Type 1 DM & Celiac Disease

Tandy Aye¹, MD : Pediatric Endocrinology
Nasim Khavari¹ MD, MPH: Pediatric Gastroenterology
Patrika Tsai² MD, MPH: Pediatric Gastroenterology

¹Lucile Packard Children’s Hospital Stanford & ²University of California, San Francisco
Type 1 DM & Celiac Disease

Tandy Aye, MD
Pediatric Endocrinology/Diabetes
Lucile Packard Children’s Hospital Stanford
Celiac Disease: It’s more than a trend!
What is Celiac Disease (CD)?

- Autoimmune enteropathy
- Gluten is a protein found in wheat, rye and barley.
- When people with CD eat or use gluten containing products, the immune system responds by destroying or damaging the villi.
How common is CD?

- 0.3 to 1% in general populations in North America and Europe OR CD found in approximately 1 in 100 or 1 in 250 people (Rewers et al 2004)
- Possible that for every 1 diagnosed with CD another 3 to 7 undiagnosed cases
- 95 to 97% carry the HLA-DQA1*0501/B1*0201 or HLA-DQA1*0301/B1*0302 allele
How common is CD in T1D?

- 1 to 16% in those with T1D
- 1 to 4% among first degree relatives with T1D
- Over 90% T1D is diagnosed first and then CD. Maybe related to the degree of symptoms.

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relatives of celiac disease patients</td>
<td>3.5%–20.0%</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus patients</td>
<td>1.0%–16.4%</td>
</tr>
<tr>
<td>First-degree relatives of type 1 diabetes patients</td>
<td>1.6%–3.5%</td>
</tr>
<tr>
<td>Autoimmune thyroid disease patients</td>
<td>4%</td>
</tr>
<tr>
<td>IgA-deficient patients</td>
<td>2%</td>
</tr>
<tr>
<td>Trisomy 21 syndrome patients</td>
<td>7%–19%</td>
</tr>
<tr>
<td>Turner’s syndrome patients</td>
<td>2%–8%</td>
</tr>
<tr>
<td>Sjögren’s syndrome patients</td>
<td>3%–15%</td>
</tr>
</tbody>
</table>

Rewers et al. *Endocrinol Metab Clin N Am* 2004
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Country</th>
<th>No.</th>
<th>Screen</th>
<th>+ve screen</th>
<th>No. biopsied</th>
<th>CD by biopsy</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1994</td>
<td>Finland</td>
<td>215</td>
<td>ARA</td>
<td>9</td>
<td>9</td>
<td>4 (-1)</td>
<td>1.43</td>
</tr>
<tr>
<td>9</td>
<td>1996</td>
<td>Finland</td>
<td>201</td>
<td>AGA</td>
<td>–</td>
<td>–</td>
<td>7</td>
<td>1.29</td>
</tr>
<tr>
<td>10</td>
<td>1997</td>
<td>Italy</td>
<td>146</td>
<td>AGA</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>1.09</td>
</tr>
<tr>
<td>11</td>
<td>1998</td>
<td>Germany</td>
<td>1032</td>
<td>AGA</td>
<td>17</td>
<td>0</td>
<td>2 (+8)</td>
<td>1.103</td>
</tr>
<tr>
<td>12</td>
<td>1991</td>
<td>Italy</td>
<td>998</td>
<td>AGA</td>
<td>30</td>
<td>22</td>
<td>16</td>
<td>1.31</td>
</tr>
<tr>
<td>13</td>
<td>1992</td>
<td>Australia</td>
<td>180</td>
<td>AGA</td>
<td>10</td>
<td>18</td>
<td>4</td>
<td>1.45</td>
</tr>
<tr>
<td>14</td>
<td>1993</td>
<td>Sweden</td>
<td>486</td>
<td>AGA</td>
<td>28</td>
<td>26</td>
<td>15 (+6)</td>
<td>1.21</td>
</tr>
<tr>
<td>15</td>
<td>1992</td>
<td>USA</td>
<td>211</td>
<td>AEA</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>1.70</td>
</tr>
<tr>
<td>16</td>
<td>1994</td>
<td>Australia</td>
<td>273</td>
<td>AEA</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>1.55</td>
</tr>
<tr>
<td>17</td>
<td>1996</td>
<td>Finland</td>
<td>776</td>
<td>AGA</td>
<td>36</td>
<td>19</td>
<td>19</td>
<td>1.41</td>
</tr>
<tr>
<td>18</td>
<td>1996</td>
<td>Italy</td>
<td>133</td>
<td>AGA</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>1.27</td>
</tr>
<tr>
<td>19</td>
<td>1996</td>
<td>Italy</td>
<td>172</td>
<td>AGA</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>1.29</td>
</tr>
<tr>
<td>20</td>
<td>1996</td>
<td>Algeria</td>
<td>114</td>
<td>AGA</td>
<td>13</td>
<td>13</td>
<td>16 (+12)</td>
<td>1.58</td>
</tr>
<tr>
<td>21</td>
<td>1996</td>
<td>Spain</td>
<td>141</td>
<td>AGA</td>
<td>12</td>
<td>12</td>
<td>4 (+2)</td>
<td>1.24</td>
</tr>
<tr>
<td>22</td>
<td>1997</td>
<td>Italy</td>
<td>200</td>
<td>AGA</td>
<td>14</td>
<td>11</td>
<td>8</td>
<td>1.25</td>
</tr>
<tr>
<td>23</td>
<td>1998</td>
<td>Canada</td>
<td>236</td>
<td>AEA</td>
<td>19</td>
<td>17</td>
<td>12</td>
<td>1.20</td>
</tr>
<tr>
<td>24</td>
<td>1998</td>
<td>UK</td>
<td>167</td>
<td>AEA</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>1.21</td>
</tr>
<tr>
<td>25</td>
<td>1998</td>
<td>Spain</td>
<td>93</td>
<td>AEA</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>1.16</td>
</tr>
<tr>
<td>26</td>
<td>1998</td>
<td>Spain</td>
<td>177</td>
<td>AEA</td>
<td>–</td>
<td>–</td>
<td>3 (+4)</td>
<td>1.25</td>
</tr>
<tr>
<td>27</td>
<td>1999</td>
<td>Sweden</td>
<td>115</td>
<td>AEA</td>
<td>9</td>
<td>6</td>
<td>5 (+2)</td>
<td>1.16</td>
</tr>
<tr>
<td>28</td>
<td>2000</td>
<td>Austria</td>
<td>403</td>
<td>AEA</td>
<td>14</td>
<td>13</td>
<td>6</td>
<td>1.67</td>
</tr>
<tr>
<td>29</td>
<td>2000</td>
<td>Germany</td>
<td>520</td>
<td>ARA</td>
<td>23</td>
<td>13</td>
<td>9</td>
<td>1.58</td>
</tr>
<tr>
<td>30</td>
<td>2001</td>
<td>Canada</td>
<td>233</td>
<td>AEA</td>
<td>19</td>
<td>18</td>
<td>14 (+4)</td>
<td>1.13</td>
</tr>
<tr>
<td>31</td>
<td>2001</td>
<td>USA</td>
<td>218</td>
<td>ARA</td>
<td>17</td>
<td>14</td>
<td>10</td>
<td>1.22</td>
</tr>
<tr>
<td>32</td>
<td>2001</td>
<td>Denmark</td>
<td>106</td>
<td>ARA</td>
<td>10</td>
<td>9</td>
<td>9 (+2)</td>
<td>1.10</td>
</tr>
<tr>
<td>33</td>
<td>2002</td>
<td>Italy</td>
<td>274</td>
<td>ARA</td>
<td>27</td>
<td>20</td>
<td>16 (+1)</td>
<td>1.16</td>
</tr>
</tbody>
</table>

*Three patients with negative serology biopsied on clinical grounds and all had coeliac disease.
Numbers in brackets indicate patients with coeliac disease diagnosed before screening.
What are the symptoms of CD?

- Diarrhea
- Weight Loss or Poor Weight Gain
- Growth Failure
- Abdominal Pain
- Chronic Fatigue
- Flatulence
- Malabsorption
- Malnutrition
- Erratic BG
- Unexplained hypoglycemia
When should you be screened?

- Incidence of T1D and CD are both increasing
- 4.5% of those with recent onset of T1D also have CD (Holmes et al 2002)
- The coexistence is even more common in those with longer standing T1D
- T1D and CD share susceptibility alleles in the same HLA region
Guidelines for screening and diagnosis of CD in children with T1D varies

- Similar to our practice
- We screen at diagnosis
- We repeat screening every 2-3 years if asymptomatic
- We repeat screening sooner if with symptoms

Fig. 6. Barbara Davis Center for Childhood Diabetes guidelines for screening and diagnosis of CD in patients with T1D.
Other suggested guidelines

- Screened at diagnosis and every 6 months x 3 years. 9/776 found at end of 2 years.
- Annually
- Every other year (1, 3, 5 years)
- Every year x 3, at 5 years then every 5 years.

Holmes et al *Arch Dis Child* 2002
A Finnish Study screens all susceptible for T1D & CD from birth until 11 years.

- Finnish children in the Type 1 Diabetes Prediction and Prevention (DIPP) Study who carried the genetic T1D and CD susceptibility were followed from birth until 11 years of age.
- Blood examined q 3 months from birth to age 2 then q 6 month to 12 months until 11 years for T1D antibodies. If T1D antibodies became positive, observed q 3 months.
- Children with HLA for both T1D and CD were screened with TGA
A Finnish Study screens all susceptible for T1D & CD from birth until 11 years.

- If positive TGA then screened for other CD antibodies. If another CD antibody positive, under went biopsy.
- Positive biopsy, then gluten free diet.
- 2052 children were observed.
- Children with HLA conferred susceptibility to T1D and CD develop CD antibodies (4.3 years) and T1D (4.5 years) within the same median age.
Genetic T1D risk screened by Dec 31, 2005

- Genotypes associated with increased T1D risk
- Continued in the DIPP study by the end of March 2007
- CD-associated and T1D-associated antibodies measured

Diagram:
- CD-Abs: 69
  - CD: 32
  - CD & ICA: 8
  - CD & T1D-Abs: 1
- CD-Abs & ICA: 19
  - ICA: 323
  - T1D-Abs: 146
  - CD-Abs & T1D-Abs: 10
    - CD & T1D: 3
    - CD-Abs & T1D: 2
    - T1D: 44
- T1D*: 2

Simell et al Diabetes Care 2010
A Swedish Study screening for CD and T1D

• To determine the prevalence and clinical and temporal relationship of CD in a population of Swedish children with T1D between 1995 to 2005, during an epidemic of CD in Sweden.
  • Prevalence of 9.1% of CD in children with T1D
  • 62% of the children were diagnosed with CD after T1D
  • Onset of CD within 24 months of diagnosed with CD
  • Presence of symptoms did not predict positivity of intestinal biopsy

Bybrant et al Scandinavian J Gastro Jan 2014
A Saudi Screen for CD in those with T1D

106 children with type 1 diabetes

Anti-TTG, EMA (IgA) and total IgA level

Group 1
-ve anti-TTG and +ve EMA
n=11

1 patient refused endoscopy

Biopsy proven CD n=9
Negative biopsy n=1

Group 2
+ve anti-TTG and +ve EMA
n=1

Biopsy proven CD n=1

Group 3
anti-TTG >50 U/ml and -ve EMA
n=4

Biopsy proven CD n=2

Group 4
Anti-TTG 20-50 U/ml and -ve EMA
n=10

Repeat of anti-TTG after 6 months
-ve anti-TTG n=5

Persistent anti-TTG 20-50 U/ml n=5

Biopsy proven CD n=0

CD= celiac disease; EMA= endomysial antibody; n= number; Anti-TTG= anti-tissue transglutaminase IgA; -ve= negative; +ve= positive

Figure 1 Flowchart for results of the serologic tests and biopsy proven celiac disease.

Who should be screened for CD?  
2014 ADA Clinical Guidelines

- Consider screening for CD in children with T1D soon after diagnosis
- Suggested screening: measuring IgA anti-tissue transglutaminase or antiendomysial antibodies in children with normal total serum IgA levels
- Use IgG anti-tissue transglutaminase or antiendomysial antibodies in children less than 2 years or with low IgG levels.
- Biopsy only if screening is positive and to consider forgoing the biopsy if positive screen and with symptoms.
Does potential CD in T1D lead to increased complications?

• Recruited 4 groups:
  • 22 T1D and + CD antibody
  • 14 T1D and new CD by biopsy
  • 24 T1D alone
  • 16 CD alone

• No significant differences in HbA1c, HDL cholesterol, creatinine, quality of life or prevalence of neuropathy among the groups

• Previously reports that having CD and T1D leads to increased complication, perhaps need to have the enteropathy. Is it old data? Further longitudinal studies are necessary.

Leeds et al NMCD 2014 in press
Celiac Disease

Nasim Khavari, MD MPH
Pediatric Gastroenterology and Nutrition
Lucile Packard Children’s Hospital Stanford
What is Celiac Disease (CD)?

- Celiac Disease is an immune-mediated disorder that occurs with increased frequency in those with T1D and other autoimmune conditions.
Prevalence of Celiac Disease

Figure 1 | Worldwide prevalence of Coeliac disease, expressed as percentage prevalence of elevated tissue transglutaminase antibody levels in unselected adult and paediatric populations.
Incidence of Celiac Disease

**Figure 1.** Incidence of celiac disease in US military stratified by age group, 1999–2008.

Am J Gastroenterology 2012
Pathogenesis of Celiac Disease

Multifactorial chronic inflammatory enteropathy

• Genetics
• Gluten Exposure
• Innate and Adaptive Immune Activity
• Environmental influences
Genetic Predisposition

- **Family Studies**
  - 1st degree relatives: 10-15% concordance
  - 75-85% monozygotic vs 20% in dizygotic twins
  - HLA identical siblings: 30%
  - HLA DQ2 /HLA DQ8 explain 40% heritability
  - Remaining 60% due to non-HLA genes which provide smaller risk
- Large Genome Wide Association study demonstrated shared chromosome regions with Type 1DM and other autoimmune conditions
Exposure to Gluten
### Exposure to Gluten

<table>
<thead>
<tr>
<th>Wheat</th>
<th>Rye</th>
<th>Barley</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulgar</td>
<td>Rye Flour</td>
<td>Ale</td>
</tr>
<tr>
<td>Couscous</td>
<td>Rye Flour</td>
<td>Barley Flakes, Flour, Pearl</td>
</tr>
<tr>
<td>Graham Flour</td>
<td>Rye Flour</td>
<td>Brewers Yeast*</td>
</tr>
<tr>
<td>Wheat Bran, Germ, Flour, Starch</td>
<td>Rye Flour</td>
<td>Malt</td>
</tr>
<tr>
<td>Matzo</td>
<td>Rye Flour</td>
<td>Lager</td>
</tr>
</tbody>
</table>
Gluten

Other environmental factors

Gliadin

Increased intestinal permeability

Villous atrophy
Crypt hyperplasia
Intraepithelial lymphocytosis

Zonulin

Overexpression of interleukin-15

Tissue transglutaminase

Intraepithelial lymphocytes

Deamidated gliadin

Lamina propria

Antigen-presenting cell

TCR

CD4 T cell

HLA-DQ2

B cell

Genetic factors

Antibodies (antigliadin, antiendomysial, and tissue transglutaminase)
Clinical Manifestations

Figure 1: The coeliac disease iceberg and spectrum of gluten sensitivity

Maki et al, Lancet 1997
### What are the symptoms of CD?

- Asymptomatic
- Diarrhea
- Weight Loss or Poor Weight Gain
- Growth Failure
- Abdominal Pain
- Rash: Dermatitis Herpetiformis
- Flatulence
- Malabsorption
- Malnutrition
- Chronic Fatigue
- Erratic BG
- Unexplained hypoglycemia
Diagnostic Testing

- Blood Testing (Serology)
  - Tissue transglutaminase antibody (Ttg IgA)
  - Endomysial Antibody (Ema)
  - Anti gliadin antibodies (<2 years of age)
  - Deamidated gliadin peptide (AGAII or DGP)
  - Genetic: HLA-DQ2/DQ8 to exclude CD
- Endoscopy
Endoscopy
Visible Vessels

Decreased Folds

Scalloping

Mosaic Pattern and Mucosal Tears

Normal
Villi Present
Figure 1. Spectrum of malabsorption and symptoms in celiac disease. The magnitude of malabsorption and symptoms in patients with celiac disease (bottom) often correlates with the extent of small intestinal mucosal injury as depicted schematically from I to IIIc according to the Marsh histologic damage score (also see Table 1).
Endoscopy Tissue

Marsh 1
Minimal Inflammation

Marsh 2

Marsh 3
Extensive Inflammation
Diagnosis: Symptomatic Child

FIGURE 1. Symptomatic patient. CD = coeliac disease; EMA = endomysial antibodies; F/u = follow-up; GFD = gluten-free diet; GI = gastroenterologist; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; OEGD = oesophagogastroduodenoscopy; TG2 = transglutaminase type 2.
Diagnosis: Asymptomatic Child

![Flowchart for the diagnosis of CD in asymptomatic children. The flowchart outlines the diagnostic process, starting with an HLA test, followed by serology (TGA and IGA), duodenal biopsy, and finally serological testing (EMA). The decision tree leads to different outcomes, such as CD+, GFD, or Not CD.]

ESPGHAN GUIDELINES 2010
Non Celiac Gluten Sensitivity

**Diagnostic Criteria:** Resolution of symptoms after gluten exclusion & exclusion of Celiac and Allergy. Must be differentiated from:

- Allergy to Wheat (IgE mediated) & Celiac Disease
- Symptoms: Abdominal pain, excema or rash, headache, fatigue, diarrhea, depression, anemia, joint pains
Management of Celiac Disease

Patrika Tsai, MD, MPH
Pediatric Gastroenterology and Nutrition
University of California, San Francisco
Treatment

- No cure at present
- Gluten free diet
  - Avoid all wheat, rye, and barley (bread, cereal, cake, pizza, beer)
- Lifelong
- Monitoring 6 months after diagnosis, then annually
- Regular follow-up with gastroenterologist
Lactose intolerance

- Intestinal mucosa injury from celiac disease often causes secondary lactase deficiency
- Improves on gluten free diet
- May require temporarily lactose free or reduced diet until celiac disease is under control
- May require calcium and vitamin D supplements
Hidden gluten sources

- Medications and supplements
- Lipstick and lipbalm
- Malt, semolina, couscous, farina, orzo, matzo flour, panko, udon
- Condiments, soy sauce, marinades
- Candy
- Lunch meat
- Imitation seafood, meat, and bacon
- Communion wafers
Oats

• Controversial
• Many with celiac disease can tolerate oats
• Oats in the U.S. are contaminated with gluten since they are processed and stored in the same facilities
Acceptable foods

- Rice
- Potatoes
- Corn
- Soy
- Tapioca
- Sago
- Quinoa
- Flax
Celiac disease and diabetes

- Gluten free grains
  - Higher carbohydrate
  - Higher fat
  - Lower fiber
- Glycemic response may be higher and faster

### CHO content of flour

<table>
<thead>
<tr>
<th>Flour</th>
<th>CHO grams per/cup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>95</td>
</tr>
<tr>
<td>Soy</td>
<td>33</td>
</tr>
<tr>
<td>Amaranth</td>
<td>130</td>
</tr>
<tr>
<td>Rice, white</td>
<td>126</td>
</tr>
<tr>
<td>Tapioca</td>
<td>128</td>
</tr>
<tr>
<td>Potato</td>
<td>134</td>
</tr>
<tr>
<td>Garbanzo</td>
<td>200</td>
</tr>
<tr>
<td>Corn starch</td>
<td>116</td>
</tr>
<tr>
<td>Quinoa</td>
<td>116</td>
</tr>
<tr>
<td>Sorghum</td>
<td>144</td>
</tr>
</tbody>
</table>

Borushek A. *Calorie, Fat and Carbohydrate Counter*. Costa Mesa, CA: Family Health Publications; 2009: 100
Lifestyle changes

- Separate toasters, peanut butter, jelly, butter
- Clean utensils, counters, cutting boards, pans
- Planning
- Financial implications
How strict do I need to be?
Inadvertent cross contamination

- Chefs and servers not knowing what contains gluten or cross contamination risks
- Gluten free pizza dough baked in same oven as regular pizza
- Gluten free baked goods placed next to regular baked goods
- Pots and pans or utensils not well cleaned after cooking foods with gluten
- Buffet tables
Crosscontamination

"Maybe she's gluten intolerant."
Nutrition labels

• Food allergen labeling and consumer act (Jan 1, 2006)
• Top 8 food allergens
• Wheat must be listed
• Law does not apply to barley, rye, or oats
• Wheat free is not gluten free
• Product recipes may change without notice
FDA “gluten-free” label

• Inherently gluten-free and unavoidable presence of gluten <20ppm
• Contains gluten-containing grain or derivative and processed to gluten<20ppm
• Gluten-free=no gluten=free of gluten=without gluten
• “No gluten ingredients” or “not made with gluten-containing ingredients” still may have cross contamination
• Not all products have to be labeled for gluten
FDA label

- Covered
  - FDA regulated foods
  - Dietary supplements (vitamins, minerals, herbs, amino acids)
  - Imported food subject to FDA
- Not covered
  - USDA foods like meat, poultry, and certain egg products
  - Medications
  - Distilled spirits or wines with 7% or more alcohol by volume and malted beverages with malted barley and hops
2013 FDA ruling

- No specific symbol
- Testing is not required but manufacturers are responsible for compliance
- Compliance by Aug 2014
Why 20 ppm?

- Globally accepted
- 10mg/day safe for most celiacs
  - 1/8 tspn flour
  - 18 slices of bread with each slice containing 20ppm of gluten or more than 1 pound!
- Testing threshold
What about medications?

- HR 2003: Gluten in Medicine Disclosure Act of 2013
- Sponsored by Rep Tim Ryan (D-OH) and Nita Lowey (D-NY)
- Would require drug labels to have statement identifying source of ingredients constituting or derived from a grain or starch
Compliance

- Depression, frustration, and anger
  - Support group
- Social settings
  - School, parties, restaurants
- Time constraints
- Education
Young children

- Disability
- Food allergy tables
- No food swaps
- Emergency treats at school
- Baking in school curriculum
- Gluten free art supplies
  - Pasta art, play dough, paper mache
College students

- Disability
- Housing with kitchen or allowance for fridge and small appliances
- Meal plan exemptions
- Gluten-free fridge or storage in main dining hall
- Care packages and online stores
- Gluten free beer
Resources

- Websites
- Apps
- Online stores
- Cookbooks and magazines
- Dining cards
- Restaurants and grocery guides
- Books and ebooks
- Diabetes camp
- Gluten-free Expo