

# Coeliakie: actualisering

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## Coeliakie: actualisering

- Prevalentie
- Genetische factoren
- diagnose (biopsies - serologische testen)
- Risico's op complicaties
  - ◆ tumoren
  - ◆ osteoporose
- Screening?
- Glutenvrij dieet: hoe glutenvrij is glutenvrij?

## Prevalence of celiac disease

**Table 2.** Prevalence of CD Based on Clinical Diagnosis or Screening Data

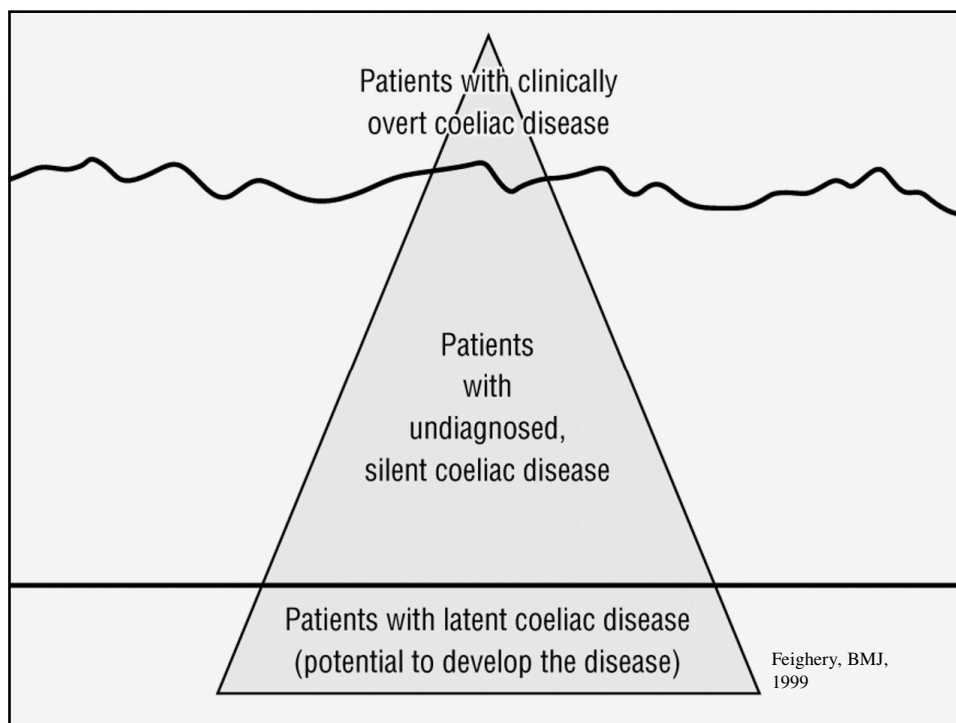
Geographic area	Prevalence on clinical diagnosis <sup>a</sup>	Prevalence on screening data
Brazil	?	1:400
Denmark	1:10,000	1:500
Finland	1:1000	1:130
Germany	1:2300	1:500
Italy	1:1000	1:184
Netherlands	1:4500	1:198
Norway	1:675	1:250
Sahara	?	1:70
Slovenia	?	1:550
Sweden	1:330	1:190
United Kingdom	1:300	1:112
United States	1:10,000	1:111
Worldwide (average)	1:3345	1:266

<sup>a</sup>Classical gastrointestinal symptoms.  
Data from references 81-85, 125-131.

From: Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120:636-51.

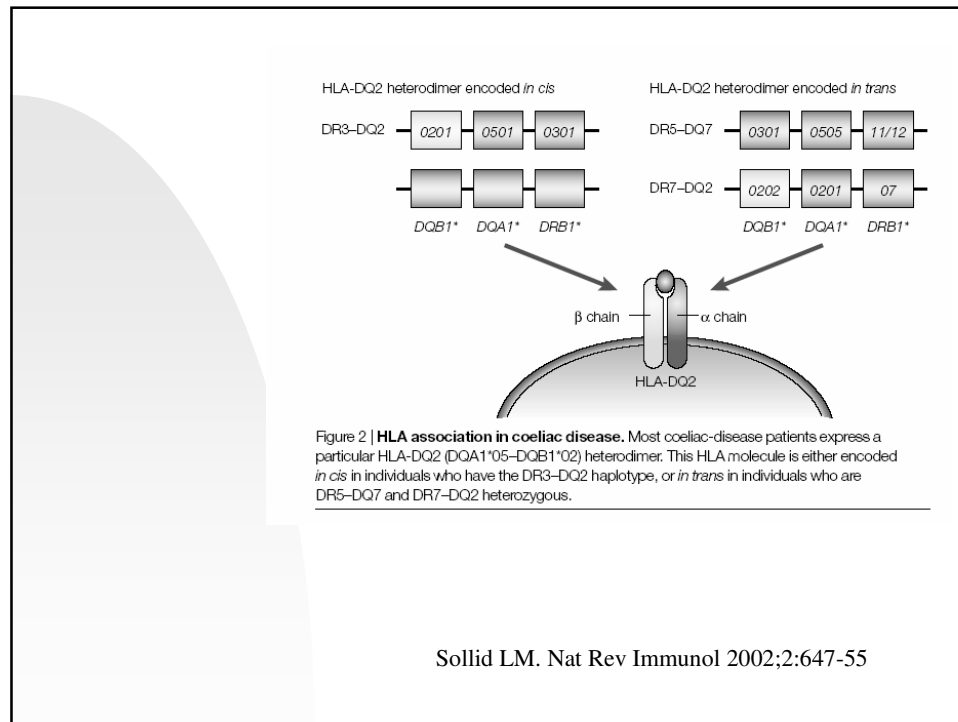
## Prevalence of celiac disease

- Also in Holland : prevalence of 1/200 found by serologic examination (in children 2-4 y) (Lancet, 1999)
- for Belgium: 1/200 would mean: more than 50.000 patients
- Many patients have few symptoms and the disease is not recognized
- The better you look, the higher the prevalence
- More and more pauci-symptomatic patients detected (how to treat them?)



## Genetic factors

- Concordance in monozygote twins: 75 %
- concordance in dizygote twins : 11 %  
(Greco et al., Gut 2002;50:624-628)
- Linked to HLA-genes (HLA-DQ2 in 95 % of patients with celiac disease, HLA-DQ8 in most of the other patients)  
HLA genes would contribute 40 % of genetic risk
- also linkage with non HLA regio (oct 2003: chromosome 19 in Dutch study, chromosome 6 and 9)
- Also importance of MHC class I antigens (MICA and MICB)



## Diagnose

- Histologie
- Serologie
- (HLA)

## Histologie

- Klassiek: villusatrofie noodzakelijk voor diagnose
- Maar vaak minder afwijkingen: partiele villusatrofie (Marsh IIIA) of zelfs geen villusatrofie (Marsh I alleen infiltratie met IE, II hyperplastische vorm):
- villusatrofie is extreme uiteinde van spectrum
- Probleem: wanneer voldoende criteria voor diagnose ?

## Histology

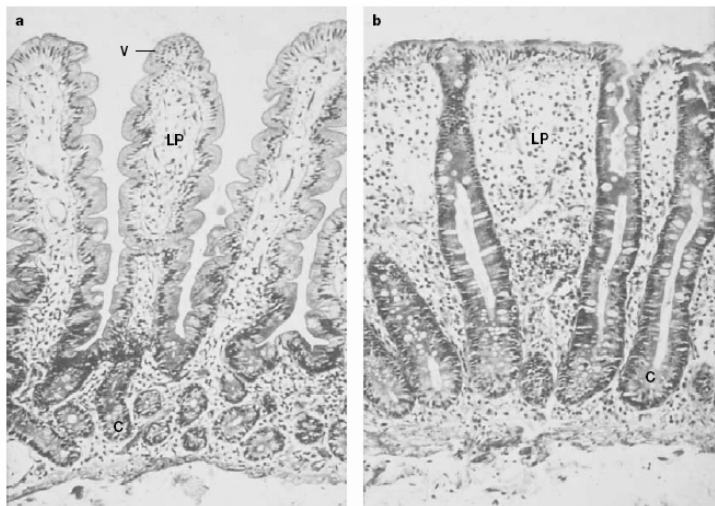
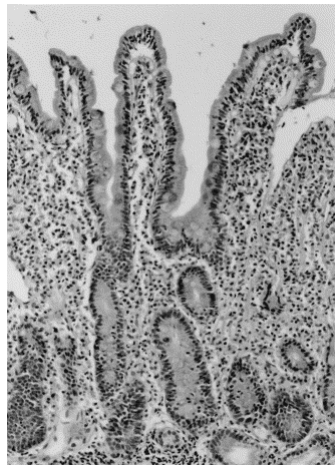


Figure 1 | Normal and coeliac-disease small-intestine mucosae. a | Histology of a normal small intestine showing villi (V) and crypts (C). The lamina propria (LP) extends between the crypts and into the core of each villus, and it contains a rich vascular and lymphatic network into which digestive products are absorbed. b | The coeliac mucosa is characterized by villus atrophy, enlarged hyperplastic crypts and increased infiltration of lymphoid cells in the lamina propria and epithelium.

Sollid LM. Nat Rev Immunol 2002;2:647-55

From : Rostami K, et al.  
*Am J Gastroenterol.* 1999;94:888-94.



Marsh II. Near-normal villi. A hyperplastic lesion comprising enlarged crypts and infiltrated by lymphocytes is seen

## Intra-epitheliale lymfocyten en “gluten sensitivity”

**Table 2.** Clinicopathologic Diagnosis in Patient and Control Subjects

Diagnosis	Patient Group (increased IEL), n = 43	Control Group (normal IEL), n = 46	<i>p</i> Value
Gluten sensitivity	4 (9.3%)	0	0.05
Immunologic diseases	6 (14%)	0	0.01
NSAIDs	6 (14%)	1 (2.2%)	0.04
Inflammatory bowel disease	5 (11.6%)	3 (6.6%)	0.30
Bacterial overgrowth	2 (4.4%)	1 (2.2%)	0.40
Tropical sprue	1 (2.3%)	0	0.10
Microscopic colitis	3 (6.9%)	5 (10.8%)	0.30
Other	16 (37.2%)	36 (78.3%)	

Kakar et al., *Am J Gastroenterol.* 2003;98:2027-33.

## Serologie

- Antistoffen tegen vreemde eiwitten (tegen gliadine)
- Auto-antistoffen:
  - ◆ tegen “endomysium”,
  - ◆ tegen “weefsel transglutaminase”

## NIH conference on celiac disease (june 28-30,2004) (I. Hill)

**Table 1.** Sensitivity and Specificity of Individual Serological Tests

Test	Age Group	Sensitivity	Specificity
AGA-IgG	Adults/Combined <sup>*(1,4,5,11)</sup>	57–100%	69–87%
	Children <sup>(2,3,7–10,12)</sup>	88–100%	47–94%
AGA-IgA	Adults/Combined <sup>(1,4,6,14,16)</sup>	54–100%	79–100%
	Children <sup>(2,3,7–10,12,13,15–17)</sup>	52–100%	71–100%
EMA	Adults <sup>(5,17,25,27,28)</sup>	87–95%	95–100%
	Children <sup>(2,8,9,15,17,19,24,25)</sup>	88–100%	90–100%
	Combined <sup>(1,4,20–23,26)</sup>	91–98%	99–100%
TTG	Children <sup>(19,25,33,34)</sup>	90–100%	94–100%
	Combined <sup>(20–32)</sup>	84–100%	91–100%
ARA	Children <sup>(7,8,36)</sup>	65–94%	93–100%

\*Combined—refers to studies involving both adults and children

## Serologie anti- endomysium AS

- klassiek heel sensitief (meer dan 95 %) en specifiek (98-99 %)?
- Andere bronnen rapporteren sensitiviteit van slechts 75-98 %
- Hoe minder histologische afwijkingen, hoe minder kans op positieve serologie (dus helpt vaak niet in echte dubieuze gevallen)
- techniek: immunofluorescentie (subjectieve beoordeling)

Low prevalence of antigliadin and anti-endomysium antibodies in subclinical/silent celiac disease (Tursi et al., Am J GE 2001)

Patients with subclinical CD					
	Marsh I	Marsh II	Marsh IIIa	Marsh IIIb	Marsh IIIc
Biopsy	2	10	18	25	30
AGA pos.	0	3 (30%)	14 (77%)	21 (84%)	27 (90%)
EMA pos	0	4 (40%)	16 (88.9%)	23 (92%)	29 (96.7%)
Patients with silent CD					
	Marsh I	Marsh II	Marsh IIIa	Marsh IIIb	Marsh IIIc
Biopsy	2	2	5	6	9
AGA pos.	0	0	3 (60%)	4 (66.7%)	7 (77.8%)
EMA pos	0	0	4 (80.0%)	5 (83.3%)	8 (88.9%)

## Anti “tissue transglutaminase”

- Substraat van anti-endomysium AS (en auto-antigen bij coeliakie) blijkt t-transglutaminase te zijn
- beste kits (recombinant humaan tTG): betrouwbaar (mogelijks sensitiever dan anti EM, en bijna even specifiek (iets minder)
- voordeel: ELISA ipv immunofluorescentie (meer objectief)
- In Belgische laboratoria: recent geïntroduceerd (nog niet terugbetaald)
- strategie in Leuven (na studie door Van Meensel et al., Clin Chem 2004):
  - ◆ IgA dosage en anti tTG
  - ◆ indien IgA deficiëntie, dan IgG anti gliadine
- door probleem met gouden standaard en selectie bias: mogelijks in realiteit minder betrouwbaar dan in studies

## Gevolgen en complicaties

- malabsorptie van allerlei nutriënten
- maligne tumoren, en mortaliteit
- osteoporose
- andere auto-immuunziekten

→ Screening ?

## Risk of intestinal lymphoma

- older studies:
  - ◆ Without a good gluten free diet :  
risk for lymphoma : 7 %
  - ◆ 30-70 X risk of somebody who has no celiac disease
- recent large Swedish study (11.000 patients) : 6 times higher risk of (T-cel intestinal) lymphoma

## Risk of lymphoma and other tumors

**Table 3.** SIRs of malignant lymphoma and of selected gastrointestinal carcinomas with 95% CI in subjects with CD (without a diagnosis of DH) 1964–1994 through 1995

	Malignant lymphoma	Oral cavity	Esophagus	Small intestine	Large intestine	Liver (primary)
No. malignancies	44	8	6	8	26	11
Overall relative risk	5.9 (4.3–7.9)	2.3 (1.0–4.5)	4.2 (1.6–9.2)	10 (4.4–20)	1.9 (1.2–2.8)	2.7 (1.3–4.7)

GASTROENTEROLOGY 2002;123:1428–1435

### CLINICAL–ALIMENTARY TRACT

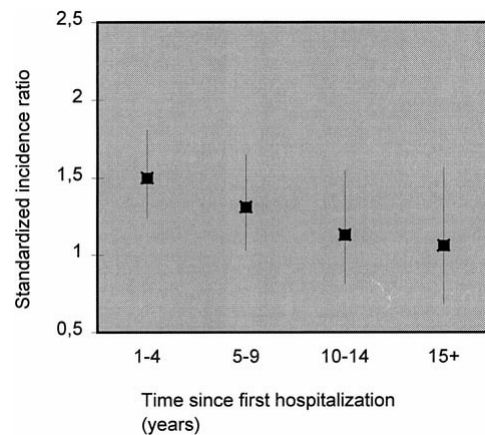
Cancer Incidence in a Population-Based Cohort of Individuals Hospitalized With Celiac Disease or Dermatitis Herpetiformis

JOHAN ASKLING,\* MARTHA LINET,<sup>†</sup> GLORIA GRIDLEY,\* TROND S. HALSTENSEN,<sup>‡</sup>  
KARIN EKSTRÖM,<sup>§</sup> and ANDERS EKBOM\*

**CLINICAL-ALIMENTARY TRACT****Cancer Incidence in a Population-Based Cohort of Individuals Hospitalized With Celiac Disease or Dermatitis Herpetiformis**

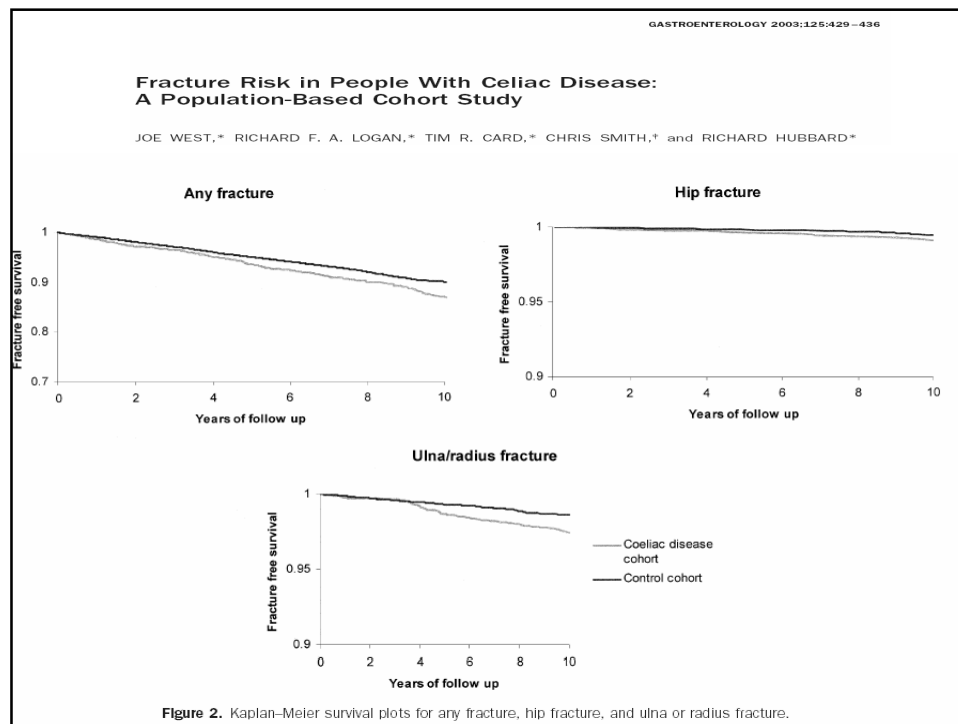
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Overall relative risk for cancer by time since first hospitalization for CD in a Swedish cohort of 11,019 individuals hospitalized with CD between 1964 and 1994.



## Risk to die from celiac disease

- Scottish study (653 pts) (Logan, Gastroenterology, 1989): approx. 2 X more risk of dying on a certain age
- risk is largest within 1 year of diagnosis
- A risk of dying 2 X larger than control population = risk of smoking
- Finnish study (249 pts): patients strictly adhering to diet have no increased risk (Collin, Gut 1994)
- Recent Swedish study in > 10.000 pts (Peters et al., Arch Int Med 2003): confirms mortality risk 2 times higher than in control population



## Screening voor coeliakie ?

Mogelijke doelgroepen:

- ◆ eerste graad verwanten (risico ± 8-10 %)
- ◆ diabetes type I (2-6 %)
- ◆ Bij osteoporose
- ◆ volledige bevolking ?
  
- ◆ case finding (vage gi klachten, anemie, ijzergebrek, gestoorde levertesten,...)

## Argumenten voor screening

(Fasano, Editorial NEJM, 2003)

### richtlijnen voor screening van de Wereld

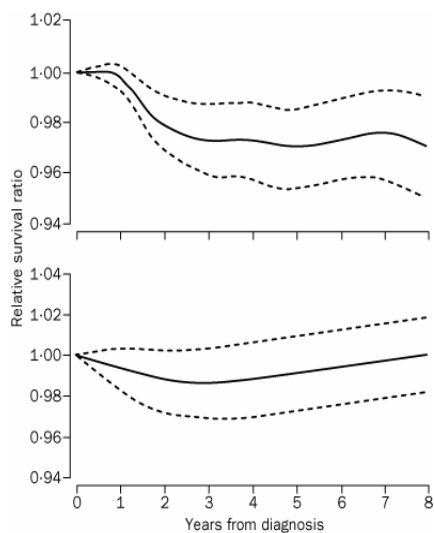
#### Gezondheidsorganisatie (WHO):

- (1) vroegtijdige detectie is moeilijk op basis van de kliniek
- (2) de aandoening is frequent en veroorzaakt significante morbiditeit (?)
- (3) er bestaat een gevoelige en specifieke screeningstest
- (4) er is een efficiënte behandeling beschikbaar
- (5) indien niet herkend, kan de ziekte aanleiding geven tot ernstige complicaties (?)

## Argumenten tegen screening

- evidentie van complicaties afkomstig van patiënten met meestal duidelijke klinische symptomen
- geen data over complicaties subklinische coeliakie
- psychologisch/ethisch probleem: iemand ziek verklaren die zich gezond voelt
- patiënten bij wie diagnose door screening gesteld wordt, zijn minder therapietrouw
- maw: noodzaak en efficiëntie screening niet overtuigend aangetoond
- beste weg op dit ogenblik: case finding (met lage drempel)  
(tot evidentie beschikbaar komt... als ze ooit beschikbaar komt)

**Relative survival ratios and corresponding 95% CI for patients with severe (upper) and mild (lower) coeliac disease (Corrao, Lancet 2001)**



**Compliance with gluten-free diet in adolescents with screening-detected coeliac disease: A 5-year follow-up study (Fabiani, J Pediatrics, 2000)**

	Group A (n = 22) detected by Screening	Group B (n = 22) Clinical symptoms
Transgressions		
Never	5	15
Once a month	7	6
Once a week	4	1
Several times a week	1	0
No GFD (normal diet)	5	0
CD markers		
IgA-AGA-positive	2	0
IgG-AGA-positive	12	5

## Screening for Celiac Disease in Children With Type 1 Diabetes: Two views of the controversy

M Freemark and L Levitsky (Diabetes Care 2003)

Table 1—Summary of published studies of children with type 1 diabetes screened for celiac disease with endomysial or tissue transglutaminase antibodies

Source	Positive screen	Positive biopsy	Symptoms	Diet improved
Denmark (56)	10/104 (9.6%)	9/9	6/9	5/6 (4 refused)
British Columbia (57)	18/232 (7.7%)	14/18	10/18	NI
Wisconsin (58)	17/218 (7.8%)	10/14	3/10	2/3
Germany (59)	13/205 (6.3%)	7/8	3/8	NI
Italy (49)	27/273 (9.9%)	16/20	2/16	2/2
New York (60)	10/211 (4.7%)	3/3	NI	NI
North Carolina/ Maryland (61)	3/81 (3.7%)	1/3	0/3	NI
Total	98/1324 (7.4%)	60/75 (80%)	24/64 (37.5%)	9/11 (81.8%)

NI, no information given.

## Aims of glutenfree diet

- Symptomatic amelioration
- Decrease risk of malignancy
- Decrease risk of metabolic complications (osteoporosis, anemia)
- in children: prevention of growth retardation

## How much gluten is allowed? Different opinions between countries

- Guidelines differ to some extent from country to country
- Most European countries allow specially prepared wheat starch (corresponding “International Gluten Free Standard” of Codex Alimentarius)
- Some countries want “zero tolerance” (No detectable gluten)  
(US, Canadian en Australian coeliac societies)  
(Canadian en Australian authorities and recently US authorities) vs European : “low gluten”.

## Prospective and randomized study: wheat starch-based gluten-free diet vs natural gluten-free diet

Per  aho et al., (Alim Pharmacol Ther 2003;17:587-594)

