Definition

Definition

Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals.

It occurs in symptomatic subjects with gastrointestinal and non-gastrointestinal symptoms, and in some asymptomatic individuals, including subjects affected by:

- Type 1 diabetes
- Down syndrome
- Turner syndrome
- Williams syndrome
- Selective IgA deficiency
- First degree relatives of individuals with celiac disease

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Expanded Definition

- Celiac disease is an autoimmune condition
- Occurs in genetically susceptible individuals
  - DQ2 and/or DQ8 positive HLA haplotype is necessary but not sufficient
- A *unique* autoimmune disorder because:
  - both the environmental trigger (gluten) and the autoantigen (tissue Transglutaminase) are known
  - elimination of the environmental trigger leads to a complete resolution of the disease

Clinical Manifestations

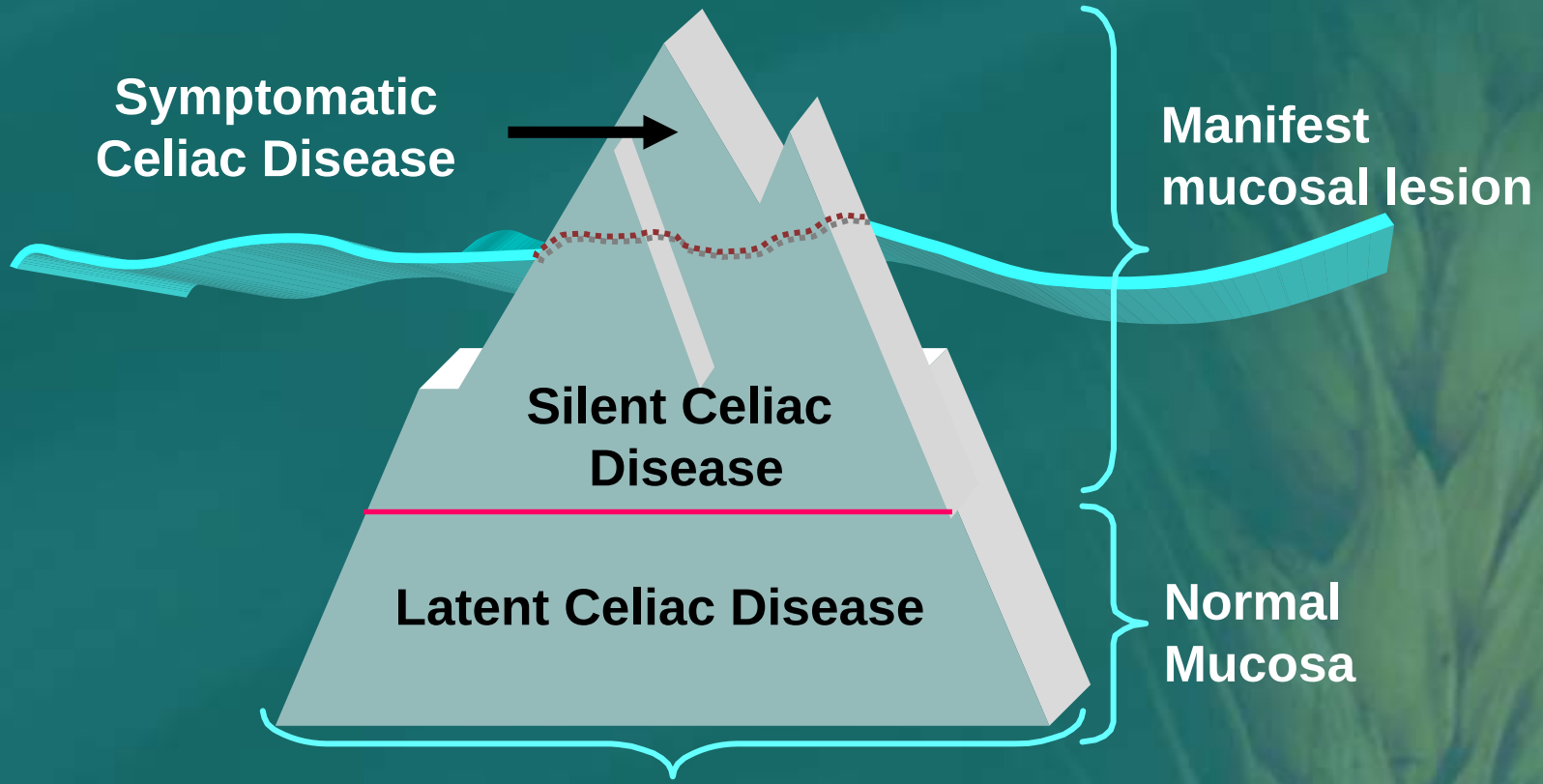
Clinical Manifestations

- **Gastrointestinal *(“classical”)***
- **Non-gastrointestinal *(“atypical”)***

- **Asymptomatic**

***In addition, Celiac Disease may be associated with other conditions, and mostly with*:**
- **Autoimmune disorders**
- **Some syndromes**

The Celiac Iceberg



Genetic susceptibility: - DQ2, DQ8
Positive serology

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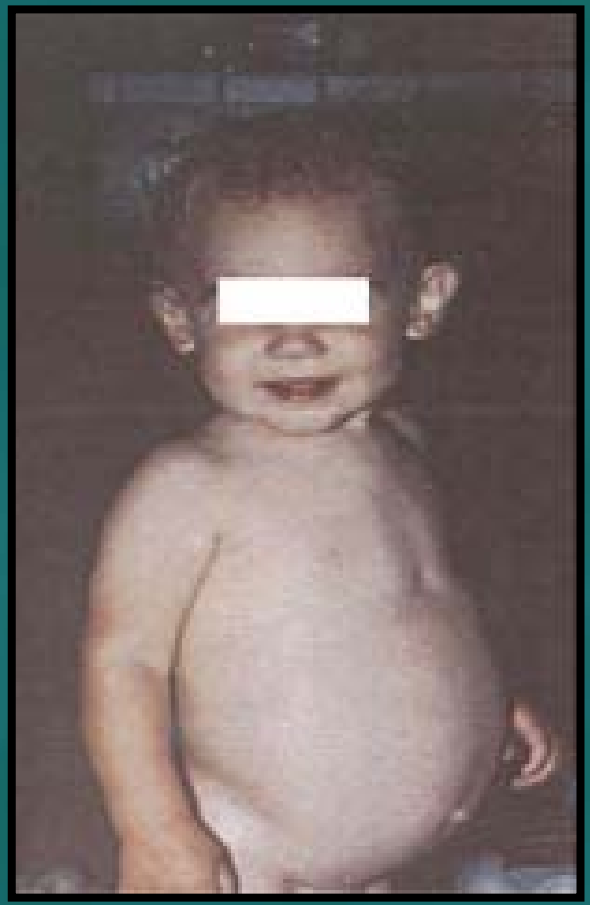
Gastrointestinal Manifestations ("Classic")

Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

***Rarely*: Celiac crisis**

Typical Celiac Disease



Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

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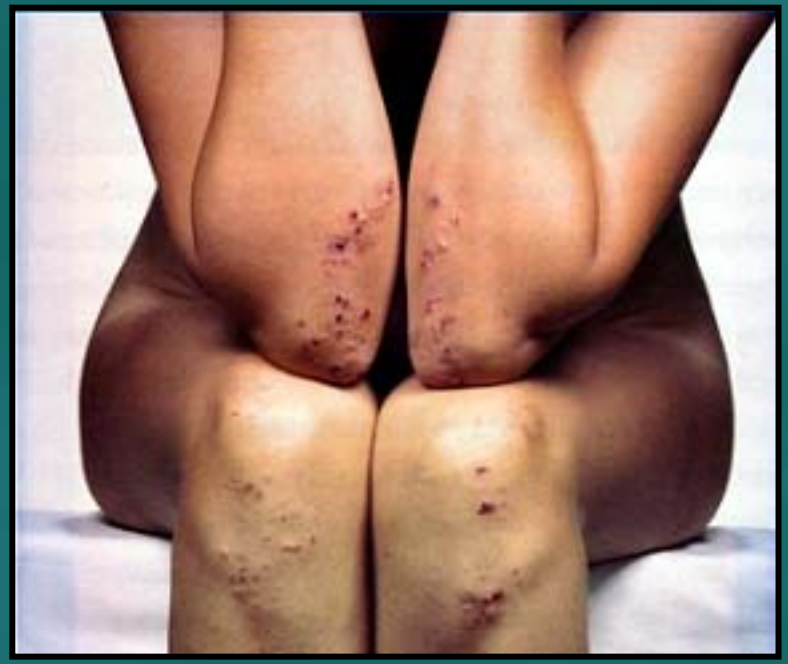
Listed in descending order of strength of evidence

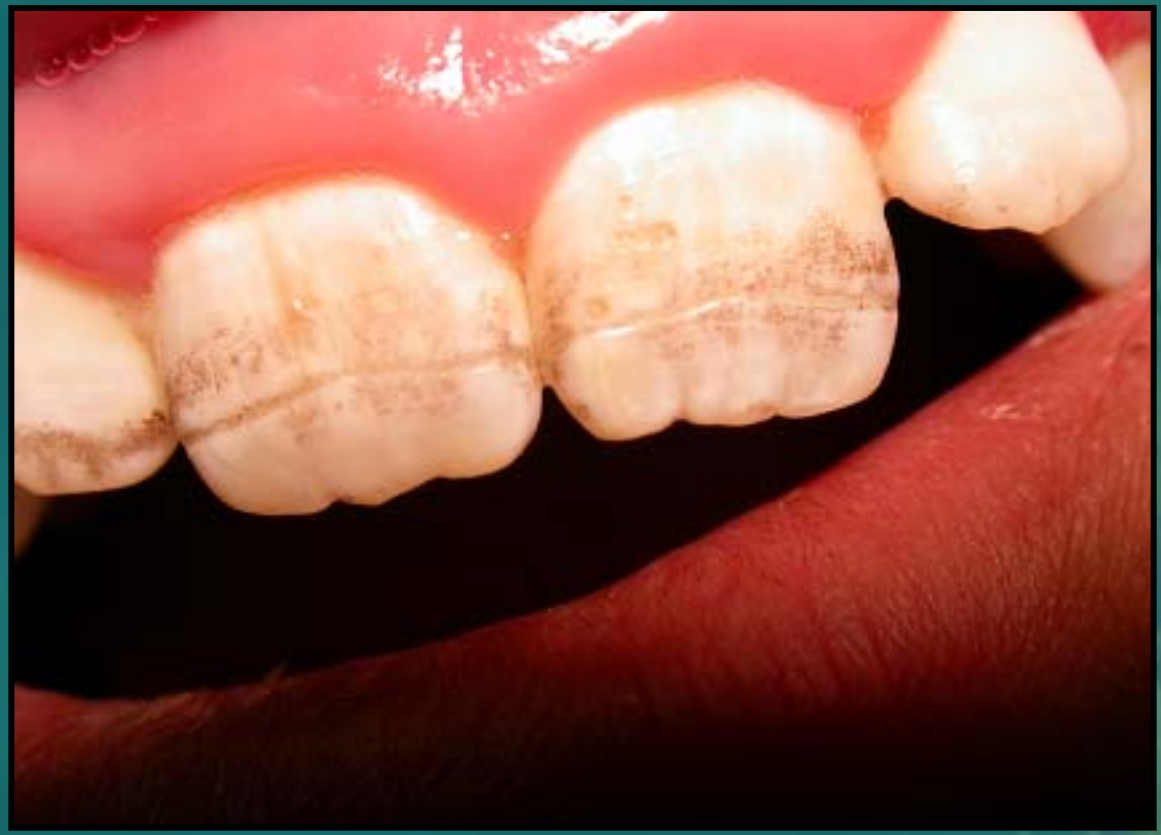
Dermatitis Herpetiformis



- Erythematous macule > urticarial papule > tense vesicles
- Severe pruritus
- Symmetric distribution
- 90% no GI symptoms
- 75% villous atrophy
- Gluten sensitive

Garioch JJ, et al. *Br J Dermatol*. 1994;131:822-6.
Fry L. *Baillieres Clin Gastroenterol*. 1995;9:371-93.
Reunala T, et al. *Br J Dermatol*. 1997;136-315-8.

Dental Enamel Defects



Involve the secondary dentition
May be the only presenting sign of Celiac Disease

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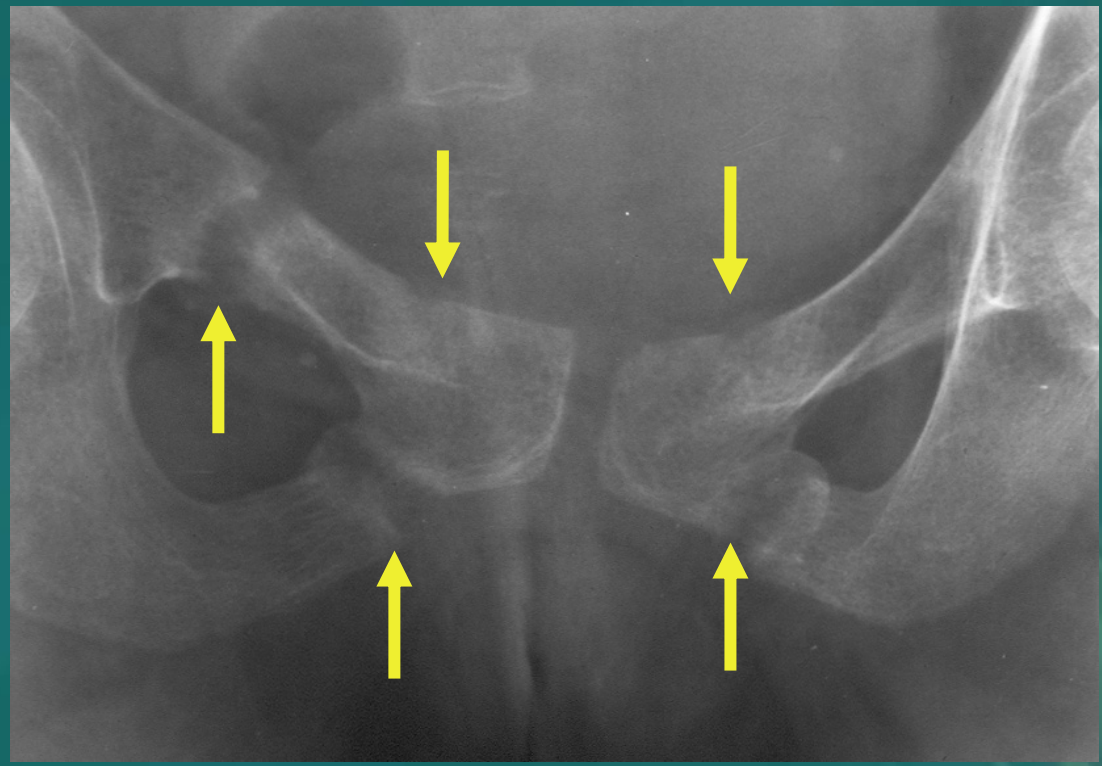
Osteoporosis



Low bone mineral density improves in children on a gluten-free diet.

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Short Stature/Delayed Puberty

- **Short stature in children / teens:**
  - **~10% of short children and teens have evidence of celiac disease**
- **Delayed menarche:**
  - **Higher prevalence in teens with untreated Celiac Disease**

Fe-Deficient Anemia Resistant to Oral Fe

- Most common non-GI manifestation in some adult studies
- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease
- In children with newly diagnosed Celiac Disease:
  - Anemia is common
  - Little evidence that Celiac Disease is common in children presenting with anemia

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Hepatitis

- Some evidence for elevated serum transaminases (ALT, AST) in adults with untreated Celiac Disease
  - Up to 9% of adults with elevated ALT, AST may have silent Celiac Disease
  - Liver biopsies in these patients showed non-specific reactive hepatitis
  - Liver enzymes normalized on gluten-free diet

Arthritis and Neurological Problems

- Arthritis in adults
  - Fairly common, including those on gluten-free diets
- Juvenile chronic arthritis
  - Up to 3% have Celiac Disease
- Neurological problems
  - Epilepsy with cranial calcifications

3 – Asymptomatic

Silent **Latent**

- **Silent:**
  No or minimal symptoms, "damaged" mucosa and positive serology

  Identified by screening asymptomatic individuals from groups at risk such:

  - **First degree relatives**
  - **Down syndrome patients**
  - **Type 1 diabetes patients, etc.**

3 – Asymptomatic

Silent **Latent**

- **Latent: *No symptoms, normal mucosa***
  - **May show positive serology. Identified by following in time asymptomatic individuals previously identified at screening from groups at risk. These individuals, given the "right" circumstances, will develop at some point in time mucosal changes (± symptoms)**

Asymptomatic

- **Asymptomatic patients are still at risk of osteopenia/osteoporosis**

- **Treatment with a gluten-free diet is recommended for asymptomatic children with proven intestinal changes of Celiac Disease who have:**

  - **type 1 diabetes**
  - **selective IgA deficiency**
  - **Down syndrome**
  - **Turner syndrome**
  - **Williams syndrome**
  - **autoimmune thyroiditis**
  - **a first degree relative with Celiac Disease**

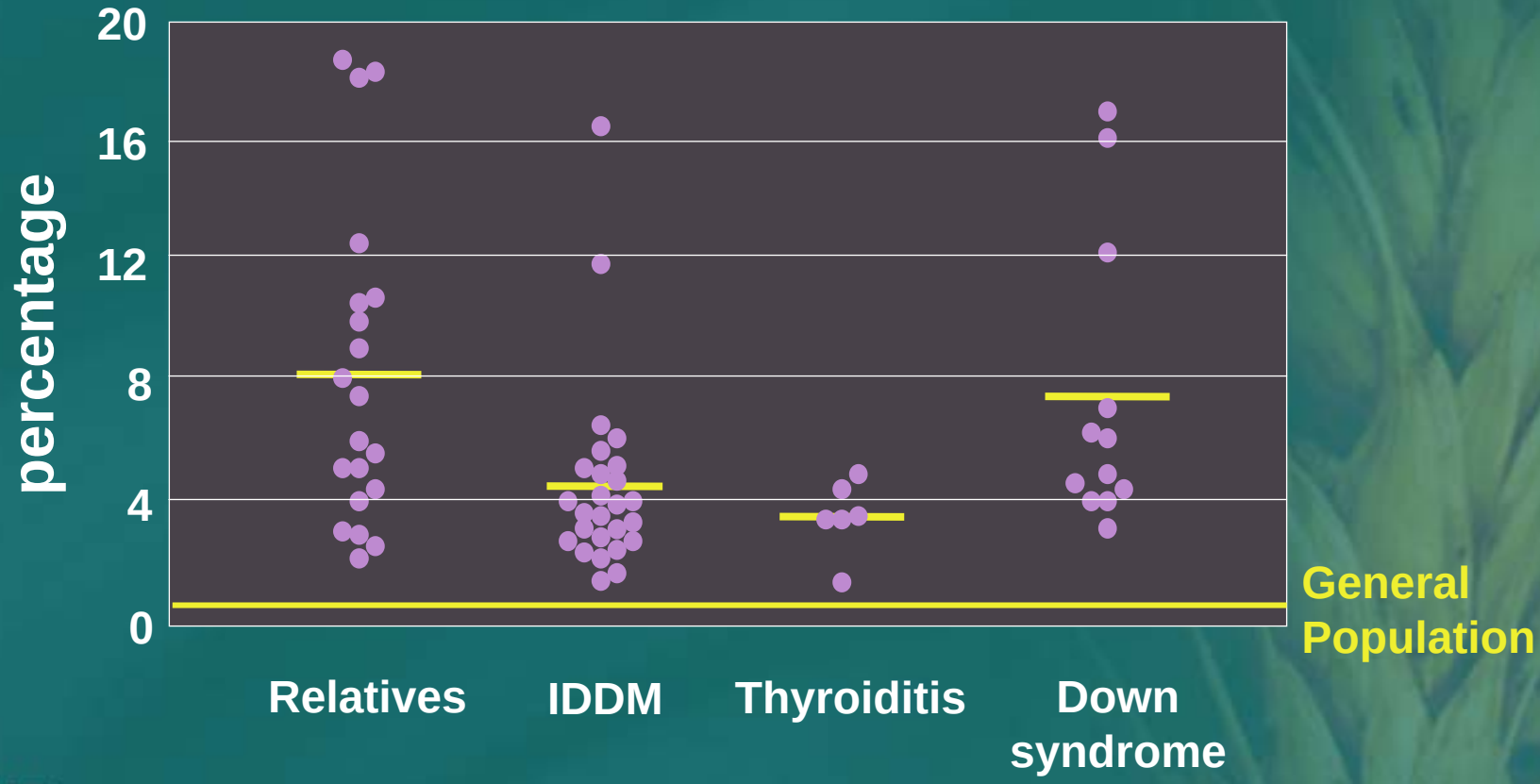
Associated Conditions

Associated Conditions

The prevalence of Celiac Disease is higher in patients who have the following:

- Certain genetic disorders or syndromes
- Other autoimmune conditions
- Relative of a biopsy-proven celiac

Associated Conditions



Genetic Disorders

- Down Syndrome: 4-19%
- Turner Syndrome: 4-8%
- Williams Syndrome: 8.2%
- IgA Deficiency: 2-3%
  - Can complicate serologic screening

Prevalence of Celiac Disease is Higher in Other Autoimmune Conditions

Type 1 Diabetes Mellitus:	3.5 - 10%
Thyroiditis:	4 - 8%
Arthritis:	1.5 - 7.5%
Autoimmune liver diseases:	6 - 8%
Sjögren's syndrome:	2 - 15%
Idiopathic dilated cardiomyopathy:	5.7%
IgA nephropathy:	3.6%

Relatives

- **Healthy population:** **1:133**
- **1st degree relatives:** **1:18 to 1:22**
- **2nd degree relatives:** **1:24 to 1:39**

Fasano, et al, *Arch of Intern Med*, Volume 163: 286-292, 2003

Type 1 Diabetes

Patients are often asymptomatic

Nocturnal hypoglycemia with seizures

TTG may be falsely positive

Gluten–free diet challenging

2 U.S. studies in pediatrics:

- **218 patients. 7.7% EMA+. 4.6% biopsy + *(Aktay et al. JPGN 2001;33:462-465)***
- **185 patients. 5% EMA+. 4/5 biopsy + *(Talal et al. AJG 1997;92:1280-84)***

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Which Came First?

Celiac Disease and Autoimmunity

- Prevalence of autoimmune disorders in celiac disease related to duration of gluten exposure
  - Diagnosed before 2 years of age: 5%
  - Age 2-10 years: 17%
  - Greater than age 10 years: 24%
- Increased incidence of autoimmune disease in patients with IDDM and ‘silent’ Celiac Disease and their first degree relatives who were EMA+

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Ventura et al, Gastro 1999; *Not , Diabetologia* 2001

Complications

Major Complications of Celiac Disease

- Short stature
- Dermatitis herpetiformis
- Dental enamel hypoplasia
- Recurrent stomatitis
- Fertility problems
- Osteoporosis
- Gluten ataxia and other neurological disturbances
- Refractory celiac disease and related disorders
- Intestinal lymphoma

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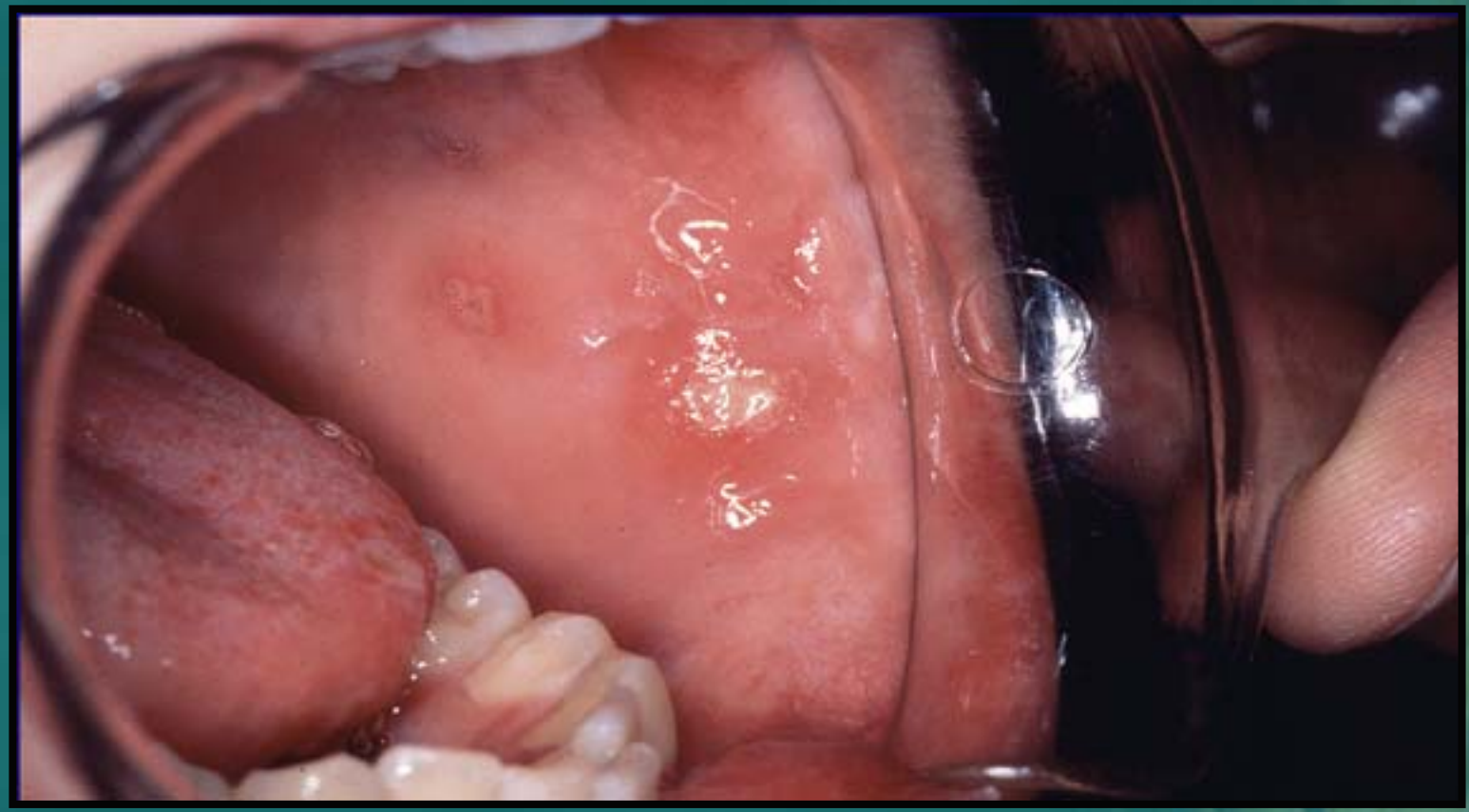
Mechanisms of Celiac Disease Complications

- Intestinal malabsorption
  - protein-caloric malnutrition
  - deficiency of specific nutrients
- Genetic background
- Autoimmunity
- IEL clonal proliferation

Celiac Disease Associated Disorders

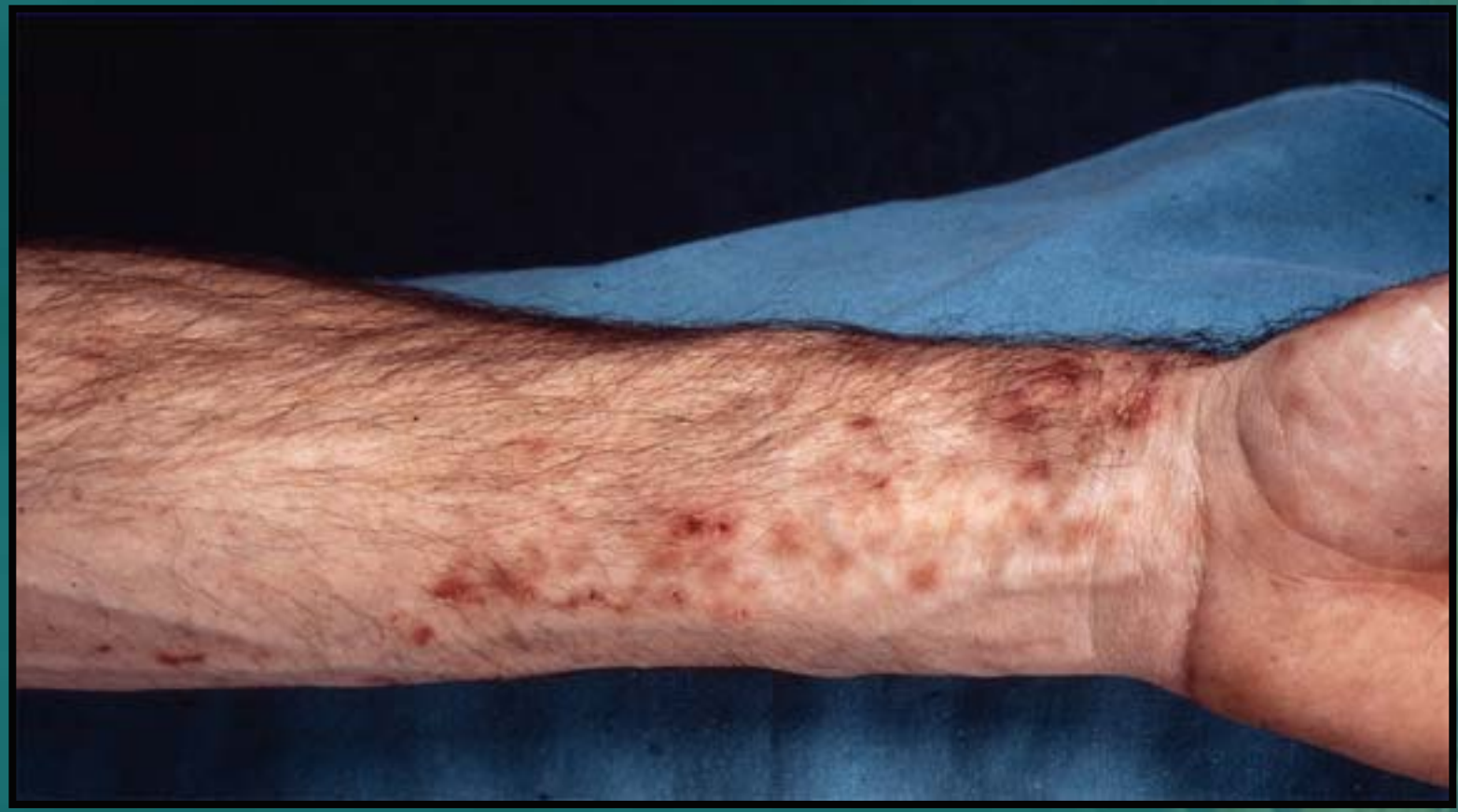
- Autoimmune diseases: type 1 diabetes, Hashimoto's thyroiditis, autoimmune hepatitis, adrenal failure
- Down syndrome
- IgA deficiency
- Turner syndrome
- Williams syndrome

Recurrent Aphtous Stomatitis



By permission of C. Mulder, Amsterdam (Netherlands)

Dermatitis Herpetiformis



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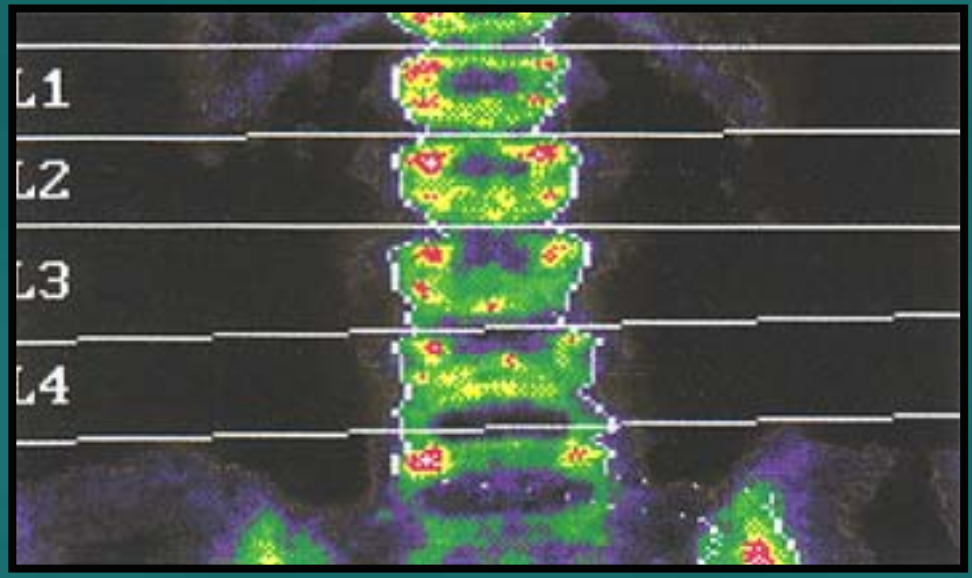
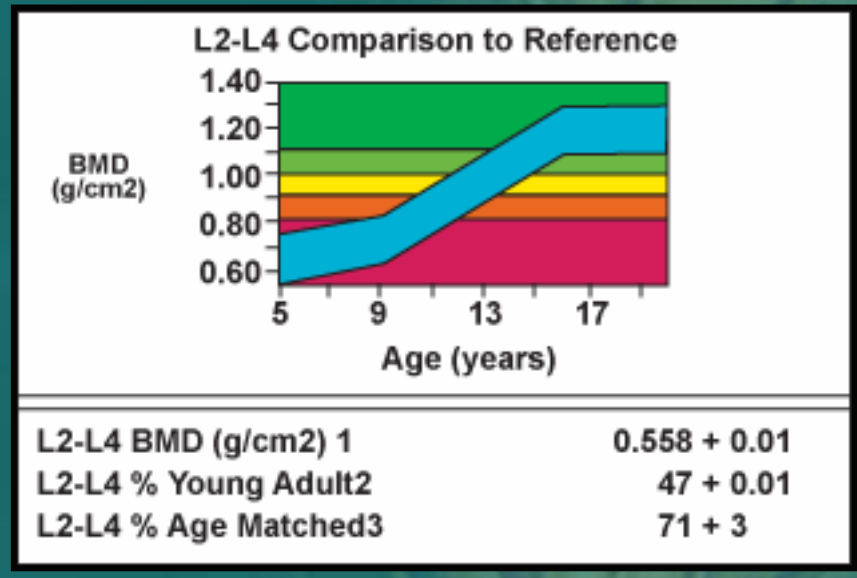
Low Bone Mineral Density (DXA) in a Child With Untreated Celiac Disease





L2-L4 BMD (g/cm2) 1	0.558 + 0.01
L2-L4 % Young Adult2	47 + 0.01
L2-L4 % Age Matched3	71 + 3

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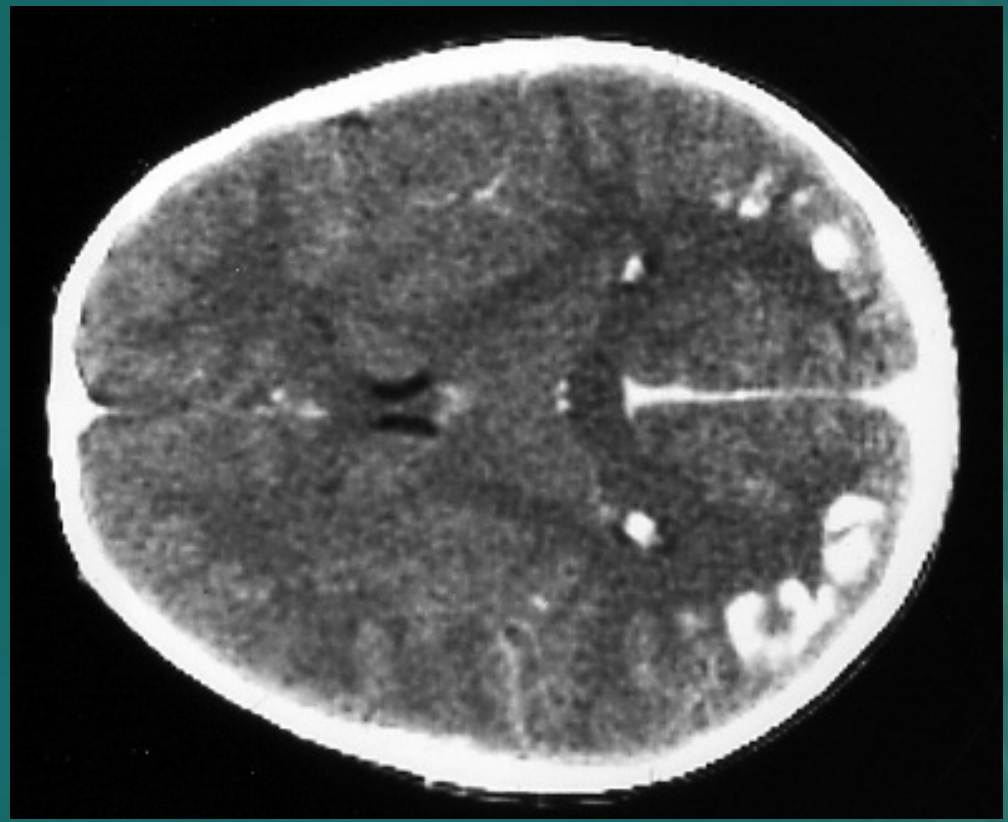
By permission of Mora S, Milan (Italy)

CT Scan Showing Occipital Calcifications in a Boy with Celiac Disease and Epilepsy



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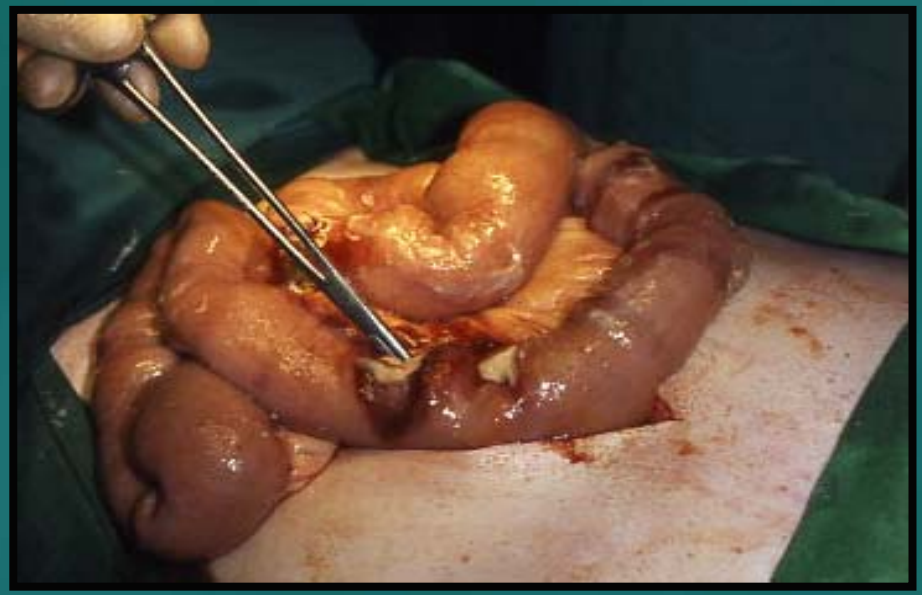
Celiac Disease Complicated by Enteropathy-Associated T-cell Lymphoma (EATL)



By permission of G. Holmes, Derby (UK)

Epidemiology

Epidemiology

The “old” Celiac Disease Epidemiology:

- **A rare disorder typical of infancy**
- **Wide incidence fluctuates in space (1/400 Ireland to 1/10000 Denmark) and in time**
- **A disease of essentially European origin**

Celiac Disease in London, Year 1938

. 2.—Photograph of five cases of coeliac disease showing the general clinical feature

The Changing Celiac Epidemiology

The availability of sensitive serological markers made it possible to discover Celiac Disease even when the clinical suspicion was low.

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“Mines” of Celiac Disease Were Found Among:

Relatives

Patients with

short stature, anaemia, fatigue, hypertransaminasemia

Associated diseases

autommune disorders, Down s, IgA deficiency, neuropathies, osteoporosis, infertility

“Healthy” groups

blood donors, students, general population

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The First Picture of the Celiac Iceberg

Coeliac disease in the year 2000: exploring the iceberg

C Catassi, I-M Rätsch, E Fabiani, M Rossini, F Bordicchia, F Candela, G V Coppa, P L Giorgi

Summary

It is now generally believed that subclinical coeliac disease is common in the general population. We have undertaken screening for this disorder in a school district in central Italy. Screening was divided into three levels: first, IgG and IgA antigliadin antibody (AGA) assay on capillary blood obtained by finger prick; second, AGA plus IgA antiendomysium antibody (AEA) test and measurement of serum immunoglobulins in venous blood; and third, intestinal biopsy.

3351 students (66% of the eligible population) aged 11-15 years attended first level screening. 71 (2%) were recalled because of AGA positivity; 18 of these satisfied second-level criteria and underwent intestinal biopsy. Coeliac disease was diagnosed in 11 subjects, most of whom had no serious symptoms. Selective IgA deficiency was found in 4 subjects, 1 of whom also had coeliac disease. The prevalence of subclinical coeliac disease in the study group was 3·28 per 1000.

Coeliac disease screening is feasible and involves only slight discomfort to the general population. Such screening can detect large numbers of cases of coeliac disease, which can be treated with a gluten free diet. Many subclinical cases of coeliac disease would not be detected by screening only a selected group of at risk patients.

Introduction

It has become apparent over the past few years that clinically manifest cases of coeliac disease represent only a small proportion of the total population with this disorder. There are many patients who are free of major symptoms but who have typical damage to the jejunal mucosa on intestinal biopsy (subclinical or "silent" coeliac disease).[1] If such patients are not treated, they risk complications such as anaemia, infertility, and malignant disorders; they may die prematurely.[2-4] Early dietary management of gluten enteropathy seems to protect coeliac disease patients from the development of malignant disorders.[4]

The serum antigliadin antibody (AGA) assay is a widespread and simple screening test for coeliac disease and is especially informative when AGA of both IgG and IgA classes is measured.[5] We undertook a pilot study on subclinical coeliac disease screening in a general school population; the first step was IgG AGA and IgA-AGA assays on blood obtained from a finger prick. Our aims were to characterise and quantify the prevalence of subclinical coeliac disease and to assess the feasibility of such screening in the general population.

Patients and methods

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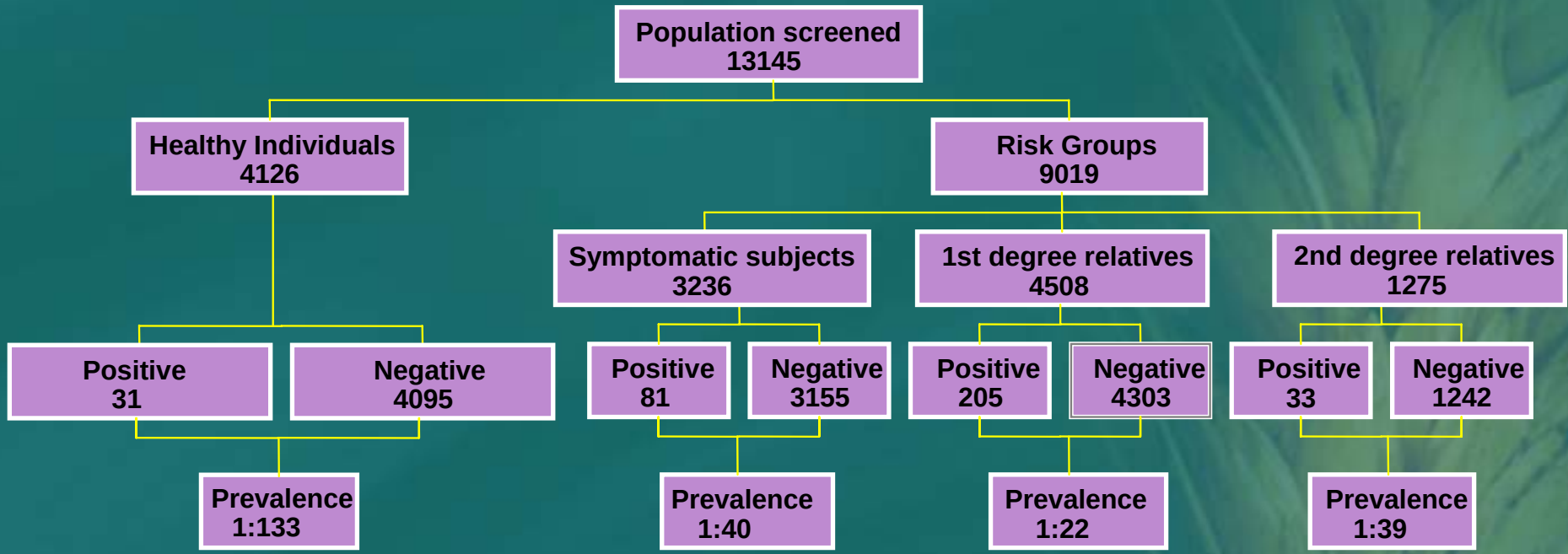
Celiac Disease Epidemiological Study in USA



Projected number of celiacs in the U.S.A.: 2,115,954
Actual number of known celiacs in the U.S.A.: 40,000
For each known celiac there are 53 undiagnosed patients.

A. Fasano et al., *Arch Int Med* 2003;163:286-292.

Celiac Disease Prevalence Data

Geographic Area	Prevalence on clinical diagnosis*	Prevalence on screening data
Brasil	?	1:400
Denmark	1:10,000	1:500
Finland	1:1,000	1:130
Germany	1:2,300	1:500
Italy	1:1,000	1:184
Netherlands	1:4,500	1:198
Norway	1:675	1:250
Sahara	?	1:70
Slovenia	?	1:550
Sweden	1:330	1:190
United Kingdom	1:300	1:112
USA	1:10,000	1:133
Worldwide (average)	1:3,345	1:266

*based on classical, clinical presentation

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Fasano & Catassi, *Gastroenterology* 2001; 120:636-651.

Celiac Societies Data in Europe and USA

(approximate estimates)

Country	Celiac Society members (n)	Population	Frequency of CD membership
United Kingdom	48,000	55,500,000	1:1146
Italy	25,000	57,000,000	1:2280
Sweden	18,000	8,700,000	1:483
Germany	15,000	80,000,000	1:5333
Finland	11,000	5,100,000	1:464
Spain	8,000	38,500,000	1:4812
Norway	6,000	4,300,000	1:716
Netherlands	4,500	15,100,000	1:3355
France	3,700	57,000,000	1:15405
Belgium	1,800	10,000,000	1:5555
Austria	2,400	7,800,000	1:3250
Switzerland	2,300	6,900,000	1:3000
Ireland	2,400	3,500,000	1:1458
Denmark	1,100	5,200,000	1:4727
Europe	149,200	354,600,000	1:2377
USA	40,000	281,421,906	1:7035

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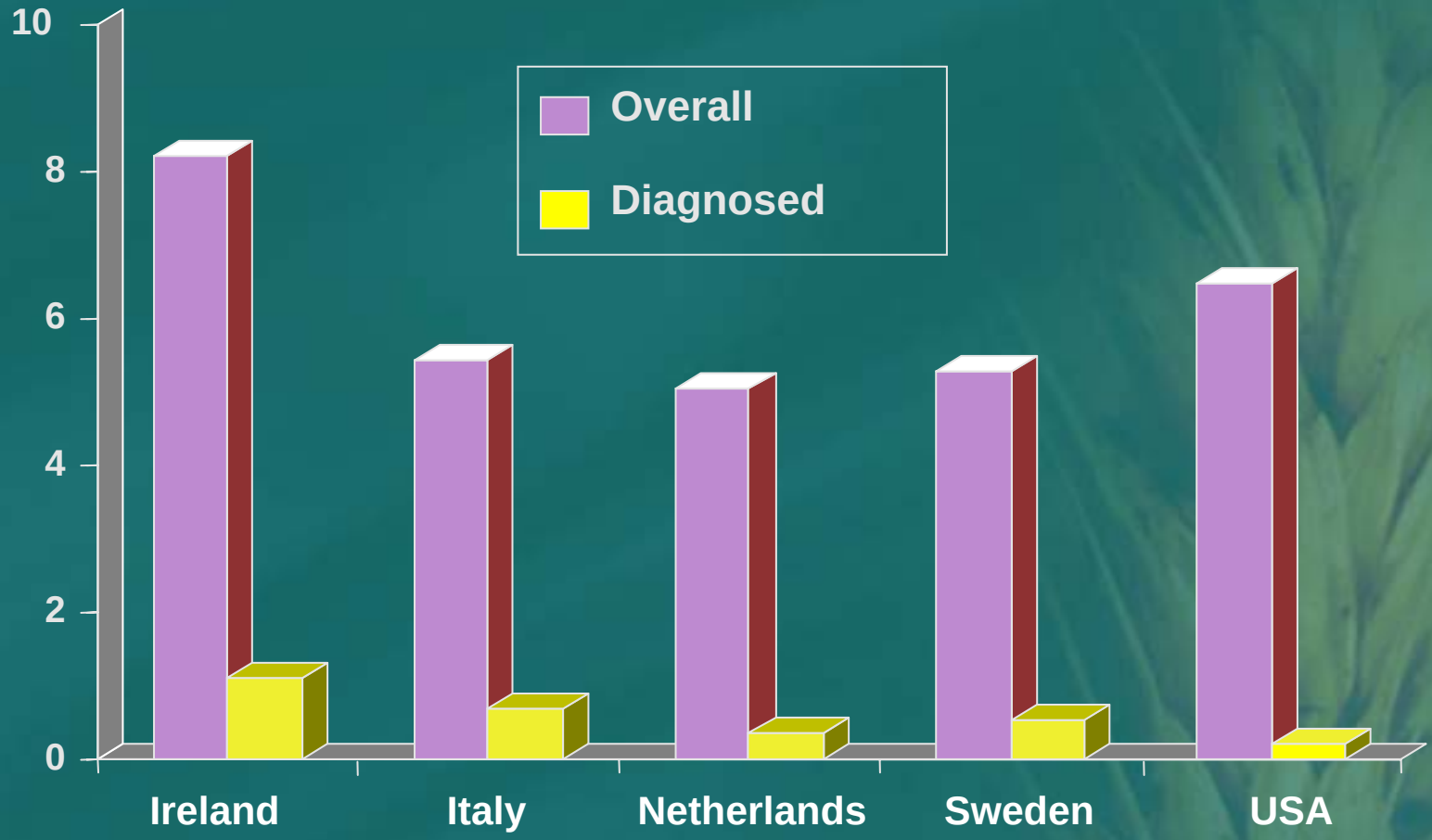
A. Catassi, A. Fasano . *Curr Gastroenterol Rep* 2002;4:238-243.

Celiac Disease Icebergs



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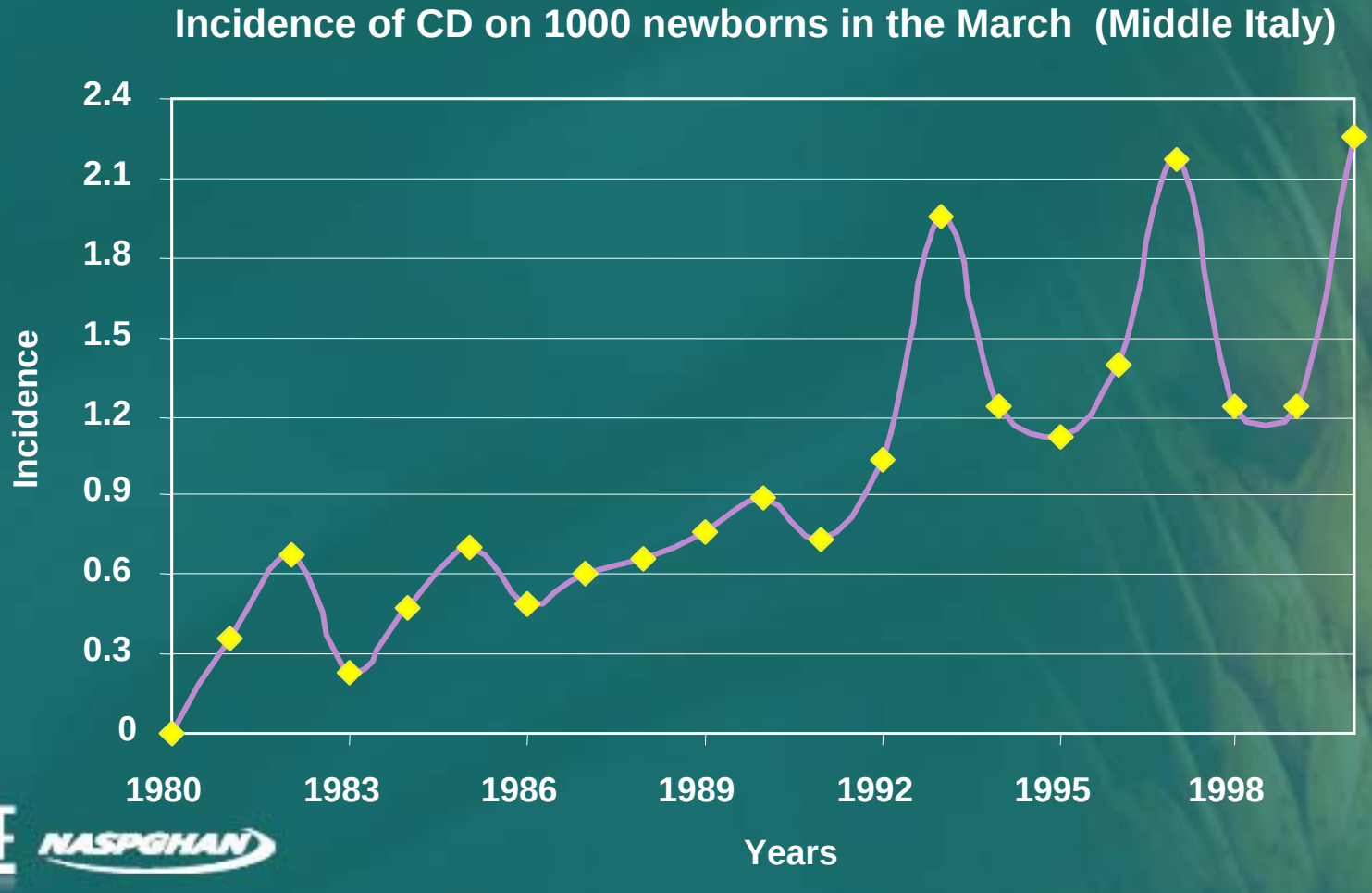
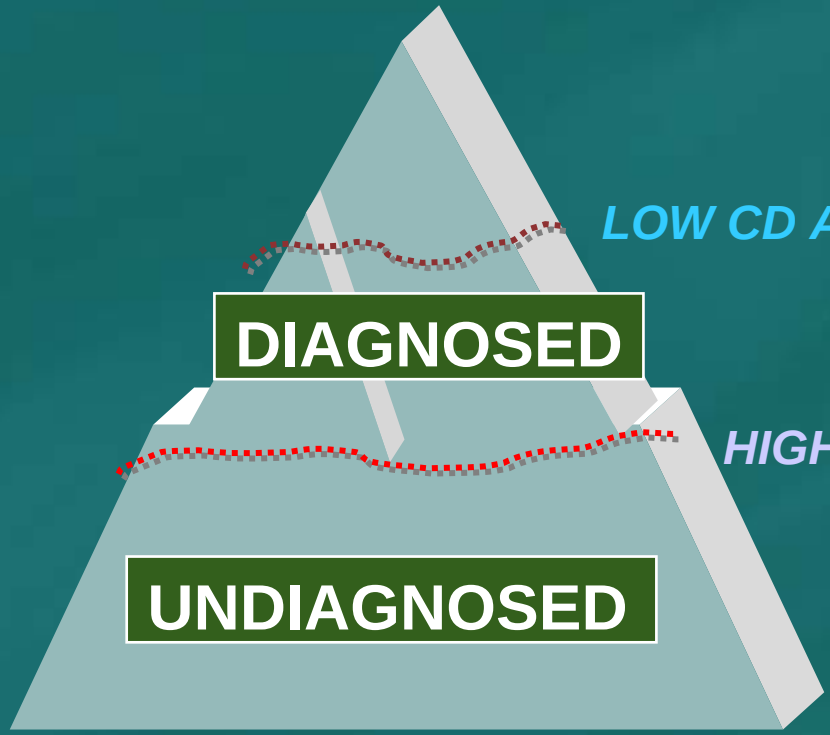
In Italy the Celiac Case-Finding is Increasingly Efficient



The Size of the Submerged Iceberg is Decreasing in Many Countries Due to Active Case-Finding



Even an intensive policy of Celiac Disease case-finding will leave at least 50 % of celiacs without a diagnosis.

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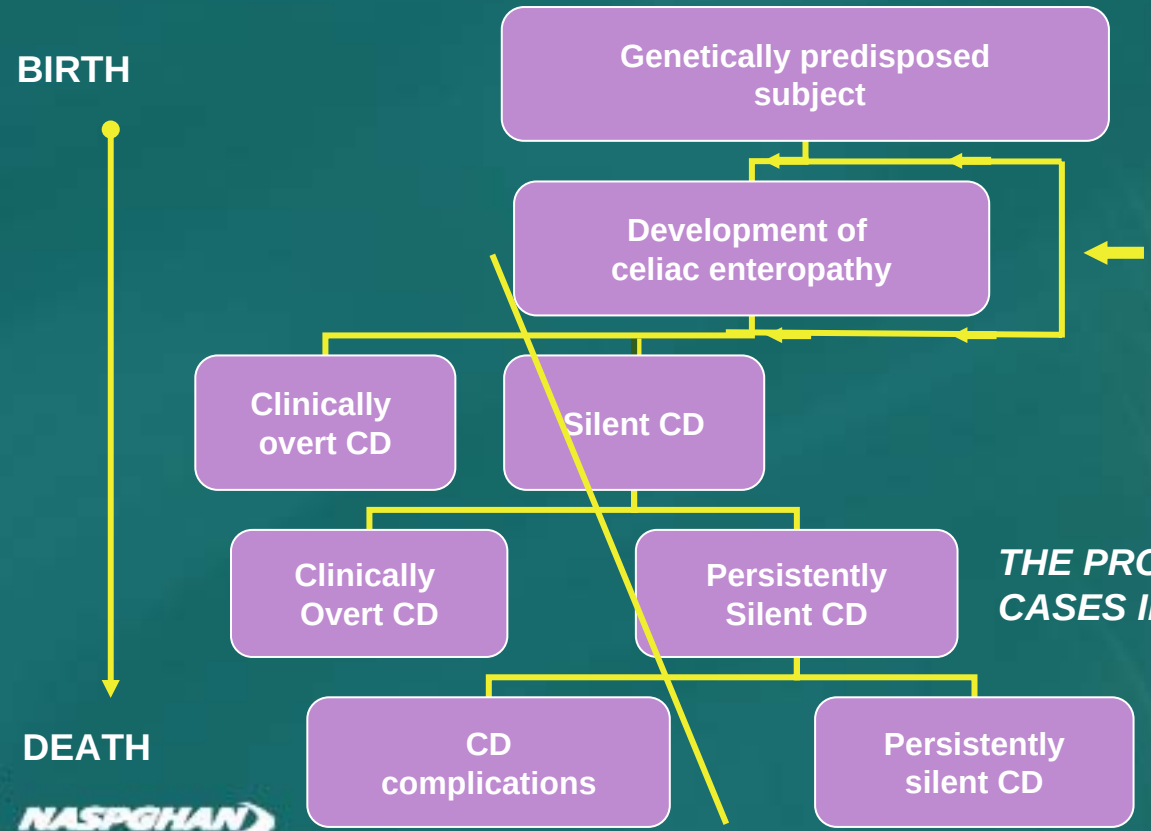
Natural History Of Celiac Disease At Glance



ENVIRONMENTAL TRIGGERS

Gluten "load"
Intestinal infections
Pregnancy
cancer

THE PROPORTION OF SYMPTOMATIC CASES INCREASES WITH AGE

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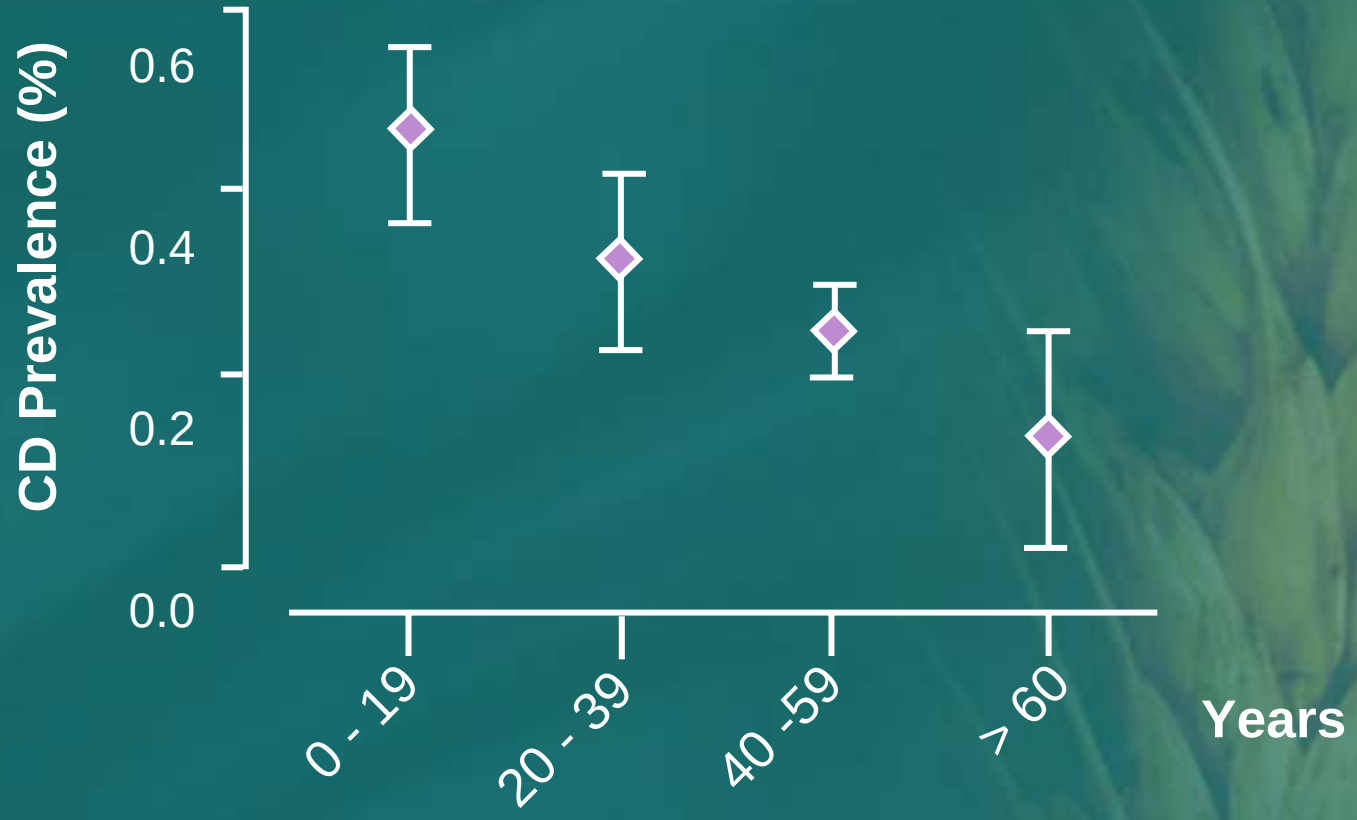
Where Have The Aging Celiacs Gone?



Increased Overall Mortality In Adult Life

AUTOIMMUNE DISEASES

OSTEOPOROSIS

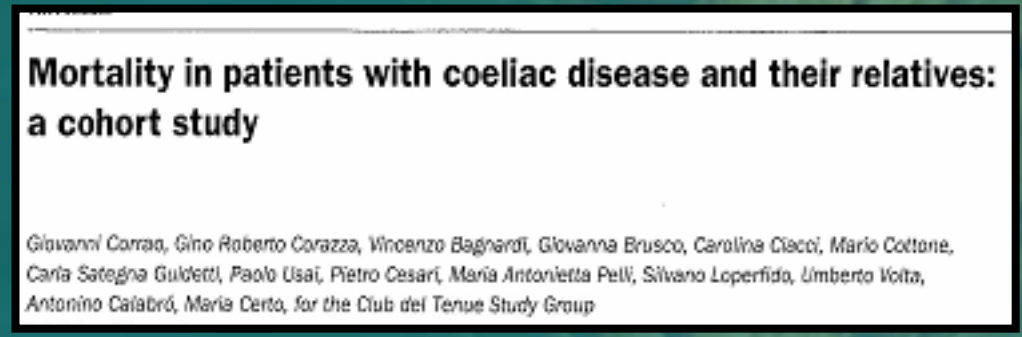
LIVER DISEASES

CANCER

ORIGINAL INVESTIGATION

Causes of Death in Patients With Celiac Disease in a Population-Based Swedish Cohort

Ulrike Peters, PhD, MPH; Johan Askling, MD; Gloria Gridley, MS; Anders Ekbom, MD, PhD; Martha Linet, MD



Mortality in patients with coeliac disease and their relatives: a cohort study

Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Silvano Loperfido, Umberto Volta, Antonino Calabrò, Maria Certo, for the Club del Tenue Study Group

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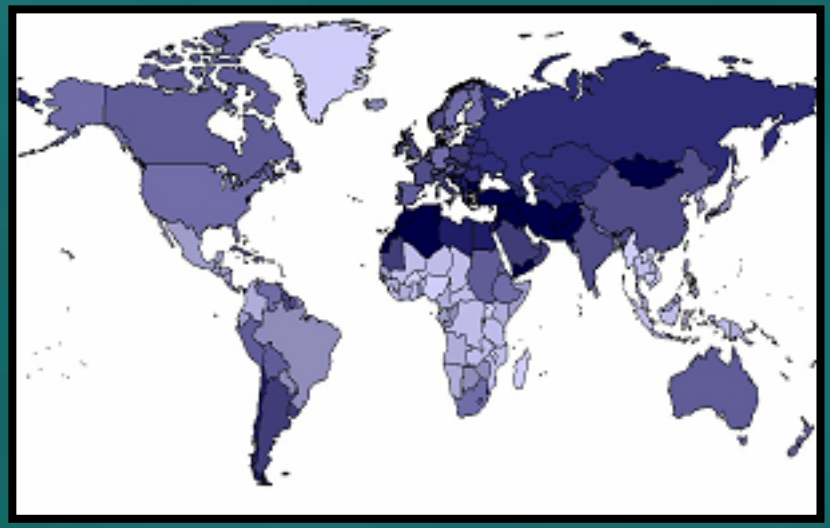
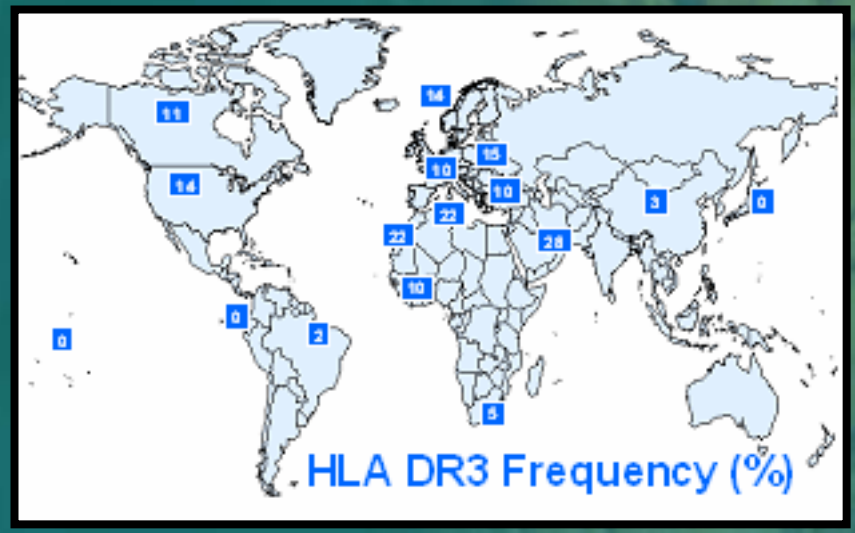
Risk Factors



The Grains

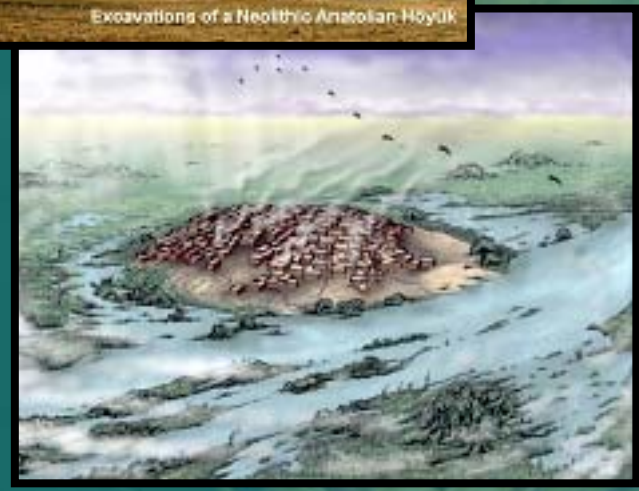
The Genes



Spreading of Agriculture and Celiac Disease

1
Cereals domestication started 10,000 years ago in the Fertile Crescent…

2
Catalhuyuc,
The first town in the world was built 9,000 y ago



3
Agricolture slowly spread with a East-West gradient (1 Km/y)…

INVERSE RELATIONSHIP BETWEEN CD FREQUENCY AND LENGHT OF TIME SINCE THE INTRODUCTION OF AGRICOLTURE ?

4
CD genes confer disadvantage in areas of high cereal consumption

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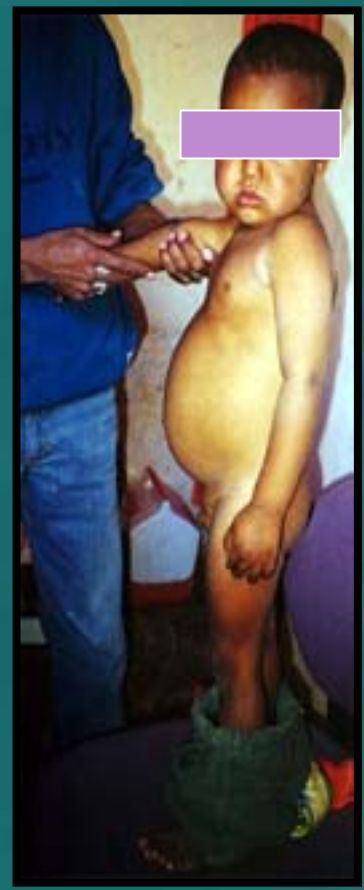
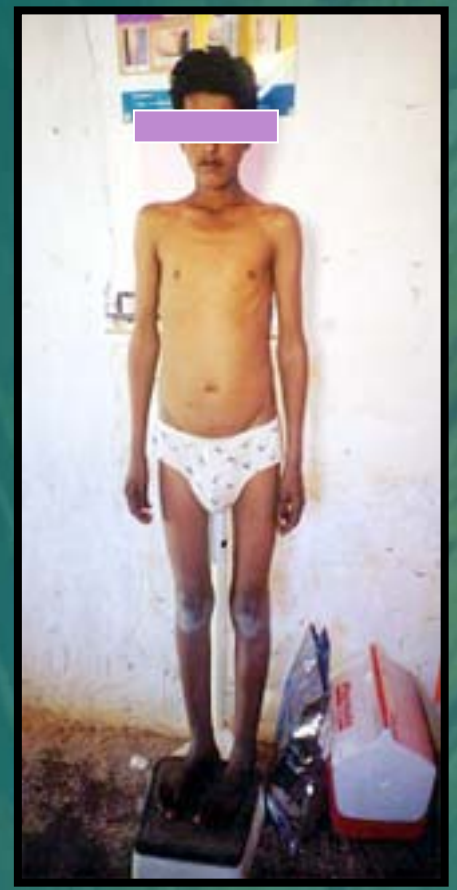
Celiac Disease in the Saharawis

- 1:18 children are affected with Celiac Disease
- Diarrhea, stunting, anemia
- EMA pos, typical jejunal damage
- High frequency of DR3/DR3 and DR3/DR4
- High mortality (especially in summer)





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Celiac Disease in Iran

- The prevalence of Celiac Disease among 2000 Iranian blood donors is one of the highest in the world (1:166).
- Celiac Disease is a common finding among patients labelled as irritable bowel syndrome (11 %).
- The theory on the East-West increasing gradient of Celiac Disease prevalence does not hold.

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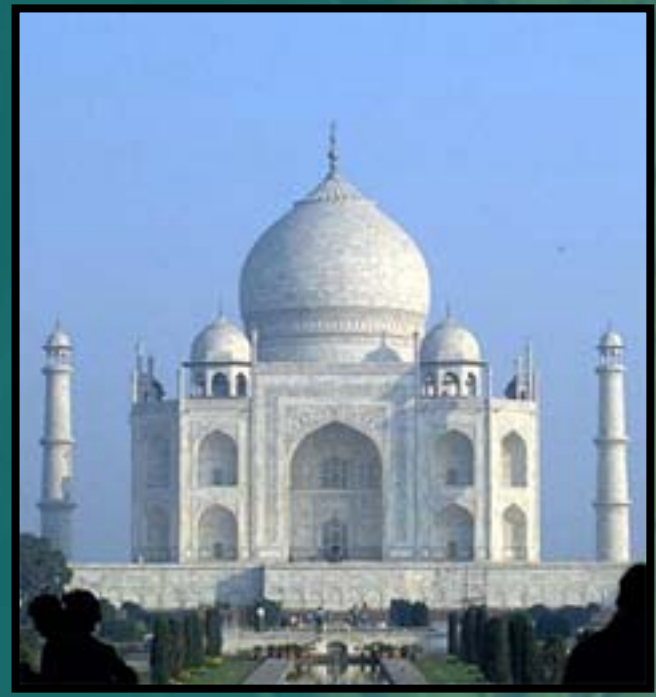
Celiac Disease in India

- Common cause of chronic diarrhea both in children and in adults
- Long diagnostic delay
- “Hypertypical” clinical presentation
- Strong association with DQ2 heterodimer and with DR3 Asian haplotypes (A26-B8-DR3)



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Celiac Disease in Developing Countries

- Worldwide circulation of gluten-containing food could cause epidemics of Celiac Disease
- Largely underestimated (e.g. along the “silk road”)
- Typical symptoms and stunting (nutritional dwarfism)
- Celiac Disease serological markers still reliable
- Formidable treatment difficulties

The Global Village of Celiac Disease

- In many areas of the world Celiac Disease is one of the commonest, lifelong disorders affecting around 1% of the general population.
- Most cases escape diagnosis and are exposed to the risk of complications.
- Active Celiac Disease case-finding is needed but mass screening should be considered.
- The impact of Celiac Disease in the developing world needs further evaluation.

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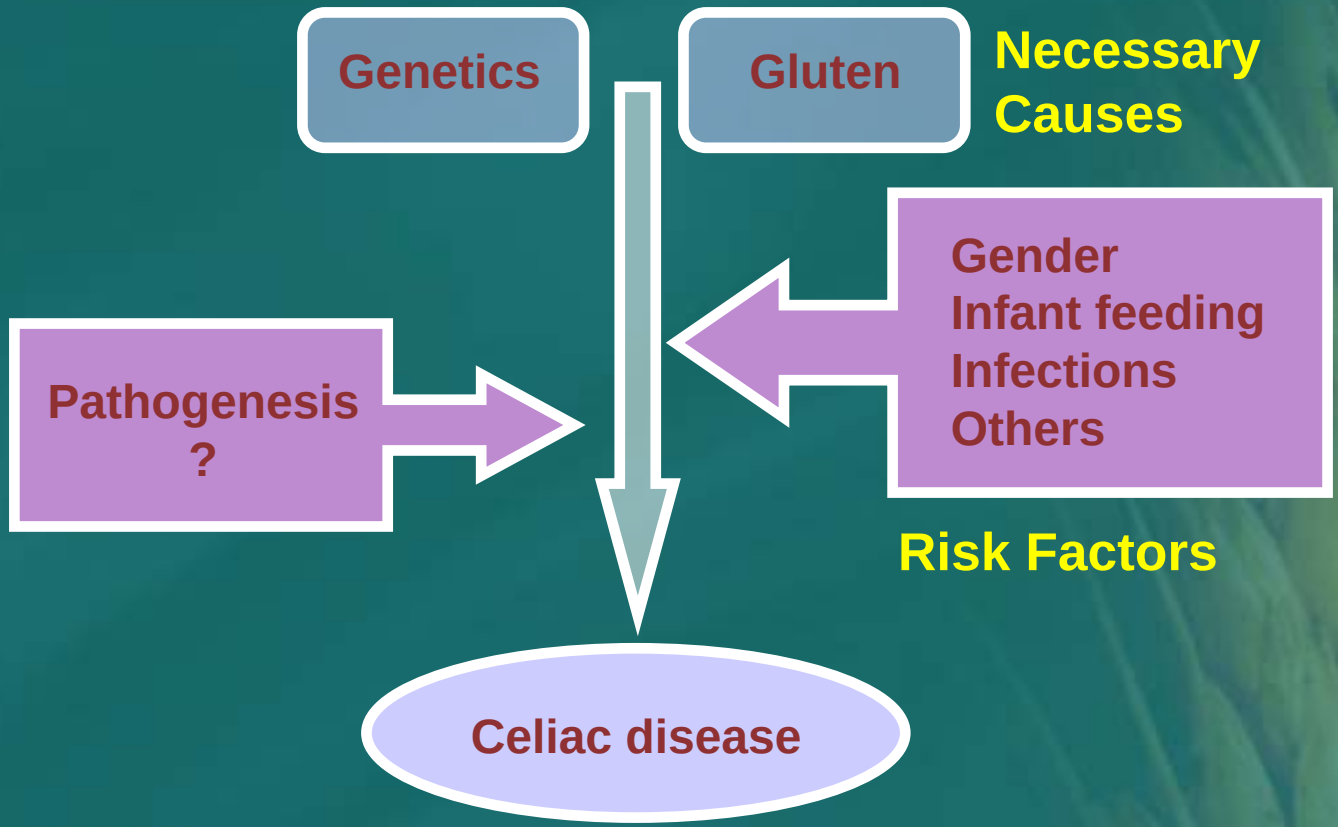
Pathogenesis

Pathogenesis

- Genetic predisposition
- Environmental triggers
  - Dietary
  - Non dietary?

Pathogenesis



Genetics

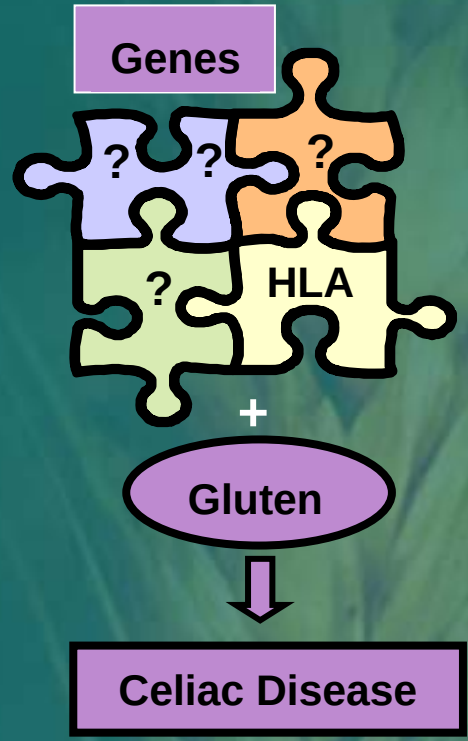
- Strong HLA association
- 90 - 95% of patients HLA-DQ2 – also found in 20 - 30% of controls
  - Most of the remainder are HLA - DQ8
- 10% of patients have an affected first degree relative

Genetics

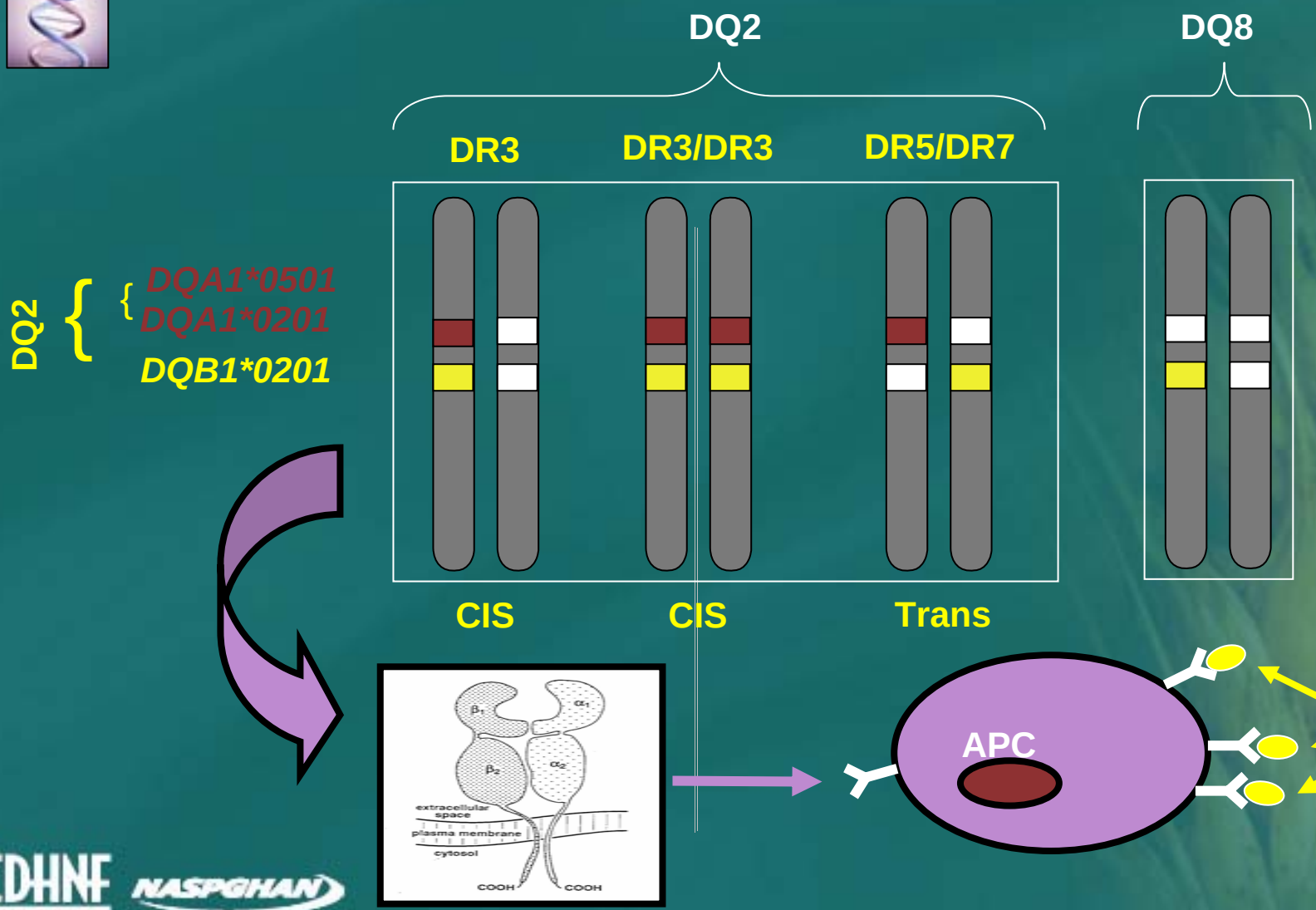
- Concordance in monozygotic twins is 70%
- Concordance in HLA-identical siblings 30 - 40%, suggesting other genes involved
- Protein binding receptors on antigen presenting cells

Genetics

- Several genes are involved
- The most consistent genetic component depends on the presence of HLA-DQ (DQ2 and / or DQ8) genes
- Other genes (not yet identified) account for 60 % of the inherited component of the disease
- HLA-DQ2 and / or DQ8 genes are necessary (No DQ2/8, no Celiac Disease!) but not sufficient for the development of the disease



Be aware DR3 should now be referred to as DR17



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Genetics

- Non-HLA Related Factors
  - Concerns about HLA factors
    - < 2% of all DQ2 carriers have Celiac Disease
    - concordance for HLA matched siblings (30-40%) is lower than for monozygotic twins (~70%)
  - Data suggests additional non HLA genes
  - Inheritance of Celiac Design most likely multigenic
  - Conflicting data for non HLA genes

Genetics

- Genetic factors associated with effector T-cell reactivity
  - CTLA-4 - negative regulation of T-cell activation
  - CTLA-4/CD28 gene locus linked to autoimmune disease (IDDM, Graves, Celiac Disease)
  - CTLA-4 polymorphism in Finnish and French patients with Celiac Disease but not in Italian and Tunisian families

Dietary Factors

The Grass Family - (GRAMINEAE)

Subfamily — Festucoideae

Tribe

Zizaneae	Oryzeae	Hordeae	Aveneae	Festuceaea	Chlorideae
wild rice	rice	wheat, rye, barley	oat	finger millet (ragi)	teff

Dietary Factors

- Wheat - (15% protein, 75% starch)

Gluten

Gliadin
(alcohol soluble)
Prolamine

Glutenin
(alcohol insoluble)

- Rye prolamines - secalins
- Barley prolamines - hordeins
- Oats are safe

Dietary Factors

Amino acid sequence of A-gliadin is rich in proline (P) and glutamine (Q).

P = 15%

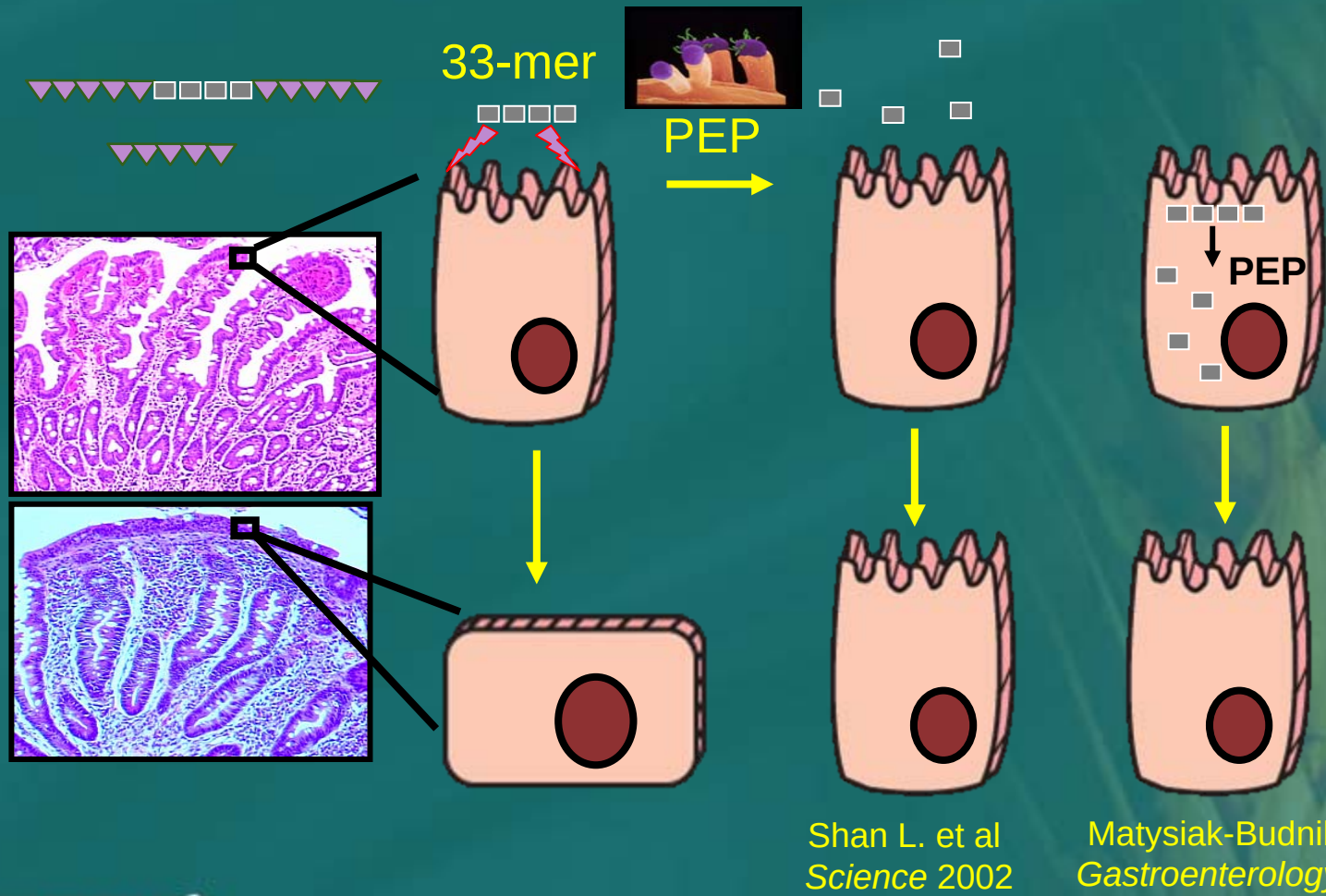
Q = 30%

No specific peptide activates disease in all Celiac Disease patients.

Dietary Factors

- 33 amino acid peptide in gliadin contains critical epitopes – high in glutamine and proline
- Resistant to digestion in lumen
- Penetrates epithelial barrier
- Modified by the enzyme tissue transglutaminase – deamidates glutamine residues to glutamic acid
- Resulting higher affinity binding to HLA DQ2 molecule on the surface of antigen-presenting cells

Toxic Peptides Digestion



Non Dietary Factors

- Infections
  - Viral infections
    - sequence homology between α-gliadin & adenovirus type 12 & 7, rubella and human herpesvirus 1
  - Parasitic infestations
    - sequence homology between a-gliadin & Plasmodium yoelli
  - Other ?

Role of Cytokines

- **Mucosal cytokines**
  - upregulation of IL2 receptor expression
  - increased γ interferon mRNA expression
  - involvement of IL15
  - in vitro gluten stimulation of mucosa from treated Celiac Disease patients
    - γ interferon mRNA
    - IL2 mRNA

T Cells Activation

- **Presentation of modified gliadin peptide in context of HLA-DQ2 leads to activation of CD4+ lamina propria T cells**

- **Gliadin-specific T cells have a Th1 functional phenotype with high secretion of IFN-γ**

Mucosal Events

- **Epithelial cell infiltration**
  - **increased IEL's -** (>90% CD8, <10% CD4)
  - **increased mucosal γ/δ T cells** (nl <10%)
  - **role of γ/δ cells in Celiac Disease unknown**
- **Mucosal surface alterations**
  - **loss of epithelial cells**
  - **proliferation of crypt epithelial cells**

Humoral Response

- Humoral response
  - enhanced antibody production
    - Anti-tissue transglutaminase
    - Anti-gliadin
    - ? other autoantigens (anti-actin)
  - mechanism of antibody production unknown

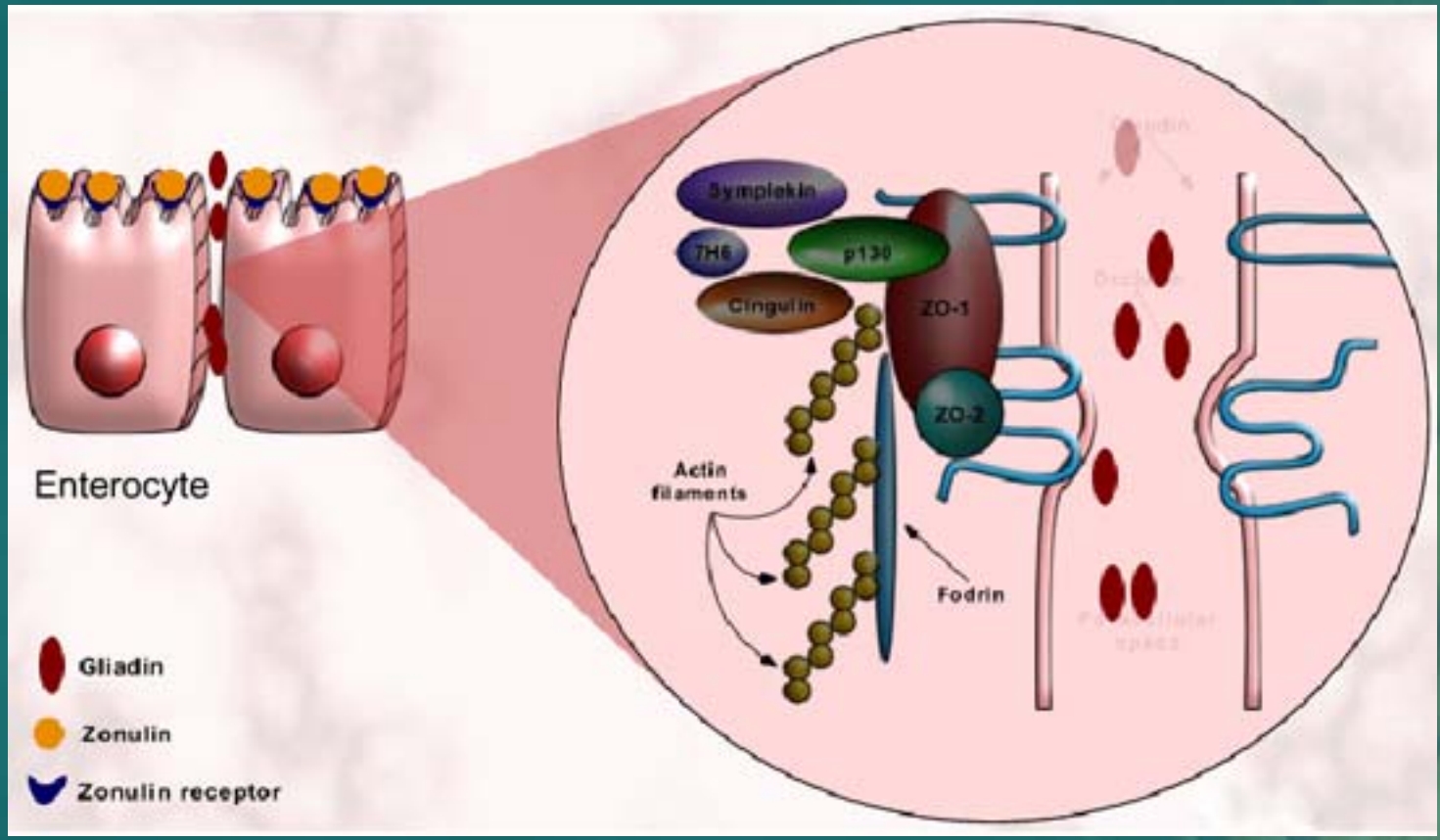
Tissue Transglutaminase (TTG)

- Normal gut enzyme released during injury and stabilizes the cross-linking of proteins in granulation tissue
- Role in Celiac Disease
  - Modification of gliadin epitopes
  - Autoantibodies against TTG correlate with active Celiac Disease - ? involved in pathogenesis

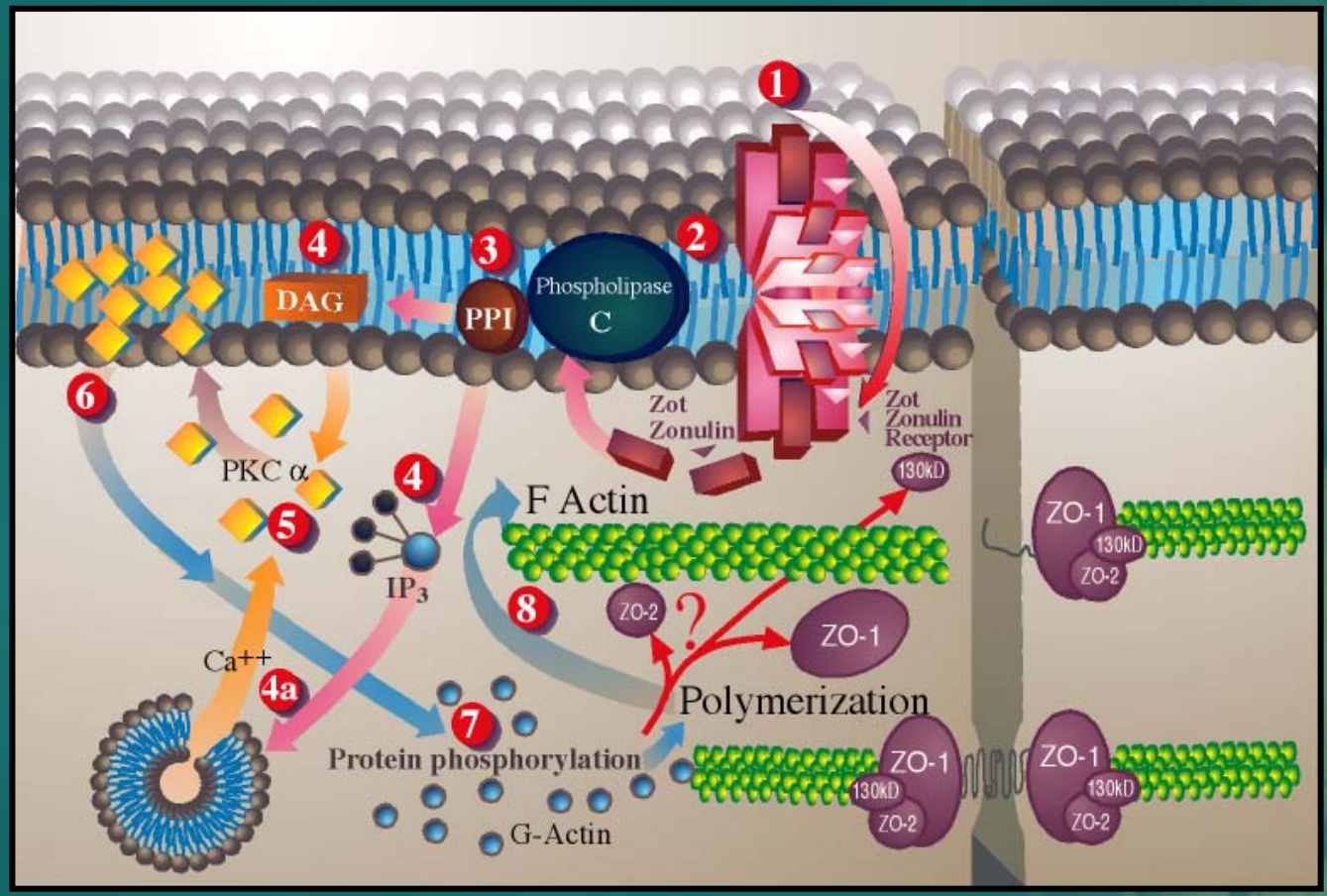
Pathophysiology Sequelae

- Malabsorption of nutrients, especially iron, folate, calcium, and vitamin D
- Increased intestinal permeability may permit entry of other toxins which might induce autoimmune diseases

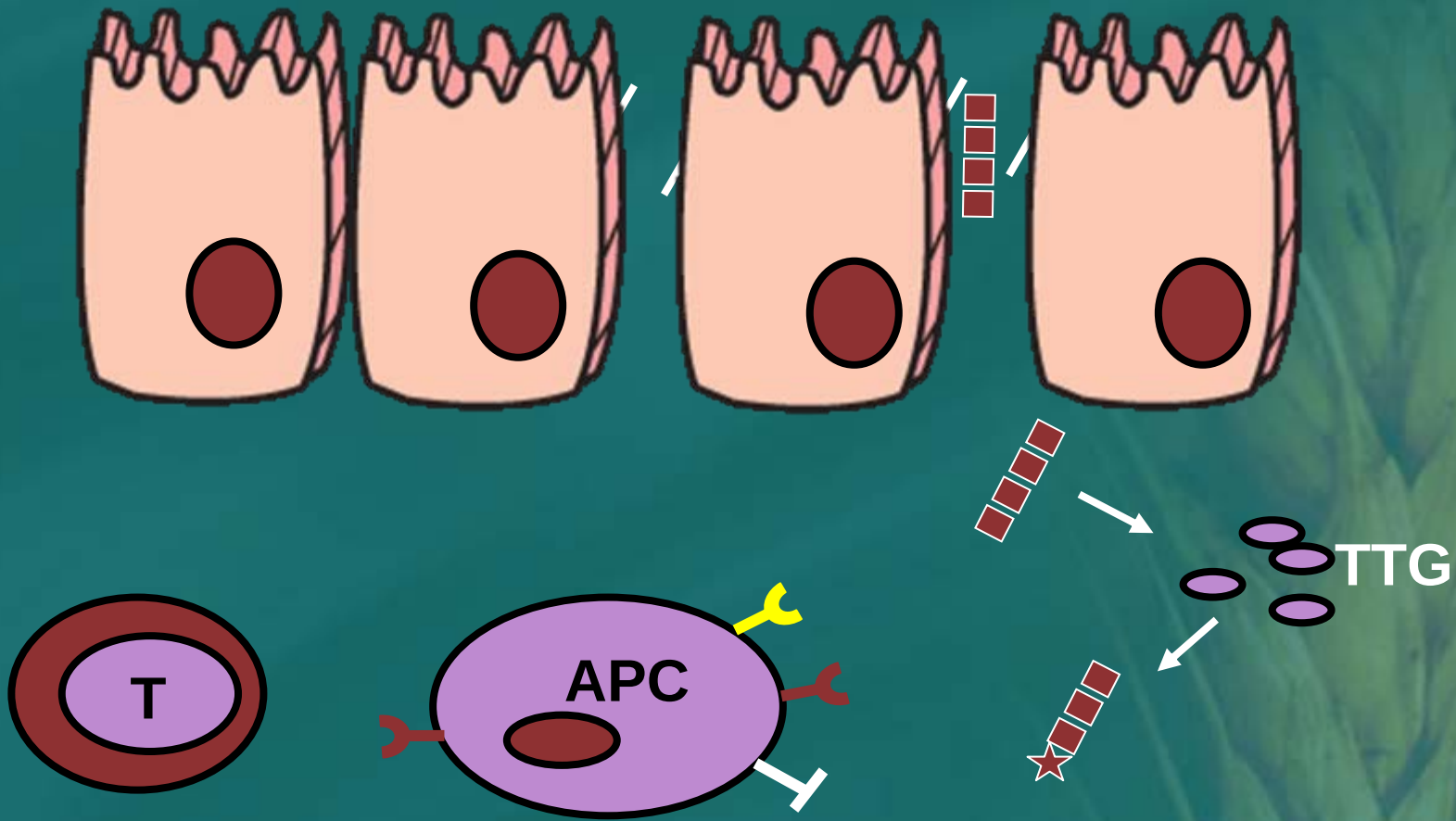
Hypothesis

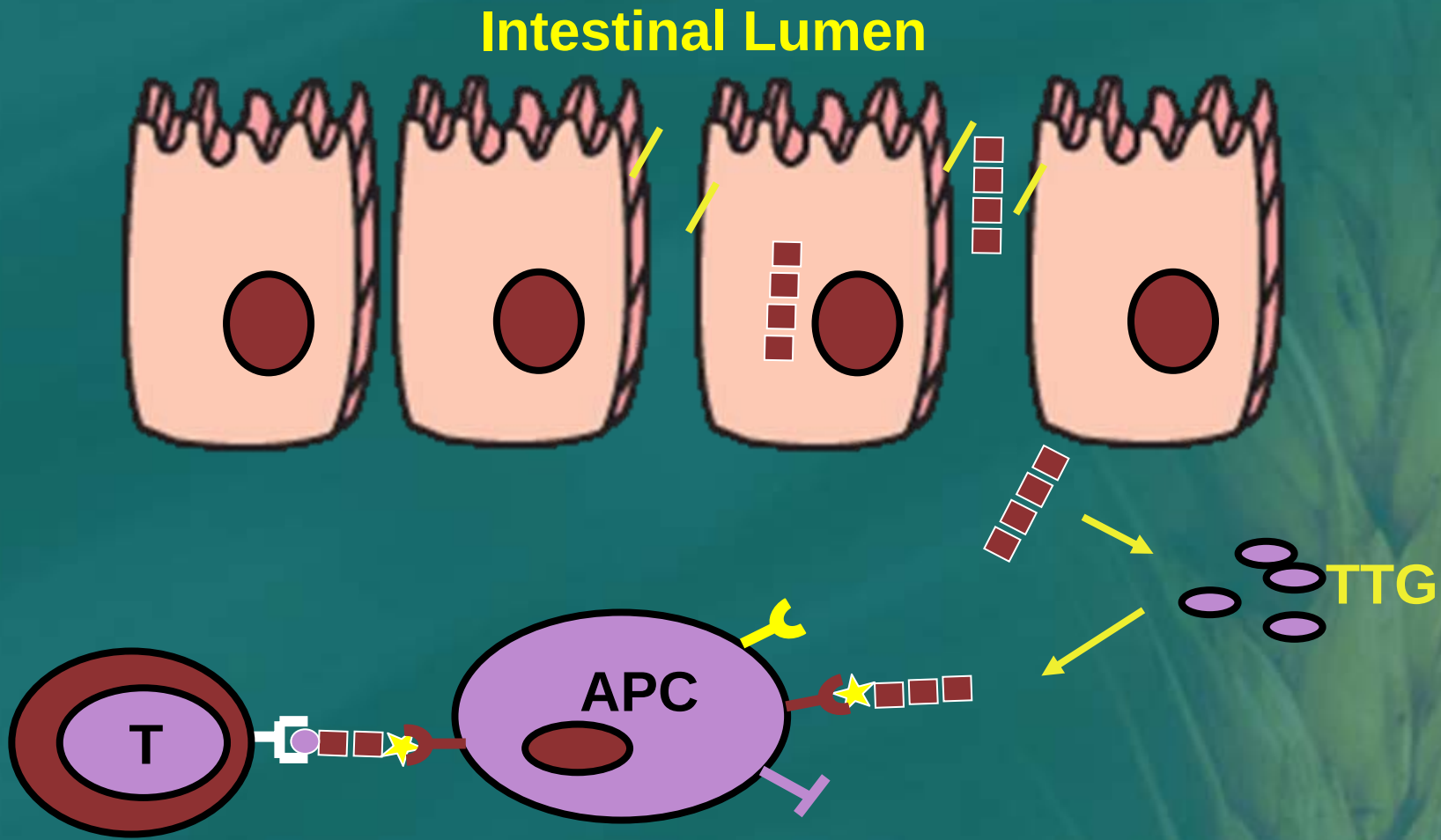

Enterocyte
Gliadin
Zonulin
Zonulin receptor
Symplekin
7H6
p130
Cingulin
ZO-1
ZO-2
Actin filaments
Fodrin

Proposed Zonulin Mechanism of Action

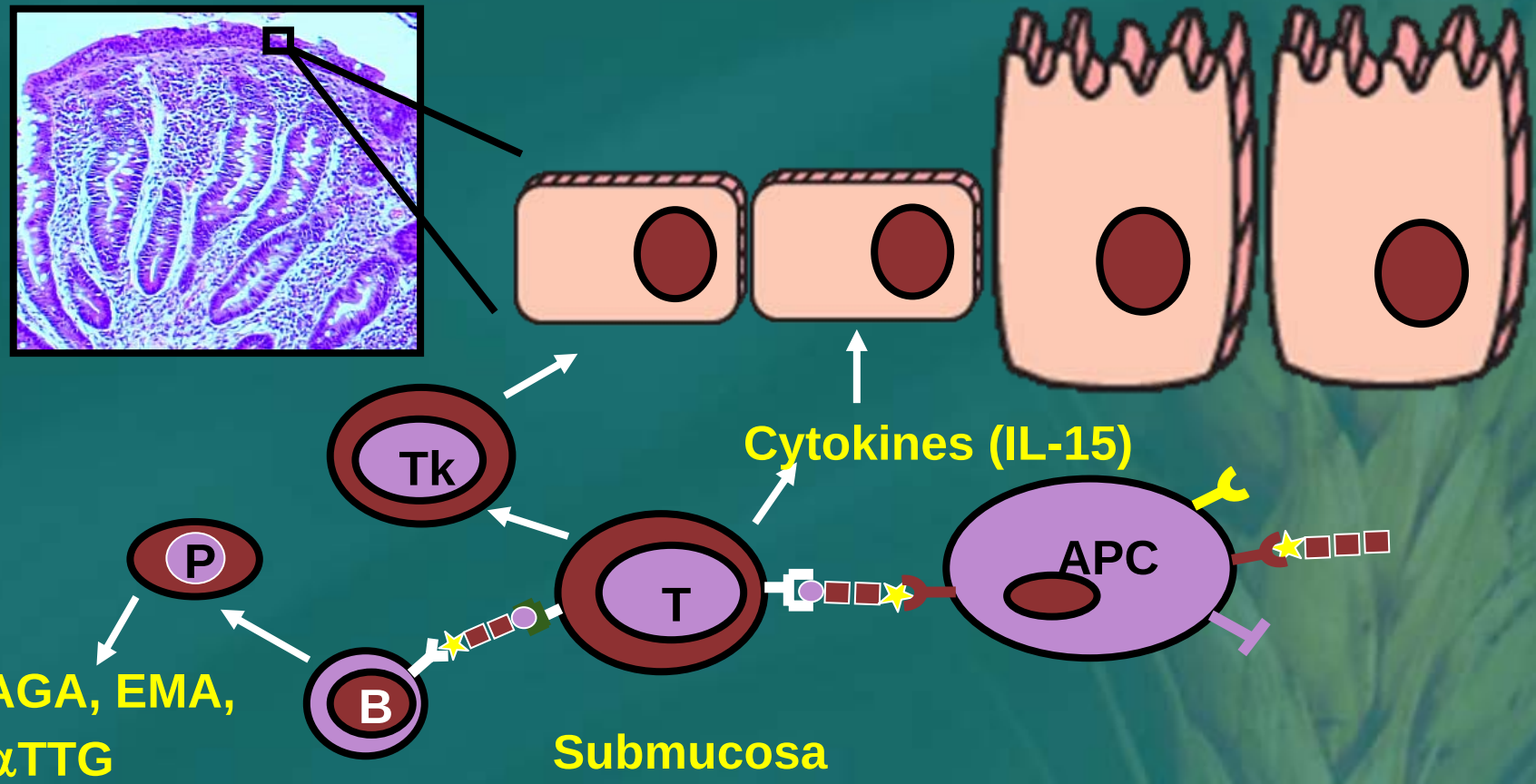


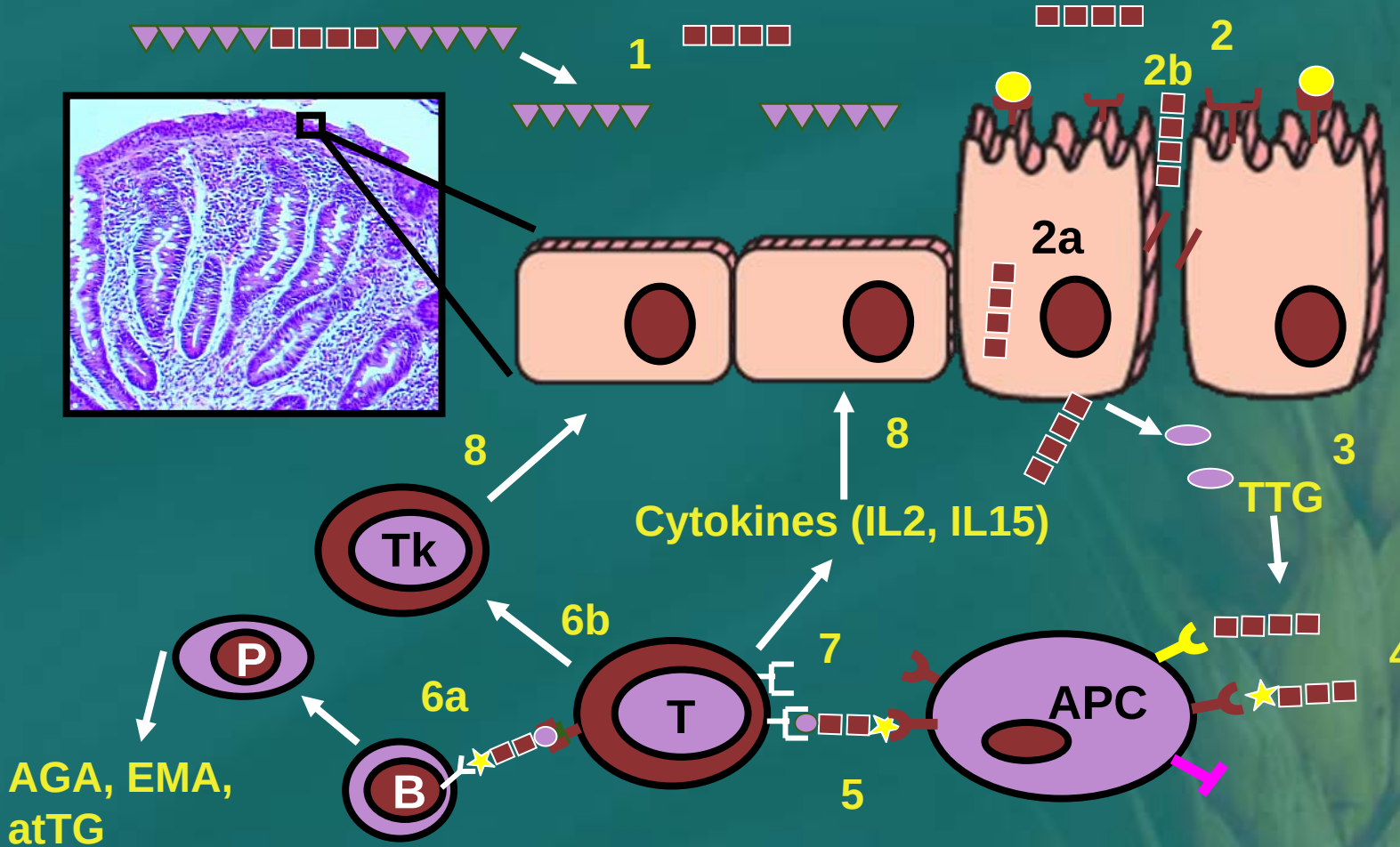
Fasano, J. Ped. Gastroenterol. Nutr., Vol. 26: 520-532, 1998


Intestinal lumen
TTG
T
APC
Submucosa


Intestinal Lumen
TTG
APC
T
Submucosa

Intestinal lumen




1
2
2b
2a
8
8
3
TTG
Cytokines (IL2, IL15)
Tk
6b
7
4
P
6a
T
APC
AGA, EMA,
atTG
B
5
Submucosa

Pathogenesis:
Unanswered Questions

Questions:

- Mechanisms for failure of gliadin tolerance
- Role of innate immunity
- What are immunodominant epitopes
- Does gluten have direct effect on mucosa
- How is mucosal TH1 response induced/maintained
- Mechanism and role of IEL's
- How is mucosal remodeling induced
- What is the role of autoantibodies

Diagnosis

Diagnosis

Diagnostic principles

- Confirm diagnosis before treating
  - Diagnosis of Celiac Disease mandates a strict gluten-free diet for life
    - following the diet is not easy
    - QOL implications
- Failure to treat has potential long term adverse health consequences
    - increased morbidity and mortality

Diagnosis

- Diagnosis of Celiac Disease requires:
  - characteristic small intestinal histology in a symptomatic child
  - complete symptom resolution on gluten-free diet
- Serological tests may support diagnosis
- Select cases may need additional diagnostic testing

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ESPGAN working group. Arch Dis Child 1990;65:909

Serological Tests

Role of serological tests:

- **Identify symptomatic individuals who need a biopsy**
- **Screening of asymptomatic “at risk” individuals**
- **Supportive evidence for the diagnosis**
- **Monitoring dietary compliance**

Serological Tests

- Antigliadin antibodies (AGA)
- Antiendomysial antibodies (EMA)
- Anti tissue transglutaminase antibodies (TTG)
  - first generation (guinea pig protein)
  - second generation (human recombinant)
- HLA typing

Antigliadin Antibodies

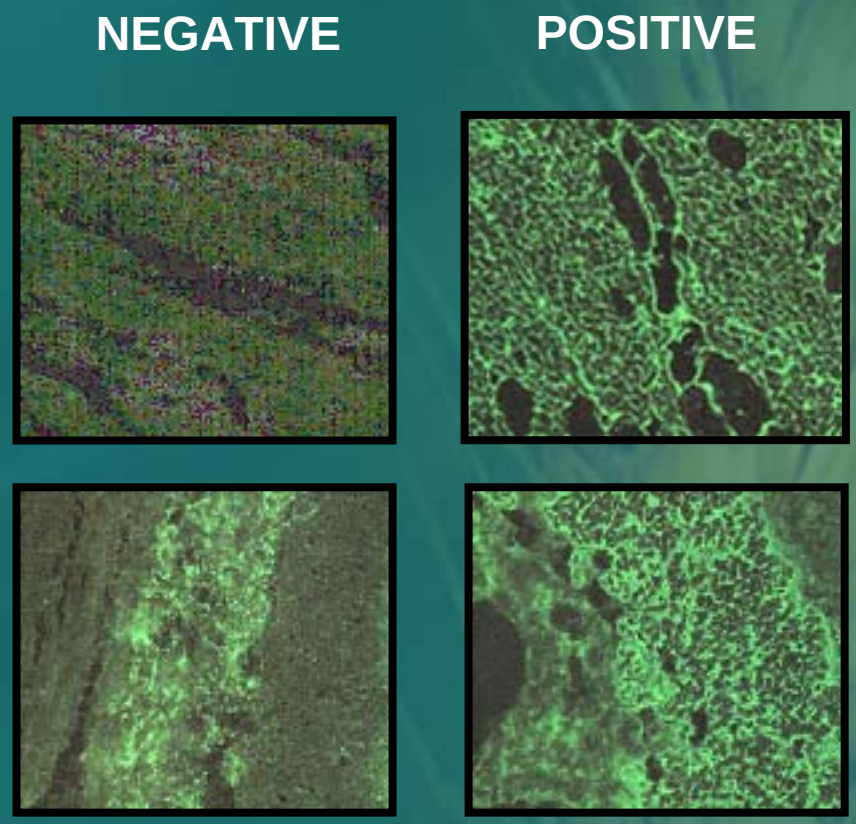
- Antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley
- Advantages
  - relatively cheap & easy to perform
- Disadvantages
  - poor sensitivity and specificity

Endomysial Antibody - EMA

- IgA based antibody against reticulin connective tissue around smooth muscle fibers
- Advantages
  - high sensitivity and specificity
- Disadvantages
  - false negative in young children
  - operator dependent
  - expensive & time consuming
  - false negative in IgA deficiency

Endomysial Antibody - EMA

Antibodies against the outer layer of the smooth muscle of monkey esophagus



Tissue Transglutaminase - TTG

- IgA based antibody against tissue transglutaminase (Celiac Disease autoantigen)
- Advantages
  - high sensitivity and specificity (human TTG)
  - non operator dependent (ELISA/RIA)
  - relatively cheap
- Disadvantages
  - false negative in young children
  - false negative in IgA deficiency
  - possibly less specific than EMA

Serological Test Comparison

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
TTG (IgA)	90 – 98	94 – 97

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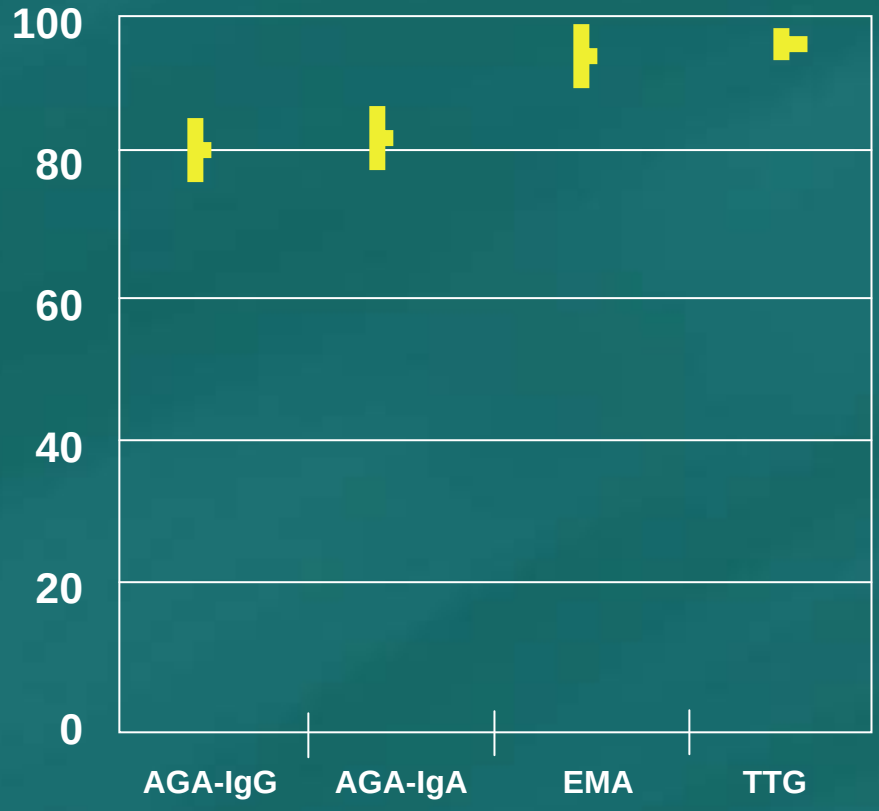
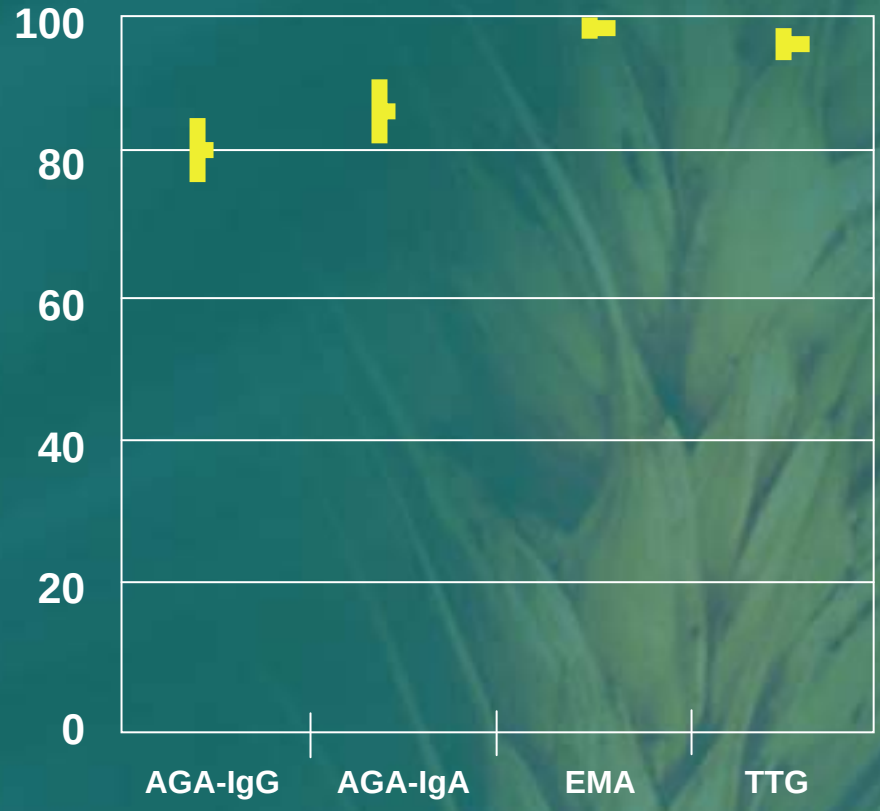
Farrell RJ, and Kelly CP. Am J Gastroenterol 2001;96:3237-46.

Sensitivity



Specificity



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Serum IgA Level

- Individuals with IgA deficiency are at increased risk for Celiac Disease
- IgA deficient individuals will have negative EMA-IgA & TTG-IgA
- Check IgA levels with Celiac Disease serology in all symptomatic individuals
- Consider IgG based tests (EMA-IgG & TTG-IgG) in IgA deficiency

HLA Tests

HLA alleles associated with Celiac Disease

- **DQ2 found in 95% of celiac patients**
- **DQ8 found in remaining patients**
- **DQ2 found in ~30% of general population**

Value of HLA testing

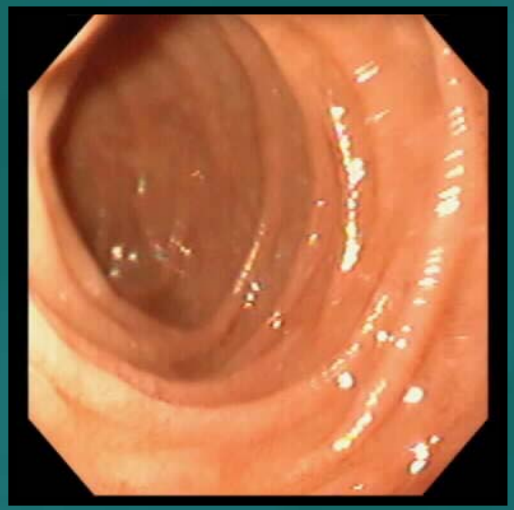
- **High negative predictive value**
  - **Negativity for DQ2/DQ8 excludes diagnosis of Celiac Disease with 99% confidence**

Schuppan. Gastroenterology 2000;119:234
Kaukinen. Am J Gastroenterol 2002;97:695

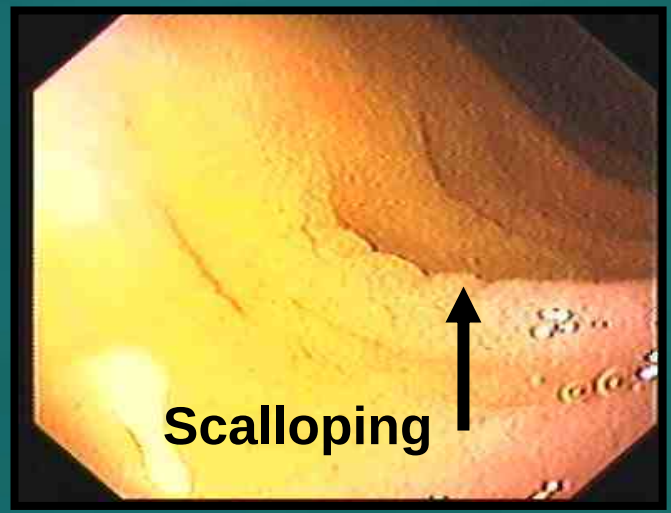
HLA Tests

- Potential role for DQ2/DQ8
  - asymptomatic relatives
  - Down, Turner & Williams syndrome
  - type 1 diabetes
  - diagnostic dilemmas

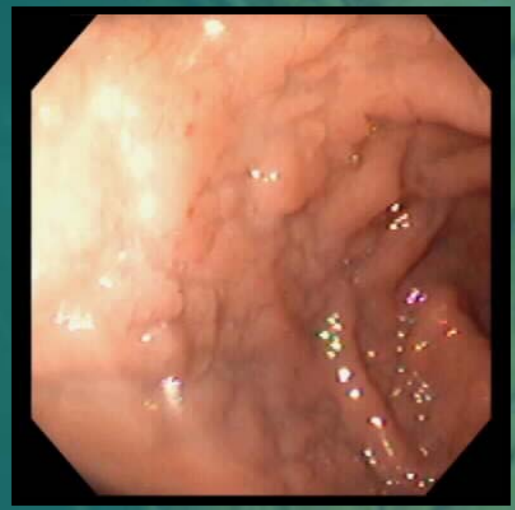
Endoscopic Findings



Normal Appearing

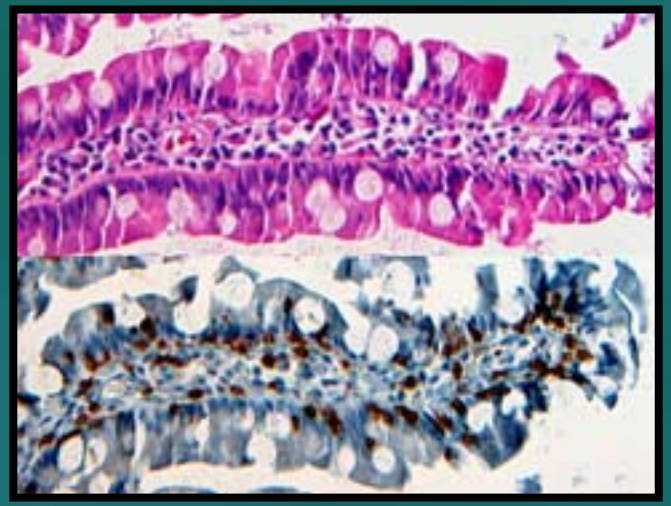


Scalloping



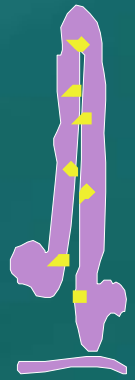
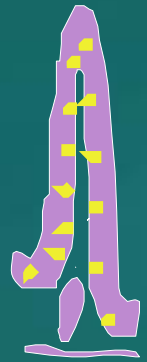
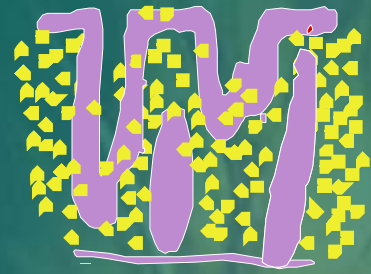
Nodularity

Biopsy Diagnosis



- Histologic Features:
  - Increased IEL's (> 30/100 enterocytes)
  - Loss of nuclear polarity
  - Change from columnar to cuboid
  - Lamina propria cellular infiltrate
  - Crypt elongation and hyperplasia
  - Increased crypt mitotic index
  - Progressive villous flattening

Patterns of Mucosal Immunopathology

Type 0	Type 1	Type 2	Type 3
			
Normal	**Infilitrative**	**Hyper plastic**	**Flat destructive**
Celiac Disease (latent)	Celiac	Celiac	Celiac
	Giardiasis	Giardiasis	Giardiasis
	Milk intolerance	Milk intolerance	Milk intolerance
	Tropical sprue	Tropical sprue	Tropical sprue
	Marasmus	Marasmus	Marasmus
	GVHR	GVHR	GVHR

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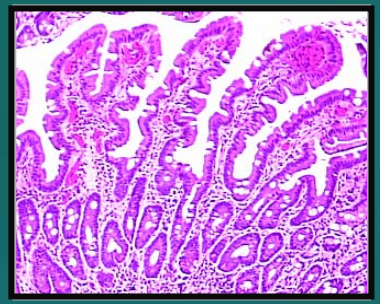
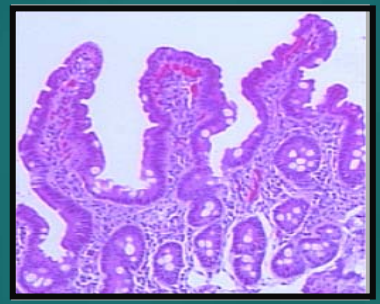
Marsh, *Gastroenterology* 1992, Vol 102: 330-354

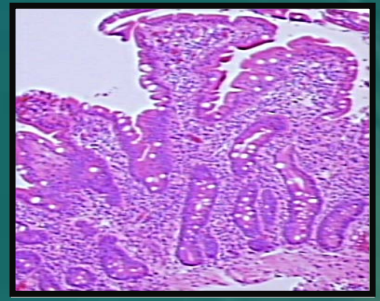
Histological Features



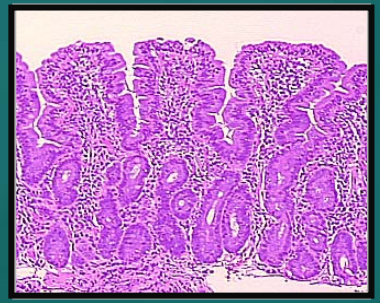
Normal 0



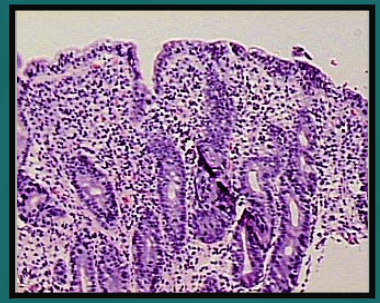
Infiltrative 1



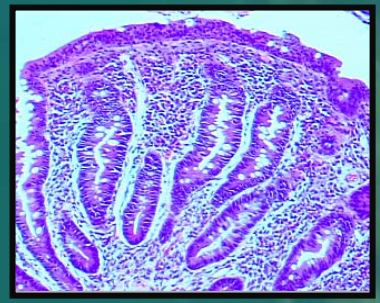
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c

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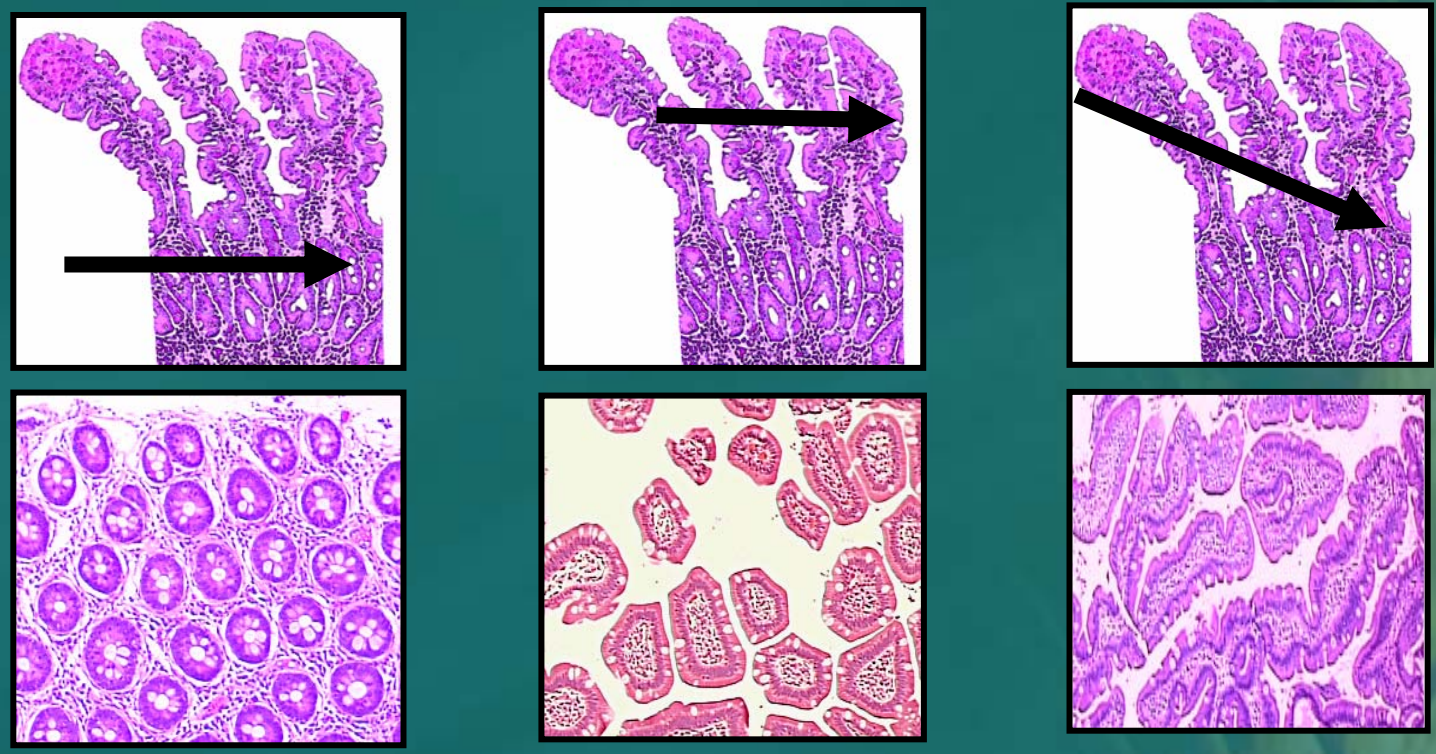
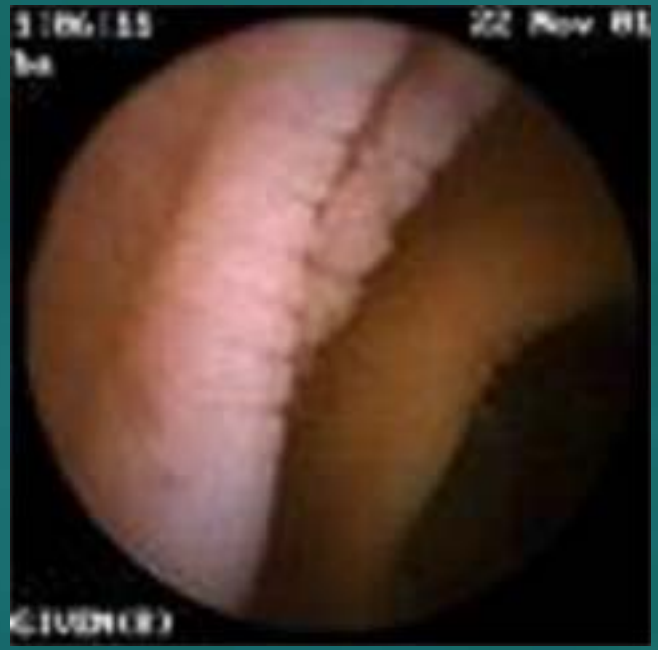
Horvath K. Recent Advances in Pediatrics, 2002.

Diagnostic Pitfalls

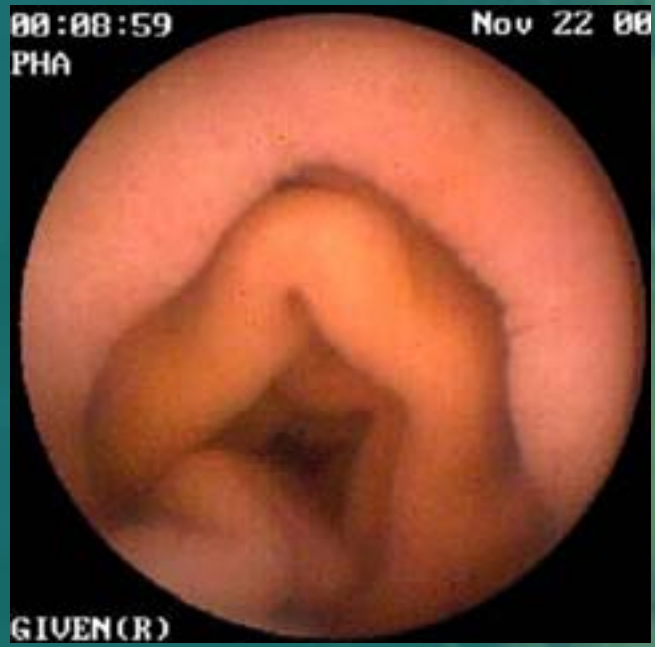
Poor Orientation



Fantastic Voyage

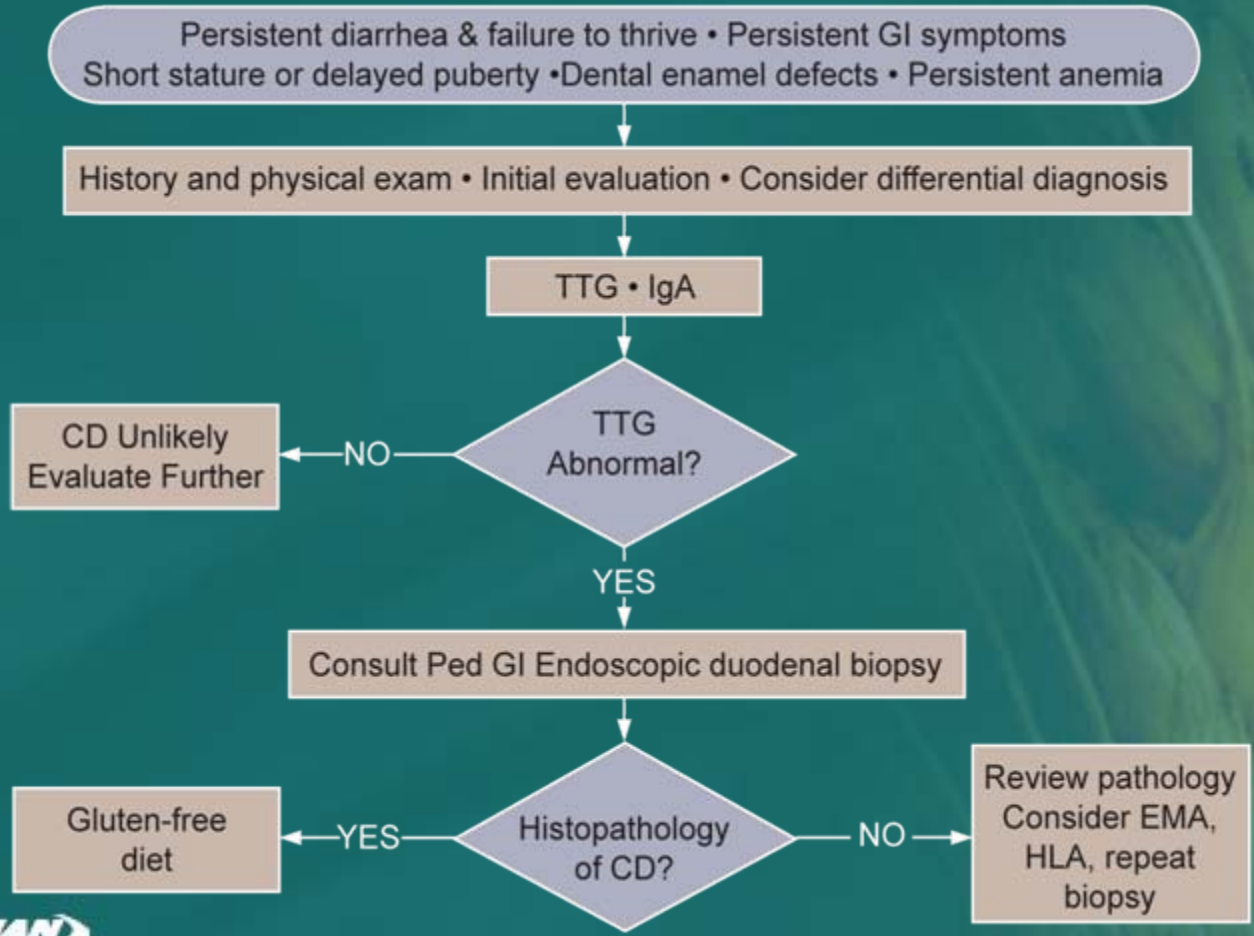


Celiac



Normal

Diagnostic Approach:
Symptomatic Child



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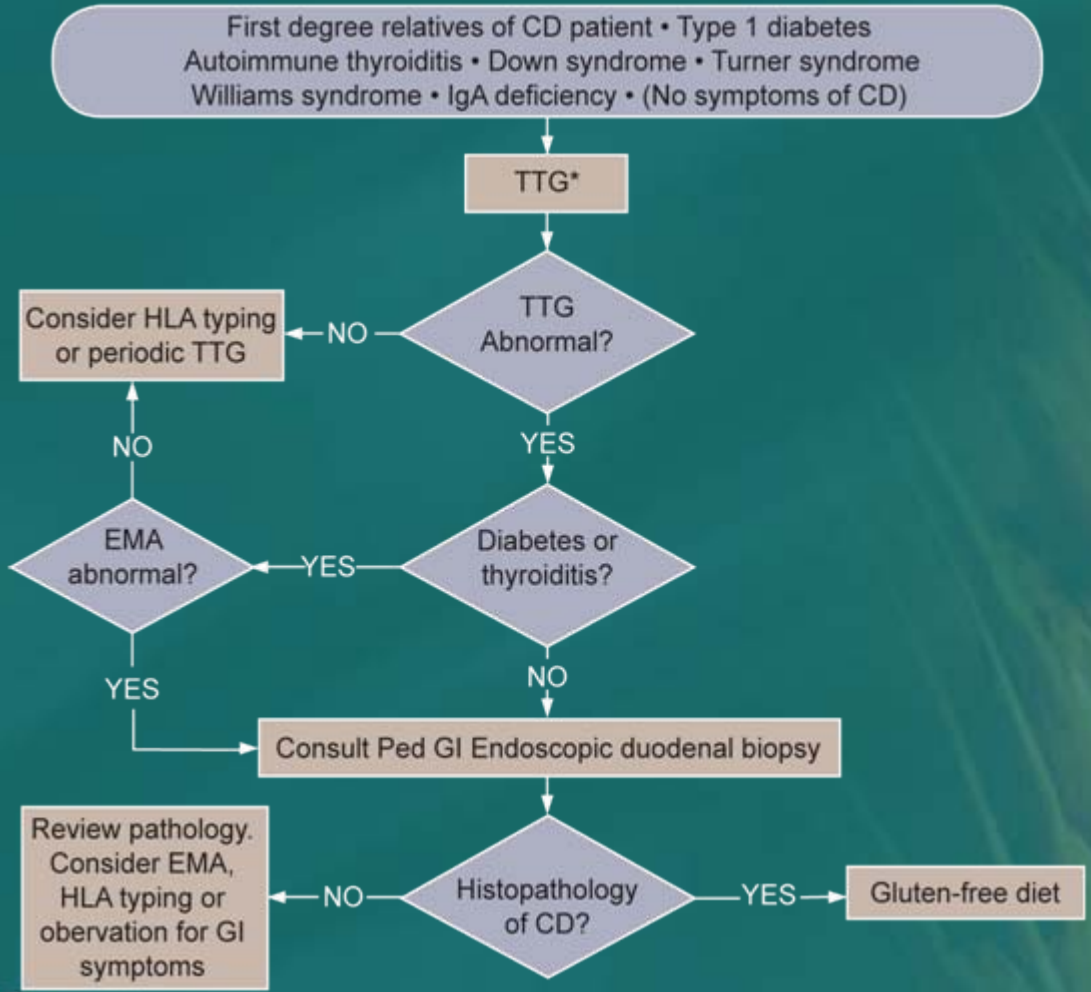
Asymptomatic Child in an at-risk group



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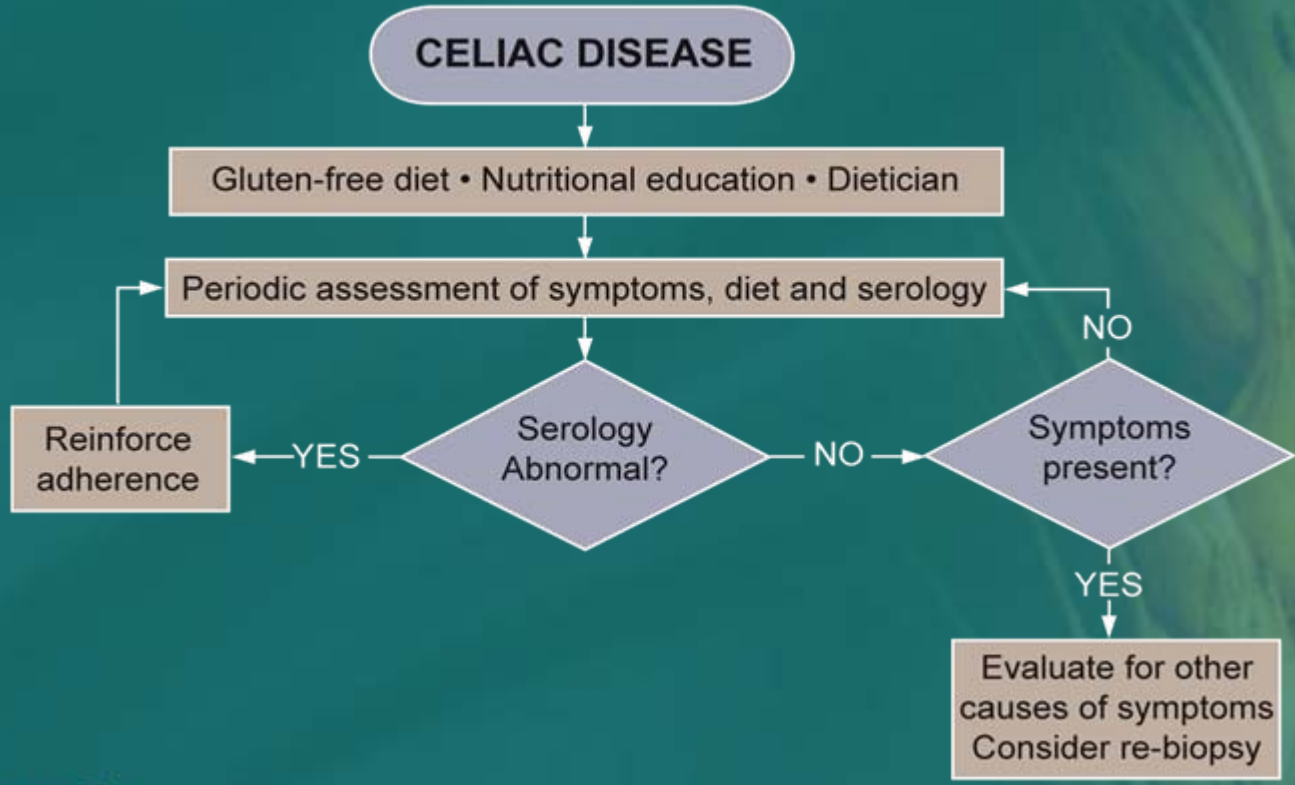
Treatment

Treatment and Monitoring



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Treatment

- **Only treatment for celiac disease is a gluten-free diet (GFD)**
  - **Strict, lifelong diet**
  - **Avoid:**
    - **Wheat**
    - **Rye**
    - **Barley**

Gluten-Containing Grains to Avoid

- Wheat
- Wheat Bran
- Wheat Starch
- Wheat Germ
- Flour/Meal
- Semolina
- Spelt
- Bulgar
- Couscous
- Durum
- Einkorn
- Barley
- Barley Malt/ Extract
- Rye
- Filler
- Graham flour
- Kamut
- Matzo
- Emmer
- Faro
- Triticale

Sources of Gluten

- **OBVIOUS SOURCES**
  - **Bread**
  - **Bagels**
  - **Cakes**
  - **Cereal**
  - **Cookies**
  - **Pasta / noodles**
  - **Pastries / pies**
  - **Rolls**

Sources of Gluten

- **POTENTIAL SOURCES**
  - Candy
  - Communion wafers
  - Cured Pork Products
  - Drink mixes
  - Gravy
  - Imitation meat / seafood
  - Sauce
  - Self-basting turkeys
  - Soy sauce

Ingredients to Question (*may* contain gluten)

- Seasonings and spice blends or mixes
- Modified food starch
- Malt/ malt extract/ flavoring
- Modified hop extract and yeast-malt sprout extract
- Dextrin
- Caramel color

Gluten-Free Grains and Starches

- Amaranth
- Arrowroot
- Buckwheat
- Corn
- Flax
- Millet
- Montina
- Oats*
- Potato
- Quinoa
- Rice
- Sorghum
- Tapioca
- Teff
- Flours made from nuts, beans and seeds

*for possible cross-contamination with gluten containing grains

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Safe Ingredients

- Starch
- Maltodextrin
  - Made from cornstarch, potato starch, or rice starch, but not from wheat
- Vinegar and Alcohol
  - Distilled vinegar and distilled spirits are gluten-free, however avoid malt vinegar and malt beverages (e.g. beer)

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Other Items to Consider

- Lipstick/Gloss/Balms
- Mouthwash/Toothpaste
- Play Dough
- Stamp and Envelope Glues
- Vitamin, Herbal, and Mineral preparations
- Prescription or OTC Medications

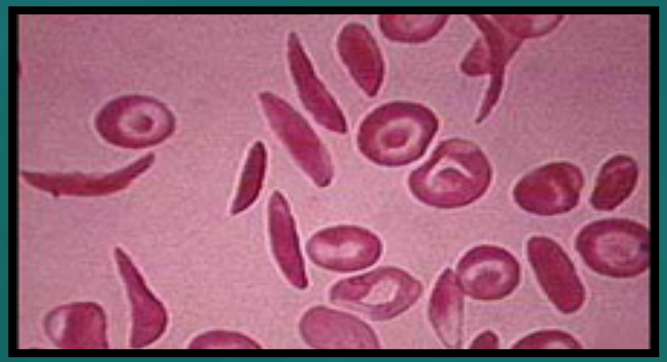
Potential Nutritional Complications in Untreated Celiac Disease

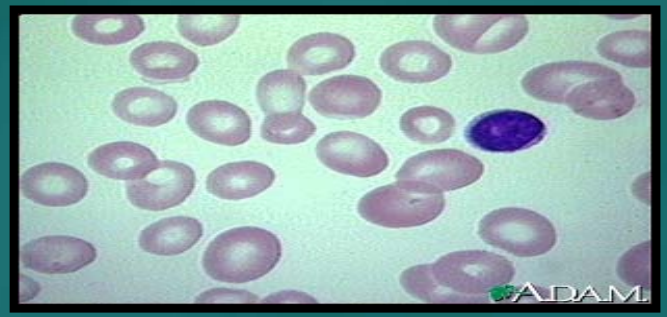
- Low Iron
- Low Folate
- Low Vitamin B-12
- Low Vitamins ADEK
- Low Thiamine
- Low Niacin
- Low B6 (rare)
- Low Beta-carotene
- Low Zinc
- Essential Fatty Acid Deficiency

Potential Nutritional Complications in Untreated Celiac Disease

- Prolonged PT
- Hypocalcaemia
- Elevated PTH
- Increased Alkaline Phosphatase
- Hypophosphatemia
- Hypomagnesaemia
- Hypoalbuminemia
- Re-feeding syndrome

Anemia in Celiac Disease





- Microcytic anemia - iron absorption most efficient in the duodenum
- Megaloblastic/Macrocytic anemia – folate is absorbed primarily in the proximal third of the small intestine (location of folate hydrolases)
- Vitamin B-12 deficiency occurs rarely

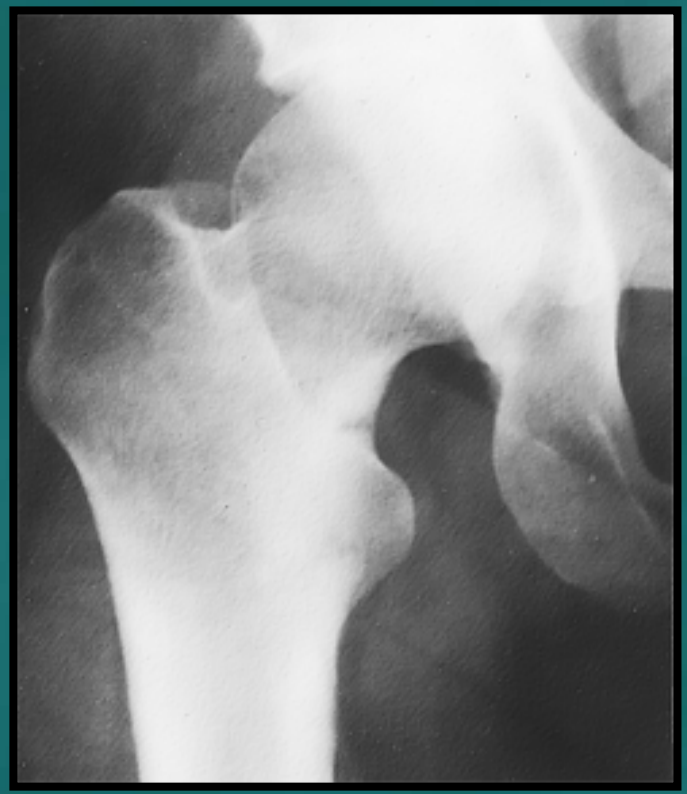
Importance of Folic Acid Supplementation

- Folate hydrolases are needed in the brush border for absorption
- Best absorbed in proximal 3rd of duodenum.
- Increased use of folate in apoptosis
- Low folate impairs cell division

Importance of Folic Acid Supplementation

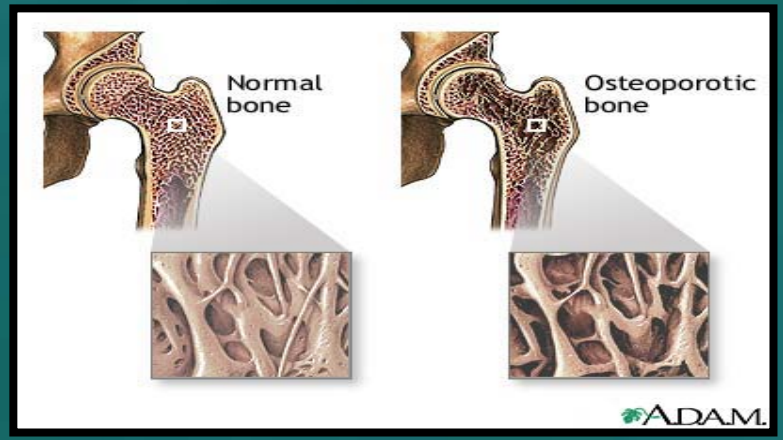
- Low folate increases irritability & forgetfulness
- Celiac Disease increases risk of GI malignancies
  - Folate supplement may have anti-cancer effect as needed for DNA replication
- Supplement Celiac Disease patients with 1 mg folic acid

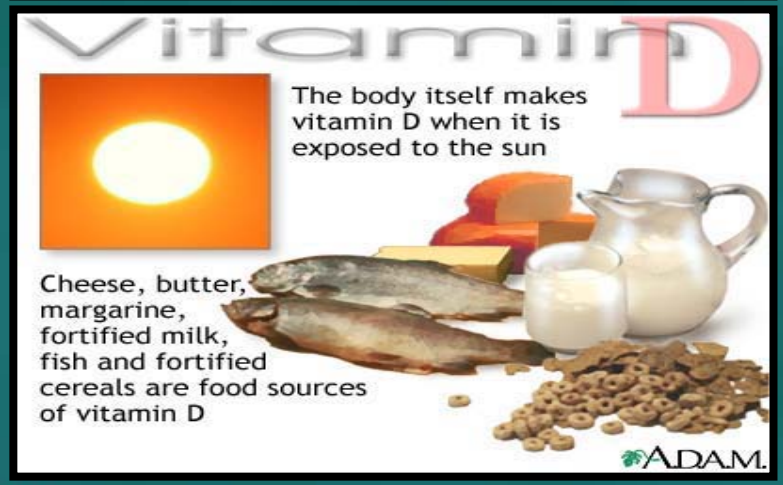
Bone Disease in Celiac Disease



- Arthritis
- Osteoporosis
- Osteopenia
- Osteomalacia
- Rickets

Calcium and Vitamin D Requirements





- 800 to 1200 mg/day of Calcium for low bone mineral density (LBMD) in males
- 1200-1500 mg/day of Calcium for treatment of LBMD in females
- 400 IU of Vitamin D daily
- Up to 2/3 of patients on a gluten-free diet have suboptimal calcium intake

Lactose Intolerance & Celiac Disease: Incidence

- Secondary lactase deficiency is estimated to be 20-40%
- Increasing lactose Intolerance with delayed diagnosis
- Increased incidence in patients with GI symptoms in Celiac Disease
- Decrease calcium and vitamin D intake in lactose intolerance

Lactose Intolerance & Celiac Disease: Treatment

- Gluten free diet
- Temporary lactose-reduction
- Lactase enzymes
- Lactose-free milk
- Gluten-free milk substitute
- Supplement with calcium & vitamin D where appropriate

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Nutrients Speculated to Play a Role in Celiac Disease Infertility and Pregnancy Outcomes

Low Levels of:

- Iron
- Zinc
- Folic Acid
- Vitamin B-12
- Protein
- Vitamin K
- Vitamin B-6
- Vitamin E

Nutritional Exam and Review of Systems

- Anemia
- Peripheral Neuropathy
- Ricketts in Children
- Bone Pain
- Tetany
- Acrodermatitis
- Easy bruising
- Coagulopathy
- Night Blindness

Nutritional Exam and Review of Systems

- Amenorrhea, Infertility
- Impotence
- Cheilosis
- Glossitis
- Stomatitis
- Purpura
- Follicular Hyperkeratosis
- Hyperpigmented dermatitis
- Edema
- Ascites

Possible Causes of GI Symptoms on a Gluten-Free Diet

- Acidic foods
- Sorbitol
- Olestra
- Guar gums
- Antibiotics
- Lactose
- Alternate flours made from beans or nuts
- Food Allergens such as Milk Protein, Soy, Nuts, Egg, Corn
- Food Intolerance to fructose
- Foods high in salicylates and amines

Eating Healthy on the Gluten-Free Diet

- **Similar to a normal diet**
  - **Moderate cholesterol**
  - **Moderate protein**
  - **Low fat, sodium, alcohol, and concentrated sugars**
  - **High fiber**
- **Variety of foods for good nutrient balance**

Improving Nutrient Density

- **Nutrient density and quality of the gluten-free diet can be improved:**
  - **Use nutrient-rich grains/seeds**

Amaranth	Montina
Bean	Rice Bran
Buckwheat	Quinoa
Teff	Sorghum
Millet	Soy

- **These grains are:**
  - **higher in protein and amino acids**
  - **moderate carbohydrates**
  - **good sources of calcium**
  - **some are higher in iron that wheat**
  - **low sodium.**

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Improving Nutrient Density

- When limiting the use of gluten-free flours to the most common sources (rice, corn), nutrient deficiencies may occur due to low fiber content and excess calories
- Rapid increases in fiber intake may lead to increased GI distress

Living Gluten-Free

- You can have a positive outlook
- Learning to live:
  - Gluten-free foods are better tasting than ever before
  - The diet gets easier as patients adjust to it
  - It is not necessary to restrict the patient's lifestyle, it is just a different way of eating
- Don't make it harder than it needs to be
  - Why following a strict gluten-free diet is vital to living a full, healthy life
- Weight management may become a concern

Dietary Adherence: A Common Problem

- Only 50% of Americans with a chronic illness adhere to their treatment regimen including:
  - diet
  - exercise
  - medication
- Dietary compliance can be the most difficult aspect of treatment

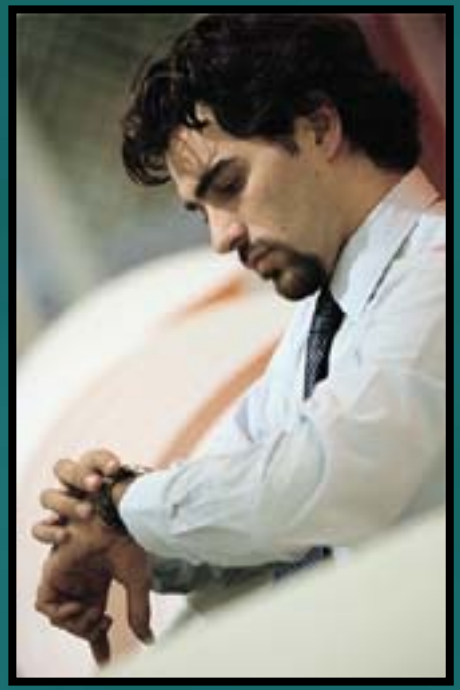
Health Beliefs of Adults with Celiac Disease

- Survey of 100 people in Celiac Disease support group (Buffalo, NY)
  - Number of people who agreed with following statements:
    - "If I eat less gluten I will have less intestinal damage." –51%
    - "I've lived this long eating gluten, how much will the gluten-free diet really help me now?" –33%
    - "My doctor should be the one to tell me when I need follow up testing." –26%
    - "Scientist/doctors still haven't proven that gluten really hurts them." –16%

Barriers to Compliance

- Ability to manage emotions – depression, anxiety
- Ability to resist temptation – exercising restraint
- Feelings of deprivation
- Fear generated by inaccurate information

Barriers to Compliance



- Time pressure – time to plan, prepare food is longer
- Planning – work required to plan meals
- Competing priorities – family, job, etc.
- Assessing gluten content in foods/label reading
- Eating out – avoidance, fear, difficult to ensure food is safe

Barriers to Compliance

- Social Events – Not wanting to look/be different
- Support of Family and Friends – “Just a little bit – it won’t hurt you”

Factors that Improve Adherence

Internal Adherence Factors Include:

- Knowledge about the gluten-free diet
- Understanding the risk factors and serious complications can occur to the patient
- Ability to break down big changes into smaller steps
  - Ability to simplify or make behavior routine
- Ability to reinforce positive changes internally
- Positive coping skills
- Ability to recognize and manage mental health issues
- Trust in physicians and dietitians

The Key to Dietary Compliance is Follow Up Care

- NASPGHAN Guidelines apply to adults and children
- The health effects are motivation
  - When one believes they are real
  - Testing measures the health effects of eating gluten
- Follow up testing provides important feedback

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The Key to Dietary Compliance is Follow Up Care

- Test results are a powerful motivator
  - especially those who do not have symptoms when they eat gluten
- Patients/parents look to the physician to tell them when follow-up testing is needed
  - Proactive follow-up measures can reinforce adherence

Resources

- Reputable websites
  - Celiac.Com (www.celiac.com)
  - National Institutes of Health (www.niddk.nih.gov)
  - American Dietetic Association (www.eatright.org)
- Local Support Groups
  - Celiac.Com (www.celiac.com)
- National Support Groups
  - The Gluten Intolerance Group – GIG (www.gluten.net)
  - Celiac Disease Foundation – CDF (www.celiac.org)
- Research and Information
  - Center for Celiac Research (www.celiaccenter.org)

Resources

- **Cookbooks**
  - Hagman, Bette, “The Gluten-Free Gourmet Cooks Fast and Healthy”
  - Saros,Connie, “Wheat-free Gluten-free Cookbook for Kids and Busy Adults”
  - Books and Magazines
  - Case, Shelley, “Gluten-Free Diet: A Comprehensive Resource Guide”
  - Gluten-Free Living
  - Sully’s Living Without (www.livingwithout.com)
- **Product information**
  - www.glutenfreemall.com

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Prevention & Future Directions

Celiac Disease-Diagnosis: The Future

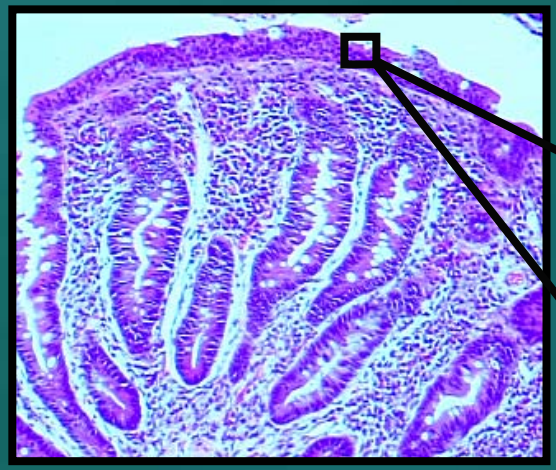
- Diagnosis Strategies
  - Mass population screening
    - Not cost effective (research tool)
    - Benefits uncertain
- Active case finding
  - Selective serological testing
  - Biopsy confirmation

Celiac Disease-Diagnosis: The Future

- Non biopsy diagnosis
  - Characteristic clinical subgroups
  - Refined (standardized) serological tests
  - Use of HLA typing
  - Discovery of biomarkers
  - Specific gene identification

Celiac Disease-Management: The Future

- Gluten free diet remains best treatment
- Refined understanding of “gluten free”
- FDA mandates better food labeling
- Commercial recognition of the “value” of gluten free products



1

2

33-mer

3

TTG

4

Cytokines (IL15)

Tk

8

7

6

5

T

APC

P

B

AGA, EMA,
αTTG

Immune
Tolerance

5+6

Submucosa

CDHNF

NASPGHAN