Endocrinology matters in celiac disease

Deborah Mitchell, MD

April 1, 2017
NO DISCLOSURES
Objectives

Endocrine disorders associated with celiac disease
• To recognize signs and symptoms of autoimmune endocrine disorders for which patients with celiac disease are at risk

Endocrine disorders as a result of celiac disease
• To understand the effects of celiac disease on growth in children
• To understand the effects of celiac disease on bone accrual, microarchitecture, and fracture risk
AUTOIMMUNE ENDOCRINE DISEASES
Predisposition to autoimmunity in patients with celiac disease

- Human leukocyte antigens (HLA) proteins help display antigens to immune system cells.
- HLA subtypes DQ2 and DQ8 are strongly associated with celiac disease - and type 1 diabetes, thyroid disease, and several other autoimmune disorders.

T cell  Antigen-presenting cell
TYPE 1 DIABETES MELLITUS
IN CELIAC DISEASE
Insulin production and type 1 diabetes

Pancreatic islet histology

**Normal**
- Ambient glucose $\rightarrow$ insulin secretion from $\beta$-cells

**Diabetes**
- Lymphocytic infiltration $\rightarrow$ destruction of $\beta$-cells
- Failure of insulin production
Consequences of insufficient insulin

- Glucose not taken up by muscles $\rightarrow$ high blood glucose
  - Short-term: increased urination, increased thirst
  - Long-term: microvascular damage to eyes, kidneys, nerves

- Glucose cannot be metabolized for energy – “starvation”
  - Accelerated breakdown of muscle and fat
  - Accumulation of acidic by-products of fat breakdown
Insulin: an “unspeakably wonderful” discovery

J.L., age 3 years
December 15, 1922
Weight: 15 lbs

J.L., 2 months later
Weight: 29 lbs

Eli Lilly and Company Archives
How common is T1DM among patients with celiac disease?

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Patients</th>
<th>T1DM in subjects with celiac disease</th>
<th>T1DM in control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyvokas et al., 2016</td>
<td>Finland</td>
<td>1358 adults</td>
<td>3.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ludvigsson et al., 2006</td>
<td>Sweden</td>
<td>9243 children</td>
<td>1.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Canova et al., 2016</td>
<td>Italy</td>
<td>1215 children</td>
<td>3.6%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Kylokas et al., BMC Gastro, 2016
Ludvigsson et al., Diab Care, 2006
Canova et al., J Peds, 2016*
Presentation of type 1 diabetes

Classic presentation:
- Increased thirst and urination (night time urination, bedwetting)
- Weight loss

Diabetic ketoacidosis: a life-threatening presentation
- 0.1-0.3% mortality
- Acidemia with organ dysfunction, cerebral edema
- 30% of patients present in DKA – stable prevalence over time
Should we measure diabetes antibodies?

Multi-national prospective study of genetically at-risk youth

- Presence and number of antibodies associates with diabetes risk
- **But:**
  - Specificity is not 100%
  - Timing of onset is unpredictable

Screening outside of a clinical research study is not recommended

Ziegler et al., JAMA 2013
Recommendations

- Patients with celiac disease and their families should be counseled about increased risk of diabetes
- Patients and families should be educated about signs and symptoms of diabetes
- **Research questions:**
  1. What is best method and frequency of education?
  2. How effective is anticipatory guidance in preventing DKA?
  3. Can we develop treatments to *prevent* diabetes in patients with islet cell antibodies?
AUTOIMMUNE THYROID DISEASE IN CELIAC DISEASE
Autoimmune thyroid disease

- Lymphocytic infiltration of thyroid gland $\rightarrow$ goiter
- **Autoimmune hypothyroidism** ("Hashimoto’s disease")
  - Injury to gland leads to impaired production of thyroid hormone
- **Autoimmune hyperthyroidism** ("Graves’ disease")
  - Antibodies against thyrotropin receptor stimulate thyroid hormone production
Signs & symptoms of hypothyroidism

Symptoms:
• Increased rates of fatigue, cold intolerance, constipation, dry skin
• Altered school performance (better and/or worse!)
• Irregular menses

Exam findings:
• Decreased growth velocity
• Puffy face, sallow complexion, delayed reflexes
• Hypothyroidism does not cause weight gain (severe hypothyroidism can lead to myxedema/fluid gain)
Signs & symptoms of hyperthyroidism

**Symptoms:**
- Poor sleep, anxiety, difficulty concentrating
- Palpitations
- Tremor
- Irregular menses

**Exam findings:**
- Lid lag, proptosis ("thyroid stare")
- Rapid heart rate, high blood pressure
- Weight loss
Prevalence of thyroid dysfunction among patients with celiac disease

**Hypothyroidism:**
- 6-12% in celiac patients vs. 0.5-2% in population

**Hyperthyroidism:**
- Much rarer, few robust population estimates
- Registry of >14,000 Swedish children with celiac disease;
  - Incidence of hyperthyroidism 5-fold higher than general population

*Elfstrom et al., JCEM 2008*
Diagnosis of thyroid disease

• Thyroid-stimulating hormone (TSH) produced by pituitary which senses amount of ambient thyroid hormone: “thermostat”
• TSH increases if thyroid hormone too low
• TSH decreases if thyroid hormone too high

Serum TSH concentration is best measure to diagnose and monitor treatment of thyroid disease
Treatment of thyroid disease

Hypothyroidism
• Hormone replacement

Hyperthyroidism
• Medical management (anti-thyroid medications)
• Surgical removal of thyroid gland
• Radioactive iodine ablation of thyroid gland
Recommendations

• Patients with celiac disease should have screening TSH measured soon after diagnosis
• Review of signs and symptoms suggestive of thyroid disease should be undertaken at follow-up
• Repeat screening of TSH should be obtained at periodic intervals
GROWTH IN CHILDREN WITH CELIAC DISEASE
How is growth regulated?

• Linear growth is due to proliferation and hypertrophy of chondrocytes (cartilage-forming cells) in the growth plate

• Requires growth hormone, thyroid hormone, sex hormones (estrogen and testosterone)

• Proinflammatory cytokines inhibit chondrocyte proliferation
Case study – 12 year old girl with poor growth

- No “red flag” symptoms
- General exam unremarkable
- Labs: TTG-IgA 17 U/mL (normal <3)
- Endoscopy:
  - Decreased folds and flattening in 2nd part of duodenum
  - Pathology: Moderate villous blunting, intraepithelial lymphocytes - Marsh 3b celiac disease
Growth failure in children with celiac disease

Systematic review

- Of asymptomatic children evaluated by an endocrinologist for short stature:
  - 2-8% had celiac disease
- Of children in whom a primary endocrine disorder (e.g. hypothyroidism) had been excluded:
  - 19-59% had celiac disease
- Consensus guidelines in pediatric endocrinology recommend testing for celiac disease in the setting of low growth velocity

Van Rijn et al., Arch Dis Child, 2004
Growth failure in children with celiac disease

Study of 177 children in Finland with celiac disease:

Compared 5 growth parameters to >50,000 unaffected children:

1. Height
2. BMI
3. Difference from parental height
4. Change in height percentile
5. Change in BMI percentile

Average height lower than reference population by 1-2 years prior to diagnosis

Saari et al., JAMA Peds, 2015
Why is growth affected in celiac disease?

- General malnutrition – decreased caloric availability, resistance to growth hormone
- Selective malnutrition – micronutrient deficiency (e.g. zinc)
- Chronic inflammation – cytokines impair cells of growth plate
- Delayed puberty
Growth recovery with gluten-free diet

• Most children display robust “catch-up growth” after institution of gluten-free diet
• However, late diagnosis may lead to permanent height deficit
  • N=585 adults with CD at Columbia, diagnosed after age 18
    • Men were 8 cm (3.1 inches) shorter than general population
    • Women were of equivalent height
  • N=290 adults with CD in Israel
    • No difference in height from general population
    • In men, final adult height is inversely correlated to age at diagnosis

Weiss et al., Am J Gastro, 2008
Sonti et al., Eur J Gastro Hepatol, 2013
Recommendations

• Growth optimized by:
  • Younger age at diagnosis
  • Degree of adherence to gluten-free diet
  • Research question: Do subtle growth deficiencies persist?
• Importance of advocacy – training physicians and other medical providers to identify and evaluate children with growth failure
BONE HEALTH IN CELIAC DISEASE
Historical/global perspective

- Severe untreated celiac disease may present with:
  - Osteomalacia
  - Rickets
- Secondary to profound calcium malabsorption
- In underdeveloped nations, this remains common

13 year old Yemeni girl with growth failure, bowed legs, inability to walk. Diagnosed with celiac disease and commenced walking 4 months later

*Al-Sharafi et al., BMC Research Notes, 2014*
Celiac disease → high risk of osteoporosis

- **Bone strength** defined by mass, microarchitecture, and material properties

- **Osteoporosis**: low mass and altered microarchitecture → risk of fragility fracture

*Dempster et al., JBMR, 1986*
Are fractures increased in celiac disease?

Conflicting data:

1. Danish study (n=1,021):
   - No increase in fracture risk

2. British study (n=4,732):
   - 30% increase risk for any fracture
   - 90% increase risk for hip fracture

3. Swedish study (n=13,724):
   - 40% increase risk for any fracture
   - 110% increase risk for hip fracture

Vestergaard et al., Am J Epi, 2002
West et al., Gastroenterology, 2003
Ludvigsson et al., Alim Pharm Ther, 2007
Celiac disease

→ 30% increase in the risk of any fracture

→ 69% increase in the risk of hip fracture

Heikkila et al., JCEM 205
Clinical consequences of fracture in older adults

**Hip fracture**
- 8-36% mortality over the following year
- <50% return to baseline level of independence

**Vertebral fracture**
- Chronic pain
- Altered mobility, restrictive lung disease

**Wrist fracture**
- ~15% with significant functional decline
Natural history of bone accrual

Bone mineral content

~95% adult bone mass attained by age 18

40-50% total body mineral accrued

Pubertal years

Age

Bailey et al., JBMR 1999
Baxter-Jones et al., JBMR, 2011
Natural history of bone acquisition

Peake bone mass

Bone mineral content

Age

Pubertal years

Berger et al., JBMR 2010
Natural history of bone acquisition

- **Bone mineral content**
- **Peak bone mass**
- **Age**
- **Pubertal years**
- **Fracture risk**
Natural history of bone acquisition

- Impaired adolescent bone accrual
  - Lower peak bone mass
  - Increased risk of osteoporosis & fracture
Is bone mineral density affected by celiac disease?

- Jatla et al. studied 44 children (mean age 10) at time of diagnosis by DXA scanning
  - Spine bone mineral content low (Z-score -0.6 vs. 0.0),
  - Whole body bone mineral content low (Z-score -0.9 vs. 0.0)
- Lower BMI and worse histological grade associated with lower bone mineral content
- Numerous other studies confirm these findings
- Several studies document lower bone density in patients diagnosed at an older age

Jatla et al., JPGN 2009
Celiac disease alters bone microarchitecture

Study of 31 young women with newly-diagnosed celiac disease

→ High-resolution peripheral quantitative CT scanning

Zanchetta et al., Bone 2015

- 3% lower cortical density
- 23% lower trabecular density
  - 18% lower trabecular number
  - 6% lower trabecular thickness
Why is bone health altered in celiac disease?

• Altered intestinal absorption:
  • Poor calcium and vitamin D status $\rightarrow$ impaired bone mineralization

• Chronic inflammation:
  • Pro-inflammatory cytokines (IL-1, IL-6, TNF-\(\alpha\)) $\rightarrow$ promote bone resorption
Effect of gluten-free diet on bone health: Data in children

• Several studies have evaluated BMD in children after initiation of gluten-free diet
• These data suggest that celiac treatment during **key period of bone growth** (peri-pubertal years) can prevent/minimize effects on bone health
• **More research** is required with larger sample size, more detailed imaging techniques (e.g. HR-pQCT) to assess for more subtle effects
Effect of gluten-free diet on bone health: Recent data in adults

• Argentinian study: 26 women re-evaluated 1 year after diagnosis of celiac disease and treatment with gluten-free diet
  → 16 strictly adherent, 7 partially adherent, 3 no data
• Overall:
  • **3% increase** in spine BMD, **4% increase** at hip
  • **8-9% increase** in trabecular BMD at the radius and tibia
  • Modest improvement in cortical density at tibia only
  • Degree of improvement correlated with ↓ in TTG-IgA
  • However, bone parameters **still** lower than control subjects

Recommendations for bone health in with celiac disease:

- Vigilant treatment of celiac itself
- Nutritional counseling
  - Calcium intake
    - 1000 mg/day (age 4-8, adults)
    - 1300 mg/day (age 9-18 – to support growth spurt)
  - Vitamin D assessment and supplementation if low
    - Maintain serum 25OHD ≥ 30 ng/mL
- Promotion of physical activity:
  - Mechanical loading of bone promotes bone formation
- DXA scanning: Post-menopausal women and men ≥ 50
  - Additional DXA scanning based on clinical concern
Questions

MGH Pediatric Endocrine and Diabetes Unit