University of Maryland – CRC
- Screened n=13,145

Healthy	4126	1/133
Relatives	5783	1/20

Fasano Arch Int Med 2003

# Disease Frequencies

- Combined Familial Hyperlipidemia 1:100
- **Celiac Disease** **1:133**
- Familial Hypercholesterolemia 1:300
- Hemochromatosis 1:400
- Down's Syndrome 1:600
- Cystic Fibrosis 1:2,500
- Phenylketonuria 1:15,000
- Wilson's Disease 1:30,000

# Celiac Dis. Clinical Presentations

1. **Classical** - (<5%)
2. **“ Atypical”/Late Onset** – IBS Like
3. **Silent** - Extra Intestinal, w/o GI Sx.
4. **Latent** – positive antibodies but normal biopsy
5. **Refractory** - Types I and II









# DERMATITIS HERPETIFORMIS



- Papules, vesicles and occ bullae on erythematous urticarial base
- On extensor surfaces, elbows, knees, upper back and buttocks
- Symmetrical / Bilateral / grouped

# Apthous Ulceration



# Atypical Celiac Presentations

- Atyp. GI Symptoms- 40% owt., 13% ob., Dickey; AJG06
- Fe Deficiency Anemia- (5% in some groups)
- Derm. Herpetiformis- (80%) only 10 % have GI Sx.
- Aphthous Ulcers- (5% of Recurrent)
- Osteopenic Bone Disease- 3-5% of Unexplained
- Migraine, P. Neuropathy, Seizure- (2.5%, Cronin)

## Increased Prevalence of Celiac Disease and Need for Routine Screening Among Patients With Osteoporosis

William F. Stenson, MD; Rodney Newberry, MD; Robin Lorenz, MD, PhD; Christine Baldus, RN, BSN; Roberto Civielli, MD

**Background:** There is an increased prevalence of osteoporosis among patients with celiac disease. However, the relative prevalence of celiac disease among osteoporotic and nonosteoporotic populations is not known, and the benefit of screening the osteoporotic population for celiac disease remains controversial.

**Methods:** We evaluated 840 individuals, 266 with and 574 without osteoporosis, from the Washington University Bone Clinic by serologic screening for celiac disease. Individuals with positive serologic test results for antitissue transglutaminase or antiendomysial antibody were offered endoscopic intestinal biopsy to confirm the diagnosis of celiac disease. Individuals with biopsy-proven celiac disease were treated with a gluten-free diet and followed up for improvement in bone mineral density.

**Results:** Twelve (4.5%) of 266 patients with osteoporosis and 6 (1.0%) of 574 patients without osteoporosis tested positive by serologic screening for celiac disease. All but 2 serologically positive individuals underwent in-

testinal biopsy. Nine osteoporotic patients and 1 nonosteoporotic patient had positive biopsy results. The prevalence of biopsy-proven celiac disease was 3.4% among the osteoporotic population and 0.2% among the nonosteoporotic population. All biopsy-positive individuals tested positive by antitissue transglutaminase and antiendomysial antibody. The antitissue transglutaminase levels correlated with the severity of osteoporosis as measured by T score, demonstrating that the more severe the celiac disease the more severe the resulting osteoporosis. Treatment of the patients with celiac disease with a gluten-free diet resulted in marked improvement in T scores.

**Conclusions:** The prevalence of celiac disease among osteoporotic individuals (3.4%) is much higher than that among nonosteoporotic individuals (0.2%). The prevalence of celiac disease in osteoporosis is high enough to justify a recommendation for serologic screening of all patients with osteoporosis for celiac disease.

*Arch Intern Med.* 2005;165:393-399

**C**ELIAC DISEASE IS AN ANTIGEN-driven enteropathy of the small intestine, resulting from an inappropriate immune response to dietary gliadin, a component of wheat proteins.<sup>1</sup> Celiac disease can have a varied clinical presentation, with most symptoms being attributed to malabsorption.<sup>2,3</sup> The discovery of tissue transglutaminase as the predominant autoantigen of celiac disease allowed for the development of standardized and quantitative serologic screening tests.<sup>4</sup> These tests have facilitated the widespread screening of asymptomatic individuals and have altered our perception of the incidence of celiac disease. However, despite the observation that celiac disease is much more common than previously appreciated, and despite the availability of serologic tests for screening, we still do not know which groups of individuals will most benefit from screening for celiac disease.

Adults with newly diagnosed celiac disease have a low bone mineral density

(BMD), and treatment of these individuals with a gluten-free diet increases their BMD.<sup>5,6</sup> However, studies<sup>7-12</sup> screening asymptomatic osteoporotic individuals for the presence of celiac disease have yielded conflicting results. Given these results, current practice for the workup of postmenopausal women presenting with osteoporosis does not include serologic screening for the presence of celiac disease. In an attempt to resolve these issues, we performed a large prospective screening trial for the presence of celiac disease in osteoporotic and nonosteoporotic individuals.

*For editorial comment  
see page 370*

### METHODS

#### PROTOCOL

The study protocol was approved by the institutional review board at Washington Univer-

**Author Affiliations:** Divisions of Gastroenterology (Drs Stenson and Newberry) and Bone and Mineral Metabolism (Ms Baldus and Dr Civielli), Washington University School of Medicine, St Louis, Mo; and Department of Pathology, University of Alabama School of Medicine, Birmingham (Dr Lorenz).  
**Financial Disclosure:** None.

**Table 2. Serologic Testing for Celiac Disease in the Osteoporotic and Nonosteoporotic Groups**

Serologic Test*			Osteoporotic Group (n = 266)			Nonosteoporotic Group (n = 574)		
Antigliadin	TTG	EMA	No. (%)	No. With Biopsy Performed	No. With Positive Biopsy	No. (%)	No. With Biopsy Performed	No. With Positive Biopsy
-	-	-	201 (75.6)	0	0	444 (77.4)	0	0
+	-	-	53 (19.9)	0	0	124 (21.6)	0	0
+	+	-	1 (0.4)	1	0	2 (0.3)	2	0
-	+	-	1 (0.4)	1	0	2 (0.3)	0	0
-	-	+	1 (0.4)	1	0	0	0	0
+	-	+	0	0	0	1 (0.2)	1	0
+	+	+	9 (3.4)†	9	9	1 (0.2)	1	1

Abbreviations: EMA, antiendomysial antibody; TTG, antitissue transglutaminase.

\*Minus sign indicates negative test result; plus sign, positive test result. Antigliadin is IgG or IgA.

† $P < .001$  compared with the nonosteoporotic group.

# Autoimmune Disease

1. Dermatitis Herpetiformis (70-80%)
2. IDDM (3-8%)
3. Sjogrens Syndrome (3-4%)
4. Liver Disease (PBC, CAH ?5% )
5. Thyroid Disease (5%)
6. Neurologic (Neuropathy, Epilepsy(2.5%), Ataxia)
7. IGA Nephropathy
8. Cardiomyopathy
9. Addisons Disease

# Fertility in Celiac Disease

- Delayed Menarche/Premature Menopause
- Amenorrhea
- Recurrent Abortions
- Relative Infertility/Woman & 4x Men ? DDW 2007
- Low Birth Weight Babies
- Increased Perinatal Mortality
- Poor Outcomes of Fertility May be Corrected by Gluten-Free Diet

# Malignant Complications

- Enteropathy- type Intestinal T Cell Lymphoma  
(30-40x, if GFD, 70x if not on diet)
- Other Lymphomas
- Small Bowel Adenocarcinoma (83x)
- Oropharyngeal Cancer (23x)
- Esophageal Squamous Cell Carcinoma (23x)
- Other Malignancies (2-3x)

# Serologic Test in Adults

Test	Sensitivity	Specificity
AGA IgA	< 80% in 50%	> 80% in most
AGA IgG	Variable	Non-specific
EMA IgA	96 – 97% ME, 90% HUV	100% ME, HUV
<b>tTG IgA</b>	<b>90% GP, 98% HR</b>	<b>95% GP, 98% HR</b>
tTG IgG	40%	98%

# Endoscopic findings

- Scalloped folds
- Decrease in Kerckring's folds, fissuring
- Flattened Folds
- normal appearing



# Histology

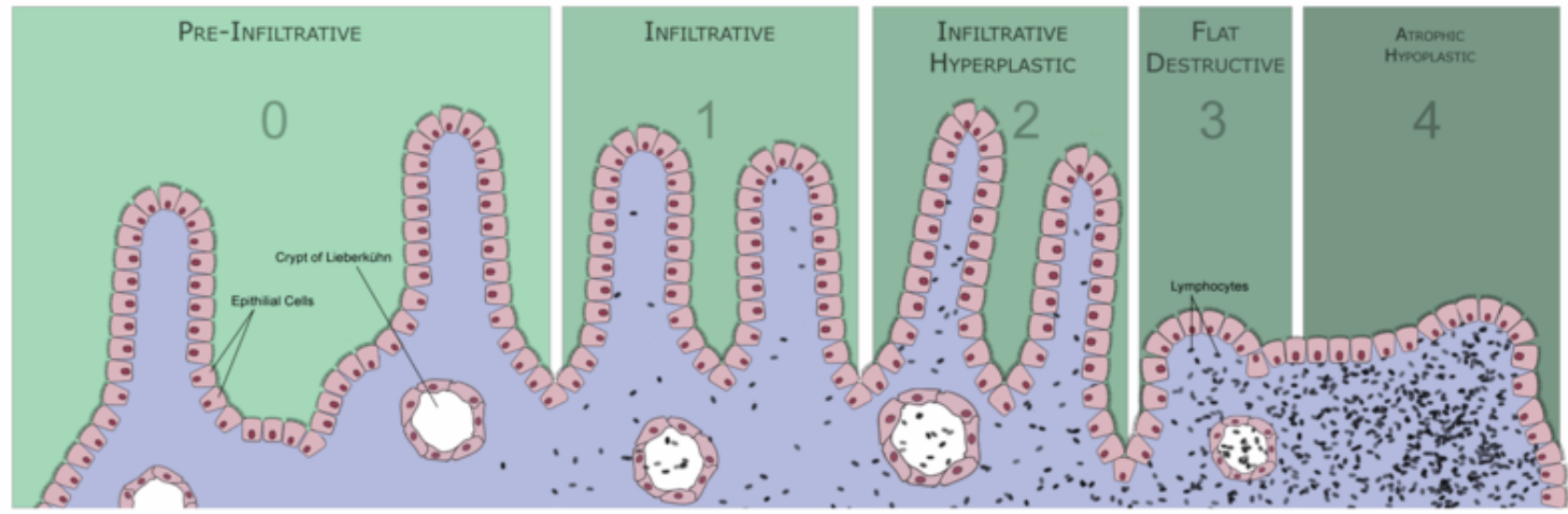
- Stage 1 - initial increase in intraepithelial lymphocytes, followed by lymphocyte infiltrate into the lamina propria
- Stage 2 - crypt hyperplasia
- Stage 3 - villous atrophy

# Differential Diagnosis of Scalloped Folds on Endoscopy/WCE

- Celiac sprue
- Tropical sprue
- Malnutrition
- Crohn's disease
- Soy protein intolerance
- Eosinophilic enteritis
- Giardiasis
- HIV enteropathy or related infections
- Amyloidosis
- Normal!

# MARSH CLASSIFICATION

## UPPER JEJUNAL MUCOSAL IMMUNOPATHOLOGY



- Stage 1 :Increased intraepithelial lymphocytes/ infiltration into lamina propria
- Stage 2: Proliferation of crypts of Lieberkühn
- Stage 3: Partial/ complete villous atrophy
- Stage 4: Hypoplasia of small bowel architecture

# What is the Treatment?



- Only treatment is to follow a **100% gluten-free diet, no wheat, rye, barley!!!**
- For most people, following this diet will stop symptoms, **heal existing intestinal damage**, and prevent further damage
- Improvements begin within **days of starting the diet**, and the small intestine is usually completely healed in **3 to 6 months**.
- It may take up to **2 years** for older adults
- **Gluten-free diet is a lifetime requirement**

# Refractory Sprue (<5%) : Diff.Dx.

1. Poor Compliance With Diet
2. Collagenous Sprue
3. Lymphoma
4. Autoimmune Enteropathy
5. Tropical Sprue
6. Ulcerative Jejunoileitis
7. Pancreatic Insufficiency
8. Bacterial Overgrowth
9. Refractory I or II

# The Future : Celiac Disease

- **Breast Feed, delay/decrease infant diet Gluten**

Farrell RJ, JAMA 05

- **“Predigest” Gluten Molecules (endopeptidases)**

Pyle AK, CG&H 06

- **Genetically Modified Wheat Strains**

- **Inhibit Zonulin which regulates Intestinal Permeability (TJ)**

Fassano A., Lancet 2000, Drago S., Gastro. 2006

- **Immunotherapy**

**Block tTG**

**Block HLA DQ2 (DQ8)**

**Block T cells or T cell Receptors**

# Summary

- **Celiac disease is not rare (1 in 100 – 300)**
- **It can present in many ways:**
  - **Iron deficiency anemia, depression, osteopenic bone disease, abnormal LFTs, non-specific or IBS-like GI symptoms, dyspepsia, DH, recurrent miscarriages, microscopic colitis**
- **Associated with autoimmune diseases**
- **Screening with tTG IgA is probably best**
- **Confirm diagnosis with duodenal biopsy**
- **Cornerstone of treatment is avoidance of gluten**
- **New therapies on the horizon but unclear if they will ever replace gluten free diet**