Coeliac disease

Coeliac disease in 2010
Markku Mäki, Tampere, Finland

Coeliac disease is an autoimmune-like systemic disorder in genetically susceptible persons perpetuated by the daily-ingested gluten cereals wheat, rye, and barley with manifestations in the intestine and in organs outside the gut. Today it is understood that the nature of celiac disease is much more complex than simply intestinal malabsorption, which, as such, is, in fact, no longer essential for the diagnosis (Walker’s Pediatric Gastrointestinal Disease, chapter 16.1. Celiac disease, 2008, BC Decker Inc, Hamilton).

- Coeliac disease is induced by gluten (1950)
- Gluten is inducing small intestinal mucosal injury (1957)
- The mucosa heals on gluten-free diet (1964)
- Gluten must be avoided life-long (1969)
Autoimmune aspects of coeliac disease

Environmental single trigger and driving force known: Gluten
Specific and narrow MHC class II: DQ2 or DQ8
Single major autoantigen, self identified: TG2

Self perpetuating if the environmental trigger is not removed
Disease-specific autoantibodies against the self

Mäki 1992

Classical presentations of coeliac disease
Coeliac disease family and HLA

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0101/2</td>
<td>0103</td>
<td>0501</td>
<td>0501</td>
</tr>
<tr>
<td>0602</td>
<td>0603</td>
<td>0201</td>
<td>0201</td>
</tr>
<tr>
<td>0402</td>
<td>0101</td>
<td>0101</td>
<td>0101</td>
</tr>
</tbody>
</table>

- **Biopsy proven healthy**
- **Index case (CD)**
- **Silent CD**
- **Bold = alleles encoding HLA DQ2**

Coeliac disease diagnosis
Small bowel mucosal morphology

Mäki M. & Collin P. Lancet 1997;349:1755-59

Walker-Smith J: Diseases of the small intestine in childhood, 1979
**Change in phenotype**

- <1 yrs: Malabsorption, Poor weight gain
- 7 yrs: Diarrhoea
- 14 yrs: Asymptomatic
- 17 yrs
- 33 yrs

- Gluten
- GFD
- Gluten-containing diet

**DH**

Kurppa et al., JPGN 2008

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**Changing pattern and shift of the age at diagnosis of coeliac disease**

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Abdominal symptoms 36%

- Malabsorption, anaemia, weight loss 9%

Extraintestinal symptoms total 30%:
- Short stature 17%
- Skin symptoms 8%
- Arthritis/arthralgia 3%
- Other 2%

By chance, routine biopsy 2%

Screening in at-risk groups total 23%:
- Family members 12%
- Autoimmune disorders 8%
- Other 3%

Presenting symptoms/signs of childhood coeliac disease at the diagnosis in 2008, N=132

Collin et al. Scand J Gastroenterol 1997;32:1129-33

Fig. 1. The 5-year incidence figures for adult coeliac disease (CD) and dermatitis herpetiformis (DH).

Collin et al. Scand J Gastroenterol 1997;32:1129-33
Coeliac disease

Daily ingested wheat-, rye-, and barley-induced manifest mucosal lesion in genetically susceptible individuals (DQ2 +ve or DQ8 +ve)

Clinically silent coeliac disease
manifest mucosal lesion

Gastrointestinal and other symptoms,
"out of sorts"
mild – severe

Risk groups
Type 1 diabetes
Thyroid disease
Sjögren’s syndrome
Down’s syndrome
IgA deficiency

Symptoms and signs of malabsorption

Extraintestinal manifestations
dermatitis herpetiformis, osteopenia and osteoporosis, dental enamel defects,
peripheral and central nervous system involvement, mental disorders, liver
diseases, arthritis, reproductive system involvement, malignancies

Permanent-tooth enamel dysplasia in coeliac disease
Aine et al.
Permanent-tooth enamel dysplasia in coeliac disease
Aine et al.

Symptoms and signs in untreated coeliac disease
Tampere area, 1995-2008

- Abdominal symptoms 40%
- Malabsorption, weight loss, anemia 16%
- Risk group screening altogether 16%
  - First degree relatives 12%
  - Autoimmune diseases 6%
- Extraintestinal symptoms altogether 25%
  - DH 10%
  - Neurological symptoms 5%
  - Arthritis/arthralgia 4%
  - Others 6%
- By chance 3%

n = 450 adults
Finland: 0.6% of the total population diagnosed clinically (biopsy-proven)

Coeliac disease

This is coeliac disease!

This is coeliac disease !!!
Cumulative risk of autoimmune disease according to compliance to a GFD

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Cosnes et al Clin Gastroenterol Hepatol 2008

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**Persistent small bowel mucosal injury on a gluten-free diet (GFD)**

- All coeliacs are routinely biopsied after 12 mo on GFD in Finland
- Not healing – inadequate diet
- Still not healing – refractory sprue, serious condition, severe symptoms and malabsorption, risk for ulcerative jejunoileitis, intestinal lymphoma, these conditions are rare in Finland
- GFD, no symptoms BUT still mucosal damage after 2 years on GFD (Kaukinen et al., 2007)
  - 13780 adult cases detected
  - all had good clinical response, further follow-up 5 years
  - osteoporosis 58%
  - two developed symptomatic refractory sprue
  - one died of lymphoma, one of carsinoid tumor
  - one gastric adenocarcinoma was operated
  - bloating, tiredness, transient diarrhoea
  - 4 asymptomatic, 3 of whom had osteopenia

**Prevalence of coeliac disease in Finland**

- **CHILDREN** 1.5 % (Mäki et al., NEJM 2003)
- **ADULTS** 2.0 % (Lohi et al., Aliment Pharm Ther 2007)
- **ELDERLY** 2.7 % (Vilppula et al., Dig Liv Dis, 2008, Vilppula et al., BMC Gastroenterol 2009)

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'Mini-Finland' 1978-80 'Health 2000'

Clinical prevalence of CD 0.03% 0.52%
Total prevalence of CD 1.1% 2.0%
95% CI 0.8 - 1.3 1.6 - 2.3


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CD

Type 1 DM

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Screening tools for coeliac disease

Serology
Gluten-dependent autoantibodies
• endomysial (EMA) and reticulin (ARA) antibodies (tissue antibodies)
• tissue transglutaminase antibodies (TG2-ab)
• whole blood rapid test (point of care EMA/TG2-ab)
• deaminated gliadin peptide antibodies
Other antibodies
• (gliadin antibodies)

HLA
• DQ2
• DQ8

Diagnosis of coeliac disease

High index of suspicion/Case finding by screening
In primary care

Classical symptoms and signs
Minor symptoms
Extraintestinal manifestations
- EMA
- tTG-ab
- DGP-ab (deamin gliadin peptide)
- whole blood rapid test

Biopsy
Antibody case finding
Risk groups
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Serum IgA-class reticulin antibody test in celiac disease


Sensitivity 97% (28/29)
Specificity 98% (241/245)

<table>
<thead>
<tr>
<th>Initial values</th>
<th>Months on gluten-free diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>IgG IgA</td>
<td></td>
</tr>
<tr>
<td>1:8000</td>
<td></td>
</tr>
<tr>
<td>1:4000</td>
<td></td>
</tr>
<tr>
<td>1:2000</td>
<td></td>
</tr>
<tr>
<td>1:1000</td>
<td></td>
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<tr>
<td>1:500</td>
<td></td>
</tr>
<tr>
<td>1:200</td>
<td></td>
</tr>
<tr>
<td>1:100</td>
<td></td>
</tr>
<tr>
<td>1:50</td>
<td></td>
</tr>
<tr>
<td>neg</td>
<td></td>
</tr>
</tbody>
</table>

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Serum IgA-class tissue transglutaminase antibody titers determined by ELISA

Sulkanen et al., Gastroenterology 1998;115:1322-38

I. Newly diagnosed untreated CD
II. CD patients on GFD
III. CD patients during gluten-challenge
IV. CD patients after gluten withdrawal
V. Disease controls with normal small bowel mucosa
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Wildtype  TG2 knockout  TG2 knockout + human rec TG2

CDIgA binding

Korponay-Szabo et al., Gut 2003

Missing endomysial and reticulin binding of celiac antibodies in transglutaminase 2 knockout tissues.

Schoolchildren

n=3,654

IgA- EMA+

IgA - tTG-

n=1

IgA - EMA+

IgA - tTG+

n=50

IgA - EMA-

IgA-tTG+

n=2

IgA - EMA-, IgG- EMA +

n=3

Symptom detected CD

n=10

IgA- EMA+  IgA- EMA+  IgA- EMA+

IgA- EMA+  IgA- EMA+  IgA- EMA+

IgA- EMA+  IgA- EMA+  IgA- EMA+

n=9

n=2

n=3

Biopsy proven CD

n=9

DQ2+ n=7

DQ8+ n=3

DQ2+ n=22

DQ8+ n=3

DQ2/DQ8+ n=1

DQ2 and DQ8+ n=1

DQ2+ n=7

DQ2/DQ8+ n=1

DQ2 and DQ8+ n=1

DQ2+ n=10

Mäki et al., NEJM 2003

Blood sampling in 1994

Serum auto-antibody testing in 2001

Small-bowel biopsies

HLA

Biopsy proven CD

Celiac trait

1:99

1:67

Not biopsied

n=10

IgA- EMA+  n=10

IgA- tTG+  n=9

Normal on biopsy

n=9

IgA- EMA+  n=7

IgA- tTG+  n=9

Screen detected CD

n=27

IgA- EMA+  IgA- EMA+  IgA- EMA+

IgA- EMA+  IgA- EMA+  IgA- EMA+

IgA- EMA+  IgA- EMA+  IgA- EMA+

n=25

n=2

n=3

Symptom detected CD

n=50

IgA- EMA+  IgA- EMA+  IgA- EMA+

IgA- EMA+  IgA- EMA+  IgA- EMA+

IgA- EMA+  IgA- EMA+  IgA- EMA+

n=1

n=2

n=3

EMA and/or tTG +

n=56

IgA-EMA+  IgA-EMA+  IgA-EMA+

IgA-EMA+  IgA-EMA+  IgA-EMA+

IgA-EMA+  IgA-EMA+  IgA-EMA+

n=1

n=2

n=3

Mäki et al., NEJM 2003
### Population-based Screening of Coeliac Disease

Coeliac disease-related HLA DR-DQ among 3,627 schoolchildren and among 56 individuals positive for serum EMA or TG-2 antibodies.

<table>
<thead>
<tr>
<th>HLA genotype</th>
<th>All N (%)</th>
<th>Ab +ve N (%)</th>
<th>O.R.</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR3-DQ2/X</td>
<td>575 (16)</td>
<td>46 (82)</td>
<td>26.45</td>
<td>8.00</td>
</tr>
<tr>
<td>DR4-DQ8/Y</td>
<td>756 (21)</td>
<td>6 (11)</td>
<td>0.45</td>
<td>0.79</td>
</tr>
<tr>
<td>DR3-DQ2/DR4-DQ8</td>
<td>80 (2)</td>
<td>2 (4)</td>
<td>1.66</td>
<td>2.50</td>
</tr>
<tr>
<td>Other genotypes</td>
<td>2216 (61)</td>
<td>2 (4)*</td>
<td>0.02</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*One individual with confirmed CD carried the DQB1*02 allele (DR7 haplotype). Mäki et al., N Engl J Med 2003

### Performance of commercial TG2 ELISA tests may be variable

1,655 hospital samples in 6 months 2001
176 TG2-antibody + (10.6%)

47 EMA +

57 patients biopsied

Positive predictive value (EMA+ and TG2+): 97%
(TG2+ only): 54%

Lock, Eur J Gastroent 2004

Routine TG2 antibody measurement before endoscopy:

Positive predictive value: 28%

Hopper, BMJ 2007
Elevated serum anti-TG2 antibodies in EMA negative non-coeliac patient groups

- Down syndrome
  
- Autoimmune and tumor patients
- Liver diseases
- Cardiac diseases
- Psoriasis

- Common childhood infections (EBV)

Comparison of 6 coeliac ab tests (n=242)

Concordance between 6 antibody tests 91%
**Finger tip whole blood assay for coeliac disease, a new rapid point of care test, Biocard Celiac-Test**


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**Principle of self TG-based rapid antibody detection**

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**Biocard Celiac Test, AniBiotech, Vantaa, Finland**
RESULTS

Screened population: 2676 (77%)
Participating nurses: 120
Screened children per nurse: 18 (4-95)

Nurse-detected coeliac disease

Biocard testing on site n=2676 (77%)

Biocard + n=28
Small bowel biopsy n=25
Coeliac disease n=25

Biocard - n=2648
Refused biopsy n=3

Prevalence of positivity: 1.1%
Positive predictive value: 100%

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BMJ 2007
Comparison of onsite and laboratory results

<table>
<thead>
<tr>
<th>Rapid test results</th>
<th>Untrained nurses n=120</th>
<th>Experienced evaluators n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>81%</td>
<td>96%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Efficiency</td>
<td>99.5%</td>
<td>98.9%</td>
</tr>
<tr>
<td>(PPV for villous atrophy)</td>
<td>(100%)</td>
<td>(87%)</td>
</tr>
</tbody>
</table>

Complete agreement with laboratory EMA/TG-Ab in 85% of nurses

**Clinical Findings**

**Clinical symptoms and signs**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal bloating, diarrhoea</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>RAP</td>
<td>13 (41%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>Chronic headache</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Slow weight gain</td>
<td>13 (41%)</td>
</tr>
<tr>
<td>Behavioural problems</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Thyroid autoimmunity</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Symptom-free</td>
<td>5 (16%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>

**Response to a gluten-free diet**

- **Hb**
  - Median: At screening 5.1 g/l, GFD for 6 mo 7 g/l
  - p<0.001

- **BMI**
  - Median: At screening 18, GFD for 6 mo 20
  - p<0.001

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BMJ 2007
GLUTEN

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Normal > IELs↑ > Crypt hyperplasia > Villous atrophy

Genetic gluten intolerance/mild enteropathy coeliac disease

Follow-up of patients positive in reticulin and gliadin antibody tests

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Follow-up 1-7 years</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>23/25</td>
<td>17/25</td>
</tr>
<tr>
<td>Slight changes</td>
<td>2/25</td>
<td>1/25</td>
</tr>
<tr>
<td>SVA</td>
<td></td>
<td>7/25</td>
</tr>
<tr>
<td>VH/CrD &gt;3</td>
<td>24/25</td>
<td>16/25</td>
</tr>
<tr>
<td>IELs &gt;30</td>
<td>2/25</td>
<td>8/25</td>
</tr>
<tr>
<td>AGA-A positive</td>
<td>21/25</td>
<td>21/25</td>
</tr>
<tr>
<td>ARA-A positive</td>
<td>6/25</td>
<td>6/25</td>
</tr>
</tbody>
</table>

Prediction of mucosal deterioration

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>ARA-A</td>
<td>83%</td>
</tr>
<tr>
<td>AGA-A</td>
<td>24%</td>
</tr>
<tr>
<td>AGA-G</td>
<td>0%</td>
</tr>
</tbody>
</table>


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**IELs (cells/mm epithelium)**

<table>
<thead>
<tr>
<th></th>
<th>Gluten-containing diet</th>
<th>Gluten-free diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>+50</td>
<td>+100</td>
</tr>
<tr>
<td>VH/CrD</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Abd symptoms</td>
<td>+ + + + + + + + + + + + + + + + + + + + - - - - - - - - - - - -Abd</td>
<td>3.1</td>
</tr>
<tr>
<td>HLA DQ2+</td>
<td></td>
<td></td>
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</table>

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Kaukinen et al., Dig Dis Sci 2001;46:879-87

**Mild enteropathy coeliac disease, randomised controlled study**

Kurppa et al., Gastroenterology, 2009
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In situ TG2-specific IgA-deposits in early developing CD

Korponay-Szabo I et al., Gut 2004; 53:641-8

Before After GFD

TG2+IgA

IgA

Predictors for forthcoming CD

"Mild enteropathy coeliac disease"

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Sens %</th>
<th>Specif %</th>
</tr>
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<tbody>
<tr>
<td>Mucosal IgA-deposits</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Serum autoantibodies</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>Mucosal villous tip IELs</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>Mucosal γδ IELs</td>
<td>76</td>
<td>60</td>
</tr>
<tr>
<td>Mucosal IELs (Marsh 1)</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>HLA DQ2 or DQ8</td>
<td>100</td>
<td>66</td>
</tr>
</tbody>
</table>

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Salimi et al., Aliment Pharmacol Ther, 2006
Deposition of IgA autoantibodies on transglutaminase in different organs of celiac subjects

Korponay-Szabó et al. Gut, 2004

IgA deposition on brain transglutaminase in gluten ataxia  Hadjivassiliou et al., Neurology 2006

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Histological parameters

- Vh/Cr D
- CD3, α/β, g/d IEL densities
- HLA DR expression
- IgA TG2-targeted deposits

Diagnosing Coeliac Disease

1. Symptoms and signs of coeliac disease
2. Case finding by screening using serology
   - high index of suspicion, primary care
3. Population-based screening – still research
4. Subtotal villous atrophy, flat lesion – criterium for clinics. BUT
5. Normal small-bowel mucosal morphology does not exclude coeliac disease. Use of IgA deposits in clinics.
6. New diagnostic criteria needed.
Future diagnostic criteria
Genetic gluten intolerance
(Coeliac trait)

Autoab +ve, correct genetics, no biopsy
Correct diagnosis in 90-95% of all coeliacs

Autoab -ve, clinics +ve or -ve
5-10% of all coeliacs
Biopsies needed + sophisticated lab methods

The sooner we are ready to meet the future, the longer we are able to stay there (Ralf Gotheni 1998)