Hypothalamic amenorrhea

- **Functional hypothalamic amenorrhea**
  - Absence of menses due to suppression of hypothalamic-pituitary-ovarian axis in which no anatomical or organic disease is identified
  - Amenorrhea > 6 months
  - 3 main types related to stress, weight loss or exercise (often all 3 present)
  - (NEJM 363;4 7/2010)
Hypothalamic-pituitary-ovarian axis in setting of hypothalamic amenorrhea

What controls GnRH pulsatility?
- We do not know why but body's assessment of energy balance plays a role
  - Calorie in = calorie out balanced
  - Calorie in < calorie out imbalance = reduction in LH pulse frequency
- Calorie composition
  - Athlete with similar calories those with fat restriction > amenorrhea

Leptin
Ghrelin
Triiodothyronine
Female Athletic Triad

Low Energy Availability/Disordered Eating

Female Athlete Triad

Bone Loss/Osteoporosis

Menstrual Disturbances/Amenorrhea

http://www.femaleathletetriad.org/

Female Athletic Triad

Restrictive Eating/High Drive for Thinness

Healthy Energy Status

Disordered Eating/Energy Deficiency

Healthy Bones

Low BMI

CBO: Amenorrhea

Osteoporosis

Amenorrhea

Anorexia

Triad of amenorrhea, weight loss and psychiatric disturbance
Postmenopausal measurements of BMD

- Postmenopausal women
  - T-score = number of standard deviations below peak BMD (WHO)
    - <1 normal
    - -1 to -2.5 osteopenia
    - >-2.5 osteoporosis

- International Society for Clinical Densitometry (ISCD) position paper states not to use these terms in children and premenopausal women

Premenopausal measurements of BMD

- Use Z score not T-score
  - Z score below -2.0 “low bone density below expected range for age” (ISCD)
  - Athletes BMD Z-score <-1.0 concerning
- No role for term osteopenia
- Osteoporosis (defined by ISCD & ACSM)
  - BMD Zscore ≤ -2.0 plus secondary risk factors AND
  - Secondary risk factors including chronic malnutrition, eating disorders, hypogonadism, glucocorticoid exposure and previous fractures

Estrogen and bones

Bone formation → Osteoblast apoptosis

Bone resorption → Estrogen deficiency

Estrogen and bones
Bone health

- Low BMD increases risk of injury 3.6x
- Stress fractures
  - 2-4x increased risk in amenorrhic athletes
  - 1.9x risk for stress fractures in 11-17yo participating in >16 hours exercise per week compared to those <4 hours

Bone Health in Female Athletic Triad

- American College of Sports Medicine Position paper states:
  - "OC should be considered in an athlete with functional hypothalamic amenorrhea over the age 16 if BMD is decreasing with nonpharmalogical management despite adequate nutrition and body weight"

  Medicine and Science in Sports and Medicine 2007

Bone Health in Anorexia

- Bone loss from anorexia may never fully recover
- Bone loss may be rapid and early in disease
- Low bone density in 92% with anorexia
  - Osteoporosis in 40% of these women
Hypothalamic amenorrhea = hypoestrogenized state = increased risk for low BMD and fracture

Estrogen is beneficial for bone health

Those with hypothalamic amenorrhea should be treated with estrogen to protect their bones

What is the evidence?

Estrogen Replacement

Randomized, controlled trial 2007
24 subjects
- Randomized to OCP + medroxyprogesterone
- Medroxyprogesterone only
- Placebo
BMD > in OCP + medroxyprogesterone group than placebo or medroxyprogesterone alone

Hergenroeder et al Am J Obstet Gynecol 1997; 176

Estrogen replacement

Randomized controlled trail 2001
64 women hypothalamic amenorrhea (stress induced)
- 3 groups
  - 30 ug EE + 0.15 mg desogestrel
  - 20 ug EE + 0.15 mg desogestrel
  - No hormone therapy (control)
- Increase in lumbar spine BMD in both OCP groups (+2.4/+2.5%) but decreased in control group (-1.1%)
- Calcium, phosphate and osteocalcin reduced by treatment group but not control

Castelo-Branco J Reprod Med 2001; 46:875-879
Estrogen replacement

- Systemic review 2006
  - 10 studies on HRT and BMD in oligo/amenorrheic premenopausal women
    - 7 showed positive effect (2 RCT, 5 cohort) - 379 subjects (88 from RCT)
    - 2 showed no effect (1 RCT, 1 cohort)
    - 1 case report negative effect
  - Trend (non-significant) was to increase BMD in the OC group
    - 1 RCT (n=45) showed decreased markers of bone resorption in oligo/amenorrheic OCP group
  - Anorexic premenopausal did not show benefit


Estrogen replacement

- Randomized control trial 2007
  - Female distance runners (18-26) randomized 2 arms
    - OCP group 30mcg EE/0.3mg norgestrel
    - No treatment
  - BMD density measured at baseline, year 1 and year 2
  - Oligo/amenorrheic women taking OCP regained significantly more whole body bone mineral content and spine BMD compared to those not on OCP (2% vs. -1%)
  - No difference in fracture in either group


Challenges with nonpharmalogical treatment

- Many with anorexia do not recover or course is prolonged so damage to bones is severe
- One study showed only 17% with anorexia had normal BMD despite weight restoration and recovery (Miller et al 2004)
- Studies indicate weight gain and menses recovery not sufficient to normalize bone accrual
Challenges with nonpharmalogical treatment

- Athletes with female athletic triad unlikely to gain weight or decrease exercise for fear of poorer performance
- While recovery ovulation may occur before menses restored resulting in unplanned pregnancy

Anorexia Nervosa and Treatment

- Data does not show HRT or OCP improves BMD with anorexic pts but treatment options are emerging and promising
- 50% of anorexic girls have BMD Z-score -1 at one or more sites and do not have increase bone mass prospectively leading to further decline in BMD

Anorexia Nervosa and Treatment

- IGF-1 is an important bone trophic hormone
- Levels are decreased in anorexia
- High dose estrogen (as in OCP) suppress IGF-1 secretion
- Possible reason OCP don’t work in anorexia is it further suppresses already decreased IGF-1 levels
- Pubertal estrogen levels do not suppress IGF-1
**Anorexia Nervosa and Treatment**

- **Randomized controlled trial 2002**
- 60 osteopenic women
  - rhIGF-I 30µg/kg sc BID plus OCP (35µg EE 0.4 norethidrone)
  - rhIGF-1 alone
  - OCP plus rhIGF-1 placebo
  - rhIGF-1 placebo only
- Combination of estrogen and subcutaneous insulin-like growth factor 1.8% increase in spinal BMD over 9 months
  
  Grinspoon J Clin Endocrinol Metab 2002;87:2883-91

**Anorexia Nervosa and Treatment**

- **Randomized, double blinded, placebo controlled trial 2011**
- 150 girls ages 12-18 with anorexia
  - Treatment group transdermal 17β-estradiol patch
  - Controls (40)
  - Anorexia and placebo (55)

  Misea et al, JBMR 6(10) 2011: 2430-2438

**Anorexia Nervosa and Treatment**

- Placebo arm
- Treatment arm
  - Mature girls 100µg patch twice weekly) with medroxyprogesterone 2.5mg daily 10days/ month
  - Immature girls escalating does
    - 3.75µg daily x 6 months → 7.5µg daily 6 months
    - → 11.25µg daily 6 months
Anorexia girls in treatment group had greater increase in BMD Z-scores at spine and hip than anorexic girls without treatment ($p=0.044$ and $0.040$).

Black AN E-  Gray AN E+  White controls

Anorexia Nervosa and Treatment

- Randomized placebo controlled trial 2013
- 94 subjects with anorexia
  - 43 50mg oral micronized DHEA + 20µg EE/0.1mg levonorgestrel
  - 37 placebo
- Estrogen therapy started with 0.3mg x 3 months that to OCP

DiVasta Metabolism 2012 7:61(7)

Anorexia Nervosa and Treatment

BMD Z-score preserved in DHEA+ COC group but bone loss in placebo

DiVasta Metabolism 2012 7:61(7)