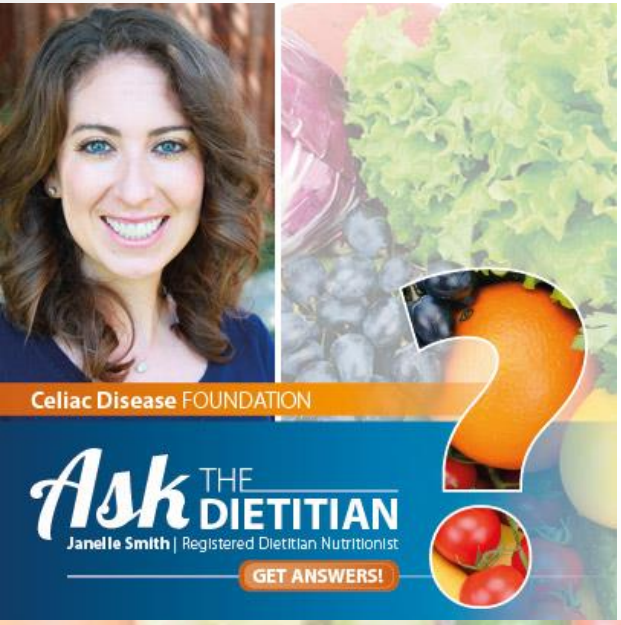
Women's Health Focus in Gluten-Related Disorders

Special guest:



Sheila Crowe, MD

Janelle Smith
CDF Registered
Dietitian Nutritionist

March 19, 2015

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Today's Webinar

- How celiac disease effects fertility and the female body – Sheila Crowe, MD

- Nutritional considerations for women with gluten-related disorders – Janelle Smith, RDN

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Sheila Crowe, MD

AGAF, FRCPC, FACP, FACG

- Professor of Medicine & Director of Research, Division of Gastroenterology, UC San Diego Medical School
- Vice President of American Gastroenterological Association
- Distinguished Educator Award, AGA 2015
- Outstanding Woman in Science, 2008
- America's Best Doctors in America since 1996
-

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A Balancing Act: Women's Health and Celiac Disease

Sheila E. Crowe, MD, FRCPC, FACP, FACG, AGAF

Director, UCSD Celiac Disease Center

Department of Medicine

University of California, San Diego

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Case Presentation

- A 28 year old woman comes to her primary care provider for possible celiac disease. She reports abdominal bloating and discomfort, increased loose stools ranging from 2 to 3 a day without blood. She also complains of fatigue and headaches.

- On the advice of a friend she went on a gluten free diet two months ago. She feels better but wants to know if she has celiac disease and if she should stay on her diet which she finds expensive and difficult to adhere to. She is planning to get pregnant and wants to know if having celiac disease could be a problem.

Issues for Consideration

- What clinical presentations suggest celiac disease
- How to screen and diagnose celiac disease
- Role of genetic testing
- How to evaluate someone already on a GFD
- What about celiac disease and fertility
- Outcomes of pregnancy in celiac disease
- Who is at risk in your family
- Should your offspring eat gluten free

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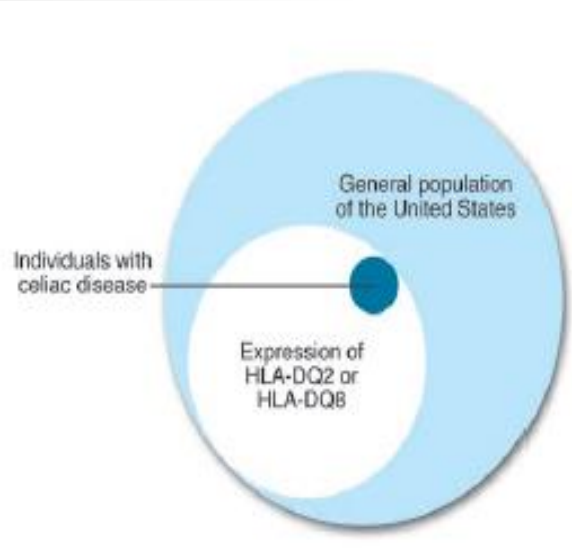
Changing Prevalence of Celiac Disease

- Prevalence of up to ~1:100 in most genetically susceptible populations, 0.71% in NHANES study
- Less than 10-15% of current cases of CD have been diagnosed in the US
- CD is 4 to 4.5 times more prevalent than 50 yrs ago
- Cause of "CD epidemic" unknown
  - Dietary – grains with increased gluten, increased wheat in diets worldwide
  - Other environmental
  - Microbiota

Fasano et al, Arch Int Med, 163:286, 2003
Rubio-Tapa et al, Gastroenterology, 137: 88, 2009
AGA Technical Review, Gastroenterology, 131:1981, 2006
Virta et al, Scand J Gatroenterol, 44:933, 2009
Rubio-Tapia, Am J Gastroenterol, 2012

Who Develops Celiac Disease? Genetic and Other Factors



- 70% concordance in twins
- 10-15% prevalence in first degree relatives

- Other genetic factors - genes on chromosomes 5, 16, ?6
- GWAS have identified at least 26 celiac genetic risk variants
  - many contain immune-related genes controlling adaptive immune response

- Increased frequency of HLA haplotypes - DR3-DQ2, DR5/7-DQ2, DR4-DQ8
- Other factors involved since most with these haplotypes do not get celiac disease (confer ~40% of risk)
-

- Environmental factors - ? Infectious agents
  - Cytokines released during infection - Affecting APCs (e.g., dendritic cells)
  - Cross-reactive amino acid sequences - Adenovirus, H. pylor*i*

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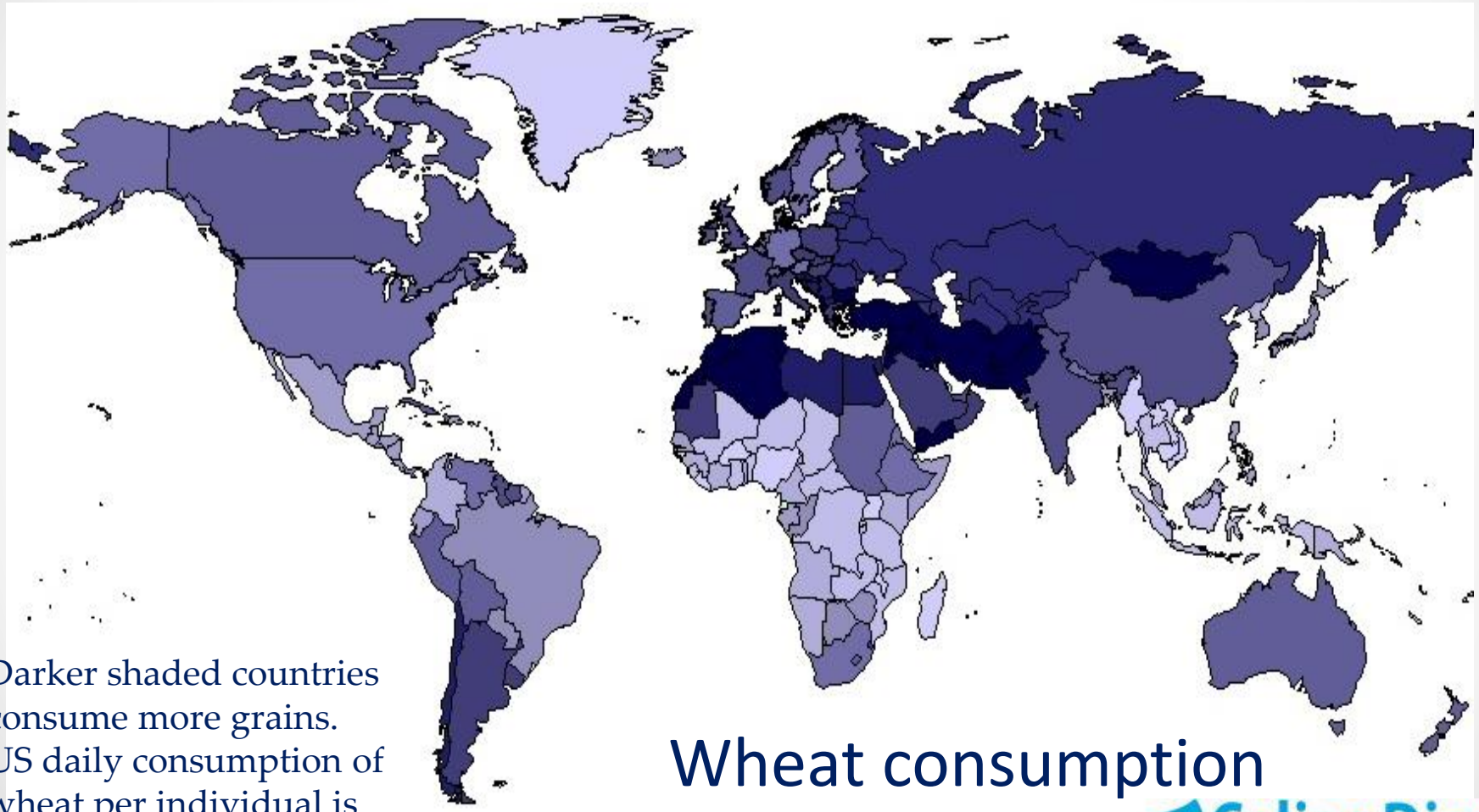
Risk Factors: The Grains



Wheat consumption

Darker shaded countries consume more grains. US daily consumption of wheat per individual is moderately high (≈ 24% to 32% of diet).

Adapted from Fasano A, Catassi C. Gas

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Varying Forms of Celiac Disease

- Classical celiac disease of childhood
- Late onset, non-specific GI symptoms
- Dermatitis herpetiformis
- Extra-intestinal presentations (many)
- Associated conditions (many)
- Silent or asymptomatic celiac disease (relatives)
- Latent or potential celiac disease

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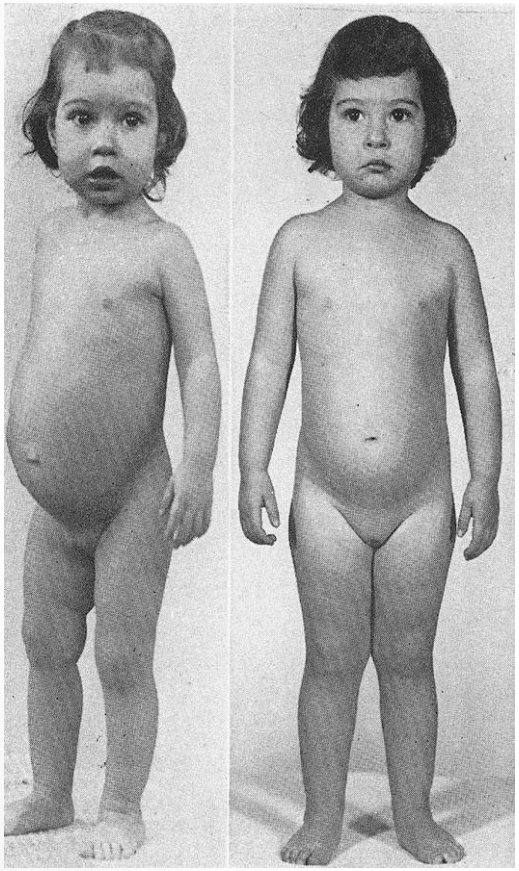
Celiac Disease: "Classical"



Haas & Haas, Management of Celiac Disease. 1951

- Failure to thrive
- Weight loss
- Protuberant abdomen
- Bloating
- Diarrhea, steatorrhea
- Abdominal pain
- Dramatic response to gluten free diet

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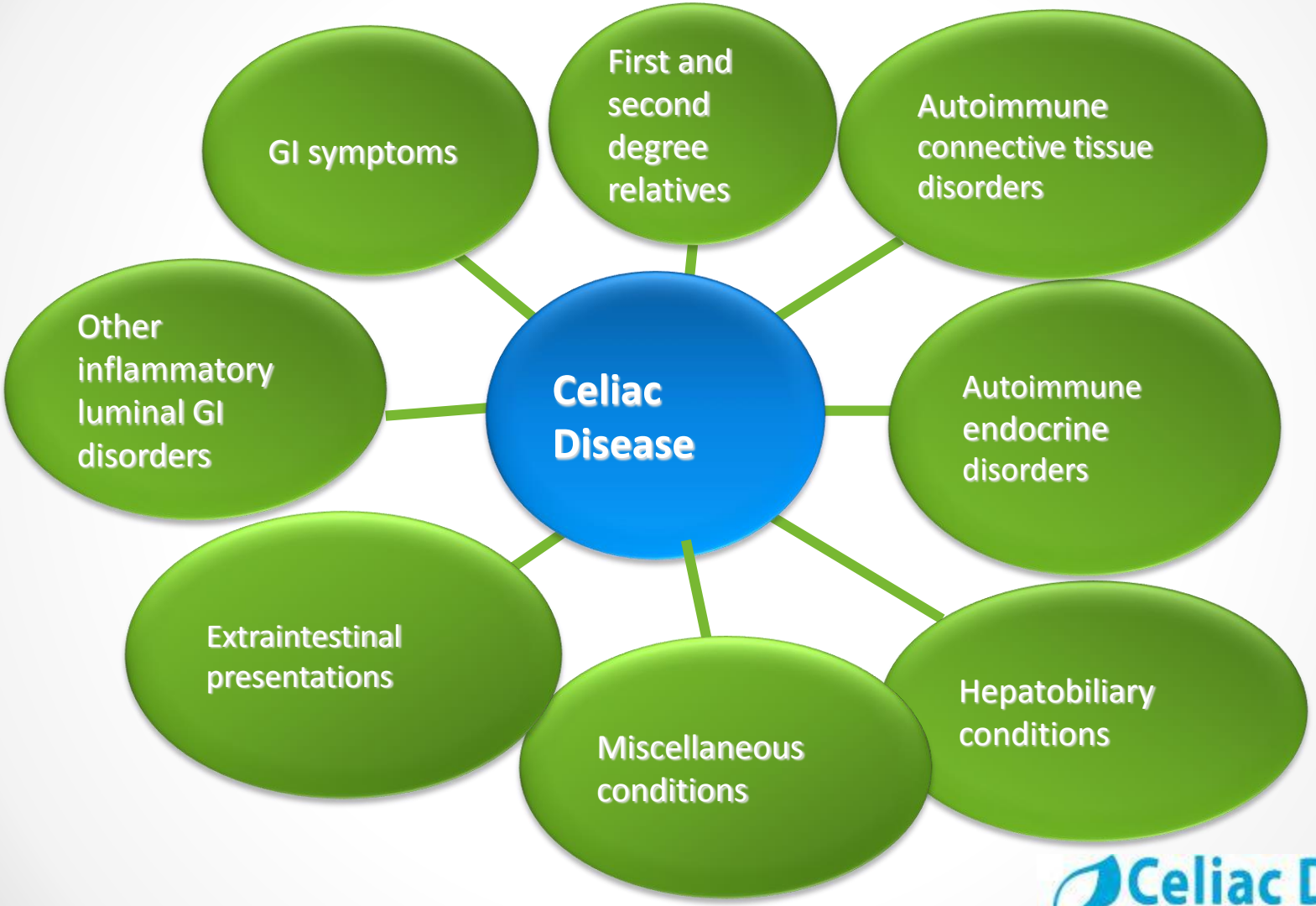
Changing Picture of Disease

- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many are overweight
- Seroprevalence M=F, diagnosis M<F (1: 2 - 3)
- Other presentations are being increasingly recognized:
  - Reproductive problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
  - Many others – true associations or chance?

Symptoms and Conditions That Should Prompt Consideration of Celiac Disease



- *Crowe, SE, In The Clinic : Celiac Disease, Ann Int Med, 154:ITC5-14, 2011*

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Common Symptoms in Celiac Disease

- Altered bowel habits
  - Diarrhea, constipation and mixed pattern
- Fatigue
- Borborygmi, flatulence
- Abdominal discomfort or pain
- Weight loss
  - Howver patients with CD can be overweight and even obese
- Abdominal distention or bloating
- Note that there are many other presentations of celiac disease including an asymptomatic state

Niewinski MM. J Am Diet Assoc. 2008;108:661-672.
Presuttii JR et al. Am Fam Physician. 2007;76:1795-1802.
Green PHR JAMA. 2009;302(11):1225-1226.
Crowe, SE, In The Clinic : Celiac Disease, Ann Int Med. 154:ITC5-14, 2011

Elevated "Risk" of Celiac Disease in:

- 1st and 2nd degree relatives
- Down's syndrome (12%)
- Type I DM (3-8%)
- Autoimmune thyroid disease (5%)
- Symptomatic iron deficiency anemia (10-15%)
- Asymptomatic iron deficiency anemia (3-6%)
- Microscopic colitis (15-27%)
- IBS (3.4%)
- Chronic fatigue syndrome (2%)
- Osteoporosis (1-3%)

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Many and Varied Presentations

- Altered bowel habit, bloating, dyspepsia, abdominal discomfort, abnormal liver tests
- Anemia (iron, folate, B12), coagulopathy
- Dermatitis herpetiformis
- Miscarriages, IUGR, infertility
- Peripheral neuropathy, ataxia, migraines, cerebral calcifications
- Fatigue, depression, irritability
- Enamel defects, osteopenic bone disease, osteomalacia, short stature

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Obstetrical & Gynecological Presentations in Untreated Celiac Disease

Medline search of English language publications 1996 - March 2000 indicate patients with untreated celiac disease sustain:

- Delayed menarche
- Earlier menopause
- Increased prevalence secondary amenorrhea
- Infertility
- Higher miscarriage rates
- Increased IUGR
- Lower birth weights

Eliakim & Sherer, Gynecol Obstet Invest, 51: 3, 2001

Studies of Fertility in Celiac Disease (England)

- 1521 women with celiac disease were compared to 7732 age- and practice-matched women without celiac disease using an English computerized primary case database
- Fertility rates similar overall
  - Crude fertility rates (live births per 1000 person years) were 48.2 (celiac) and 47.7 (non-celiac)
  - Celiacs had lower fertility rates when younger but greater when older compared to controls

Tate et al, Gastroenterology, 128: 849, 2005

Studies of Fertility in Celiac Disease (England)

- Risks moderately higher for:
  - C-section - OR 1.33 (CI 1.03-1.70)
  - Miscarriage - rate ratio 1.31 (CI 1.06-1.61)
- Risks of other outcomes similar
  - Assisted birth, breech birth, preeclampsia, postpartum hemorrhage, ectopic pregnancy, stillbirth, termination

Tate et al, Gastroenterology, 128: 849, 2005

Studies of Fertility in Celiac Disease (Israel)

- Retrospective comparison of all pregnancies of women with and without celiac disease delivered during years 1998-2002
  - 48 with, 143,663 without known celiac disease
- In celiac women there were higher rates of:
  - Labor induction (29.2 vs 11.9%, $p < 0.001$)
  - IUGR (6.3 vs 2.1%, $p < 0.042$)
- No difference for fertility treatments, recurrent abortion, or perinatal mortality

Shelner et al, Eur J Obstet Gynecol Repro Biol, 129: 41, 2005

Studies of Fertility in Untreated Celiac Disease (Italy)

Case-control comparison of treated (94) and untreated (31) Italian women with celiac disease

- RR of miscarriage 8.9 (CI 1.19-66.3)
- RR of low birth weight 5.84 (CI 1.07-31.9)
- RR of shorter duration of breast feeding 2.54

None of these outcomes were associated with severity of disease

Ciacci et al, Am J Gastroenterol, 91: 718, 1996

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Obstetrical & Gynecological Presentations: Effect of Treatment

- In a small before and after treatment study GFD significantly reduced risks of:
  - miscarriage (by 9.18 fold)
  - low birth weight babies (29.4% to 0%)

  (Ciacci et al, Am J Gastroenterol, 91: 718, 1996)
- Prognosis for future pregnancies improved if mother on GFD

  (Martinelli et al, Gut, 46: 332, 2000)

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Screening for Celiac Disease during Pregnancy

- Endomysial Ab screening of all women attending an obstetrical department in Naples, Italy over 90 day period
  - 12 of 845 pregnant woman identified with celiac disease – 3 previously diagnosed but not on GFD, 9 subsequently diagnosed by intestinal biopsy
  - Unfavorable outcome of pregnancy in 7 of 12
  - 6 healthy babies born to mothers on 1 yr of GFD
  - Anemia, history of miscarriages
- Authors suggest pregnant women should be routinely screened for celiac disease given their findings

Martinelli et al, Gut, 46: 332, 2000

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Screening for Celiac Disease in Infertility and Recurrent Miscarriages

- Some European studies suggest higher prevalence of celiac disease among infertile women compared to general population especially if also anemic and having GI symptoms *(Meloni et all, Human Reprod, 14:2759, 1999; Collin et al, Gut, 49: 382, 2001,)*
- Similar results in study from Israel *(Shamaly et al, Acta Obstet Gynecol Scand, 83: 1184, 2004)*
- Not all European studies report this however *(Kolho et al, Br J Obstet Gynecol, 106: 171, 1999; Tiboni et al, Hum Reprod, 21:376, 2006)*
- Californian study found only 1 of 121 (0.8%) using tTG and EMA *(Jackson et al, Fertil Steril, 2007)*

Value of screening in infertile women remains unclear

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Obstetrical & Gynecological Presentations in Untreated CD

Patients with untreated celiac disease sustain:

- Delayed menarche
- Earlier menopause
- Increased prevalence secondary amenorrhea
- Infertility
- Higher miscarriage rates (9-fold increase)
- Increased IUGR
- Lower birth weights
- Premature births

Reviewed in Eliakim & Sherer, Gynecol Obstet Invest, 51: 3, 2001
Soni & Badawy, J. Reprod Med, 55:3, 2010 and Ozgor, B & MA, Selimoglu, Scand J Gastroenterol, 45:395, 2010

Recent Study of Fertility in Celiac Disease (England)

- 2, 426,225 women with prospective UK primary care records between 1990 and 2013 during child-bearing years. Age-specific rates of newly recorded fertility problems among women with or without celiac disease were estimated.
- Stratified for CD diagnosis before or after infertility problems
- Age-specific rate of new clinically recorded fertility problems in 6506 women with celiac disease were similar to the rates in women without celiac disease
- Rates were 41% higher among women diagnosed with celiac disease during the age of 25-29 yrs (incident rate ratio of 1.12 [0.88-1.42] in age 25-29 yrs)

Dhalwani, NN et al, Gastroenterology, 147: 1267, 2014

Dietary Response to a Gluten Free Diet: Is this Diagnostic?

- Placebo response in IBS up to 70%
- Gluten (increased prolamines) is hard to digest, increases stool volume
- Gluten free diet often eliminates other dietary factors
- Potentially other mechanisms explain benefit
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study

Campanella et al, Scand J Gastroenterol, 43:1311, 2008

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Diagnosis

- Characteristic histological findings
- Clinical, serological, and in some cases, histological response to a gluten free diet
- Rarely necessary to observe clinical and histological response to gluten challenge
- Intestinal biopsies are the only method by which celiac disease can be diagnosed
- However, for dermatitis herpetiformis a classical skin biopsy is often sufficient

AGA Technical Review, Gastroenterology, 131:1981, 2006

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Take Home Message

- Celiac disease is not rare (1 in 100)
- It can affect the body in many ways including the reproductive system and its function
- Women diagnosed with celiac disease and are treated have increased fertility and better pregnancy outcomes than those untreated
- Role of screening not established but should consider assessing for celiac disease in women with recurrent miscarriages, a history of IUGR, especially with anemia and/or GI symptoms

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Nutrition in Women's Health

- Nutrition for fertility & breastfeeding
- Nutrition for bone health
- Nutrition for iron-deficiency anemia

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Fertility

Nutritional factors influencing infertility:

- Unhealthy body weight – both under and over
  - effect production of female reproductive hormones
- Insulin insensitivity - can impair ovulation
- Inadequate fat intake, esp monounsaturated
- Inadequate protein intake

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Fertility

Nutrients often lacking in gluten-free diet that play a role in fertility and fetal health:

- Folic acid – 400 mcg/day
- Calcium – 1,000 – 1,200 mg/day
- Zinc – 15 mg/day
- Iron – 27 mg/day
- Omega-3 fatty acids for DHA – 300 mg/day
- Choline – 450 mg/day

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Nutrient Comparison: C

Nutrition Facts

Serving size 1/2 cup (30g)
Servings per container 10

Amount Per Serving

Calories 120	**Calorie from fat** 10
	% Daily Value*
Total Fat 1g	2 %
Saturated Fat 0g	0 %
Trans Fat 0g	
Cholesterol 0mg	0 %
Sodium 120mg	5 %
Total Carbohydrate 26g	9 %
Dietary Fiber 1g	4 %
Sugars 4g	
Protein 1g	

Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 0%

daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Saturated Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Nutrition Facts

Serving Size ¾ cup (30g)
Servings Per Container 17

Amount Per Serving	Apple Cinnamon Cheerios	with ½ cup skim milk
Calories	120	160
Calories from Fat	15	15
		% Daily Value**
Total Fat 1.5g*	**3%**	**3%**
Saturated Fat 0g	**0%**	**0%**
Trans Fat 0g		
Polyunsaturated Fat 0.5g		
Monounsaturated Fat 1g		
Cholesterol 0mg	**0%**	**1%**
Sodium 115mg	**5%**	**8%**
Potassium 65mg	**2%**	**8%**
Total Carbohydrate 24g	**8%**	**10%**
Dietary Fiber 2g	**8%**	**8%**
Sugars 10g		
Other Carbohydrate 12g		
Protein 2g		
Vitamin A	10%	15%
Vitamin C	10%	10%
Calcium	10%	25%
Iron	25%	25%
Vitamin D	10%	25%
Thiamin	25%	30%
Riboflavin	25%	35%
Niacin	25%	25%
Vitamin B_6	25%	25%
Folic Acid	50%	50%
Vitamin B_{12}	25%	35%
Phosphorus	6%	20%
Magnesium	6%	8%
Zinc	25%	30%

* Amount in cereal. serving of cereal plus skim milk provides

Fertility Foods

- Folic Acid: beans, leafy greens, whole grains
- Zinc: nuts, meat, shellfish
- Choline: cauliflower, egg yolks, pork, cod
- DHA: fatty fish

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Breastfeeding

- Naturally helps with post-partum depression, movement of hips back to original position, and weight normalization
- Calorie needs approx. 500 more to produce breast milk
- Increased needs of most vitamins and minerals as well… continue taking prenatal vitamins!
  - May need extra calcium, magnesium and iron
  - Women may lose 3-5% of bone mass during breastfeeding, but it recovers after weaning

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Breastfeeding in Celiac Mothers

- Breastfeeding women with low body weight or malnutrition may have difficulty producing adequate amounts of breast milk

- Breastfeeding women with low body weight and/or low energy intake have infants more likely to experience failure to thrive

Is Breastfeeding Protective for CD?

- No strong research shows that breastfeeding effects development of celiac disease in infants
  - At most, may delay onset of celiac disease but not prevent onset

"Breast-feeding, regardless of whether it was exclusive or whether it was ongoing during gluten introduction, did not significantly influence the development of celiac disease"

- Vriezinga S.L. et al., New Engl J Med 2014

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Infant Feeding & Gluten

- Gluten is not passed through breast milk, but other wheat allergens may be
- Formula generally does not contain gluten, but infants may not tolerate other ingredients well

- Most recent research suggests that introducing gluten at 6 months is ideal time for infants. For those at high risk for CD (have 2 sets of HLA-DQ2 genes), both earlier and later might increase risk
  - Vriezinga S.L. et al., New Engl J Med 2014

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Bone Health

Why are Women Special ?

- Estrogen prevents resorption of calcium from bones by turning on/off the genes to make osteoclasts
- Lower muscle mass -> lower bone density

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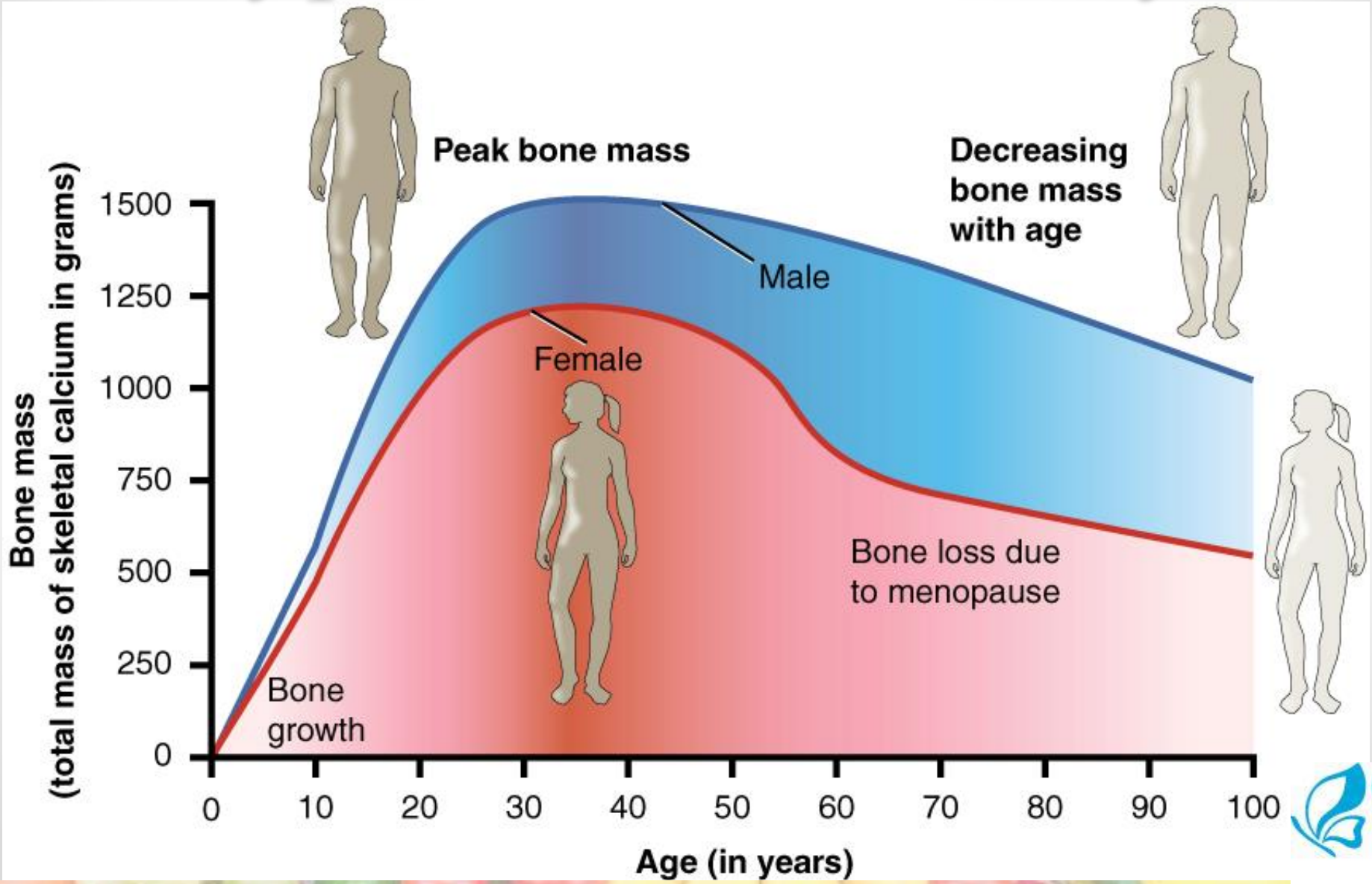
Typical Bone Density



Bone Disorders

- **Osteomalacia:** (i.e. Rickets) new bone constructed is abnormal, "soft bones", usually due to Vit D deficiency
  - Bones may bend or break
  - Muscle weakness, achy bone pains

Deterioration of existing bone tissue:

- Due to malnutrition – inadequate Ca, Phos, vit D, magnesium
- Natural aging process & menopause
- Resorption of calcium from the bones d/t above

- **Osteopenia:** -1.0 to -2.5 SD below "normal"
- **Osteoporosis:** < -2.5 SD below "normal"

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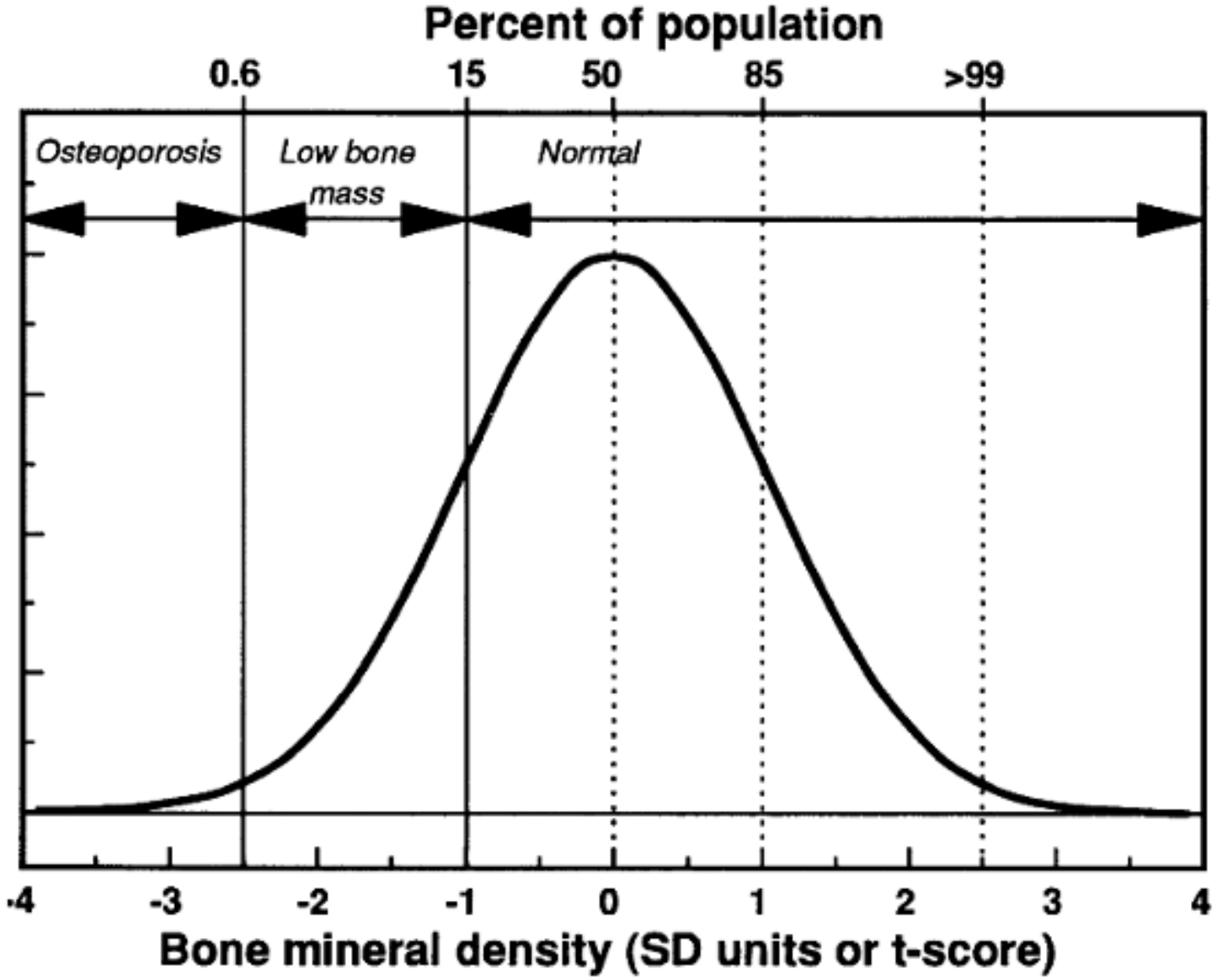
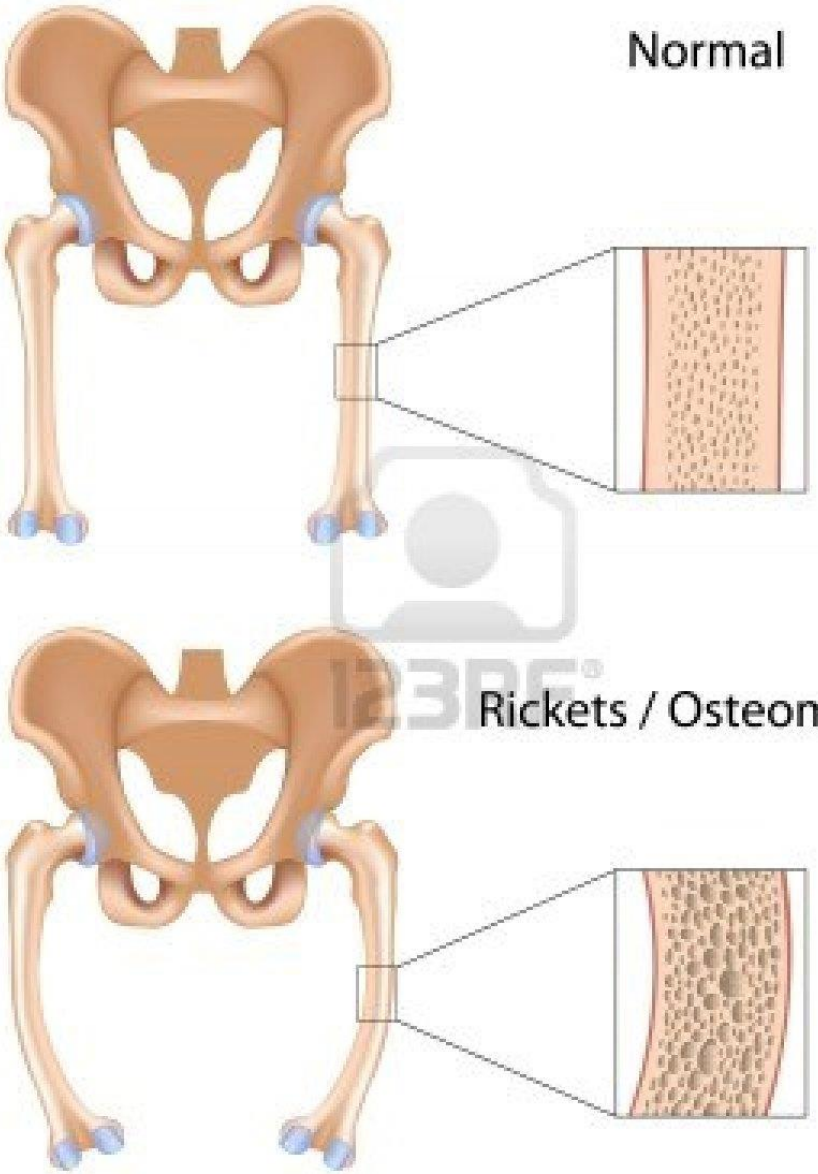
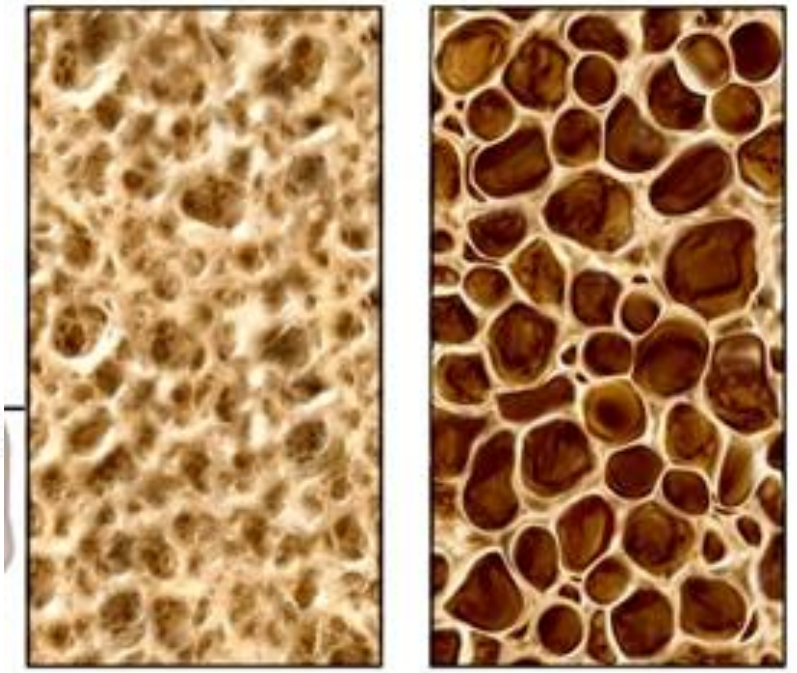


Fig. 1. Diagnostic thresholds for women based on the distribution of bone mineral density in the young healthy female population.





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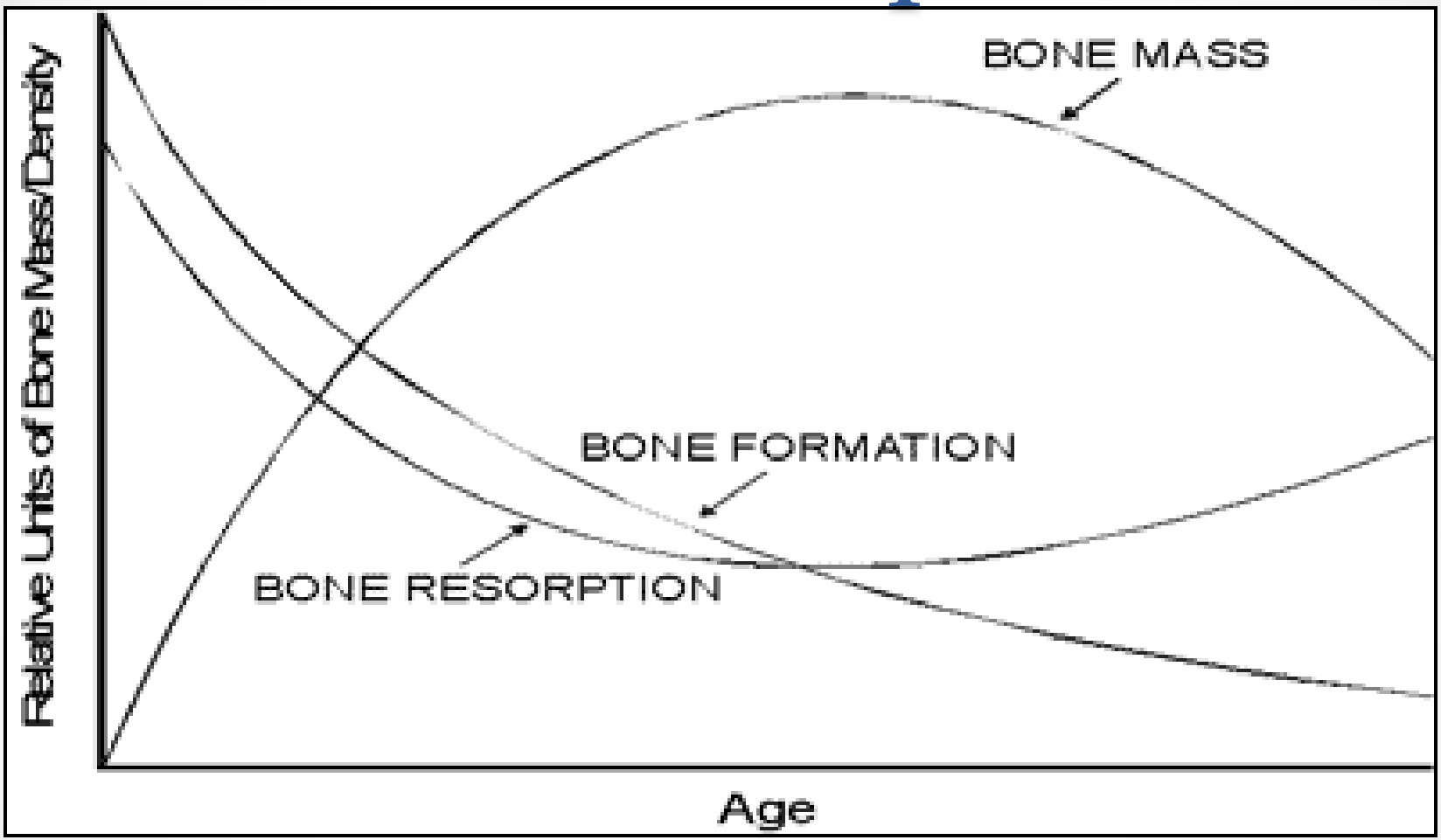
Bone Resorption



When bone breakdown out-rates bone formation, bone density decreases leading to osteopenia or osteoporosis

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When to Scan?

- At time of celiac diagnosis
- If you have bone pain
- If had an eating disorder or other malnutrition for prolonged period of time
- If amenorrheic for prolonged period of time
- If post-menopausal
- If undergone chemotherapy/radiation, steroids
- If have parathyroid disorder

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Bone Health risks

Why to care about bone health?

- Motility, independence
- Movement ability may effect cardiovascular health
- Infections (osteomyelitis) from undetected fractures can lead to sepsis, amputation

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Nutrition for Bone Health

- **Calcium**: 1200 mg/day (menstruating)
  1500 mg/day (post-menopausal)
  May be higher when treating for bone disease

- **Vitamin D**: 600 IU/day RDI
  1000-2000 IU/day over-the-counter
  May be higher medical dose treating for deficiency

- **Magnesium**: 320 mg/day
  400 mg/day RDI (pregnant/lactating)
-

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Non-Dairy Sources

- **Vitamin D**:
  - Mushrooms
  - Fatty fish (herring, mackerel, salmon, halibut)
  - Fortified soy milk or orange juice
  - Egg yolk
- **Magnesium**
  - Nuts
  - Leafy greens
  - Soy
  - Beans
- **Calcium**
  - White beans, black eyed peas
  - Canned salmon or sardines with bones
  - Leafy greens
  - Seaweed
  - Fortified orange juice or soy milk
  - Tofu

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Bone Health Salad

- Mixed greens
- Roasted chickpeas
- Cashew nuts
- Avocado
- Roasted cauliflower
- Grilled tofu

Dressing:

- ½ tbsp olive oil
- ½ tbsp balsamic vinegar
- Juice from ½ lemon
- Black pepper

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Lifestyle Interventions

- Weight-bearing activity – 30 min/day
- Sunshine or UV light – 20 min/day without sunscreen (discuss with physician if at risk for skin cancer)
- Alcohol – limit to 1-2 servings/day
  - Women drinking more than 2 /day have higher risk of osteoporosis
- Caffeine intake – limit if already at risk
  - For every 100 mg caffeine, takes away 6 mg Ca from bones
  - Not significant in healthy diet and low risk individuals
  - Keep in mind in osteopenia or osteoporosis
- Smoking
- Soda intake – high phosphorous content

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Iron-Deficiency Anemia

- Most common deficiency for women worldwide
- Most common symptom of celiac disease in adults

Definition:

- Abnormal red blood cells (anemia) due to inadequate iron stores in the body

- Low ferritin (iron stores)
- Low hemoglobin (protein that carries iron in your red blood cells)
- Cells are small in size because of inadequate hemoglobin

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Symptoms

- Fatigue, lethargy
- Irritability, depression
- Poor concentration, memory
- Shortness of breath when physically active
- Brittle nails or spoon nails
- Pale skin
- Pica – desire to eat ice, non-food items
- Dizziness, light-headedness

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Dietary Treatment

- Dietary sources
  - Red meat, dark meat poultry, liver
  - Tofu, beans, pumpkin seeds
  - Pair "heme" (animal) sources with nonheme (plant) sources to maximize absorption
  - Separate from sources of calcium (dairy)
  - Eat with vitamin C
- Oral supplements
  - Chelated iron / ferrous bisglycinate

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Non-Responsive to Diet/Oral Therapy

- Follow gluten-free diet to promote intestinal absorption!
- Investigate any blood loss
- Investigate malabsorption
  - Bacterial overgrowth?
  - Gluten in diet?
  - Medication causes?

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Women's Health Chili

- Contains 32% daily value iron, 19% DV calcium, 24% DV folate, 20% DV magnesium, 43% DV vit C to enhance absorption

- 1 tsbp canola oil, 2 cloves minced garlic, 1.5 tbsp chili powder, 1 tsp ground cumin, 1 tsp brown sugar, ¼ tsp salt
- 30 oz canned red kidney beans, rinsed
- 1/3 cup red quinoa
- 1 lb lean ground turkey
- 2 large onions
- 36 oz canned tomatoes
- 1 carrot, chopped

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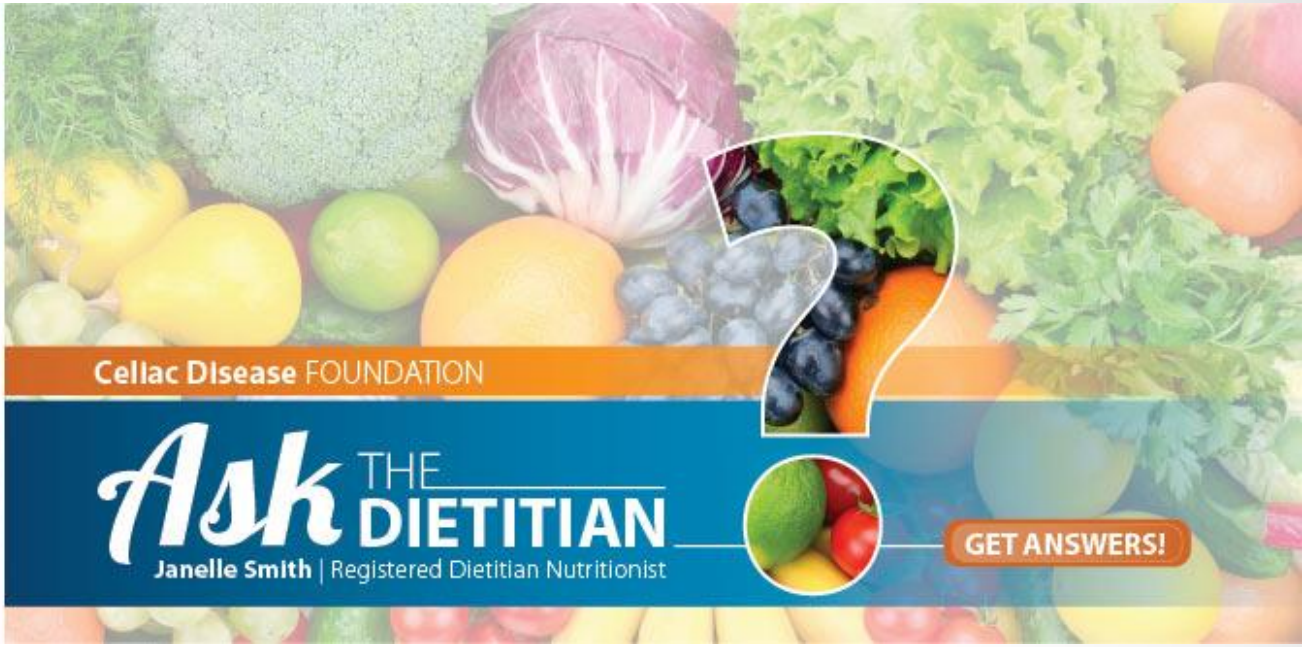

Next CDF Ask the Dietitian Webinar:

Countdown to the Conference

Wednesday April 15th, 9 am PST

Joseph Murray, MD

Celiac Disease FOUNDATION
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