Female Athlete Triad

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Disclosures
• None

Prevalence of Components of Triad

• Systematic Review of 65 studies:
  - All 3 Triad conditions: 0-15.9% (9 studies; n=991)
  - Menstrual disorder and low BMD: 0-7.5% (4 studies; n=460)
  - Menstrual disorder and disordered eating: 2.7-50.0% (8 studies; n=1,136)
  - Low BMD and disordered eating: 0.9-3.2% (2 studies; n=298)
  - Menstrual disorder and low energy availability: 17.5% (1 study; n=80)
  - Low BMD and low energy availability: 3.75% (1 study; n=80)
• Up to 78% of high school varsity female athletes found to have 1 or more components of the Triad

Relative Energy Deficiency in Sport (RED-S)

Consequences of Aspects of the Triad

SERIOUS PHYSICAL HEALTH PROBLEMS FROM RED/S
• Fluid/electrolyte imbalances
• Acid-base abnormalities
• Cardiac arrhythmias & even death
• Anorectics have 6x the mortality rate vs. the general population

EFFECTS OF RED/S ON MENTAL HEALTH AND RELATIONSHIPS
• Isolating
• Stressful
• Misunderstood
• Less able to relate to others & form friendships/romantic relationships

EFFECTS ON PERFORMANCE, INJURY & RECOVERY
• Decreased energy & earlier fatigue
• Decreased coordination, concentration & speed
• More frequent muscle strains/sprains & fractures
• More frequent illnesses
• Longer to recover from work-outs and competitions

EFFECTS ON LONG-TERM HEALTH
• OSTEOPOROSIS!
• Possible infertility complications
• Bad lifetime habits which can lead to full-blown, life-threatening disorders
Potential Performance Effects of RED-S

Leanness Sports

| Endurance sports | Cross-country skiing, cycling, rowing, running, speed skating, swimming |
|------------------|---------------------------------------------------------------------|
| Aesthetic sports | Cheerleading, dance, figure skating, gymnastics, synchronized swimming |
| Weight-class sports | Boxing, judo, kickboxing, lightweight rowing, mixed martial arts, taekwondo, weightlifting, wrestling |
| Anti-gravitational sports | Cycling, swimming, synchronized swimming |

Age of Onset

- Adult elite athletes diagnosed with DE/EDs report having started dieting and developing problems during puberty/adolescence
  - Peak onset is adolescence, when females especially experience rapid changes in body composition and shape

Low Energy Availability

- **Eating disorder**: clinical mental disorder defined by DSM-5 and characterized by abnormal eating behaviors, an irrational fear of gaining weight, and false beliefs about eating, weight, and shape.
- **Disordered eating**: various abnormal eating behaviors including restrictive eating, fasting, frequently skipped meals, diet pills, laxatives, diuretics, enemas, overeating, binging, and purging.

Low Energy Availability

- **Energy Availability (EA)**: dietary energy intake (EI) - exercise energy expenditure (EEE) normalized to fat free mass
  - EA = (EI - EEE)/FFM
  - Ex. EI = 2000 kcal/d, EEE = 600 kcal/d, FFM = 51 kg
  - (2000 - 600)/51 = 27.5 kcal/kg of FFM/d

Menstrual Cycle

- **Follicular phase**: 5 days
- **Ovulation**: Day 14
- **Luteal phase**: 16 days
- **Menstrual phase**: 5 days

Caveats:

- Energy intake (EI) - Exercise energy expenditure (EEE) normalized to fat-free mass
- Likely individual variability
- Higher needs in kids

- Exercise energy expenditure: energy expended during exercise in excess of energy that would have been expended in non-exercise activity during same time interval

*Mountjoy, M. et al. Br J Sports Med. 2014;48(5):491-497.*
Menstrual Dysfunction

- **Eumenorrhea**: menstrual cycles at intervals near the median for young adult women (28 days ± 7 days)
- **Oligomenorrhea**: menstrual cycles longer than 35 days
- **Luteal Suppression**: menstrual cycle with a luteal phase shorter than 11 days or with a low concentration of progesterone
- **Anovulation**: menstrual cycle without ovulation
- **Amenorrhea**: no menstrual cycles for > 90 days

Energy Availability and Menstrual Function

Dose-response relationship between energy availability and LH pulsatility

Bone Mass over the Lifespan

- 90% of women’s peak bone mass is accrued by age 18

Bone Measurement Techniques

- **DXA**:
  - Clinical gold standard
  - Limitations:
    - 2-dimensional or areal measurement of bone
    - Underestimates true BMD of small bones and overestimates BMD of large ones
  - Quantitative computed tomography (QCT):
    - QCT and peripheral QCT (pQCT) provide direct measurement of volumetric BMD
    - Can distinguish between cortical and trabecular bone
    - High-resolution pQCT (HRpQCT) can even provide information about bone microarchitecture
- **Z-score < -1.0 in weight-bearing athletes considered abnormal**
Bone Density and Structure in Adolescent and Young Adult Endurance Athletes 14-21 yo

BMI 10th-90th %iles
- Endurance athletes with amenorrhea (AA)
- Endurance athletes with eumenorrhea (EA)
- Non-athletic Controls (NAC)
- Bone mineral density (DXA)
- Bone structure assessed by HRpQCT
  - Distal radius (non weight-bearing bone)
  - Distal tibia (weight-bearing bone)

Bone Density and Structure in Adolescent Athletes
- Athletic activity → ↑ cross-sectional bone area at tibia
- Amenorrhea in athletes →
  ↓ trabecular # & ↓ cortical thickness →
  ↓ trabecular & total BMD → decreased stiffness and failure load (i.e. weaker bones!)

Interrelationship of Components of the Triad
- Negative Energy Balance → Disruption of Hypothalamic-Pituitary-Ovarian (HPO) axis

Interrelationship of Components of the Triad
- As energy availability ↓ below 30 kcal/kg FFM/day
  - Bone protein synthesis and mineralization ↓
  - Insulin, which enhances amino acid uptake, ↓
  - IGF-1 ↓
  - T3 ↓
- These effects occurred within 5 days of the onset of energy deficiency, and without a reduction in estrogen concentration!
Lean Mass is an Important Predictor of Bone Density in AA

Christo K, et al. Pediatrics, 2008.

Low Estrogen Contributes to Low Bone Density in Adolescent AA

Estrogen: antiresorptive

Lumbar BMD & WB BMD are predicted:
- Positively by estradiol
- Negatively by duration of amenorrhea and age at menarche

Studies of efficacy of oral estrogen not definitive
- ↑, no change, ↓ in BMD

Low IGF-1 Levels in Amenorrheic Athletes Compared with Controls Predict Bone Density

IGF-1: ↑ bone formation

- Oral estrogen: suppresses IGF-1
- Transdermal estrogen: does not suppress IGF-1

Screening for Triad

- An athlete with 1 component of the Triad should be evaluated for the other 2!

Diagnosis: Low Energy Availability/Eating disorder

- Suspect when:
  - Weight loss
  - Fall off of growth curve
  - Decline in performance
  - Change in mood
  - Frequent injury/illness
  - Stress Fracture
  - Low BMD
  - Menstrual dysfunction
  - Poor score on Eating Questionnaire
Diagnosis: Menstrual Dysfunction

- Suspect when:
  - ED/DE
  - Low BMI
  - Delay in developing secondary sexual characteristics
  - Weight loss
  - Stress Fracture

Diagnosis: Low BMD

- Suspect when:
  - Stress Fracture
  - ED/DE
  - Menstrual dysfunction
  - Malabsorption syndrome
    - Celiac Disease
    - Irritable Bowel

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**Component of Triad**

**Diagnostic Testing**

**Low Energy Availability**
- CBC
- Complete Metabolic Panel
- +/- ECG

**Menstrual Dysfunction**
- hCG
- Follicle Stimulating Hormone (FSH)
- TSH and Free T4
- Proctolin

If suspect hyperandrogenism:
- LH (to assess LH:FSH ratio)
- Total Testosterone
- Sex hormone binding globulin (SHBG)
- DHEA-S
- 17-OH Progesterone

To confirm estrogen status:
- Progesterone challenge

**Low Bone Mineral Density**
- DXA and T/U labs

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**Treatment**

- Interdisciplinary Team!
  - Therapist/Sports Psychologist/Psychiatrist
  - Dietitian/Nutritionist
  - Exercise Physiologist
  - MD/NP/RN: Primary Care, Sports Med, Endocrine, Ortho, etc.
  - Support Group
  - Teammates
  - Family/Friends

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**Medical Treatment**

- Aircast boot?
- Bone stimulator?
- Medications???
  - Antidepressant
  - Progestin challenge
  - OCP
  - Androgens
  - IGF-1
  - Leptin
  - Bisphosphonates
  - PTH
  - Estrogen
Potential Treatments for Triad-OCPs?

• Data limitations

• Studies of efficacy of OCPs on BMD not definitive
  • Increase, no change, decrease in BMD

• Recent guidelines from Endocrine Society recommending against use

Gordon CM, Ackerman KE, et al. J Clin Endocrinol Metab, May 2017, 102(5):1–27.

Androgens? IGF-1?

• Testosterone and DHEA replacement in women with anorexia nervosa (AN)
  – Changes in bone turnover markers, but no improvements in BMD
  – DHEA + OCP in adolescents & young adults with AN prevented further decrease, but did not increase BMD

• Recombinant human IGF-1 + OCP in AN
  – Improved lumbar BMD
  – Not yet tested in young women with Triad

Huang J, Li, et al. Osteoporosis Int, 2011.
DiVasta AD, et al. Metab, 2012.
Fajardo A, et al. J Clin Endocrinol Metab, 2012.

Leptin?

• 20 amenorrheic female athletes randomized to recombinant methionyl human leptin (metreleptin) or placebo
  – Lumbar spine BMD trended higher at 9 months in treatment group

• In subjects who completed the entire 2-year study, metreleptin significantly increased lumbar BMD (but n=41)

• Major side effect: weight loss!

Sternlieb E, et al. Metab, 2011.

Bisphosphonates?

• Antiresorptive agents that inhibit osteoclast function

• Low energy availability and amenorrhea can both increase bone loss and suppress bone formation, but bisphosphonates do not address issue of reduced bone formation

• Long half-life of drug (can stay in bone for 10 years) and teratogenic risk

• No studies in Triad

Grinspoon S, et al. J Clin Endocrinol Metab, 2002.

Teriparatide?

• Teriparatide (Forteo®) is an anabolic agent used in some forms of osteoporosis

• Used off-label to accelerate fracture healing

• 21 adult women (mean age 47 yo) with AN randomized to teriparatide or placebo:
  – At 6 months, lumbar BMD increased significantly more with treatment

• No studies yet in Triad and not appropriate for adolescents

Fazeli PK, et al. J Clin Endocrinol Metab, 2014.

Transdermal Estrogen?

• Anorexia patients (n=112, ages 12 - 18 yrs) randomized to either a transdermal patch of estradiol + cyclic oral progesterone or placebo
  – 18 months: both spine and hip BMD ↑ vs. placebo

Misra M, et al. J Bone Miner Res, 2011.
Female Athlete Triad Coalition’s Return to Play Approach

| Risk Factors | Low Risk → 4 points each | Moderate Risk → 1 point each | High Risk → 2 points each |
|--------------|---------------------------|-------------------------------|---------------------------|
| Ex-E, E or without RED | No dietary restriction | Semi-dietary restriction; current/past history of ED* | More than 15% weight loss for ED** |
| Ex-RM | BMI > 15.5 or 10% EEN** or weight stable | BMI 15.5 > 16.5 or 10% EEN* | BMI 15.5 > 16.5 or > 10% weight loss |
| Menstrual Anomaly | Menarche < 17 years | Menarche > 17 years | Menarche > 17 years |
| Independent and/or competitive | 0 to 9 months to 17 months* | 0 to 9 months to 12 months* | 0 to 6 months to 12 months* |
| Ex-RM | 2-scores > 1.5 | 2-scores > 1.5 to 2.5 | 2-scores > 2.5 |

Cumulative Risk Score (total score):

- 0-4 points = Low Risk
- 5 points = Moderate Risk
- > 5 points = High Risk

De Souza MJ, et al. Br J Sports Med. 2014 Feb;48(4):289.

FATC’s Return to Play

| Cumulative Risk Score* | Low Risk | Moderate Risk | High Risk |
|------------------------|----------|--------------|-----------|
| Full Clearance | 0 – 1 point | | |
| Provisional Clearance | 2 – 5 points | Provisional Clearance | Limited Clearance |
| Restricted from Training and Competition | 6 points | | Restricted from Training; Competition Provisional |
| Disqualified | | | Disqualified |

De Souza MJ, et al. Br J Sports Med. 2014 Feb;48(4):289.

IOC’s RED-S CAT

- Level of concern: low, medium, high
- Red flags: exercise restriction, amenorrhea, loss of muscle mass, loss of sexual interest
- Red-S score: 0 to 3 (low), 4 to 6 (medium), > 6 (high)

De Souza MJ, et al. Br J Sports Med. 2014 Feb;48(4):289.

Future Directions

- Studies exploring other health and performance effects of low energy availability in female athletes and other populations
- Studies determining efficacy of RTP Protocols
- Comparison of treatment approaches for ED/DE in athletes:
  - Complete exercise restriction vs. reduced exercise
  - Psychotherapy early (CBT, DBT, FBT) in some vs. all Triad patients
- Definitive hormonal and other therapy studies
- Further research on consequences of energy deficiency in female athletes and other populations
- More awareness and prevention programs

De Souza MJ, et al. Br J Sports Med. 2014 Feb;48(4):289.

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- Massachusetts General Hospital Sports Endocrine Research Lab
- Our Patients

De Souza MJ, et al. Br J Sports Med. 2014 Feb;48(4):289.
GOOD RESOURCES

BJSM
FTR Female Athlete Triad: Oxfam Campaign. The 2014 report, led by Kathryn Ackerman, was a call to action to "take a stand" for female athletes and to "fclose the gender gap." Kathryn Ackerman is a fellow in adolescent medicine at Children's Hospitals Boston and the Harvard Medical School.

UpToDate
Functional hypothalamic amenorrhea: Pathophysiology and clinical manifestations
Authors: Kathryn E Ackerman, MD, MPH, Shuchanda Mira, MD, MPH
Section Editors: Robert L Radtke, MD, William F Crowley, Jr, MD
Deputy Editor: Kathryn A Marks, MD

JCEM
Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline
Authors: Catherine M. Grady,1 Kathryn E. Ackerman,2,4 Sarah L. Bengtson,2,4 Jay L. Kaplan,1 Deborah Roberts,1 Shuchanda Mira,3,4 M. Hasan Murad,2,4 Karuna P. Samoto,2 and Michele P. Marceus2

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