Management of Stress Fractures in the Active Woman

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Until every child is well™

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

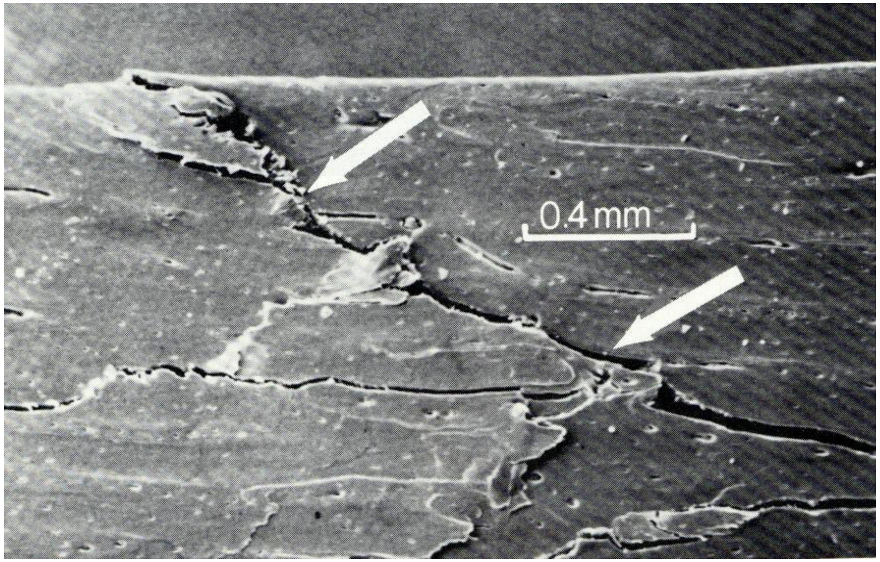
Disclosures

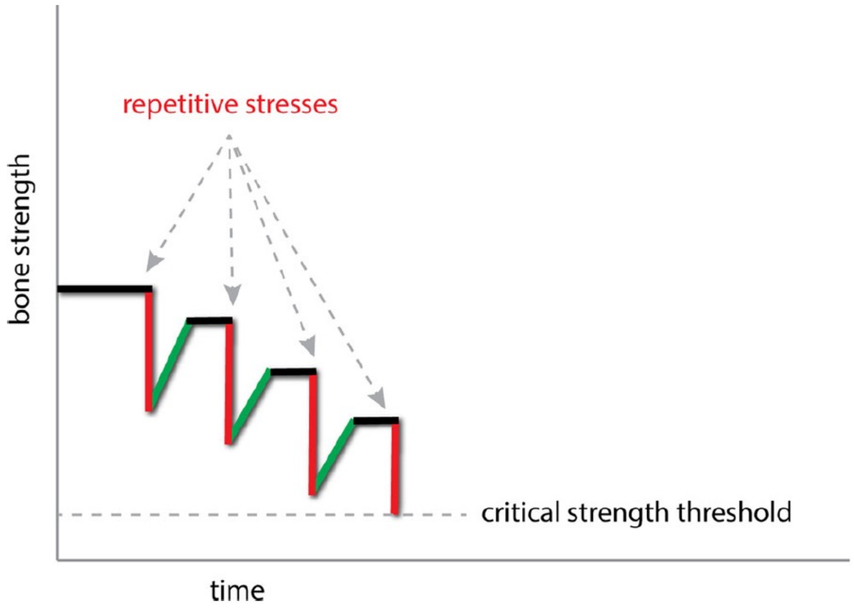
- Paid speaker and consultant:
  - Gatorade Sports Science Institute
  - Hologic
  - US Olympic and Paralympic Committee

Stress Fractures/Bone Stress Injuries

- Microfractures in cortical bone as a result of abnormal bone remodeling in the setting of repetitive stress impact

- Bone stress injuries account for up to 20% of injuries seen in sports medicine clinics



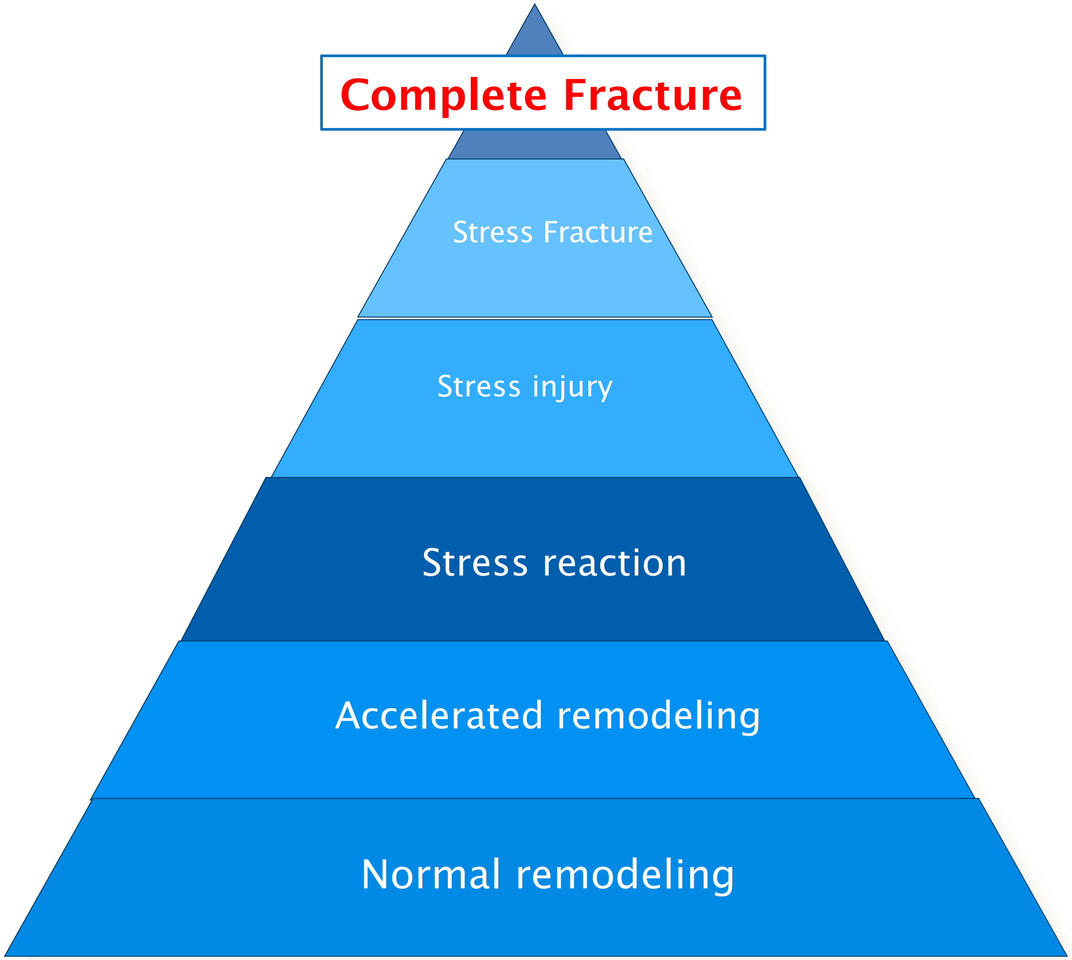


Fredericson M, et al. Top Mag Reson Imag, 2007.   Mandell JC, et al. Skeletal Radiol, 2017.

Semantics

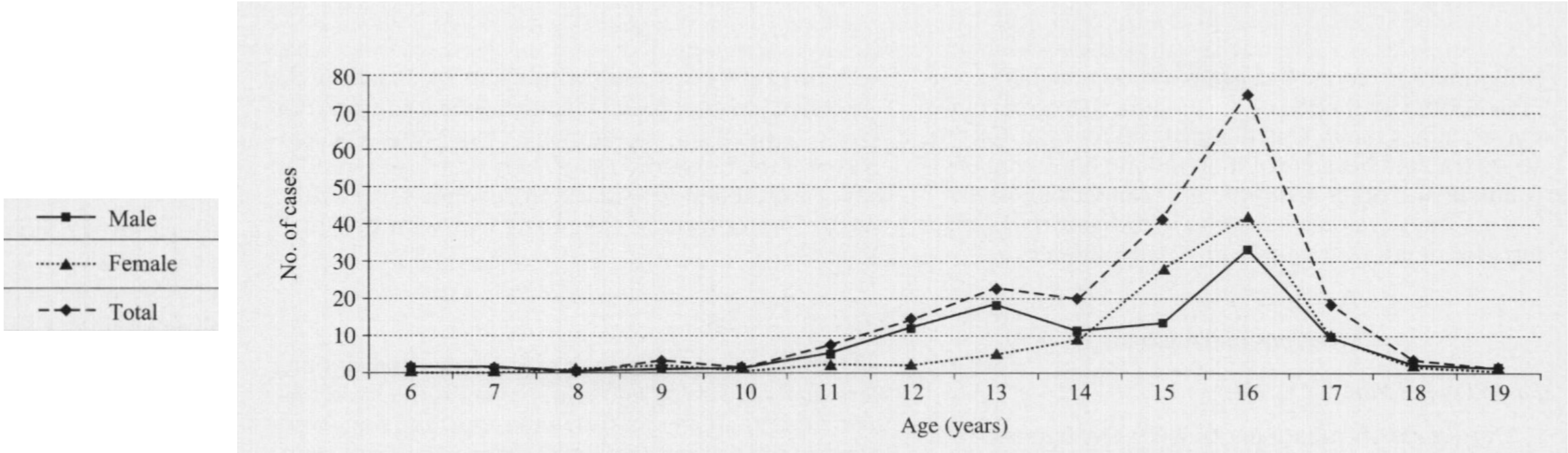
- Stress fractures are sometimes divided into fatigue fractures and insufficiency fractures
  - A *fatigue fracture* occurs from repeated stress on a “normal bone”
  - An *insufficiency fracture* occurs with relatively normal activity on a “weakened bone”
- Stress Fracture/Fatigue Fracture/Bone Stress Injury

Continuum of Bone Stress Injuries



Stress Fractures/Bone Stress Injuries

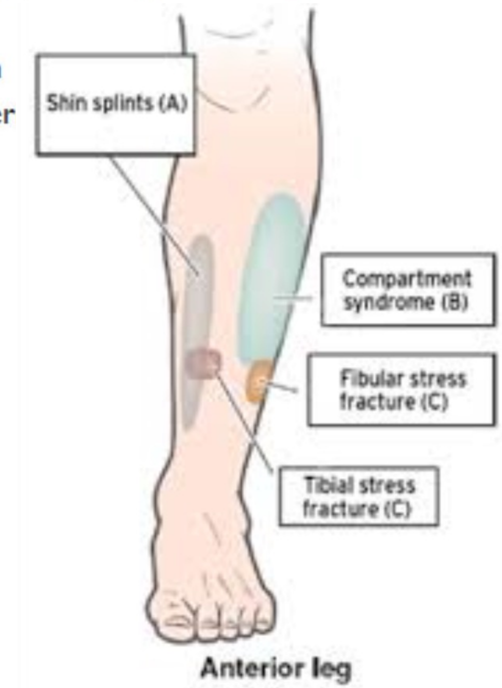
- Runners who average >25 miles per week are at increased risk for stress fractures
- More common in women than men
- The tibia, fibula, and metatarsal bones are the most frequently affected sites
- In children there are peak times of susceptibility



Moreira CA and Bilezikian JP. J Clin Endocrinol Metab, 2017. Ohta-Fukushima M, et al. J Sports Med Phys Fitness, 2002.

Common Locations of BSI

Stress fracture location	Differential diagnosis	History and physical evaluation
Tibia – medial	• Medial tibial stress syndrome • Meniscal pathology (medial tibial condyle) • Ligamentous injury (medial malleoli, tibial condyle) • Malignant tumor (medial tibial condyle)	• Focal pain during weight-bearing/or activity along tibial shaft • Pain with percussion
Tibia – anterior	• Compartment syndrome • Tendinopathy	• Focal pain during weight-bearing/or activity along tibial shaft • Pain with percussion
Fibula	• Meniscal injuries • Lateral ligament sprains	• Focal pain and tender • Referred knee pain



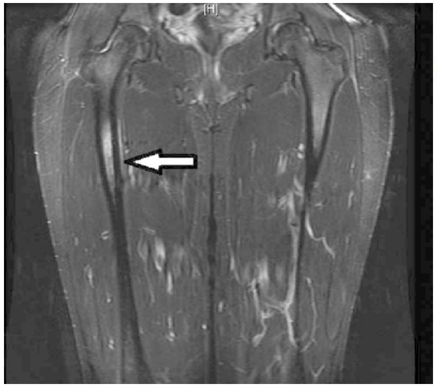
Kahanov L, et al. Open Access J Sports Med, 2015.

Common Locations of BSI

Stress fracture location	Differential diagnosis	History and physical evaluation
Great toe sesamoid	• Sesamoiditis • Avascular necrosis • Synchondrosis • Partite sesamoid • Osteomyelitis • Bursitis	• Focal point tenderness and swelling • Pain on dorsiflexion • Pain during weight bearing and push off • Increasing pain with activity
Metatarsals	• Strain • Plantar fasciitis • Morton's neuroma • Metatarsalgia	• Pain during weight bearing • Focal swelling • Focal tenderness

Kahanov L, et al. Open Access J Sports Med, 2015.

Common Locations of BSI

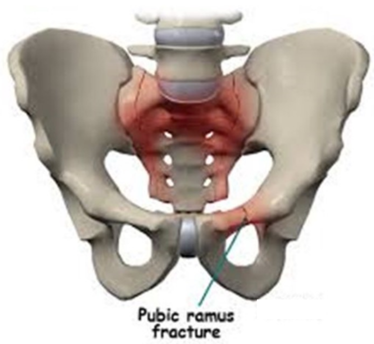


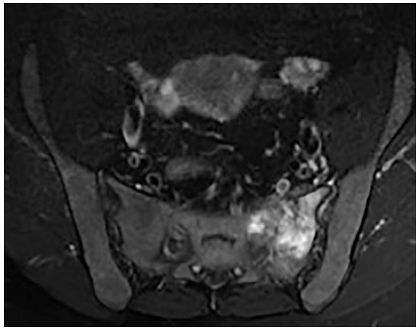
Stress fracture location	Differential diagnosis	History and physical evaluation
Femur/femoral shaft	• Rectus femoris strain • Adductor strain	• Dependent on location of injury o Groin o Anterior thigh o Gluteal o Knee • Activity related pain • Hip pain at end ranges of motion • Pain with one leg hop • No pain on palpation • Night pain may be present
Femoral neck	• Trochanteric bursitis • Strain in hip musculature	• Anterior groin pain • Increasing pain with activity • Pain with straight leg raise • Pain with log roll • Pain with one leg hop

Kahanov L, et al. Open Access J Sports Med, 2015.

Common Locations of BSI

Stress fracture location	Differential diagnosis	History and physical evaluation
Pelvis (pubic rami)	• Strain of adductors • Bursitis	• Groin, buttock, or thigh pain • Focal tenderness • Pain with single leg stance on affected side • Positive hop test • Point tender (may be extreme) on pubic rami
Sacrum	• Sciatica • Disk pathology • Sacroiliac joint pathology • Strain of gluteus maximus • Strain deep external rotators or piriformis • Strain hamstring	• SI and/or buttock pain during palpation and load bearing activity • Low back pain • Radiculopathy • Additional physical examinations are typically unremarkable





Kahanov L, et al. Open Access J Sports Med, 2015.

Low-risk and High-Risk

High Risk	Low Risk
Region of Maximal Tensile Load	Compression Load
Poor natural history: progression to complete fracture	Good natural history
Zone of diminished blood flow	Good blood flow
Chronic Pain	Chronic Pain
Delayed Union / Non Union	Good healing
Predilection for protracted recovery	Good recovery
Complete Fracture needs surgery	Symptomatic: activity modification
Incomplete fracture needs Strict NWB or Surgery	Asymptomatic: need no x-ray follow up

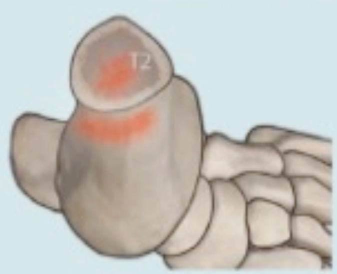
Kaeding CC, et al. Clin J Sports Med 2005; Diehl JJ, et al. Clin J Sports 2006; McInnis KC & Ramey LC, PM R, 2016. *Courtesy of Dr. Juan Manuel Alonso*

Low-risk and High-Risk

Low Risk	High Risk
Iliac Crest	Sacrum
Pubic Ramii	Femoral Neck
Femoral Shaft	Patella
Fibula	Anterior cortex of tibia
Posteromedial Tibia	Medial Malleolus
Lateral Malleolus	Talus (lateral process)
Calcaneus	Tarsal Navicular
Cuboid	Proximal Diaphysis of MT5
Cuneiforms	Base of MT2-MT4
Diaphysis of MT1-MT4	Great-toe sesamoids

Kaeding CC, et al. Clin J Sports Med 2005; Brukner & Khan´s Clinical Sports Medicine, 2017. *Courtesy of Dr. Juan Manuel Alonso*

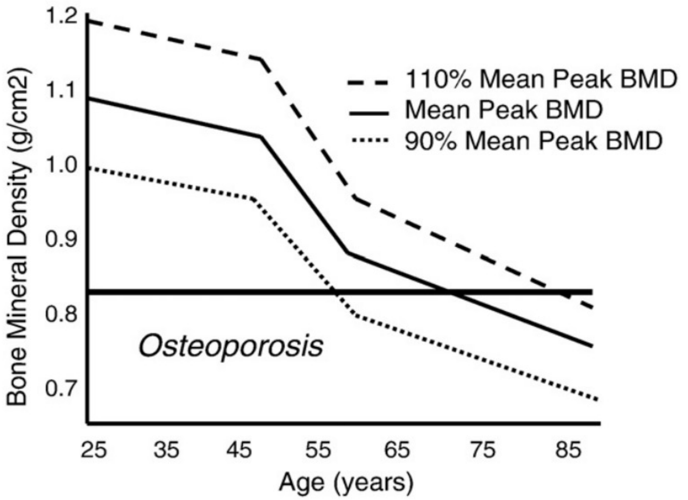
Common MRI Grading (Fredericson with Kijowski modification)

Grade	Illustration	Grade	Illustration
Grade 0: Normal MR		**Grade 3:** Moderate bone marrow edema seen on both T2-weighted images and T1-weighted images *return to sport in mean 39-44 days*	
Grade 1: Periosteal edema only *return to sport in mean 16 days*		**Grade 4a:** Cortical signal abnormality, not linear in morphology *return to sport in mean 39-44 days*	
Grade 2: Mild bone marrow edema seen on T2-weighted images only *return to sport in mean 39-44 days*		**Grade 4b:** Linear cortical signal abnormality *return to sport in mean 71 days*	

Mandell JC et al. Skeletal Radiol, 2017. Fredericson M, et al. Am J Sports Med, 1995. Kijowski R,et al. Am J Roentgenol, 2012.

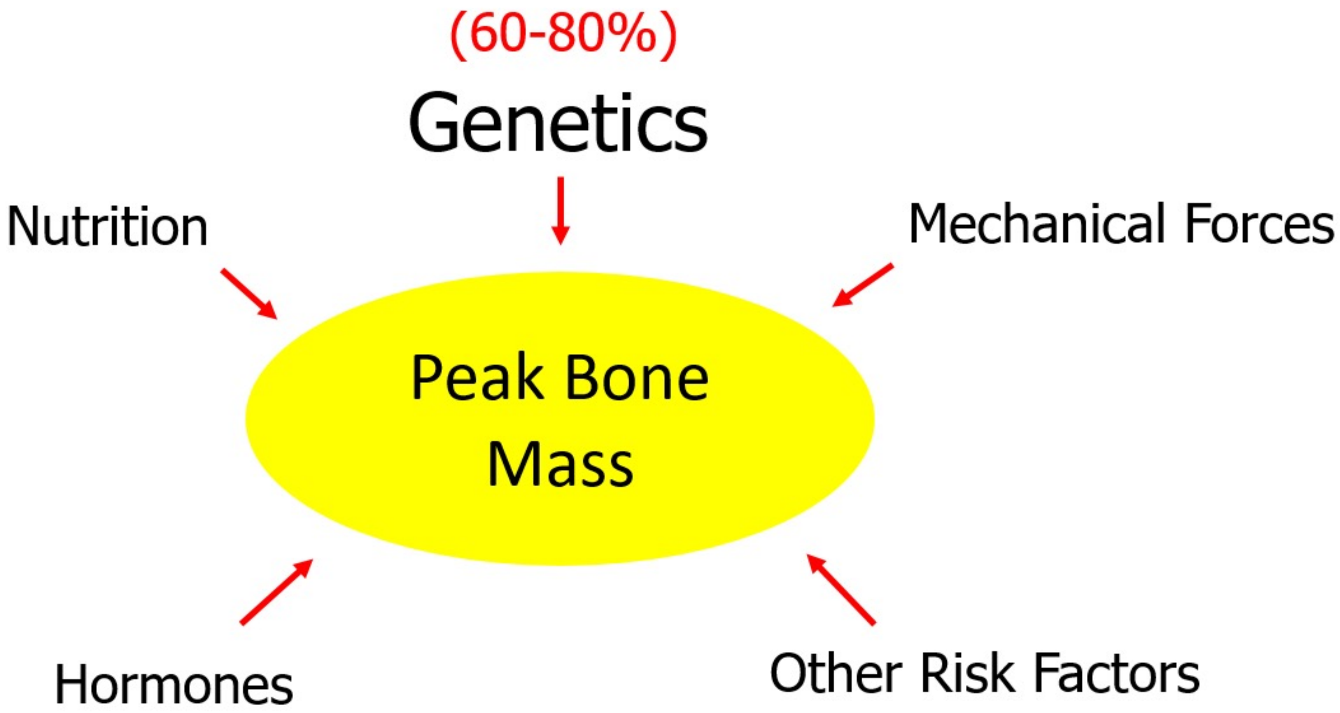
Peak Bone Mass

- Peak Bone Mass attained during childhood and adolescence is a major determinant of bone mass and fracture risk later in life
  - We build 90% of our peak bone mass by age 18
  - If a young adult’s BMD is just 10% higher than the mean, it may decrease stress fracture and fracture risk and delay the age of crossing the osteoporosis threshold by 13 years!



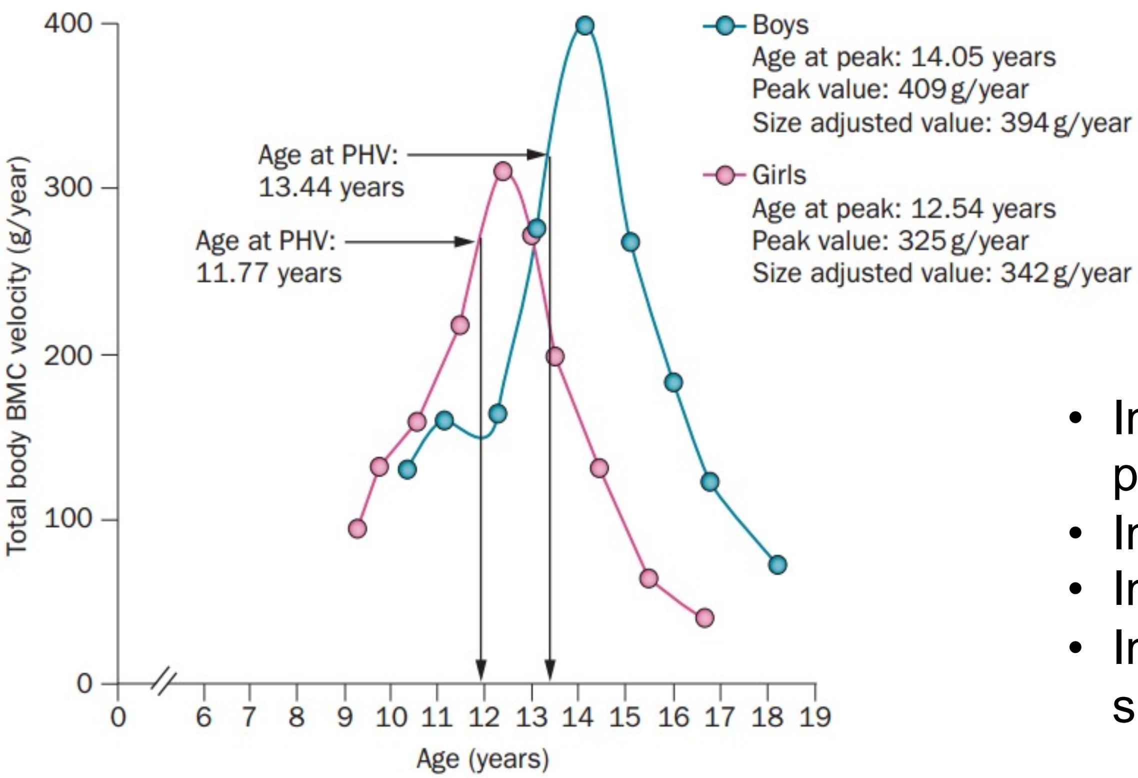
Rizzoli R, et al. Bone, 2010.
Hernandez CJ, et al. Osteoporos Int, 2003.

Determinants of Peak Bone Mass (and Risk of BSI)



Rizzoli R, et al. Bone, 2010.

Bone Accrual and Growth



- Increased cortical porosity
- Increased sports volume
- Increased fragility
- Increased fracture susceptibility

Bailey DA, et al. J Bone Miner Res, 1999.
Farr JM and Khosla S. Nat. Rev. Endocrinol, 2015.

Primary Conditions associated with Bone Fragility

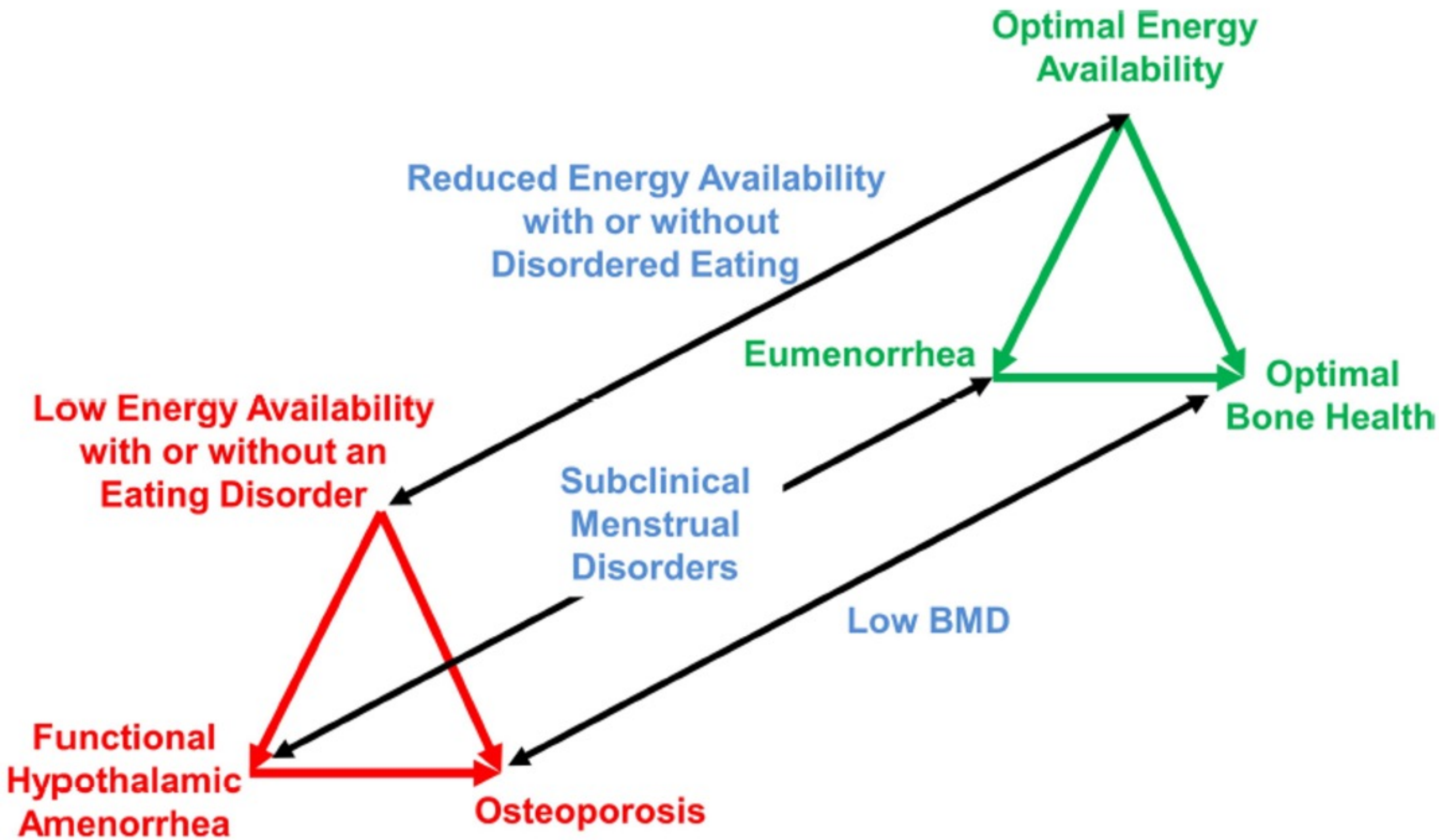
- Impaired collagen gene expression/modification/cross-link formation
  - Osteogenesis Imperfecta, Bruck syndrome
- Connective tissue defects
  - Ehlers-Danlos syndrome, Marfan syndrome, Homocystinuria
- Defective bone mineralization from low alk phos activity
  - Hypophosphatasia
- Impaired cell signaling and osteoblast function
  - Osteoporosis pseudoglioma syndrome
- Idiopathic Juvenile Osteoporosis

Secondary Conditions associated with Bone Fragility

- Medication induced
  - Glucocorticoids, Antiepileptic meds, Anticoags, Depo-medroxyprogesterone
- Decreased weight-bearing or muscle bulk
  - Duchenne muscular dystrophy, Cerebral palsy
- Infiltrative conditions
  - Leukemia, Thalassemia
- Chronic inflam. conditions
  - Juvenile idiopathic arthritis, Inflam. bowel disease
- Endocrine abnormalities
  - Hypogonadism, GH deficiency, Hyperpara, Hyperthyroidism, Hypercortisolism
- Vitamin and nutritional deficiencies
  - Vit D deficiency, Celiac disease, Eating disorder, Cystic fibrosis
- Renal disease
  - Renal failure w/ 2° hyperpara, Idiopathic hypercalciuria

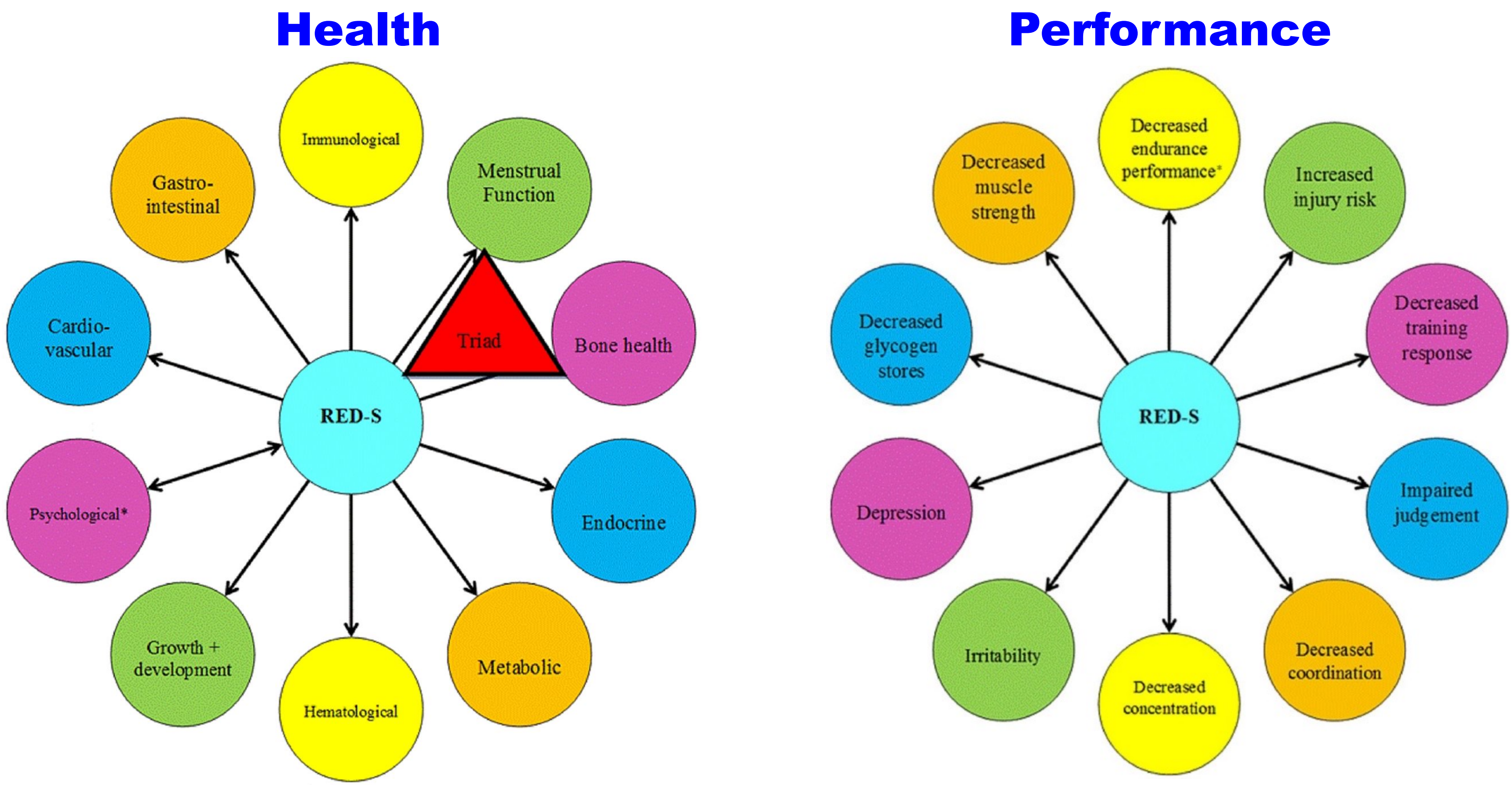
Harrington J and Sochett E. Pediatr Clin North Am, 2015.

Female Athlete Triad



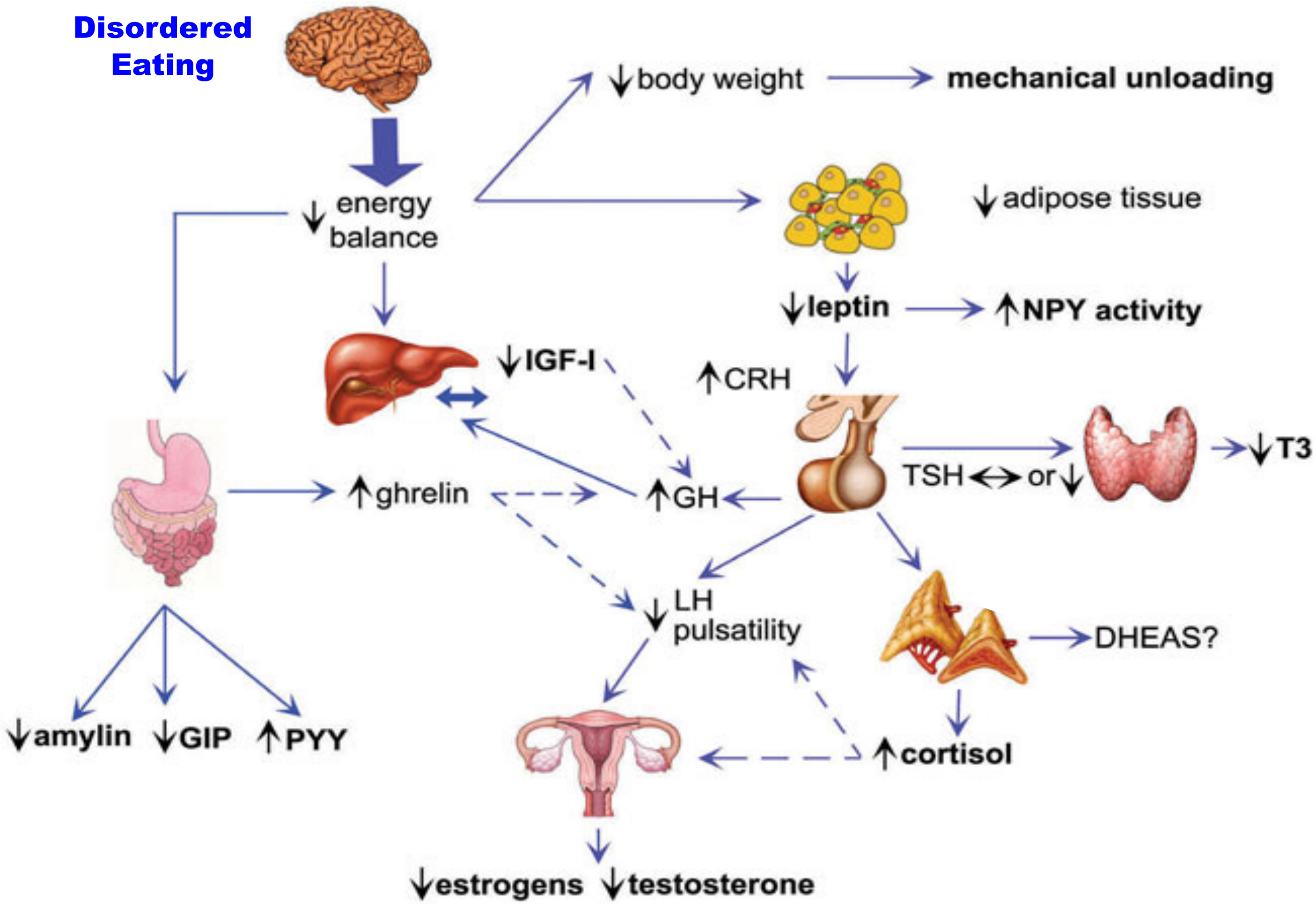
Nattiv A, et al. Med Sci Sports Exerc, 2007.
De Souza MJ, et al. Br J Sports Med, 2014.

Relative Energy Deficiency in Sport (RED-S)



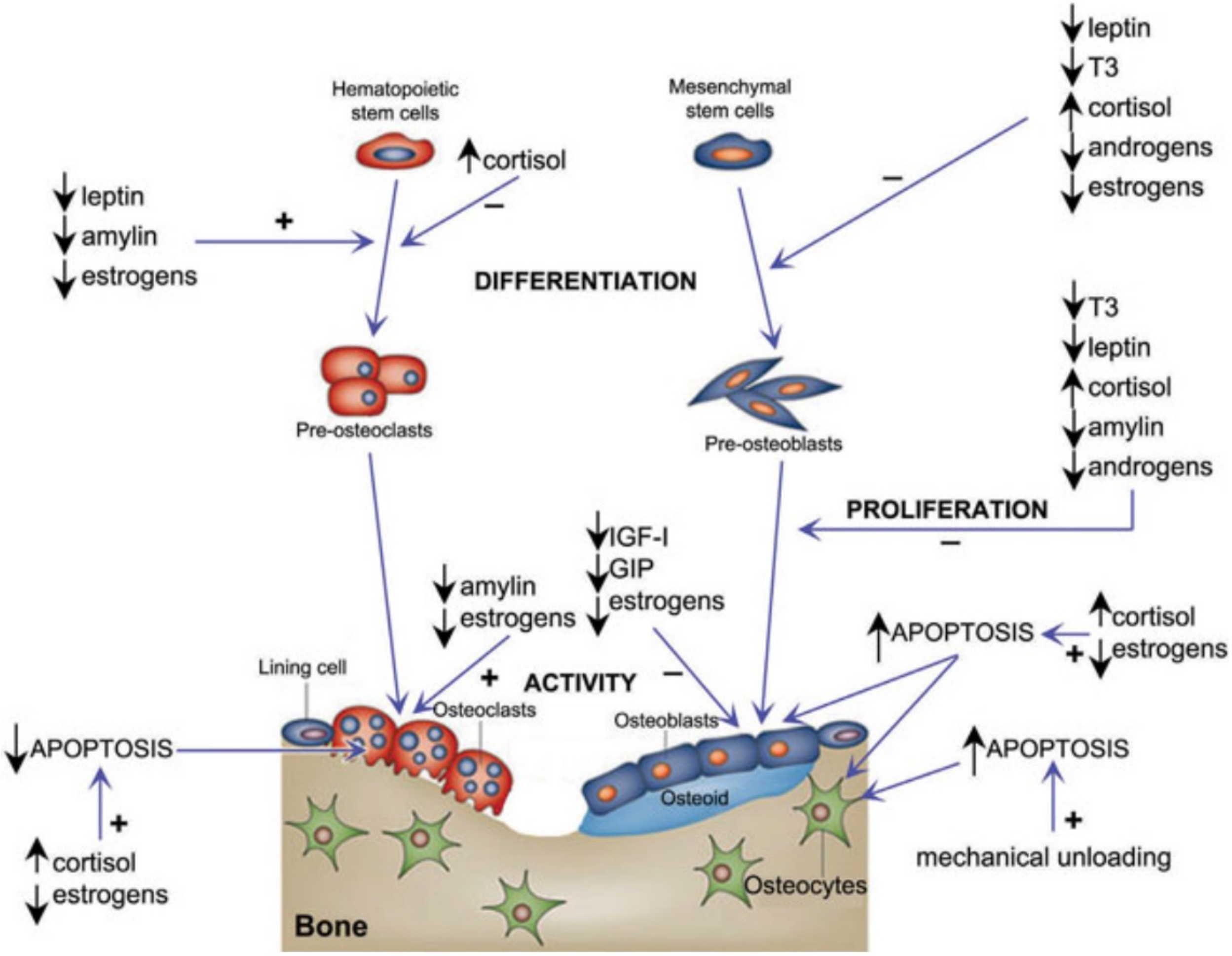
Mountjoy M, et al. Br J Sports Med, 2014, 2018.

Mechanisms of adaptive alterations similar to Anorexia Nervosa



Dede AD, et al. Hormones, 2014.

Hormonal Effects on Bone



Dede AD, et al. Hormones, 2014.

Endocrine Changes with Low EA

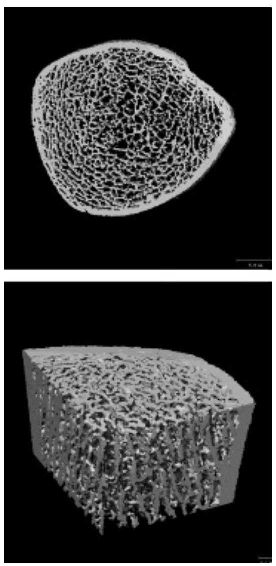
	Females	Males
Hypothalamic-Pituitary-Gonadal Axis		
LH	↔, ↓	↑, ↔, ↓
FSH	↔	↓
Estradiol	↓	↓
Testosterone	↑, ↔, ↓	↔, ↓
Progesterone	↓	
Energy Homeostasis, Appetite		
Resting metabolic rate	↓	↓
Leptin	↓	↓
Adiponectin	↑, ↔	
Ghrelin	↑	↔
Peptide YY	↑	↑
Oxytocin	↓	↓
Insulin	↓	↓
Amylin	↓	

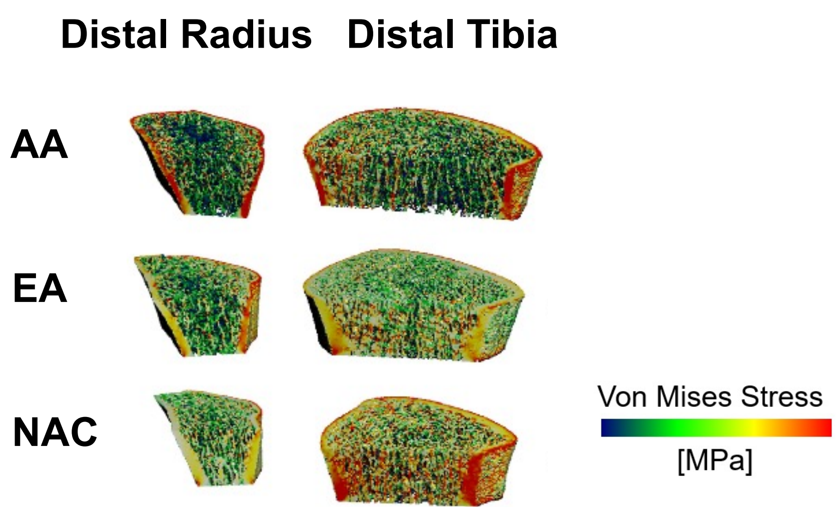
	Females	Males
Hypothalamic-Pituitary-Adrenal Axis		
Cortisol	↑, ↔	↔
Hypothalamic-Pituitary-Thyroid Axis		
TSH	↔	↔
T3	↓	↓
Free T3	↓	↓
T4	↑, ↔, ↓	↓
Free T4	↔, ↓	↓
Growth Hormone and IGF-1 Axis		
GH	↑	↑
IGF-1	↔, ↓	↑, ↓
IGF binding protein-1	↑	↑

Elliott-Sale Elliott-Sale KJ, Tenforde AS, Parziale AL, Holtzman B, Ackerman KE. Int J Sport Nutr Exerc Metab, 2018.

Bone Density and Structure in Adolescent and Young Adult Female 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!)**

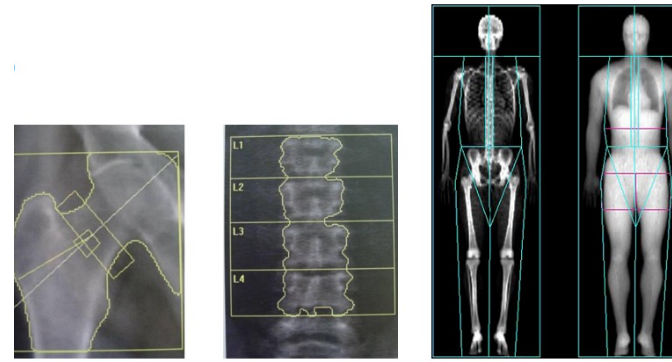


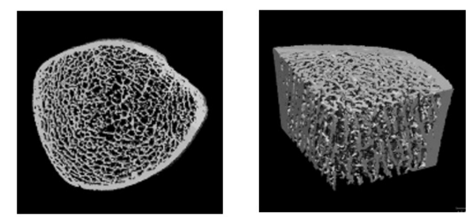


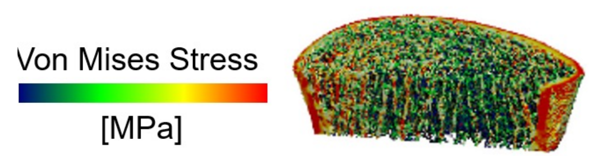
Ackerman KE, et al. J Clin Endocrinol Metab, 2011; Ackerman KE, et al. Bone, 2012.

Fractures in Relation to Menstrual Status and Bone Parameters in Young Athletes

- 175 females 14-25 year olds were studied
  - 100 oligo-amenorrheic athletes (AA)
  - 35 eumenorrheic athletes (EA)
  - 40 non-athlete controls (NA)
- Lifetime fracture history was obtained through participant interviews
- Areal BMD was assessed by DXA at the spine, hip and whole body
- Bone structure was assessed by HRpQCT at the radius and tibia, and strength by finite element analysis

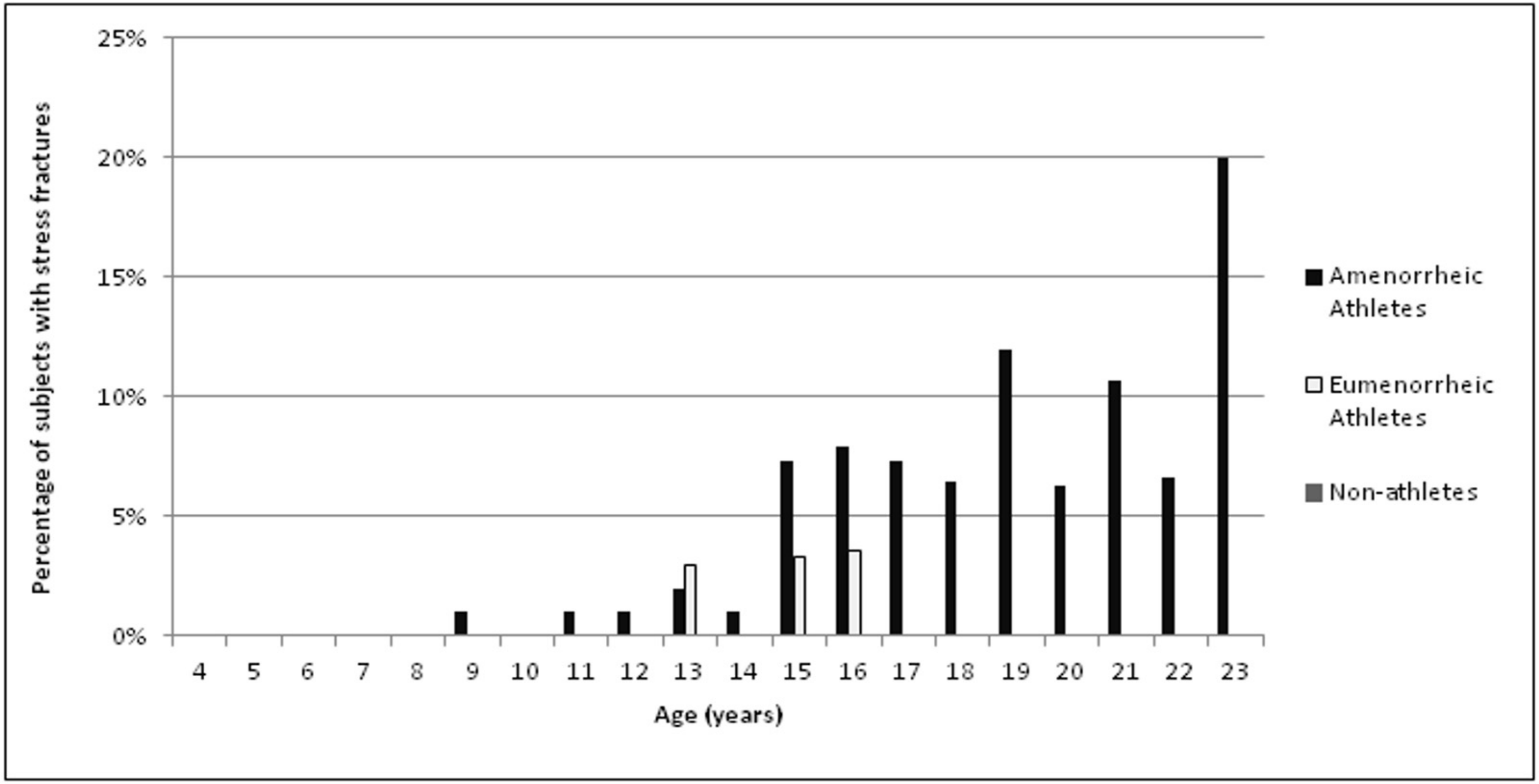






Ackerman KE, et al. Med Sci Sports Exerc, 2015.

Proportion of Subjects with *Stress Fracture* each Year



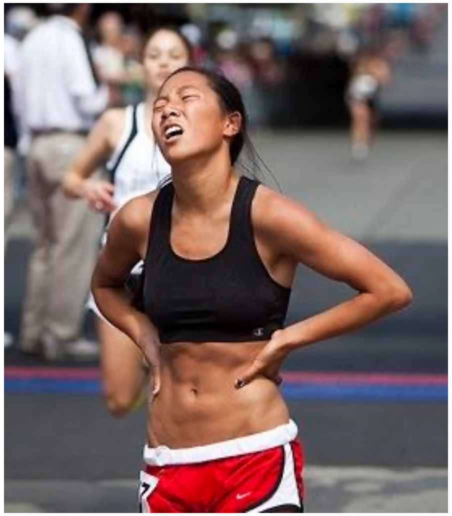
Ackerman KE, et al. Med Sci Sports Exerc, 2015.

DXA and HRpQCT Data in AA according to Stress Fracture History

	< 2 Stress Fx	≥2 Stress Fx	P
DXA (BMD Z-scores)	n=84	n=16	
Lumbar Spine	-0.61±1.20	-1.58±0.87	**0.003**
Whole Body	-0.55±1.02	-1.09±0.94	**0.05**
HRpQCT Radius	n=71	n=13	
Total area (mm^2)	267.9±45.8	240.7±32.9	**0.045**
Ct. porosity (%)	1.2±0.9	0.8±0.5	**0.07**
Tb. thickness (mm)	0.071±0.011	0.067±0.009	**0.25**
Tb. vBMD (mg HA/cm^3)	168.5±32.2	148.1±21.2	**0.03**
Outer Tb. vBMD (mg HA/cm^3)	226.8±31.1	204.5±21.0	**0.02**
Inner Tb. vBMD (mg HA/cm^3)	128.3±33.8	109.0±21.9	**0.05**
Stiffness (kN/m)	74.3±13.7	63.0±12.1	**0.007**
Failure load (kN)	3.78±0.68	3.18±0.60	**0.004**
HRpQCT Tibia	n=73	n=14	
Stiffness (kN/m)	230.7±30.3	213.8±28.0	**0.05**
Failure load (kN)	11.5±1.5	10.7±1.4	**0.048**

Ackerman KE, et al. Med Sci Sports Exerc, 2015.

What questions to ask



- ROS
- Medical hx
  - fracture hx (location, when, etc.)
  - growth hx
- Medications
- Pubertal/menstrual hx
- Pregnancy/lactation hx?
- Sexual function?
- Training hx
- Dietary hx
- Fam hx
  - fractures, osteoporosis, delayed puberty, endocrine disorders

What to look for on Physical Exam

- Height & weight (BMI)
- BP and pulse (orthostatics prn)
- HEENT: blue sclera, proptosis, gross visual fields, dentition, thyromegaly, LA
- CV
- Lungs
- Abdomen
- Maturation
- Bone pain/deformities
- Reflexes
- Flexibility/laxity
- Skin color
- Tremor?

Imaging to Consider- DXA

- DXA (with bone age in kids/adolescents)

- Z-score < -1.0 in a weight-bearing athlete
  - Investigate further

Labs to Consider

- BASIC:
  - Complete Metabolic Panel
  - Phos
  - Mg
  - PTH
  - 25(OH) Vitamin D
  - CBC
  - Urine Calcium/Creatinine
  - TSH
  - Iron studies
  - *Celiac screen (Total IgA and TTG IgA)*
  - *ESR, CRP*

- PRN:

  - Other endocrine labs (prolactin, FSH, estradiol, etc.); Further GI work-up; Myeloma screen; Genetic testing (COL1A1, COL1A2, karyotype, etc.)

At a minimum- What everyone should know about optimizing bone health

- Weight-bearing activity with adequate recovery and caloric intake is important
- General Calcium and Vit D Recommendations

AGE	CALCIUM RDA	VITAMIN D RDA	VITAMIN D LEVEL
4-9	1000 mg in divided doses	600 IU*	30-50 ng/mL
9-18	1300 mg in divided doses	600 IU*	30-50 ng/mL
19-menopause	1000 mg in divided doses	600 IU*	30-50 ng/mL
menopause	1200 mg in divided doses	600 IU*	30-50 ng/mL

* May need more vitamin D to reach level > 30, so many bone specialists recommend ≥800-1000 IU/day

- Some literature suggests that athletes may need higher doses of calcium

Treatment Options

- Interdisciplinary Approach-
  - Address Biomechanical, Behavioral, and Biological Factors

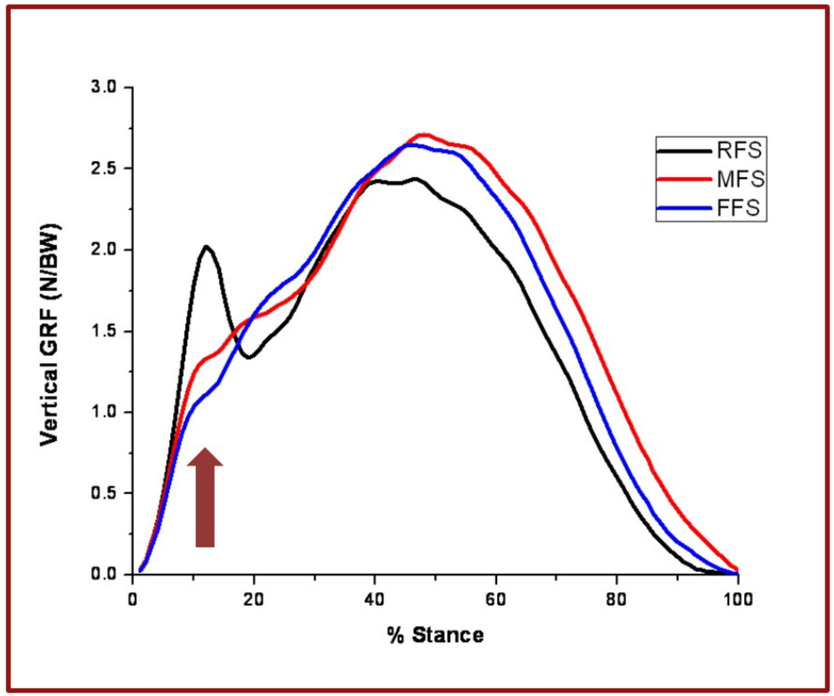
Gordon CM, Ackerman KE, et al. Functional Hypothalamic Amenorrhea:
An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab; May 2017.

Biomechanics- Strengthening, Stretching, Gait Assessment/Retraining


RFS


MFS


FFS



Images courtesy of A. Tenforde, MD

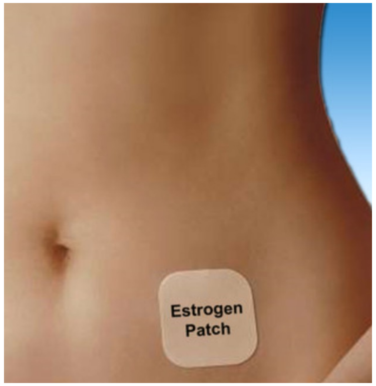
Nutrition and Training Modification

Transdermal Estrogen?

- 121 oligo-amenorrheic athletes 14-25 years old were randomized to receive:
  - 100 mcg 17-β estradiol transdermal patch applied continuously with cyclic oral micronized progesterone (200 mg for 12 days of each month) (PATCH group)

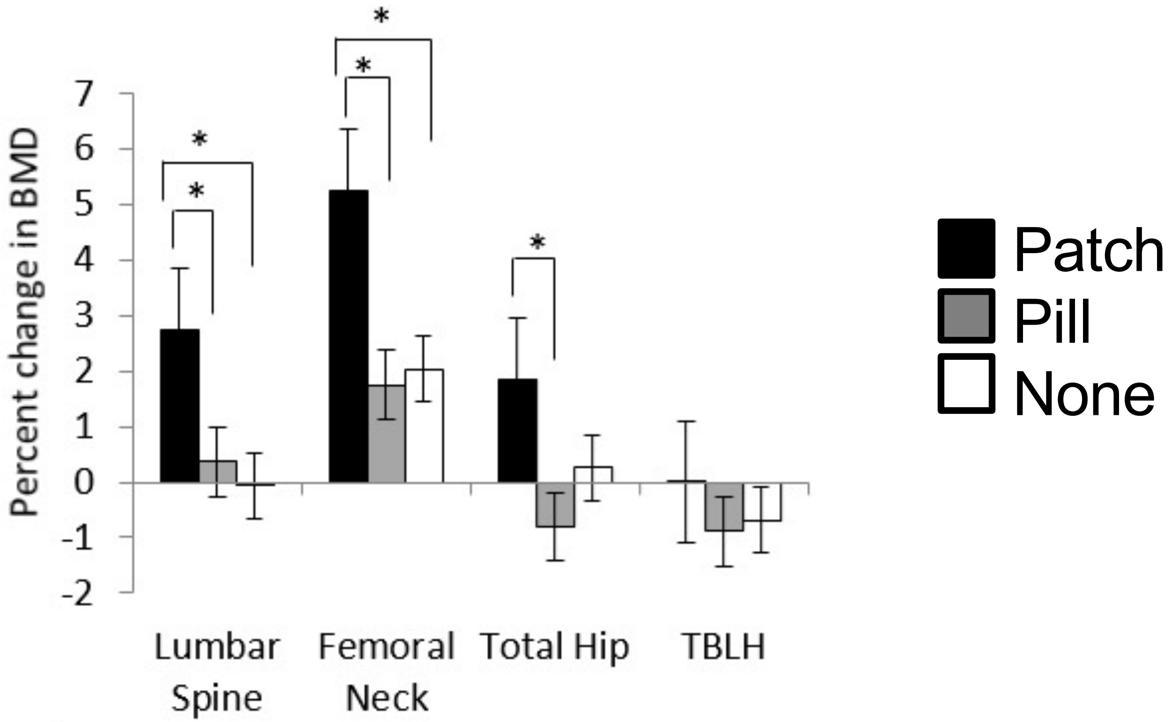
    or
  - 30 mcg ethinyl estradiol oral pill with 0.15 mg desogestrel daily with a week of placebo pills every month (PILL group)

    or
  - no estrogen/progesterone (NONE)



Transdermal Estrogen + Cyclic Oral Progesterone: Greater Increases in BMD

1 year of treatment



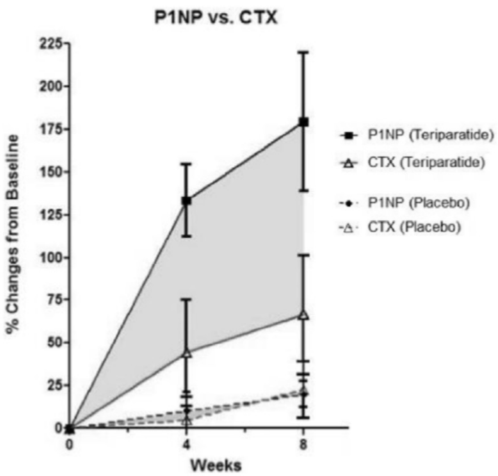
Ackerman KE, et al. Br J Sports Med, 2018.

Bisphosphonates

- Antiresorptive agents that inhibit osteoclast function
- Have been used in case series/case reports
- Used off label in professional athletes
- Low energy availability and amenorrhea can both increases bone loss and suppress formation, but bisphosphonates do not address issue of reduced bone formation
- Not recommended in premenopausal women secondary to the long half-life of these drugs (up to 10 years) and their potential teratogenic effects
- Not FDA-supported

Teriparatide?

- An anabolic agent used in some forms of osteoporosis
- A PTH analog that activates osteoblasts more than osteoclasts when used intermittently (e.g., daily injection)
- Used off-label to accelerate fracture healing
  - Almiral et al.: trial for stress fracture tx in women (6 teriparatide vs. 7 placebo)
    - Better anabolic window
    - larger cortical area and thickness vs. placebo at the tibia (placebo group had a greater total tibia and cortical density
    - MRI: 83.3% of the teriparatide and 57.1% of the placebo-treated group had improved or healed stress fractures (p = 0.18).

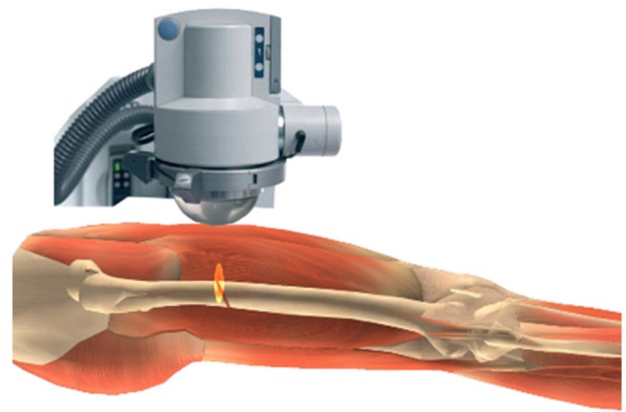


- Fazeli et al. randomized 21 adult women (mean age 47 y) with anorexia nervosa to teriparatide or placebo:
  - At 6 months, spine BMD increased significantly more with treatment (PA spine, 6.0% ± 1.4%; lateral spine, 10.5% ± 2.5%) vs. placebo (PA spine, 0.2% ± 0.7%; lateral spine, -0.6% ± 1.0%)
- No studies yet in Triad/RED-S and not appropriate for adolescents
- Not FDA-supported

Almiral EA, et al. J Clin Transl Endocrinol, 2016. Fazeli PK, et al. Clin Endocrinol Metab, 2014.

Bone Stim? Shockwave?

- capacitively coupled electrical field, CCEF
- pulsed electromagnetic fields, PEMFs
- low intensity pulsed ultrasound system, LIPUS
- extracorporeal shockwave therapy, ESWT

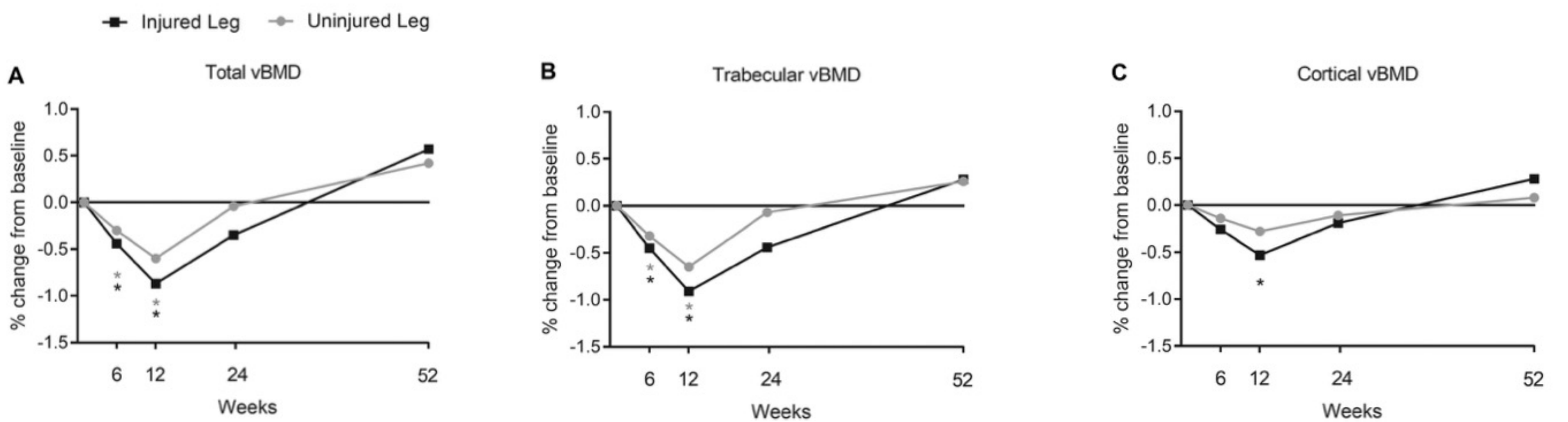


Massari L, et al. Int Orthop, 2019.

Reilly JM, et al. PM R, 2018.

Changes in Bone Microarchitecture after Tibial BSI

- 30 women ages 18-30 yrs with tibial BSIs followed for 1 year



Popp KL, et al. Am J Sports Med, 2021.

Sport and Triad Risk Factors Influence Bone Mineral Density in Collegiate Athletes

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- All Triad risk factors were associated with lower BMD Z-scores in univariable analyses
- Only low BMI and oligomenorrhea/amenorrhea were associated with lower BMD in multivariable analyses (all $p<0.05$)

TABLE 4. Influence of sports participation, Triad risk factors, and body composition for low BMD (LS or TB BMD *z*-score < −1.0) reported as rate ratios.

Categories	Unadjusted Model[a]	*P*	Model Adjusted for Triad Risk Factors[a]	*P*	Model Adjusted for Triad Risk Factors and Body Composition[a]	*P*
Sport						
Low-impact (*n* = 47)	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
Nonimpact (*n* = 81)	0.71 (0.32–1.59)	0.4	1.26 (0.50–3.18)	0.63	1.16 (0.45–2.89)	0.75
Multidirectional (*n* = 58)	0.18 (0.04–0.79)	0.0235	0.31 (0.06–1.53)	0.15	0.20 (0.03–1.48)	0.115
High-impact (*n* = 53)	0.10 (0.01–0.75)	0.0251	0.15 (0.02–1.18)	0.072	0.17 (0.03–1.33)	0.092
Triad risk factors						
Oligomenorrhea/amenorrhea, per point added risk[b]			2.05 (1.27–3.31)	0.0031	2.12 (1.34–3.35)	0.0013
Low BMI, per point added risk[b]			2.01 (1.15–3.51)	0.0145	0.98 (0.59–1.65)	0.95
Body composition						
Lean mass (kg)					0.92 (0.87–0.98)	0.0057
Height (in)					1.21 (0.98–1.48)	0.071

[a]Values represent rate ratio (95% confidence interval).
[b]Quantified risk factor additional point in risk assessment score per De Souza et al. (10).

Tenforde AS, et al. Med Sci Sports Exerc, 2018.

PREVENTION: FATC's Return to Play Approach

Risk Factors	Magnitude of Risk Low Risk = 0 points each	Moderate Risk = 1 point each	High Risk = 2 points each
Low EA with or without DE/ED	☐ No dietary restriction	☐ Some dietary restriction‡; current/past history of DE;	☐ Meets DSM-V criteria for ED*
Low BMI	☐ BMI ≥ 18.5 **or** ≥ 90% EW** or weight stable	☐ BMI 17.5 < 18.5 **or** < 90% EW **or** 5 to < 10% weight loss/month	☐ BMI ≤17.5 **or** < 85% EW **or** ≥ 10% weight loss/month
Delayed Menarche	☐ Menarche < 15 years	☐ Menarche 15 to < 16 years	☐ Menarche ≥16 years
Oligomenorrhea and/or Amenorrhea	☐ > 9 menses in 12 months*	☐ 6-9 menses in 12 months*	☐ < 6 menses in 12 months*
Low BMD	☐ Z-score ≥ -1.0	☐ Z-score -1.0*** < - 2.0	☐ Z-score ≤ -2.0
Stress Reaction/Fracture	☐ None	☐ 1	☐ ≥ 2; ≥ 1 high risk or of trabecular bone sites†
Cumulative Risk (total each column, then add for total score)	**_____ points +**	**_____ points +**	**_____ points = _____ Total Score**

De Souza MJ, et al. Br J Sports Med, 2014.

Conclusions

- Bone Stress Injuries happen and have intrinsic and extrinsic factors
- We need an interdisciplinary approach to address biological, biomechanical, and behavioral issues for treatment and prevention
- Enhanced knowledge of athletes, providers, and coaches is needed
- Currently hormonal treatments are off-label and not recommended
- Screening tools may be helpful
- More research is needed to determine appropriate loading during healing and return to play

Thank you!
Questions?

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