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RELATIVE ENERGY DEFICIENCY IN SPORT (RED-S)

OBJECTIVES

At the conclusion of this session, the learner will be able to:

- Describe 2 key differences between RED-S and the Female Athlete Triad.
- Describe the concept of energy availability and its principal role in RED-S.
- List 3 of the systems affected by RED-S.
- List 2 risk factors for the development of RED-S.
- List 3 symptoms of RED-S.
- Describe the components of an appropriate assessment for RED-S

RED-S

"…RED-S refers to 'impaired physiological functioning caused by relative energy deficiency and includes, but is not limited to, impairments of metabolic rate, menstrual function, bone health, immunity, protein synthesis and cardiovascular health."

"The aetiological factor of this syndrome is low energy availability"

EPIDEMIOLOGY

- Disordered eating:
  - Present in 25 - 31% of elite female athletes in endurance, thin-build, wt class sports.
    - 5.5 - 9% in general population.
- Impaired bone health:
  - 22-50% of female athletes (osteopenia), 0-13% (osteoporosis)
    - 12% and 2.3% respectively in non-athletes
- Menstrual Dysfunction: 6-79% of athletes.
  - 2ndary amenorrhea: 69% dancers, 65% runners
    - 2-5% in general population.
    - Young runners (<15 yo): 67%.
      - 9% in older female runners.
- Consistently lower bone mineral density in amenorrheic athletes vs eumenorrheic athletes.
- 90% of peak bone mass is achieved by the age of 18.

TIMELINE OF EVENTS

Female Athlete Triad and its development

1992

Concerning triad identified

ACSM convenes panel of experts to discuss concerning triad in female athletes

1997

1st ACSM position statement

ACSM publishes its first position statement on the Female Athlete Triad.

1998-2006

More studies

Show negative health consequences from less severe conditions than those identified in 1997

2007

2nd ACSM position statement

Emphasizes energy availability

Identified triad existing on a spectrum vs clinical endpoints

Some discussion on males.

2014

IOC position statement on RED-S

Identifies multiple systems affected by low energy availability and the consequences.

Some focus on males.

Focus on risk assessment

2018 UPDATE

IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update

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INTRODUCTION

In 2014, the IOC published a consensus statement entitled 'Beyond the Female Athlete Triad: Relative Energy Deficiency in Sport (RED-S)'. The syndrome of RED-S refers to 'impaired physiological functioning caused by relative energy deficiency and includes, but is not limited to, impairments of metabolic rate, menstrual function, bone health, immunity, protein synthesis and cardiovascular health'. The aetiological factor of this syndrome is low energy availability (LEA).[1]

The publication of the RED-S consensus statement stimulated activity in the field of Female Athlete Triad science, including some initial controversy[2 3] followed by numerous scientific publications addressing:

1. The health parameters identified in the RED-S conceptual model (figure 1).[1 4]
2. Relative energy deficiency in male athletes.
3. The measurement of LEA.
4. The performance parameters identified in the RED-S conceptual model (figure 2).[1 4]

The IOC RED-S consensus authors have reconvened to provide an update summary of the interim scientific progress in the field of relative energy deficiency with the ultimate goal of stimulating advances in RED-S awareness, clinical application and scientific research to address current gaps in knowledge.

Low energy availability

LEA, which underpins the concept of RED-S, is a mismatch between an athlete's energy intake (diet) and the energy expended in exercise, leaving inadequate energy to support the functions required by the body to maintain optimal health and performance. Operationally, energy availability (EA) is defined as:

Energy Availability (EA)
= Energy Intake (EI) (kcal)
−Exercise Energy Expenditure (EEE) (kcal)/
Fat Free Mass (FFM) (kg)

where exercise energy expenditure (EEE) is calculated as the additional energy expended above that of daily living during the exercise bout, and the overall result is expressed relative to fat-free mass (FFM), reflecting the body's most metabolically active tissues.[5 6] Rigorously controlled laboratory trials in women have shown that optimal EA for healthy physiological function is typically achieved at an EA of 45 kcal/kg FFM/day (188 kJ/kg FFM/day).[7 8] Meanwhile, although some caveats are noted in relation to differential responses of various body systems,[9] many of these systems are substantially perturbed at an EA <30 kcal/kg FFM/day (125 kJ/kg FFM/day), making it historically a targeted threshold for LEA. However, recent evidence suggests that this cut-off does not predict amenorrhoea in all women.[10 11] In addition, and not withstanding differences across body sizes and pubertal age, it is noted that an EA of 30 kcal/kg/FFM roughly equates to the average resting metabolic rate (RMR).[5] Because LEA has proven robust in explaining markers of suboptimal health and function in both laboratory[7 8] and field settings,[12 13] it seems logical that an EA assessment could serve as a diagnostic tool in the prevention or management of RED-S.

Measurement of EA

Despite the primary importance of determining whether an athlete has adequate EA, several barriers prohibit the direct measurement of EA from being a practical and reliable option. First, there is no standardised or reference protocol for undertaking an EA assessment (eg, the number of collection days, methodologies for assessing energy intake, exercise energy expenditure or FFM). Furthermore, there are significant concerns over the reliability and validity of each of these metrics. The greatest challenge is to gain an accurate record of usual energy intake from self-reported sources.[9 14] Other challenges include the measuring of exercise energy expenditure during many of the training/competition activities performed by athletes and accounting for their additional recreational/lifestyle activity.[9 15] These problems may partially explain why many field studies report considerable discrepancies between EA calculations and symptoms associated with LEA.[9 14 16–18] However, other explanations for these observations include: (1) the temporal dissociation between the period of mismatched eating and exercise behaviour that created the LEA problems and the occasion on which the EA assessment was undertaken and (2) the interaction of other dietary characteristics that often co-exist with LEA and may exacerbate its effects (eg, high intake of fibre, stimulants and artificial sweeteners; low energy density foods; high dietary restraint and poor spread of energy within a day).[19–23] Even if these problems

ENERGY AVAILABILITY (EA)

- **The amount of dietary energy remaining after exercise, for all other physiological functions.**
- EA = Energy Intake (EI) – exercise energy expenditure (EEE)/ fat free mass (FFM)
  - EEE: additional energy expended during exercise, above that of daily living
- Adequate EA females: 45 kcal/kg of FFM/day

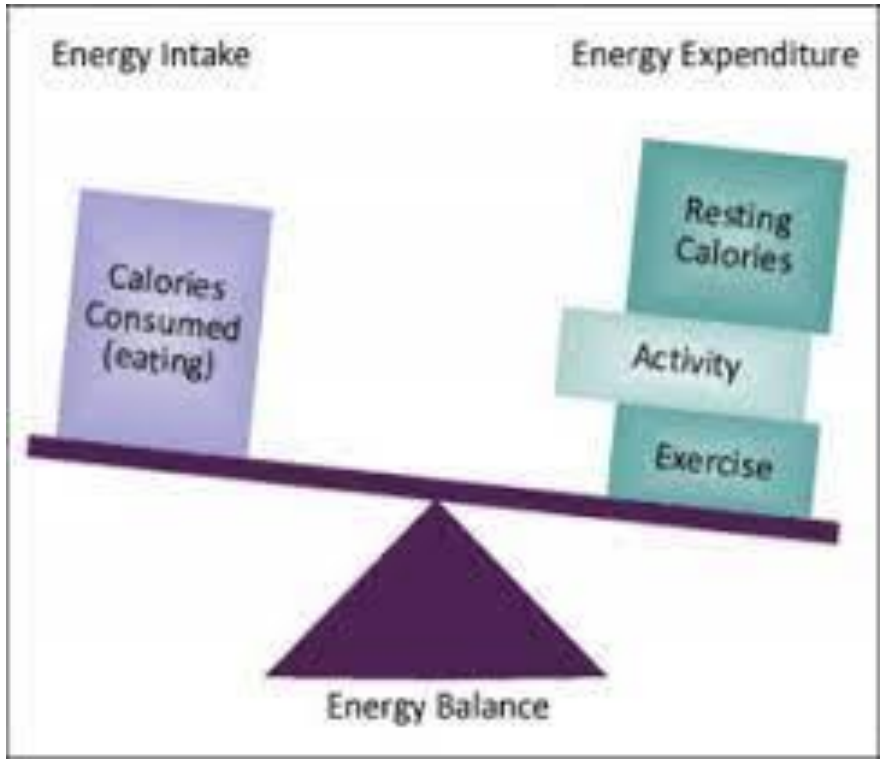
LOW ENERGY AVAILABILITY

Mismatch between energy intake and energy used in exercise

- Inadequate energy to support optimal health and performance.

Can occur due to decreased intake and/or increased expenditure

Historically defined: <30 kcal/kg FFM/day



CAUSES OF LOW ENERGY AVAILABILITY

Disordered eating, Eating disorders

Increase in training volumes without subsequent increase in energy intake

Difficult competition/travel schedules limiting access to nutrition

Poorly timed energy intake

Inadequate access to quality nutrition

Poorly designed training/coaching plans

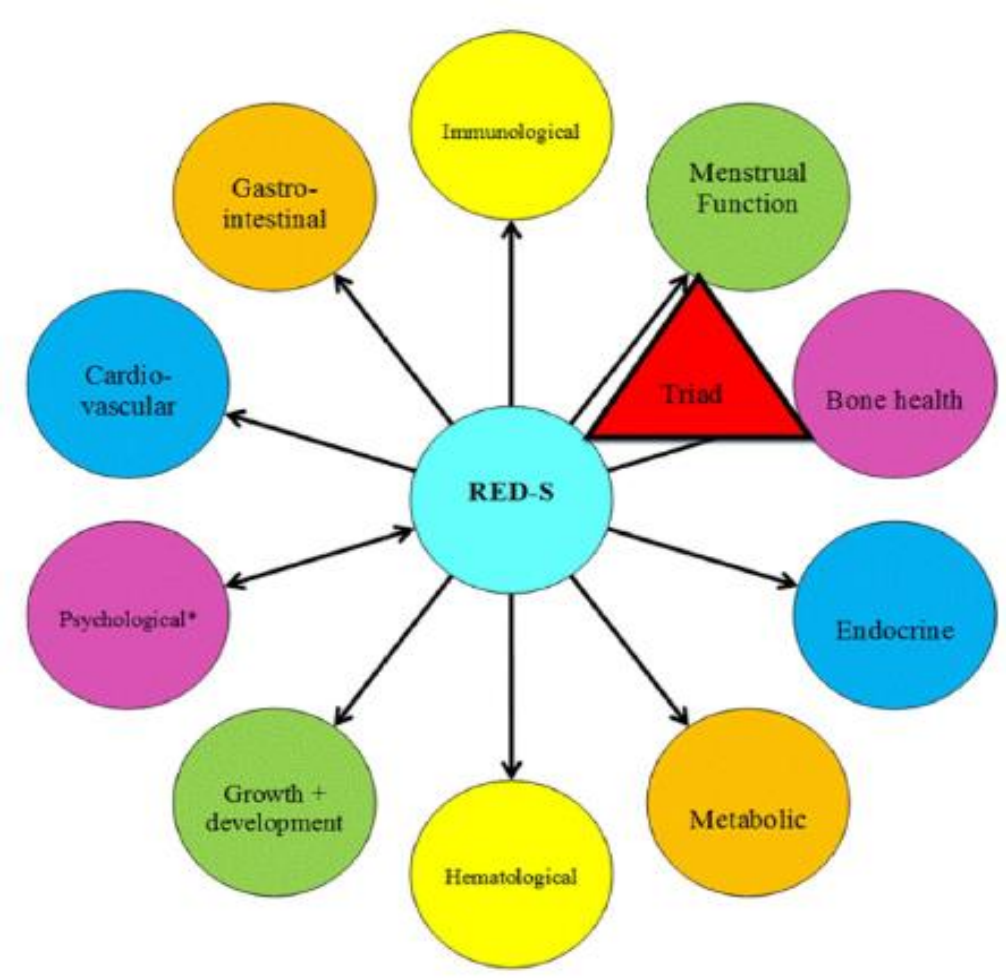
External pressures

RISK FACTORS

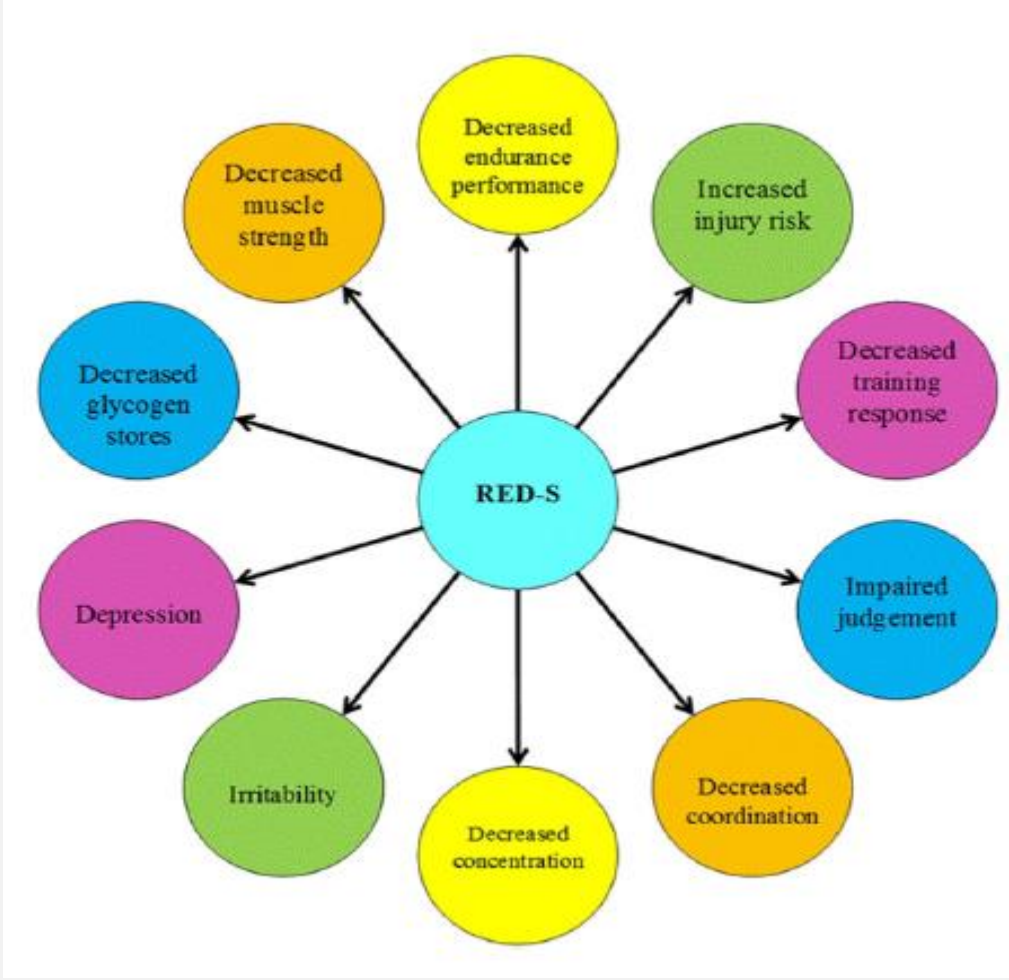
- Weight category sports:
  - Wrestling, boxing
- Endurance sports:
  - Cycling, running, triathlon
- Judged sports with emphasis on aesthetic:
  - Gymnastics, figure skating

LOW EA CONSEQUENCES

HEALTH



PERFORMANCE

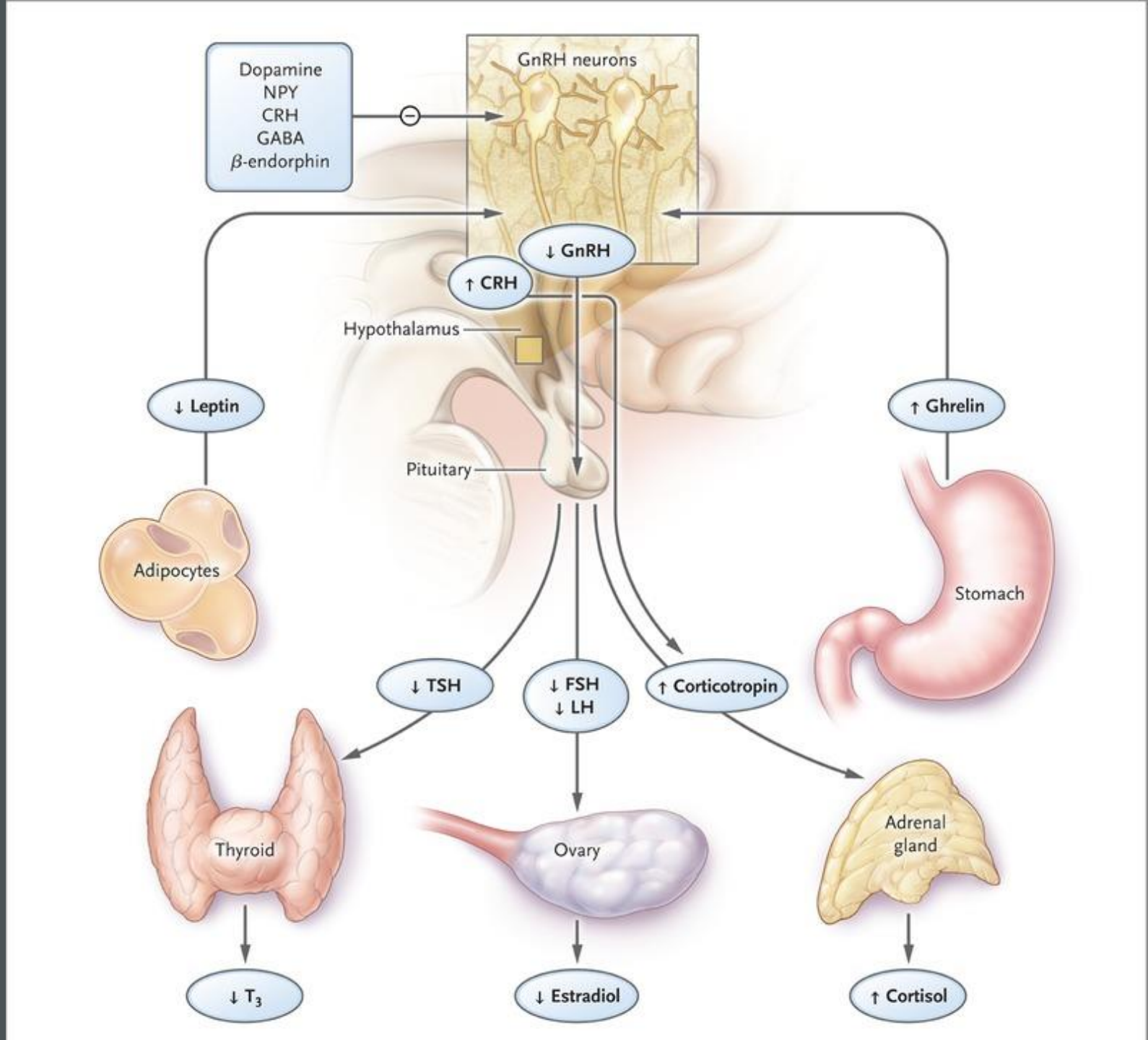


CONSEQUENCES: ENDOCRINE

- Disruption in of hypothalamic-pituitary-gonadal axis → menstrual dysfunction
- Alterations in thyroid function
- Changes in appetite regulating hormones
  - Decreased leptin and oxytocin (normally decreases appetite)
  - Increased grehlin (normally increases appetite)
- Decreased insulin, ILGF
- Increased GH resistance
- Increased cortisol

MENSTRUAL FUNCTION

- Low EA:
  - Disruption in GnRH pulsatility → alterations of LH, FSH → decreased estradiol and progesterone
  - End result: Functional hypothalamic amenorrhea



ENERGY AVAILABILITY'S IMPACT ON FEMALE REPRODUCTIVE HORMONES

- Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab. 2003 Jan;88(1):297-311. doi: 10.1210/jc.2002-020369. PMID: 12519869.
- Randomized, repeated measures, prospective study
- 19 female subjects, 18-30 yo, sedentary at baseline.
  - Menstrual length 26-32 days
  - Average luteal phase 11d determined by LH assay
- Disqualified if: significant chronic diseases (thyroid, heart, kidney disease, diabetes), known menstrual disorders, pregnant, lactating, intake <35 or > 55 kcal/kg LBM per day.

DESIGN

- Performed controlled exercise daily for 5 days in an energy balance, and again in one of three restricted energy intake treatment groups:
  - Energy balance: 45 kcal/kg LBM/day
  - Restricted energy groups (kcal/kg LBM/day): 30, 20, 10.
- Urine and blood samples done daily in the AM, starting 3 days prior to the intervention.
- Observed for 24 hrs in the hospital at completion of the 5-day intervention, with repeat blood samples done Q 10 mins for LH pulsatility.

TABLE 1. Demographic characteristics of the women who have received the balanced (45 kcal/kg LBM-d) and one of the three restricted energy availability treatments

Characteristics	Units	Restricted energy availability treatments (kcal/kg LBM · d)			*P*
		10	20	30	
n		10	11	8	
Calendar age	yr	21 ± 1	20 ± 1	22 ± 1	0.47
Age of menarche	yr	13 ± 0.4	13 ± 0.5	13 ± 0.4	0.78
Gynecological age	yr	8 ± 1	8 ± 1	9 ± 1	0.61
Menstrual cycle length	d	29.5 ± 0.6	30.2 ± 0.5	29.1 ± 0.4	0.34
Luteal length	d	12.6 ± 0.4	12.3 ± 0.5	12.8 ± 0.2	0.67
Height	cm	164.5 ± 2.0	162.6 ± 1.4	165.1 ± 2.3	0.61
Weight	kg	59.7 ± 1.3	59.1 ± 1.2	60.0 ± 1.9	0.92
Body fat	%	24.9 ± 1.2	26.2 ± 0.9	25.1 ± 1.4	0.68
LBM	kg	44.8 ± 1.2	43.6 ± 0.7	44.9 ± 1.6	0.60
VO_{2max}	ml O_2/kg BW · min	42.3 ± 1.4	38.3 ± 1.3	39.4 ± 1.3	0.10
Dietary intake	kcal/d	2000 ± 100	2000 ± 70	1830 ± 120	0.36
Dietary intake	kcal/kg LBM · d	45.8 ± 1.8	45.5 ± 1.5	40.6 ± 1.6	0.08

Data are presented as mean ± SE.

DEMOGRAPHICS

RESULTS

Decreased LH pulse frequency and increased LH pulse amplitude for 10 and 20 kcal/kg LBM

- P < 0.04

20 kcal/kg LBM/d:

- Suppressed frequency by 16% (P< 0.01)
- Increased amplitude by 21% (P <0.05).

10 kcal/kg LBM/d

- Suppressed frequency by 39%
- Increased amplitude by 109%
  - both P< 0.01

10 kcal group: 15% reduction in E2 levels

- Mean 95 to 79 pmol/liter, P<0.01

No changes in FSH

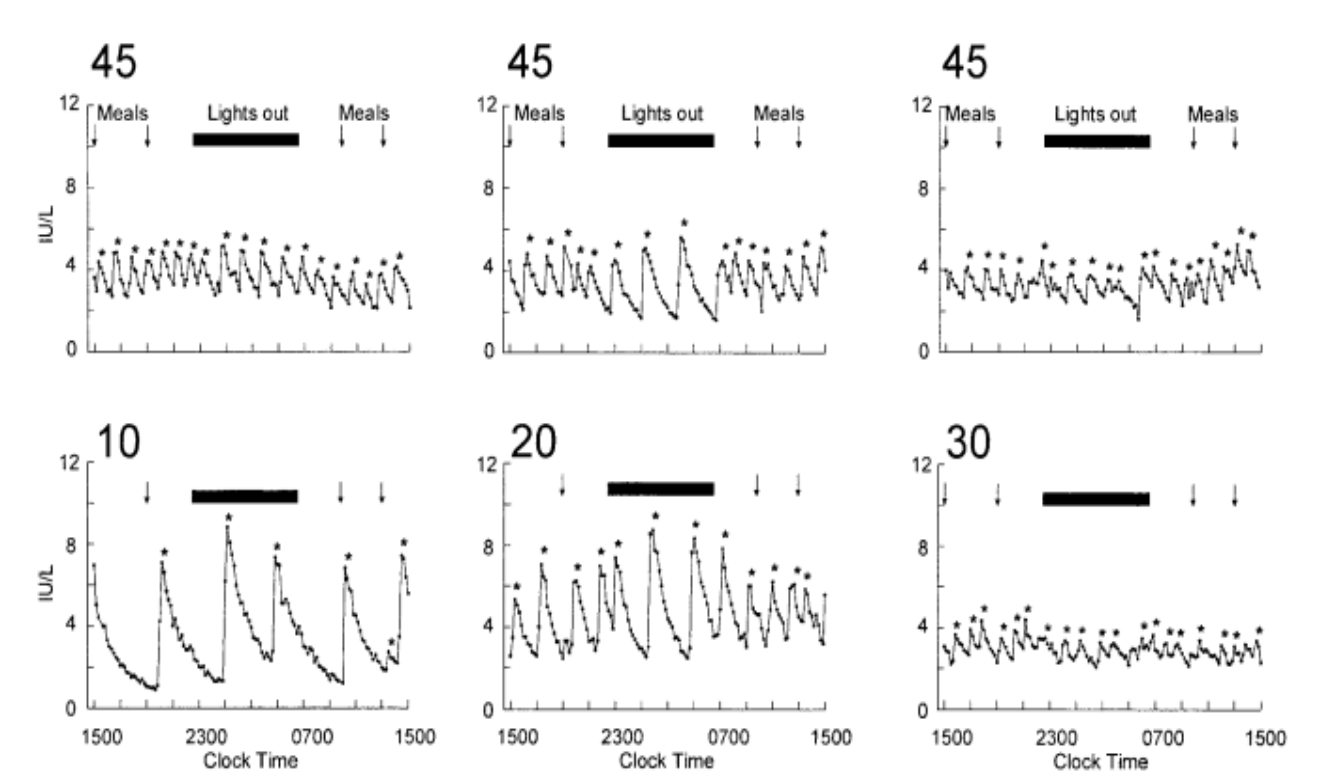


FIG. 3. LH pulse profiles. Twenty-four-hour LH pulse profiles for representative women after the balanced energy availability treatments of 45 kcal/kg LBM·d (*top*) and the paired restricted energy availability treatments of 10, 20, and 30 kcal/kg LBM·d, *left* to *right*, respectively (*bottom*). *Asterisks* indicate LH pulses. The *black bar* indicates when lights were turned off. *Arrows* indicate meals.

METABOLIC CHANGES

- Plasma glucose: reduced across all interventions.
  - 10 kcal group showed most severe reductions, present even when feeding
- Insulin concentrations: decreased linearly across the groups
- Non-linear increase in cortisol, greatest at < 20 kcal/kg LBM/d
- Decreased T3 below 30 kcal/kg LBM/d: $P < 0.05$

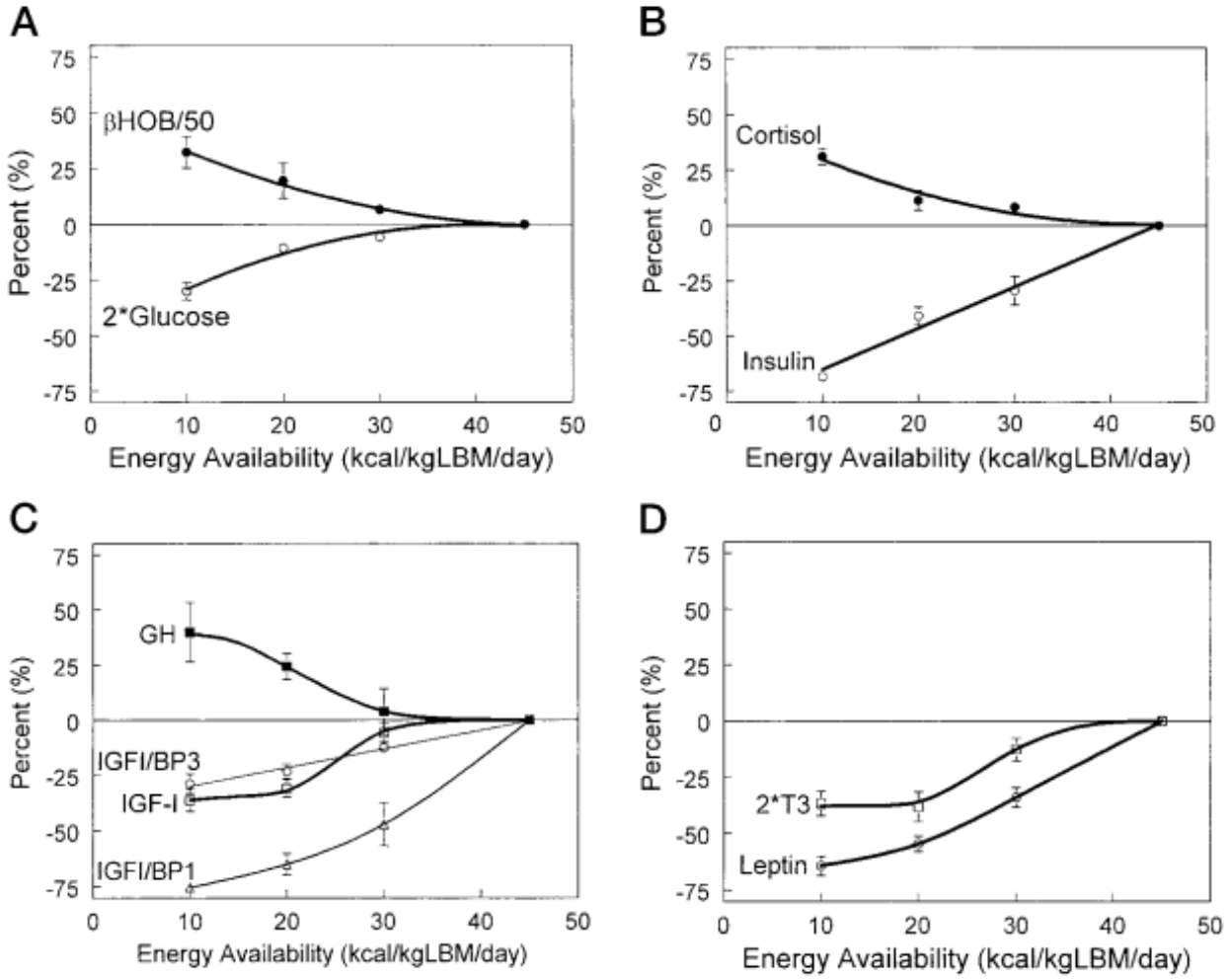


FIG. 5. Incremental effects of restricted energy availability on metabolic substrates and hormones. A, Incremental effects on the metabolic substrates β-HOB (●, *top*) and plasma glucose (○, *bottom*). Effects are shown relative to values at 45 kcal/kg LBM·d. Effects on β-HOB have been divided by 50, and effects on plasma glucose have been doubled for graphical symmetry. Effects on β-HOB and glucose become progressively more extreme as energy availability decreases. B, Incremental effects on the metabolic hormones cortisol (●, *top*) and insulin (○, *bottom*). Effects are shown relative to values at 45 kcal/kg LBM·d. Insulin declines linearly with energy availability, whereas effects on cortisol become progressively more extreme as energy availability decreases. C, Incremental effects on the somatotrophic metabolic hormones GH (■, *top*) and IGF-I (□, *bottom*) and the ratios IGF-I/IGFBP-1 (△) and IGF-I/IGFBP-3 (○). Effects are shown relative to values at 45 kcal/kg LBM·d. Effects on GH and IGF-I tend to flatten out below 20 kcal/kg LBM·d as GH resistance becomes more extreme. Both estimates of bioactive IGF-I have declined significantly and substantially at 30 kcal/kg LBM·d. D, Incremental effects on the metabolic hormones T_3 (□, *top*) and leptin (○, *bottom*). Effects are shown relative to values at 45 kcal/kg LBM·d. The effect on T_3 is doubled for graphical clarity. Both T_3 and leptin have declined significantly and substantially at 30 kcal/kg LBM·d. These effects tend to flatten out below 20 kcal/kg LBM·d.

DOES AN ENERGY THRESHOLD EXIST?

- Common number seen in the literature:
  - intake of < 30 kcal/kg LBM/day
- Some studies point to magnitude of energy deficit relative to baseline needs

WILLIAMS ET AL

- Williams NI, Leidy HJ, Hill BR, et al. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. Am J Physiol Endocrinol Metab 2015;308:E29–E39.
  - Prospective, randomized design.
  - Female, sedentary subjects (n=34), randomized to 1 of 4 groups
    - Exercise + adequate energy intake
    - Energy deficit 1: - 8% energy deficit
    - Energy deficit 2: -22% energy deficit
    - Energy deficit 3: -42% energy deficit

WILLIAMS ET AL

- Menstrual cycles were tracked prior to (at least 2 cycles) and during the intervention (3 cycles)
  - Determined follicular phase, luteal phase, ovulatory status
- All food intake was tightly controlled
- Tightly controlled exercise expenditure

DEMOGRAPHICS

ble 2. *Baseline demographic characteristics of study subjects categorized by group*

	EXCON (n = 8)	ED1 (n = 6)	ED2 (n = 12)	ED3 (n = 8)	P Value Group Effect
Demographics					
Age, yr	20.5 ± 0.4	20.5 ± 0.8	20.2 ± 0.6	20.4 ± 0.7	0.989
Height, cm	165 ± 3.0	165 ± 3.0	164 ± 2.0	164 ± 2.0	0.945
Weight, kg	57.9 ± 2.2	56.4 ± 1.2	59.8 ± 1.2	59.8 ± 1.5	0.385
BMI, kg/m^2	21.4 ± 1.3	20.7 ± 0.7	22.2 ± 0.5	22.4 ± 0.6	0.496
Body Composition					
%Body fat	26.5 ± 2.4	27.4 ± 1.5	28.8 ± 1.0	29.6 ± 1.3	0.528
Fat mass, kg	15.6 ± 2.0	15.5 ± 1.2	17.3 ± 0.8	17.8 ± 1.5	0.511
Fat-free mass, kg	42.3 ± 1.0	40.9 ± 0.6	42.6 ± 1.0	42.1 ± 1.2	0.729
Reproductive Characteristics					
Age at menarche, yr	12.3 ± 0.7	12.2 ± 0.2	11.9 ± 0.3	12 ± 1.0	0.949
Baseline cycle length, days	28.6 ± 0.9	27.8 ± 0.6	28.7 ± 0.5	30.2 ± 0.8	0.165
Training/diet characteristics					
$\dot{V}O_{2peak}$, ml·kg^{-1}·min^{-1}	36.1 ± 1.4	38.4 ± 2.1	37.6 ± 1.4	38.1 ± 1.7	0.797
Baseline caloric intake, kcal[a]	1,548 ± 195	2,150 ± 271	2,032 ± 154	1,881 ± 177	0.198
Energy Balance Parameters					
RMR, kcal/24 h	1,205 ± 57	1,293 ± 27	1,285 ± 64	1,242 ± 62	0.732
Nonexercise PA, kcal/24 h	593 ± 64	576 ± 47	737 ± 68	623 ± 64	0.276
24-h Energy Expenditure, kcal	1,797 ± 92	1,870 ± 53	2,021 ± 105	1,865 ± 77	0.341

Values are expressed as means ± SE. EXCON, exercise controls; ED, energy deficit (*groups 1–3*); PA, physical activity. [a]Data from 3-day diet logs.

RESULTS

- No changes in menstrual cycle length or follicular phase length
- Luteal phase length decreased significantly across all groups ($P < 0.0001$)
  - Disturbances increased as intervention progressed:
    - 21→ 34% of all subjects (cycle 1→3)
  - Frequency (occurring in at least 1 cycle) increased as energy deficit increased:
    - EXCON 13% subjects → ED3 88% subjects
  - No changes between groups in oligo/amenorrhea frequency
  - Percentage/amount of weight loss was not a predictor of menstrual irregularity

Table 5. *No. and corresponding percentage of subjects with at least 1 of each type of menstrual disturbances/total subjects in each group for each intervention cycle*

	EXCON	ED1	ED2	ED3	Total All Groups	*P* Value
LPDs						
Intervention cycle 1						
Subjects with at least 1 LPD/no. of subjects (%)	0/8 (0)	0/6 (0)	5/12 (42)	2/7 (29)	7/33 (21)	0.07 ($\chi^2 = 7.0$)
Intervention cycle 2						
Subjects with at least 1 LPD/no. of subjects (%)	1/8 (13)	1/6 (13)	4/10 (40)	4/6 (67)	10/30 (33)	0.14 ($\chi^2 = 5.5$)
Intervention cycle 3						
Subjects with at least 1 LPD/no. of subjects (%)	0/8 (0)	1/6 (29)	4/9 (44)	5/6 (83)	10/29 (34)	0.008 ($\chi^2 = 11.8$)
Intervention total						
Subjects with at ≥1 LPD/no. of subjects (%)	1/8 (13)	1/6 (38)	10/12 (83)	7/8 (88)	19/34 (56)	0.001 ($\chi^2 = 16.8$)
Oligomenorrheic cycles						
Intervention cycle 1						
Subjects with at least 1 oligomenorrheic cycle/no. of subjects (%)	1/8 (13)	0/6 (0)	0/12 (0)	0/8 (0)	1/34 (3)	0.34 ($\chi^2 = 3.3$)
Intervention cycle 2						
Subjects with at least 1 oligomenorrheic cycle/no. of subjects (%)	0/8 (0)	0/6 (0)	0/12 (0)	1/8 (13)	1/34 (3)	0.34 ($\chi^2 = 3.3$)
Intervention cycle 3						
Subjects with at least 1 oligomenorrheic cycle/no. of subjects (%)	0/8 (0)	0/6 (0)	1/12 (8)	2/7 (29)	3/33 (9)	0.20 ($\chi^2 = 4.6$)
Intervention total						
Subjects with at least 1 oligomenorrheic cycle/no. of subjects (%)	1/8 (13)	0/6 (0)	1/12 (8)	2/7 (29)	4/33 (12)	0.43 ($\chi^2 = 2.8$)
Anovulatory cycles						
Intervention cycle 1						
Subjects with at least 1 anovulatory cycle/no. of subjects (%)	0/8 (0)	0/6 (0)	0/12 (0)	1/8 (13)	1/34 (3)	0.34 ($\chi^2 = 3.3$)
Intervention cycle 2						
Subjects with at least 1 anovulatory cycle/no. of subjects (%)	0/8 (0)	0/6 (0)	2/12 (17)	2/8 (25)	4/34 (12)	0.32 ($\chi^2 = 3.5$)
Intervention cycle 3						
Subjects with at least 1 anovulatory cycle/no. of subjects (%)	0/8 (0)	1/8 (13)	3/12 (25)	0/7 (0)	4/33 (12)	0.12 ($\chi^2 = 5.7$)
Intervention total						
Subjects with at least 1 anovulatory cycle/no. of subjects (%)	0/8 (0)	0/6 (0)	5/12 (42)	2/8 (29)	7/34 (21)	0.07 ($\chi^2 = 7.0$)

LPD, luteal phase defect. Note: intervention totals reflect the no. of subjects that had at least one menstrual disturbance during *intervention cycles 1–3*. If subjects had more than one disturbance they were counted only once. The Total All Groups column reflects the no. of subjects who had at least one disturbance when all groups were considered. If subjects had more than one disturbance, they were counted only once.

SIGNIFICANCE

- The magnitude of the energy deficit relative to baseline (vs precise energy intake cutoff) is important
- The most common menstrual irregularity is a decreased luteal phase
  - Other studies have shown more subtle menstrual changes (ie: LPDs) precede more severe changes (ie: amenorrhea).
- → Relying on presence of menstrual cycle alone may be falsely reassuring
- Weight is not a reliable metric

BONE HEALTH

MENSES AND BONE HEALTH

- Duckham RL, Peirce N, Meyer C, et al. Risk Factors for stress fracture in female endurance athletes: a cross-sectional study. *BMJ Open* 2012;2:e001920.doi:10.1136/bmjopen-2012-001920.
  - 70 female athletes: All highly competitive
    - Mean age 26 +/- 7.4 yrs
    - 2 groups: hx of stress fx vs no hx of stress fxs (controls).
  - Results:
    - Stress fx group:
      - Higher prevalence of current amenorrhea/oligomenorrhia
        - p = 0.008
      - Higher prevalence of prior amenorrhoea
        - p = 0.035
    - Amenorrhea, oligomenorrhia are independent risks for stress fx.
      - OR: 4.7 (95% CI: 1.5-15.0).

ROLE OF ESTROGEN

- Musculoskeletal:
  - Limits bone resorption.
    - Stimulates calcitonin → Inhibits osteoclasts.
  - Promotes renal retention of calcium.

LOW EA: MENTAL HEALTH

- Mental health consequences: May be caused by or precede LEA
- Drive for thinness as proxy for LEA?
  - Eating Disorder Inventory: high drive for thinness scores asscd with markers of LEA (lower T3 levels, higher ghrelin levels, and reduced resting energy expenditure)
- Adolescent females with FHA:
  - Higher incidence of depressive traits, psychosomatic disorders, and difficulty managing stress.

PERFORMANCE CONSEQUENCES

- LEA has been shown to impair protein synthesis, glycogen storage, reduced mental capacity.
- Tornberg *et al*:
  - Lower neuromuscular performance and reaction time in subjects with secondary FHA
- Vanheest *et al*: young elite female swimming performance velocity over 400 m time trial after 12 wks of training:
  - 10% decline in performance in subjects with ovarian suppression due to energy deficiency
  - 8% improvement in eumenorrhoeic teammates

ENERGY AVAILABILITY, LIMITATIONS

- Measurement is difficult:
  - No direct measurement exists
  - No standardized protocol to assess EI, EEE, FFM
    - Reliability and validity are a concern
      - Self reported dietary intake
      - How to account for recreational/lifestyle activities
    - Often requires specialized equipment: DEXA
    - Requires athlete motivation, compliance
- Male athletes:
  - less data: thresholds/duration of LEA to induce RED-S unknown

SCREENING

- Consider screening for any athlete presenting with:
  - Eating d/o, disordered eating
  - Lack of normal growth/development
  - Endocrine dysfunction
  - Recurrent injuries
  - Wt loss, very low BMI (< 17.5)
  - Mood disorder
  - Decreased performance/performance variability

RED-S CLINICAL ASSESSMENT TOOL (RED-S CAT)

Allows risk stratification: red, yellow green

HIGH RISK: NO START RED LIGHT	MODERATE RISK: CAUTION YELLOW LIGHT	LOW RISK: GREEN LIGHT
- Anorexia nervosa and other serious eating disorders - Other serious medical (psychological and physiological) conditions related to low energy availability - Use of extreme weight loss techniques leading to dehydration induced hemodynamic instability and other life threatening conditions.	- Prolonged abnormally low % body fat measured by DXA* or anthropometry - Substantial weight loss (5–10 % body mass in one month) - Attenuation of expected growth and development in adolescent athlete	- Appropriate physique that is managed without undue stress or unhealthy diet/exercise strategies
	- Low **EA of prolonged and/or severe nature	- Healthy eating habits with appropriate EA
	- Abnormal menstrual cycle: functional hypothalamic amenorrhea >3 months - No menarche by age 15y in females	- Healthy functioning endocrine system
	- Reduced bone mineral density (either in comparison to prior DXA or Z-score <-1 SD). - History of 1 or more stress fractures associated with hormonal/menstrual dysfunction and/or low EA	- Healthy bone mineral density as expected for sport, age and ethnicity - Healthy musculoskeletal system
- Severe ECG abnormalities (i.e. bradycardia)	- Athletes with physical/psychological complications related to low EA+/-disordered eating; - Diagnostic testing abnormalities related to low EA +/-disordered eating	
	- Prolonged relative energy deficiency - Disordered eating behavior negatively affecting other team members - Lack of progress in treatment and/or non-compliance	

"RED"
NO CLEARANCE FOR PARTICIPATION

- Anorexia nervosa, other serious eating d/o
- Serious psychological, physiological conditions related to LEA:
  - Poorly controlled OCD/anxiety, extreme bradycardia, electrolyte disturbance
- Use of extreme weight loss methods leading to hemodynamic instability

"YELLOW"
CLEARED WITH TX PLAN & SUPERVISION

- ≥ 5% wt loss in 1 month
- Attenuation of normal growth in adolescent athlete
- Abnormal menstrual cycle > 3 months
- No menarche by age 15
- Reduced BMD: Z score < -1
- ≥ 1 stress fx related to menstrual dysfunction or LEA
- Diagnostic testing abnormalities related to LEA
- Lack of progress in tx, non-compliance

"GREEN"
FULL SPORT PARTICIPATION

- Appropriate physique managed without unhealthy diet, exercise strategies
- Health eating habits, appropriate EA
- Healthy functioning endocrine system
- Normal BMD
- Healthy MSK system

MANAGEMENT

Mostly non-pharmacologic

Multimodal team: physician, ATC, coach, sports dietitian, behavioral health

Engage the athlete

- Emphasis on improving performance
  - Focus on "adding" vs "taking away"
- Discuss prior injuries, how LEA may have played a role
- Small changes
- Encourage broader perspective: long-term health
- Include family members

MANAGEMENT

Address energy deficits

- Decrease activity workloads: focus on key workouts only
- Enhance energy intake:
  - Timing of intake
  - Quality of intake

Evaluate for specific deficiencies:

- Vitamin D: < 30 ng/mL of 25-OH D asscd with bone stress injury
  - goal intake 600-800 IU QD
- Calcium:
  - 1000 mg/day for 19050 yo males/females
  - 1300 mg/day for 9-18 yo males/females.

RETURN TO PLAY

STEPS	RISK MODIFIERS	CRITERIA	RED-S SPECIFIC CRITERIA
STEP 1 Evaluation of Health Status	MEDICAL FACTORS	- Patient Demographics - Symptoms - Medical History - Signs - Diagnostic Tests - Psychological Health - Potential Seriousness	- Age, sex - See Yellow Light column in RED-S Risk assessment model - Recurrent dieting, menstrual health, bone health - Weight loss/fluctuations, weakness - Hormones, electrolytes, electrocardiogram, DXA - Depression, anxiety, disordered eating/ eating disorder - Abnormal hormonal and metabolic function - Cardiac arrhythmia - Stress fracture
STEP 2 Evaluation of Participation Risk	SPORT RISK MODIFIERS	- Type of Sport - Position Played - Competitive Level	- Weight sensitive, leanness sport - Individual vs. team sport - Elite vs. recreational
STEP 3 Decision Modification	DECISION MODIFIERS	- Timing and Season - Pressure from Athlete - External Pressure - Conflict of Interest - Fear of Litigation	- In/out of season, travel, environmental factors - Mental readiness to compete - Coach, team owner, athlete family, sponsors support - If restricted from competition

Return to Play Model

Following clinical reassessment utilizing the 3 step evaluation outlined above, athletes can be re-classified into the "High Risk – Red Light", "Moderate Risk – Yellow Light" or "Low Risk – Green Light" categories. The RED-S Risk Assessment Model is adapted to aid clinicians' decision making for determining an athlete's readiness to return to sport/physical activity.

RETURN TO PLAY
STEP WISE APPROACH

- Step 1: evaluate health status
  - Testing: labs, EKG, DXA
  - Wt changes
  - Behavioral health screens
- Step 2: participation risk
  - Type of sport, competition level
- Step 3: modifiers
  - Timing within season
  - External pressure(s)
  - Conflict of interest

PHARMACOLOGIC TX

- Data lacking on efficacy specific to BMD and fracture risk/accelerated healing
- When to Consider:
  - Presence of osteoporosis.
  - Athletes with multiple fracture hx.
  - Lack of response to non-pharmacological tx after 1 year.
  - If new fx's occur during non-pharmacological management.
  - Clinically diagnosed eating disorder.
  - Comorbid conditions:
    - anxiety, depression, OCD.

ORAL CONTRACEPTIVES

Do not restore spontaneous menses.

Do not normalize metabolic factors which impair bone health.

Not proven to improve BMD in amenorrhoeic athletes.

May muddy the picture:

- When does spontaneous menstruation start?

TRANSDERMAL ESTROGEN

- Misra M, Katzman D, Miller KK, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. *J Bone Miner Res* 2011;26:2430-8.
  - RCT
  - Subjects: anorexic females.
  - Tx: transdermal estrogen (100 mcg, twice per wk) + cyclic progesterone (2.5 mg QD X 10 days of each month
- Results:
  - Bone accrual rates approximated those of normal-weight controls.
  - BMD Z scores were maintained.
  - "Catch up" of BMD never occurred

TRANSDERMAL ESTROGEN INITIATION

Z-score ≤ -2.0 + 1 additional triad risk factor

- Low BMI.
- Late menarche.
- ED or DE.
- A/Oligomenorrhia.

Lack of response to non-pharm tx:

- Worsening Z scores after 1 yr.
- New fxs during tx course.

PREVENTION

- Increased awareness: surveys show poor knowledge of triad components amongst key stakeholders
  - <50% of physicians, coaches, PT's, ATCs could identify the triad components
  - 19% of 370 US HS nurses could ID all 3 components
  - Study of regularly active Australian woman:
    - 1/3 believed irregular periods were normal
- Effective programs should target athlete and non-athletes (family members)

SUMMARY

- RED-S should be screened for at all well child checks and sports physicals
- RED-S can affect numerous systems, most prominently the endocrine, musculoskeletal, and psychological
- Risk stratification can be done via the RED-S CAT tool
- Management should involve a multi-disciplinary team, and focus on engaging the athlete specific to performance and long-term health
- Pharmacologic interventions are rarely required
- The primary goal should be in increasing energy availability.

RESOURCES

- Mountjoy M, Sundgot-Borgen JK, Burke LM, et al. IOC consensus statement on relative energy deficiency in sport (RED-S): 2018 update Br J Sports Med 2018;52:687–697
- YEAGER, KIMBERLY K.; AGOSTINI, ROSEMARY; NATTIV, AURELIA; DRINKWATER, BARBARA The female athlete triad, Medicine & Science in Sports & Exercise: July 1993 - Volume 25 - Issue 7 - p 775-777
- Otis, Carol L. M.D., FACSM, (Chair); Drinkwater, Barbara Ph.D., FACSM; Johnson, Mimi M.D., FACSM; Loucks, Anne Ph.D., FACSM; Wilmore, Jack Ph.D., FACSM ACSM Position Stand: The Female Athlete Triad, Medicine & Science in Sports & Exercise: May 1997 - Volume 29 - Issue 5 - p i-ix
- Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab. 2003 Jan;88(1):297-311. doi: 10.1210/jc.2002-020369. PMID: 12519869.
- Williams NI, Leidy HJ, Hill BR, et al. Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. Am J Physiol Endocrinol Metab 2015;308:E29–E39.
- RED-s CAT: Br J Sports Med 2015;49:421–423. doi:10.1136/bjsports-2014-094559