

Celiac Disease

Rob Squires, M.D.
Clinical Director, Gastroenterology
Children's Hospital of Pittsburgh of UPMC

Professor of Pediatrics
University of Pittsburgh

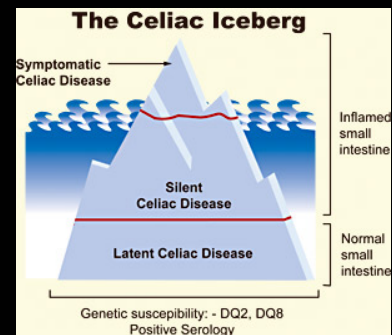
Celiac Disease

- Prevalence in the US and Europe approaches 1% of the population
- Triggered by the ingestion of wheat gluten and related proteins (barley, rye)
- Gluten molecules provoke an inflammatory response within the bowel resulting in a histological spectrum that includes:
 - villous atrophy
 - crypt hyperplasia
 - lymphocytic infiltration
- Symptoms and mucosal lesions resolve following removal of gluten from the diet.
- The condition is "life long".

Celiac Disease

- Classic symptoms
 - Gastrointestinal symptoms
 - Partial/total villous atrophy
- Non-classic symptoms
 - Extra-intestinal manifestations
 - Partial/total villous atrophy
- Silent
 - Minimal complaints/symptom free
 - Partial/total villous atrophy
- Potential
 - No symptoms, positive antibodies, predisposing genotype (DQ2 or DQ8)
 - Normal or minimally normal (increase intraepithelial lymphs)

Scope of the Problem



Gastrointestinal manifestations

- Chronic diarrhea
- Constipation
- Anorexia
- Vomiting
- Recurrent pain
- Intussusception
- Dyspepsia
- Reflux
- Occult blood in stool
- Hepatic steatosis
- Acute hepatitis
- Autoimmune hepatitis
- Acute liver failure
- Pancreatitis
- Pseudoobstruction
- Lymphocytic gastritis

Chand N. J Clin Gastro. 2006;40:3

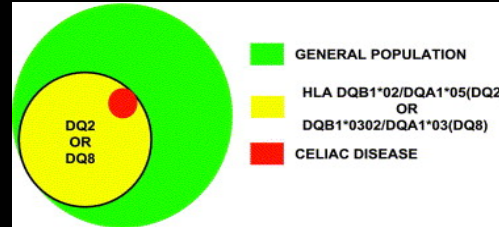
Extra-intestinal Manifestations of Celiac Disease

- Hematologic
 - Chronic anemia (folate, B12, stool loss)
- Dermatologic
 - Dermatitis herpetiformis
- Neurologic
 - Peripheral neuropathy, cerebral ataxia, depression, autism (?)
- Bone disease
 - Osteoporosis, bone pain, growth retardation
- Endocrine
 - Type 1 diabetes, autoimmune thyroid disease, addison disease, reduced fertility
- Cancer/lymphoma
 - Intestinal lymphoma

Conditions Associated with CD

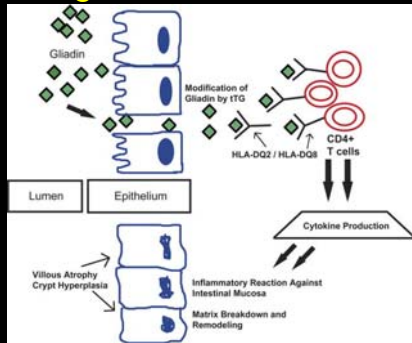
- Immune mediated disorders
 - Type 1 diabetes
 - Autoimmune hepatitis
 - Sclerosing cholangitis
 - Hashimoto's thyroiditis
 - Myocarditis
 - Addison's
- High risk populations
 - Down's syndrome
 - Turner's syndrome

Genetic Susceptibility



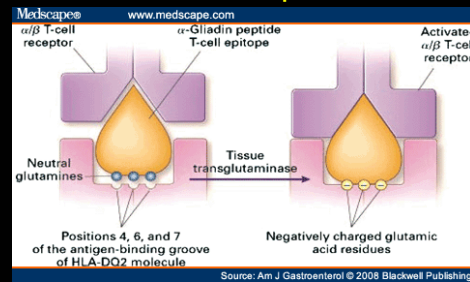
Kagnoff MF Gastroenterol 2005;128:S10

Pathogenesis of Celiac Disease



Chand, N. J Clin Gastro 2006;40:

Modification of the Gluten Protein in the Susceptible Host



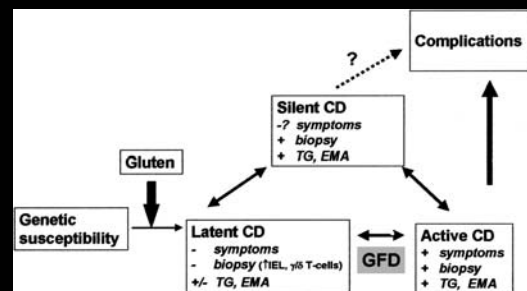
Farrell RJ, Kelly CP in N Engl J Med 2002;346:180-8

Multi-organ autoimmune disorder

General <ul style="list-style-type: none"> • pubertal & growth delay • malignancies • anemia 		Central nervous system <ul style="list-style-type: none"> • ataxia, seizures • depression
GI system <ul style="list-style-type: none"> • diarrhea, vomiting • distention, abdominal pain • malnutrition, weight loss • hepatitis, cholangitis 		Heart <ul style="list-style-type: none"> • carditis
Bone <ul style="list-style-type: none"> • osteoporosis, fractures • arthritis • dental anomalies 	Skin & mucosa <ul style="list-style-type: none"> • dermatitis herpetiformis • aphthous stomatitis • hair loss 	Reproductive <ul style="list-style-type: none"> • miscarriage • infertility

Rewers M Gastroenterol 2005;128:S47

Natural History of Celiac Disease

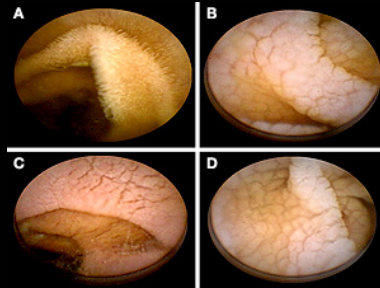


Rewers M Gastroenterol 2005;128:S47

Tools used for screening and diagnosis

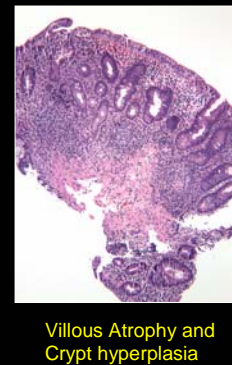
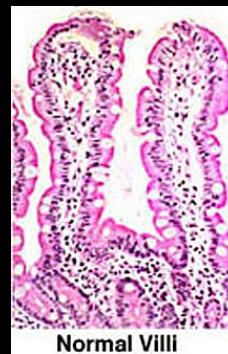
- Screening
 - IgA tissue transglutaminase (IgG isotype)
 - IgA antiendomysial antibody (IgG isotype)
 - Measure IgA
 - Antigliadin antibody---not helpful
- Intestinal biopsy
 - Multiple biopsies beyond the ampula of Vater
 - Repeat biopsy if needed
- HLA testing
 - HLA-DQ2 and HLA-DQ8
 - +ve in 98% of pts with CD; 30-40% of general population
 - -ve result would argue against CD

Endoscopic findings: "Scalloping"



Modified Marsh Classification of Celiac Disease

Marsh type		Intraepithelial lymphocytes (IELs)	Inflammatory response in lamina propria	Crypt hyperplasia	Villous atrophy
0	Normal mucosa	Normal	Normal	Absent	No
I	Infiltrative lesion	Increased	Normal or mild increase in cellularity	Absent	No
II	Hyperplastic type	Increased	Mild increase in cellularity	Present	No
IIIa	Destructive lesion	Increased	Increased cellularity	Present	Mild/partial atrophy
IIIb	Destructive lesion	Increased	Increased cellularity	Present	Marked/sub-total atrophy
IIIc	Destructive lesion	Increased	Increased cellularity	Present	Total atrophy



"All that flattens is not sprue."

- Kwashiorkor
- Acute infectious enteritis
- Milk protein intolerance
- Eosinophilic gastroenteropathy
- Immunodeficiency
- Giardia infestation
- Bacterial overgrowth
- Radiation
- Autoimmune enteropathy
- Graft-versus-host disease

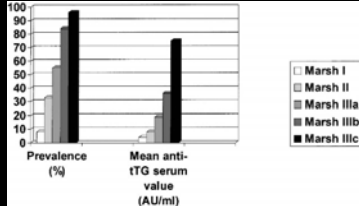
Katz A, Grand R. Gastroenterology 1979;76:375

Dermatitis Herpetiformis



TTG will miss CD with mild histology

- 119 consecutive adult patients were studied
- EGD (6 biopsies) and IgA-TTG were obtained in all patients
- Table reflects the prevalence of a positive test and mean value of TTG (lower limit of positivity = 7 UA/ml)
- Conclusion: TTG is not sensitive when histology is not severe.



Turci A. Am J Gastro 2003;26:210

tTG Sensitivity by Degree of Villous Atrophy

	Sensitivity (%)	95% confidence
Overall	70.1	60.8-79.2
Total atrophy	90	79.5-96.2
Partial atrophy	42.9	27.7-59.0
Lab 1		
Total atrophy	10/13 (77.9%)	
Partial atrophy	2/17 (11.8%)	
Lab 2		
Total atrophy	39/40 (97.5%)	
Partial atrophy	12/19 (63.2%)	

Abrams, JA Clin Gastro Hepatol 2006;4:726

Can TTG replace biopsy?

- Retrospective chart review of 103 patients who had both TTG and BX (denominator is unknown)
- Cost savings of 31% if GI is not consulted for TTG >100

Biopsy	Number with TTG level			Total
	1-19 U	20-100 U	>100 U	
Positive	3*	7	48	58
Negative	35	9	1**	45
Total	38	16	49	103

* = 2 with IgA deficiency, 1 with biopsy near ulcer
 ** = CF + duodenal ulcer

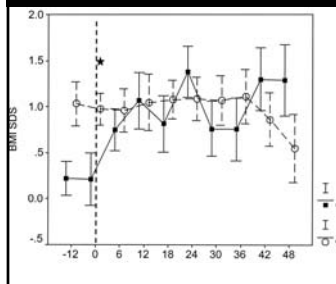
Barker C Pediatrics 2005;115:1341

Type 1 diabetes and celiac disease

- CD found in 2-5% of patients
- High false positive serology in diabetic patients reported
- Frequency of type 1 diabetes in CD patients is 1-10%
- Most cases of CD are clinically unrecognized due to lack of GI symptoms
- Hypoglycemia and reduced insulin requirements should raise possibility of CD

Chand N. J Clin Gastro. 2006;40:3
 Fasano, A. Best Prac Res Clin Gastro 2005;19:467

BMI in patients with type 1 diabetes with (●) and without (○) celiac diseases

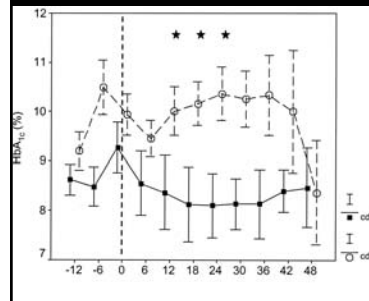


- 230 type 1 diabetic children
- Oxford, UK
- Annual screen with AEA
- Longitudinal, case-controlled
- 11 positive; bx proven
 - Duration of DM 3.8 y (0.9-7)
 - Screen tests mean 4 (1-7)
 - 6 f/u biopsy: c/w treatment
- 22 age-matched controls
 - no biopsy or GFD
- CD treated gluten-free diet
 - Antibody neg. in 6-8 mo

- Results
 - CD pts with low BMI
 - 12 mo to recover

Months after Diagnosis of CD
 Amin, R. Diabetes Care 2002;25:1117

Hgb A1c in patients with type 1 diabetes with (●) and without (○) celiac disease



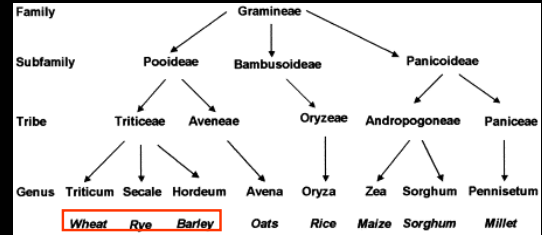
- Lower Hgb A1c in CD
 - 8.9 v 9.8 (p=.002)
- Lower insulin need in CD
 - 0.8 v 1.0 (p=.54)

Months after Diagnosis of CD

Diabetes Care 2002;25:1117

Treatment

- Gluten-free diet
 - 20 ppm gluten (20 mg / 1 kg)
 - 100 ppm
 - 200 ppm
 - 400 ppm
- Monitor nutrient deficiencies
 - Iron
 - Calcium
 - Vitamin D
 - Magnesium
 - Folate, niacin, thiamin, B12, riboflavin



Kagnoff MF Gastroenterol 2005;128:S10

Psychological stress associated with dietary compliance

- Higher rate of anxiety and depression symptoms
- Higher scores in harm avoidance, somatic complaints
- May be gender differences
- QOL for parents of children with CD is also impacted

DeLorenzo CM, et.al. Qual Life Res. 2011
Mazzone L, et. al. BMC Pediatrics 2001;11:46

Monitoring Compliance

- Diet compliance may not impact height/weight
- 57% of non-compliant patients are asymptomatic
- tTG elevation may not occur with mild dietary transgression
- Clinical follow-up is not consistent

Mozer-Glassberg Y, et.al. Digestion 2011;83:283
Errichiolo S, et.al. JPGN. 2010;50:54

