International Journal of Sport Nutrition and Exercise Metabolism, 2018, 28, 335-349
https://doi.org/10.1123/ijsnem.2018-0127

Human Kinetics
SCHOLARLY REVIEW

Endocrine Effects of Relative Energy Deficiency in Sport

Kirsty J. Elliott-Sale
Nottingham Trent University

Adam S. Tenforde
Spaulding Rehabilitation Hospital, Brigham and Women's Hospital, and Harvard Medical School

Allyson L. Parziale and Bryan Holtzman
Boston Children's Hospital

Kathryn E. Ackerman
Boston Children's Hospital, Massachusetts General Hospital, and Harvard Medical School

The term Relative Energy Deficiency in Sport was introduced by the International Olympic Committee in 2014. It refers to the potential health and performance consequences of inadequate energy for sport, emphasizing that there are consequences of low energy availability (EA; typically defined as <30 kcal·kg^{-1} fat-free mass·day^{-1}) beyond the important and well-established female athlete triad, and that low EA affects populations other than women. As the prevalence and consequences of Relative Energy Deficiency in Sport become more apparent, it is important to understand the current knowledge of the hormonal changes that occur with decreased EA. This paper highlights endocrine changes that have been observed in female and male athletes with low EA. Where studies are not available in athletes, results of studies in low EA states, such as anorexia nervosa, are included. Dietary intake/appetite-regulating hormones, insulin and other glucose-regulating hormones, growth hormone and insulin-like growth factor 1, thyroid hormones, cortisol, and gonadal hormones are all discussed. The effects of low EA on body composition, metabolic rate, and bone in female and male athletes are presented, and we identify future directions to address knowledge gaps specific to athletes.

Keywords: exercise-hypogonadal male condition, female athlete triad, low energy availability, sports endocrinology

Relative Energy Deficiency in Sport (RED-S), a term first described by the International Olympic Committee in 2014, refers to the potential health and performance consequences of inadequate energy for sport (Mountjoy et al., 2014). The concept was derived from initial work on the female athlete triad (Triad), defined as the interrelationship of energy availability (EA), menstrual function, and bone health (Nattiv et al., 2007). More recent studies in female and male athletes have demonstrated that low EA can lead to other physiological and performance decrements (Logue et al., 2018; Mountjoy et al., 2014). RED-S was proposed to expand upon the Triad and to include both female and male athletes. It suggests 10 physiological and 10 performance-related effects of low EA (Mountjoy et al., 2014).

Elliott-Sale is with Musculoskeletal Physiology Research Group, Sport, Health and Performance Enhancement Research Centre, School of Science and Technology, Nottingham Trent University, Nottingham, United Kingdom. Tenforde is with the Dept. of Physical Medicine & Rehabilitation, Spaulding Rehabilitation Hospital, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA. Parziale, Holtzman, and Ackerman are with the Division of Sports Medicine, Boston Children's Hospital, Boston, MA. Ackerman is also with the Neuroendocrine Unit, Massachusetts General Hospital, Massachusetts General Hospital, and Harvard Medical School, Boston, MA. Address author correspondence to Kathryn E. Ackerman at Kathryn.Ackerman@childrens.harvard.edu.

In this paper, we will focus specifically on the endocrine effects of RED-S, or what the RED-S model lists as "metabolic," "endocrine," "menstrual function," and "bone health" consequences (Mountjoy et al., 2014). While it is well accepted that low EA affects reproductive hormones, resulting in menstrual dysfunction, it is important to clarify what is and is not known about other endocrine pathways and to identify sex differences to better inform future research and treatment of RED-S. We have summarized the key findings in Table 1.

Concept of Relative Energy Deficiency

EA has been defined as energy intake (EI, measured in kcal) minus exercise energy expenditure (EEE, measured in kcal), divided by fat-free mass (FFM, measured in kg), or the amount of dietary energy remaining for normal physiological functioning after exercise (Loucks, 2007). Such functioning includes cell maintenance, thermoregulation, growth, and reproduction (Wade & Schneider, 1992). From an evolutionary perspective, low EA (typically defined as <30 kcal·kg^{-1} FFM·day^{-1}) due to periods of food scarcity or extraordinary energy expenditure causes physiological adaptations necessary to sustain life (Loucks & Thuma, 2003; Wade & Schneider, 1992). In all mammals, bodily energy is diverted away from processes not needed for immediate survival, such as fat accumulation, growth, and development. Female

Table 1 Summary of Endocrine Changes Using Direct or Surrogate Measures of Low EA

Hormone	Females	Males
HPG axis		
FSH	↔ Gordon et al. (2017), Laughlin and Yen (1996), Loucks et al. (1989), and Loucks and Thuma (2003)	↓ Berg et al. (2008)
LH	↔ Gordon et al. (2017), Laughlin and Yen (1996), Loucks and Thuma (2003), and Rickenlund et al. (2004)	↑ Hackney et al. (1988)
		↔ Berg et al. (2008), Hackney et al. (1998), and Hooper et al. (2017)
	↓ Ackerman et al. (2012b)	↓ MacConnie et al. (1986) and McColl et al. (1989)
estradiol	↓ Loucks and Thuma (2003)	↓ Ackerman et al. (2012a)
progesterone	↓ Loucks et al. (1989)	
testosterone	↑ Lagowska and Kapczuk (2016) and Rickenlund et al. (2004)	↔ MacConnie et al. (1986)
	↔ Rickenlund et al. (2004)	↓ Berg et al. (2008), Chan et al. (2003), Hackney et al. (1988, 1998), Heikura et al. (2017), Hooper et al. (2017), and McColl et al. (1989)
	↓ Christo et al. (2008), Miller et al. (2007), and Russell et al. (2009)	
Energy homeostasis, metabolism, and appetite		
RMR	↓ De Souza et al. (2007), Melin et al. (2015), and Myerson et al. (1991)	↓ Thompson et al. (1993)
leptin	↓ Ackerman et al. (2012b), Christo et al. (2008), Corr et al. (2011), Donoso et al. (2010), Estour et al. (2010), Grinspoon et al. (1996), Hilton and Loucks (2000), and Loucks and Thuma (2003)	↓ Gomez-Merino et al. (2002), Hagmar et al. (2013), Karamouzis et al. (2002), Koehler et al. (2016), Leal-Cerro et al. (1998), and Roupas et al. (2013)
adiponectin	↑ Donoso et al. (2010) and O'Donnell and De Souza (2011)	
	↔ Russell et al. (2009)	
ghrelin	↑ Ackerman et al. (2012b), Christo et al. (2008), De Souza et al. (2004, 2007), Scheid et al. (2011), and Tolle et al. (2003)	↔ Koehler et al. (2016) and Misra et al. (2008)
PYY	↑ Misra et al. (2006), Russell et al. (2009), and Scheid et al. (2011)	↑ Misra et al. (2008)
oxytocin	↓ Lawson et al. (2011, 2013)	↓ Chicharro et al. (2001)
insulin	↓ Laughlin and Yen (1996), Loucks and Thuma (2003), Loucks et al. (1998), and Rickenlund et al. (2004)	↓ Chan et al. (2003), Koehler et al. (2016), and Maestu et al. (2010)
amylin	↓ Wojcik et al. (2010)	
HPA axis		
cortisol	↑ Ackerman et al. (2013), Laughlin and Yen (1996), Loucks et al. (1989, 1998), Loucks and Thuma (2003), Rickenlund et al. (2004), and Tornberg et al. (2017)	↔ Hooper et al. (2017)
	↔ De Souza et al. (1994), Laughlin and Yen (1996), and Schaal et al. (2011)	
Hypothalamic–pituitary–thyroid axis		
TSH	↔ Berga et al. (1989) and Loucks et al. (1992)	↔ Skolnick et al. (2016)
total T3	↓ Berga et al. (1989), De Souza et al. (2007), Harber et al. (1998), Heikura et al. (2017), Loucks and Callister (1993), Loucks and Heath (1994), Loucks et al. (1992, 1998), and Loucks and Thuma (2003)	↓ Heikura et al. (2017) and Skolnick et al. (2016)
free T3	↓ Estour et al. (2010), Loucks and Heath (1994), and Loucks et al. (1992)	↓ Skolnick et al. (2016)
total T4	↑ Loucks and Callister (1993)	↓ Skolnick et al. (2016)
	↔ Loucks and Heath (1994)	
	↓ Berga et al. (1989), Harber et al. (1998), and Loucks et al. (1992)	
free T4	↔ Loucks and Callister (1993)	↓ Skolnick et al. (2016)
	↓ Estour et al. (2010), Loucks and Heath (1994), and Loucks et al. (1992)	

(continued)

Table 1 *(continued)*

Hormone	Females	Males
GH and IGF-1 axis		
GH	↑ Counts et al. (1992), Estour et al. (2010), Loucks and Thuma (2003), Loucks et al. (1998), Misra et al. (2003, 2004), and Stoving et al. (1999)	↑ Rigotti et al. (1986), Roemmich and Sinning (1997), and Thienpont et al. (2000)
IGF-1	↔ Laughlin and Yen (1996)	↑ Geesmann et al. (2016), Hagmar et al. (2013), and Maestu et al. (2010)
	↓ Counts et al. (1992), Estour et al. (2010), Loucks and Thuma (2003), Loucks et al. (1998), Misra et al. (2003, 2004), and Stoving et al. (1999)	↓ Berg et al. (2008)
IGF binding protein-1	↑ Laughlin and Yen (1996) and Loucks and Thuma (2003)	↑ Hagmar et al. (2013)

Note. ↑ denotes a higher level/increase with low EA, ↓ denotes a lower level/decrease with low EA, ↔ denotes no difference/change with low EA. Examples of surrogates for low EA include eating disorders, menstrual dysfunction, low BMI, participation in leanness sports, and prolonged exercise. EA = energy availability; RMR = resting metabolic rate; GH = growth hormone; PYY = peptide YY; HPA = hypothalamic–pituitary–adrenal; IGF-1 = insulin-like growth factor 1; HPG = hypothalamic–pituitary–gonadal; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

mammals are particularly vulnerable to inadequate EA, as pregnancy and lactation are energetically expensive (Dufour & Sauther, 2002; Jasienska, 2003). Thus, it is not surprising that reproduction is closely linked to EA in mammals, including humans.

The RED-S concept highlights that low EA not only affects the reproductive system, but also influences other hormonal pathways resulting in numerous endocrine-derived physiological consequences. While the RED-S health effects diagram appropriately centers energy in the model—emphasizing its importance and influence on multiple physiological systems—it is important to note that many hormonal and other physiological changes are interrelated. Altering hormonal secretion to minimize reproductive function and maximize survival efficiency may be a well-designed solution to energy deficiency and beneficial for the maintenance of the human species; however, this strategy is not optimal for an athlete's health and performance.

Such reproductive suppression in times of low EA is a form of functional hypothalamic amenorrhea (FHA), which manifests as persistent anovulation with no identifiable organic cause (Gordon et al., 2017). Aberrant gonadotropic releasing hormone (GnRH) pulsatility at the hypothalamus leads to abnormal pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), resulting in decreased estradiol and progesterone, inadequate folliculogenesis, and anovulation (Gordon et al., 2017). Athletes with FHA typically have lower EA than eumenorrheic athletes and nonathletic controls, although a specific EA threshold cannot necessarily predict the menstrual status of all females (Kaiserauer et al., 1989; Kopp-Woodroffe et al., 1999; Lieberman et al., 2018; Reed et al., 2015; Williams et al., 2015). In a prospective study of typically sedentary, eumenorrheic women aged 18–30 years, manipulations of EA by diet and exercise led to EA as low as 58% of baseline (Lieberman et al., 2018; Williams et al., 2015). The probability of developing menstrual dysfunction was greater than 50% as absolute EA dropped below 30 kcal·kg^{-1} FFM·day^{-1} (Lieberman et al., 2018). There was a dose–response relationship between relative energy deficit (percentage decrease in EA from baseline) and frequency of menstrual disturbances (luteal phase defects, anovulation, and oligomenorrhea), but the severity of menstrual disturbances did not correlate with the magnitude of energy deficiency (Williams et al., 2015). These more recent findings may suggest "RED-S" as a more descriptive term for the increased risk of menstrual dysfunction in athletes with inadequate energy, rather than relying on the term "low EA," which is typically defined as <30 kcal·kg^{-1} FFM·day^{-1} (Loucks & Thuma, 2003).

Potential Hormonal Effects of Relative Energy Deficiency

Although studies have suggested that physiological functioning is optimized at an EA ≥ 45 kcal·kg^{-1} FFM·day^{-1}, there may be individual variability for appropriate EA cutoffs to affect physiological processes such as menstrual function (Loucks, 2007; Loucks & Thuma, 2003). In addition, no standard protocol for EA assessment has been established, with current measurements often relying on self-reported EI and/or EEE (Koehler et al., 2013; Loucks, 2007). Therefore, some of the understanding of hormonal changes with RED-S has relied on studying populations assumed to be in a state of low EA. For example, FHA has been used as a surrogate marker for low EA. Women with anorexia nervosa (AN) and athletes with oligo-amenorrhea not from an organic cause can both be categorized as having FHA and have been studied to determine hormonal changes in these states (Gordon et al., 2017). Some studies focused on chronic low EA states, while others focused on hormonal changes after short-term energy deficit. In addition, athletes participating in sports that emphasize leanness have been presumed to have lower EA than those in nonleanness sports, and their hormonal profiles have been compared (Ackerman et al., 2012a; Loucks, 2007; Reinking & Alexander, 2005). Thus, in the following sections, the hormonal consequences of RED-S, as determined by EA measurement, will be emphasized, but it is important to acknowledge that, given the infancy of RED-S, some of the hormonal findings are reported in populations with surrogate markers for low EA; in such cases, this is clearly stated.

Body Composition and Metabolic Rate

Various reports indicated that amenorrheic athletes have lower body mass index (BMI) than eumenorrheic athletes and sedentary controls (Ackerman et al., 2015; Christo et al., 2008; Corr et al., 2011). Amenorrheic athletes have also demonstrated lower absolute and relative body fat compared with their eumenorrheic counterparts (Ackerman et al., 2013; Christo et al., 2008; Corr et al., 2011). In contrast, in one study of collegiate swimmers, the ovarian suppressed athletes had slightly higher BMI and fat mass compared with the eumenorrheic athletes (Vanheest et al., 2014). In collegiate male athletes, distance runners (a sport that emphasizes leanness) had lower BMI and fat mass compared with golfers, and lower BMI than off-season wrestlers (another leanness sport, though not subjected to weight cycling at the time of study), but not lower fat mass (Ackerman et al., 2012a).

A reduced resting metabolic rate (RMR) has been reported in amenorrheic athletes compared with eumenorrheic athletes and controls, as well as in elite endurance athletes with low EA (<45 kcal·kg^{-1} FFM·day^{-1}) compared with "optimal EA" (≥45 kcal·kg^{-1} FFM·day^{-1}; De Souza et al., 2007; Melin et al., 2015; Myerson et al., 1991). Similar results in RMR have been seen in elite male endurance athletes with low EI compared with those with adequate EI (Thompson et al., 1993). Despite similar EEE, BMI, and body composition, the athletes with low EI consumed an average of 1,490 fewer kcal·day^{-1} than the adequate EI group and were routinely eating 1,116–1,395 kcal/day below the perceived energy requirements (Thompson et al., 1993). RMR was 8% lower in the low EI (low EA) group, suggesting an energy conserving mechanism for maintenance of BMI and bodily function (Thompson et al., 1993).

Dietary Intake Regulating Hormones

Numerous hormones have been implicated in appetite regulation and in behavioral (reward related) food intake. Effects of low EA on such hormones are described below, including what is known in each sex.

Adipokines

Variation from optimal nutritional intake and reductions in body fat can influence the normal hormonal activity of adipose tissue. The adipokine leptin, an anorexigenic adipose hormone also involved in reproduction, is lower in states of low EA and is reduced in amenorrheic athletes (Ackerman et al., 2012b; Christo et al., 2008; Corr et al., 2011; Donoso et al., 2010; Grinspoon et al., 1996;

Hilton & Loucks, 2000). Leptin strongly correlates with fat mass in various populations, including females with AN, female athletes (regardless of menstrual status), and sedentary females (Ackerman et al., 2012b; Grinspoon et al., 1996). Baseline leptin levels positively predicted sex hormone concentrations (estradiol and testosterone) in adolescents, and overnight leptin secretory parameters were positively associated with LH secretory parameters in adolescent female athletes and nonathletes (Ackerman et al., 2012b; Christo et al., 2008). Moreover, recombinant leptin administration has been shown to resume ovulatory cycles in some women with FHA (Chou et al., 2011; Welt et al., 2004).

Adiponectin, another anorexigenic adipokine, is higher in dancers with delayed menarche and low EA, and in some, but not all, amenorrheic athletes (Donoso et al., 2010; O'Donnell & De Souza, 2011; Russell et al., 2009). Higher adiponectin levels have been reported in exercisers in general compared with nonathletes, and correlate positively with lean mass and negatively with BMI and fat content in some studies; results are inconsistent (Donoso et al., 2010; O'Donnell & De Souza, 2011; Russell et al., 2009; Simpson & Singh, 2008). Adipokines likely collectively inform the hypothalamus about EA, but the exact regulatory role and consequences of adipokines, such as adiponectin, are not well elucidated (O'Donnell & De Souza, 2011; Russell & Misra, 2010).

Similar to female athletes, reductions in serum leptin have been described in male athletes, particularly those participating in endurance sports and sports emphasizing leanness. Acute reductions in leptin have been reported in males after intense exercise in rowing, running, and swimming endurance events of various durations (Jurimae et al., 2007; Karamouzis et al., 2002; Leal-Cerro et al., 1998; Roupas et al., 2013). Koehler et al. (2016) assessed the effects of EA manipulation through diet and exercise on hormone levels, including leptin, in six male habitual exercisers. Each participant experienced four separate, 4-day conditions (with adequate washout): EA of 15 kcal·kg^{-1} FFM·day^{-1} with and without exercise (EEE 15 kcal·kg^{-1} FFM·day^{-1}) and 40 kcal·kg^{-1} FFM·day^{-1} with and without exercise (EEE 15 kcal·kg^{-1} FFM·day^{-1}). Fasting leptin was 53–56% lower after the two low EA conditions, regardless of exercise, compared to baseline. The higher EA conditions did not lead to significant changes in leptin levels compared to baseline (Koehler et al., 2016). A study of Swedish male Olympic athletes showed that men in leanness sports (e.g., gymnastics, judo, triathlon, skating) had lower leptin levels compared with men in other sports (e.g., soccer, handball, ice hockey, snowboarding; Hagmar et al., 2013). Male marathon runners were shown to have lower fat mass and leptin levels compared with sedentary males, with a positive correlation between leptin and total fat mass in both groups; similar to findings in women (Leal-Cerro et al., 1998). Lower leptin levels have also been observed in men addicted to exercise, another potential surrogate for low EA. A cross-sectional observational study by Lichtenstein et al. (2015) evaluated 20 men with exercise addictions, as assessed by the Exercise Addiction Inventory (Griffiths et al., 2005), compared with 20 men matched for age and BMI. Mean serum leptin values were nearly 75% lower in the exercise-addicted population, even after controlling for fat mass (Lichtenstein et al., 2015). Similarly, Gomez-Merino et al. (2002) showed that 5 days of military training, which induced an energy deficiency, led to a mean decrease in leptin of 67% in men.

Adiponectin levels have been measured after various durations, intensities, and types of exercise in men, but EA was not directly assessed (Simpson & Singh, 2008). Cross-sectional studies that controlled for BMI and fat demonstrated a positive association with physical activity and adiponectin, but studies examining adiponectin levels after acute bouts of exercise did not control for BMI/body composition and noted either no change or decreases in adiponectin concentrations (Simpson & Singh, 2008). For example, immediately following a 180-km ultramarathon in which the athletes were estimated to accrue a mean energy deficit of 5,000 kcal, adiponectin levels were unchanged from baseline, though the levels dropped slightly 17–22 hr after completion of the race (Roupas et al., 2013). We are not aware of any research that has examined adiponectin levels in males in chronic low EA states.

Ghrelin and Peptide YY

Ghrelin is an orexigenic hormone predominantly produced in the stomach and is thought to act upon the hypothalamus and pituitary, affecting secretion of GnRH, adrenocorticotropic hormone (ACTH), growth hormone (GH), FSH, and LH. Ghrelin is elevated in women with AN and in amenorrheic athletes (Ackerman et al., 2012b; Christo et al., 2008; De Souza et al., 2004, 2007; Tolle et al., 2003). Ghrelin is considered a marker of energy status—higher ghrelin levels indicate a lower energy state—and various pulse parameters correlate negatively with fat mass (Ackerman et al., 2012b; Misra et al., 2005). Following a 3-month diet and exercise intervention in young women, increased fasting ghrelin was shown in those with decreased EA and weight loss (Scheid et al., 2011).

While a negative correlation has been observed between BMI and ghrelin levels (Shiiya et al., 2002), ghrelin may have different effects in individuals of different BMI values. Exogenous ghrelin infusion increased caloric intake and hunger and appetite scores in normal weight and obese subjects (Druce et al., 2005). A separate exogenous ghrelin infusion study found that hunger scores increased less in patients with AN than in controls (Miljic et al., 2006). A lower ghrelin dose increased caloric intake for obese but not normal weight subjects (Druce et al., 2005). Women with AN and FHA have a high drive for thinness and high dietary restraint, suggesting that some female athletes with decreased EA may have a psychological suppression of ghrelin's ability to stimulate appetite (Scheid & De Souza, 2010). Overnight ghrelin secretion correlated negatively with LH secretion in amenorrheic athletes, even after controlling for fat mass, consistent with studies showing ghrelin administration suppressing LH and FSH pulsatility in animals and humans (Ackerman et al., 2012b; Misra, 2014).

Peptide YY (PYY) is released by intestinal cells in response to caloric intake and acts at the hypothalamus to decrease appetite and food ingestion. Interestingly, PYY is elevated in females with decreased EA and in amenorrheic athletes; levels correlate negatively with BMI and resting energy expenditure and positively with body fat percentage (Misra et al., 2006; Russell et al., 2009; Scheid et al., 2009). Animal models have demonstrated decreased LH release following PYY administration, and other studies have shown that PYY inhibits ghrelin-activated neurons (Fernandez-Fernandez et al., 2005; Riediger et al., 2004). In addition, an inverse relationship between PYY and testosterone was reported in adolescent female athletes and controls (Russell et al., 2009). Thus, PYY has been hypothesized to play a role in compounding disordered eating behaviors in AN and FHA, contribute to ghrelin resistance, and directly or indirectly contribute to the downregulation of GnRH and gonadotropin release (Scheid & De Souza, 2010). More work is needed in humans, and, specifically, in athletes with low EA, to test these theories.

In a study of males with AN, PYY was higher than in healthy controls, but ghrelin did not differ between groups (Misra et al., 2008). Koehler et al. (2016) assessed the effects of altered EA,

through diet and exercise, on hormone levels in six male habitual exercisers and showed that the low EA conditions (15 kcal·kg^{-1} FFM·day^{-1}) did not result in a significant change in ghrelin from baseline or when compared with the adequate EA conditions (40 kcal·kg^{-1} FFM·day^{-1}). With limited data, it is unclear if appetite-regulating hormones respond differently to low EA in male versus female athletes.

Oxytocin

Oxytocin is a hormone predominantly produced by the hypothalamus and released by the posterior pituitary. It has many roles, such as effects on lactation and uterine contraction in women. More recently, oxytocin has been implicated in inhibiting reward-related eating behaviors, suppressing hypothalamic–pituitary–adrenal (HPA) axis activity, and modifying the glucoregulatory response to caloric consumption (Lawson, 2017; Ott et al., 2013). Oxytocin may also have anxiolytic and antidepressant effects (Afinogenova et al., 2016).

Interestingly, young female amenorrheic athletes had lower overnight oxytocin secretion than regularly menstruating nonathletes when controlling for estradiol, as estradiol is thought to stimulate oxytocin release (Lawson et al., 2013). Females with AN had lower overnight oxytocin secretion than controls (Lawson et al., 2011). Lawson et al. (2014) also reported positive correlations of fasting oxytocin levels and surrogate measures of EA (weight and BMI), REE, and secretion of hormones involved in energy homeostasis in young amenorrheic athletes. It is conceivable that the enhanced eating behaviors expected with low oxytocin are overridden by increased anxiety and depressive symptoms that may occur with decreased oxytocin in low EA states.

In a study of 12 professional male cyclists and 10 sedentary controls, oxytocin levels did not increase after exercising to exhaustion in either group, but preexercise, during exercise, and postexercise oxytocin levels were lower in the athletes versus controls (Chicharro et al., 2001). Because of the various roles of oxytocin and dearth of literature of oxytocin in athletes, it is important for further research to clarify how oxytocin changes in low EA states and its predominant effects.

Insulin, Amylin, and Incretins

Insulin regulates the storage of energy (carbohydrates, protein, and fat). In low EA states, insulin is typically downregulated to allow for more substrate availability (Martin et al., 2008). Increased insulin sensitivity and reduced insulin levels have been reported in amenorrheic athletes compared with eumenorrheic athletes and nonathletic controls (Laughlin & Yen, 1996; Rickenlund et al., 2004). In addition, insulin affects GnRH signaling. Studies evaluating 12- and 24-hr hormonal secretion have shown that insulin's pulsatile area under the curve (AUC) positively correlates with LH pulsatility (Laughlin & Yen, 1996; Rickenlund et al., 2004). When female runners with luteal phase defects were studied, such runners demonstrated lower insulin levels compared with ovulatory sedentary runners and controls (De Souza et al., 2003).

Following four different 4-day EA conditions (15 kcal·kg^{-1} FFM·day^{-1} with exercise, 15 kcal·kg^{-1} FFM·day^{-1} without exercise, 40 kcal·kg^{-1} FFM·day^{-1} with exercise, and 40 kcal·kg^{-1} FFM·day^{-1} without exercise), Koehler et al. (2016) showed significant decreases in insulin (−34% to −38%) in both low EA states (15 kcal·kg^{-1} FFM·day^{-1} with and without exercise) in male exercisers. Similar results have been seen in males who underwent three 72-hr fasting states, where insulin levels were significantly lower on the final day of the fast compared with the initial day for each fasting period (Chan et al., 2003). In male bodybuilders who underwent 11 weeks of decreased EI with continued training to decrease body fat for competition, insulin was significantly reduced (Maestu et al., 2010). The authors noted a strong correlation between insulin and lean mass, and suggested that similar to animal models, humans may need a critical circulating level of insulin for protein synthesis and anabolism after exercise (Maestu et al., 2010).

Amylin, a peptide hormone secreted along with insulin from the pancreatic beta cells, is reduced in fasting females with AN compared with healthy controls (Wojcik et al., 2010). Amylin contributes to glucose regulation and satiety, but we are not aware of any research evaluating amylin levels by EA in either male or female athletes.

Incretins, such as glucagon-like peptide 1 and gastric inhibitory peptide, are gut hormones that stimulate insulin release and inhibit glucagon release. Scheid et al. (2009) demonstrated that glucagon-like peptide 1 concentrations were similar among sedentary ovulatory, exercising ovulatory, and exercising amenorrheic women, even though the exercising amenorrheic women represented an energy deficient population. In contrast, reduced incretin hormone concentrations have been reported in female patients with AN (Misra & Klibanski, 2014). These inconsistencies, and the paucity of information regarding many of the metabolic consequences of RED-S in male and female sporting populations, highlight the need for future work in this area.

GH/Insulin-Like Growth Factor 1

GH, a pituitary peptide, is necessary for muscle and bone anabolism and the metabolism of carbohydrates, proteins, and lipids. GH is stimulated by hormones such as ghrelin, and some of the effects of GH are heavily mediated by insulin-like growth factor 1 (IGF-1), a peptide produced in the liver. Females with AN have increased GH secretion and reduced IGF-1 levels, suggesting a low EA-acquired resistance to GH at the liver (Misra & Klibanski, 2014). Of interest, the effects of GH on carbohydrate metabolism and lipolysis are not mediated by IGF-1 and are preserved in AN. For example, GH can help maintain euglycemia in states of low EA by withdrawing energy sources from fat stores (Misra & Klibanski, 2014). As proof of concept, GH administration in women with AN led to decreased fat mass, although IGF-1 levels were unchanged (Fazeli et al., 2010; Misra & Klibanski, 2014).

Studies evaluating the effect of EA in regularly menstruating untrained women showed that compared with an adequate energy state (45 kcal·kg^{-1} FFM·day^{-1}), GH increased and IGF-1 decreased when energy was restricted to 10 or 20 kcal·kg^{-1} FFM·day^{-1} (Loucks & Thuma, 2003; Loucks et al., 1998). When comparing eumenorrheic nonathletes to amenorrheic and eumenorrheic athletes, Laughlin and Yen (1996) found that the two athlete groups had higher 24-hr mean GH concentrations than the nonathletes. The three groups had similar IGF-1 levels. However, due to differences in IGF binding protein-1 levels, the amenorrheic athletes had the lowest bioactivity of IGF-1 (Laughlin & Yen, 1996).

Increases in GH secretion have been observed in male wrestlers during a competitive wrestling season that involved dietary restriction and weight loss (Roemmich & Sinning, 1997). By the end of the season, the wrestlers had elevated GH concentrations and significantly reduced IGF-1 concentrations, suggesting dietary

restraint causes a partial GH resistance (Roemmich & Sinning, 1997). Case studies of men with AN have also indicated that inadequate caloric intake increases GH levels (Rigotti et al., 1986; Thienpont et al., 2000). Reductions in IGF-1 have also been seen in male cyclists competing in a 1,230 km ultraendurance event, with suppression of IGF-1 strongly associated with energy deficit (Geesmann et al., 2016). In the previously mentioned 11-week male bodybuilder study, the low EI group also had significant reductions in IGF-1, which correlated with changes in insulin (Maestu et al., 2010). In addition, when comparing male Olympic athletes, those participating in endurance sports had higher IGF binding protein-1 compared with nonendurance athletes, suggesting less bioavailable IGF-1 (Hagmar et al., 2013).

Thyroid Hormones

The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are important for growth, reproduction, and metabolism. Both thyroid excess and deficiency can stunt growth and inhibit reproductive function (Martin et al., 2008). In response to periods of low EA, the hypothalamic-pituitary-thyroid axis adapts in order to reduce energy expenditure and a "sick euthyroid" profile is often noted (Misra & Klibanski, 2014). Women with FHA and AN and athletes with amenorrhea have demonstrated consistently decreased T3 levels, but variable levels of T4 and thyroid-stimulating hormone (TSH; higher, lower, and similar) compared with eumenorrheic women (Berga et al., 1989; Counts et al., 1992; De Souza et al., 2007; Estour et al., 2010; Gordon, 2010; Harber et al., 1998; Loucks & Heath, 1994; Loucks et al., 1992; Misra et al., 2003, 2004; Stoving et al., 1999).

In a study by Loucks and Callister (1993), 46 women were randomized to groups of 4 days of "normal" or "low" EA (30 vs. 8 kcal·kg^{-1} FFM·day^{-1}) involving no exercise, low-intensity exercise, or high-intensity exercise resulting in six different testing conditions. Low EA decreased total T3 by 15% and free T3 by 18% compared with baseline. Total T4 increased by 7% and reverse T3 increased by 24%, but free T4 was unchanged. Exercise quantity and intensity did not affect any thyroid hormone testing result (Loucks & Callister, 1993). When 27 untrained, eumenorrheic women performed supervised aerobic exercise over 4 days, but were provided food to allow for four different levels of EA (10.8, 19.0, 25.0, and 40.4 kcal·kg^{-1} FFM·day^{-1}), decreases in total T3 and free T3 occurred abruptly between 19 and 25 kcal·kg^{-1} FFM·day^{-1}and increases in free T4 and reverse T3 occurred abruptly between 10.8 and 19 kcal·kg^{-1} FFM·day^{-1} (Loucks & Heath, 1994). This study suggests a positive association of T3 and EA and that low T3 values may be a helpful marker of low EA.

In a cross-sectional study of elite female and male endurance track and field athletes, Heikura et al. (2017) showed significantly lower free T3 values in amenorrheic versus eumenorrheic females and in males with testosterone within the lowest quartile of the reference range compared with males with testosterone values above this threshold. These groups, amenorrheic and low testosterone athletes, represent populations who commonly experience low EA.

A cross-sectional study comparing 27 male elite runners (13 sprinters and 14 marathoners) to 27 healthy, sedentary, lean men showed that TSH and TSH:Free T3 ratios were lower in the athletes (Perseghin et al., 2009). Free leptin index was independently associated with the TSH:Free T3 ratio, suggesting that leptin plays a role in the adaptive response of the hypothalamic–pituitary–thyroid axis (Perseghin et al., 2009). However, there were no differences between groups for free T3 and T4 (Perseghin et al., 2009). A case series of four males with AN revealed signs of hypothyroidism, including total T3, total T4, free T3, and free T4 measurements below normal ranges. However, TSH for each patient was within the normal range (Skolnick et al., 2016). More work is needed in both women and men to fully understand adaptations of thyroid function to acute and chronic changes in EA.

Cortisol

The HPA axis plays a critical role in energy balance, particularly in relation to food intake, energy storage, and energy mobilization. Cortisol measures have demonstrated a *U*-shaped relationship with BMI and adiposity; both extremely underweight and overweight states potentially activate the HPA axis, resulting in higher cortisol levels (Schorr et al., 2015). Although cortisol likely contributes to increased adiposity during energy abundance, cortisol is also an important catabolic hormone secreted by the adrenal cortex in response to prolonged exercise, starvation, glycogen depletion, and stress (Schaal et al., 2011). Studies of severe caloric restriction and fasting have demonstrated increases in circulating cortisol in animals and humans (Martin et al., 2008; Nakamura et al., 2016). Of interest, in animal models, stress-related reproductive feedback may begin in the upper digestive tract, where decreased EI activates vagal afferents to stimulate the brain, eventually causing noradrenergic input at the hypothalamus, thus increasing cortisol releasing hormone (CRH) activity. Increased CRH at the hypothalamus directly affects GnRH-positive neurons, modulating GnRH release and attenuating pituitary LH pulsatility in animals (Martin et al., 2008).

Loucks et al. (1989) showed no differences in ACTH secretion or cortisol pulse frequency in amenorrheic athletes versus eumenorrheic athletes or controls, but 24-hr urine cortisol measurements were higher in the amenorrheic athletes than in the other two groups. Higher baseline cortisol and higher overnight cortisol pulse amplitude, mass, half-life, and AUC have been reported in amenorrheic athletes versus eumenorrheic athletes and controls (Ackerman et al., 2013; Rickenlund et al., 2004). However, Laughlin and Yen (1996) found higher 24-hr serum cortisol levels in female athletes regardless of menstrual status compared with nonathletes, consistent with the stress of exercise significantly contributing to cortisol secretion. De Souza et al. (1994) reported a blunted cortisol response to ACTH stimulation in amenorrheic athletes versus eumenorrheic athletes and nonathletes, but similar peak cortisol values were achieved in all groups. Schaal et al. (2011) did not show any difference in cortisol levels at baseline or in response to different exercise intensities between amenorrheic and eumenorrheic athletes, but a blunted catecholamine (norepinephrine and epinephrine) response to high-intensity exercise was observed in the amenorrheic athletes.

Because CRH stimulates ACTH, which typically results in increased cortisol, it is unclear if the disruption of GnRH pulsatility in amenorrheic athletes is more directly affected by increased CRH or hypercortisolemia. Hypercortisolemia may directly influence reproductive function or simply be a biomarker of stress and reproductive dysfunction in amenorrheic athletes (Ackerman et al., 2013; Berga et al., 1989; Villanueva et al., 1986). In a study using cognitive behavioral therapy in the treatment of FHA, cortisol levels decreased and eumenorrhea was restored in some patients (Michopoulos et al., 2013). Because women with FHA have reported psychogenic difficulties accompanying behaviors that result in energy deficit and metabolic stress, the

authors suggest that cognitive behavioral therapy may have decreased cortisol and altered eating and exercising behaviors (Michopoulos et al., 2013). Tornberg et al. (2017) showed that amenorrheic athletes had higher cortisol levels and lower blood glucose levels than eumenorrheic athletes; they linked the changes to decreased neuromuscular performance. Because of the interplay between physical stress and psychological stress, and the relationship between CRH, ACTH, cortisol, and other stress hormones, more work is needed to completely understand cortisol's role in low EA in athletes.

In a small study of nine long-distance male runners with low EA (mean 27.2 ± 12.7 kcal·kg^{-1} FFM·day^{-1}) versus eight nonathletes with adequate EA (45.4 ± 18.2 kcal·kg^{-1} FFM·day^{-1}), one-time measures of cortisol were not significantly different between groups (Hooper et al., 2017). More in-depth work is needed to better understand the effects of low EA on adrenal function in male athletes.

Hypothalamic–Pituitary–Gonadal Axis

Both female and male athletes in states of low EA may experience alterations in normal sex hormone concentrations and function (Ackerman & Misra, 2015; Hooper et al., 2017; Loucks & Thuma, 2003). As previously mentioned, it is well established that low EA leads to menstrual cycle disruption, reproductive system suppression, and FHA in females, as a mechanism of energy conservation for processes more vital than procreation (De Souza et al., 2007, 2014; Gordon et al., 2017; Jasienska, 2003). Understanding the effects of prolonged low EA on reproductive hormones without confounding by FHA is difficult. Amenorrhea is characterized by changes in reproductive hormones. Nevertheless, Loucks and Thuma (2003) showed severe low EA (10 kcal·kg^{-1} FFM·day^{-1}) reduced estradiol levels in regularly menstruating women. This seminal study found that LH pulse frequency was diminished and amplitude was higher during low EA (10 and 20 kcal·kg^{-1} FFM·day^{-1}), though mean 24-hr LH and FSH concentrations were unchanged (Loucks & Thuma, 2003). In adults, LH pulse frequency has been shown to be highest in regularly menstruating controls, lower in eumenorrheic athletes, and lowest in amenorrheic athletes, with inconsistent findings in LH pulse amplitude and total LH secretion (Laughlin & Yen, 1996; Loucks et al., 1998; Rickenlund et al., 2004). A study of amenorrheic athletes, eumenorrheic athletes, and female nonathletes aged 14–21 years found no difference among groups in 8-hr overnight LH pulse frequency; lower pulse amplitude and total pulsatile secretion in amenorrheic athletes compared with controls; and no differences in LH parameters between amenorrheic and eumenorrheic athletes (Ackerman et al., 2012b). Such variability in findings likely reflect differences in blood collection timing and frequency, phase of menstrual cycle, and data analysis methods of frequent sampling.

As expected, urinary estradiol and progesterone are low in amenorrheic athletes, but progesterone was also found to be lower in eumenorrheic athletes during the luteal phase compared with eumenorrheic nonathletes (Loucks et al., 1989). Both athlete groups were inferred to have lower EA than the nonathletes based on food records, training recall, and exercise testing (Loucks et al., 1989).

Studies evaluating testosterone levels in females with low EA or surrogates for low EA have produced inconsistent results, with testosterone either being elevated, unchanged, or lowered in those with low EA (see Table 1; Christo et al., 2008; Lagowska & Kapczuk, 2016; Miller et al., 2007; Rickenlund et al., 2004; Russell et al., 2009). When using menstrual dysfunction as a surrogate for low EA, care must be taken in interpreting the results regarding testosterone, as polycystic ovarian syndrome (characterized by hyperandrogenism) can be the source of the menstrual dysfunction in addition to or instead of an energy deficit (Rickenlund et al., 2004). Further research is needed to understand how testosterone levels change in response to low EA in females.

Importantly, males can also experience disruptions in their normal reproductive hormone profiles in states of low EA. Healthy males participating in a 72-hr fast had a marked reduction in total testosterone levels compared with prefast values (Chan et al., 2003). In this same study, when men were given replacement doses of recombinant leptin during fasting, total testosterone was not reduced when compared with baseline, suggesting similar roles of leptin signaling effects on the hypothalamic–pituitary–gonadal axis in men as in women (Chan et al., 2003). In a study of nine male athletes who competed in a team, mixed ultraendurance race >800 km (median duration 6.3 days, range 5.2–7.3 days), free and total testosterone levels measured immediately after the race were significantly reduced compared with prerace values (Berg et al., 2008). These lower levels were coupled with a reduction in subcutaneous and visceral adipose tissue in all of the athletes, and decreased FSH and total and free IGF-1, but not LH (Berg et al., 2008). The authors estimated EI and EEE in three of the athletes and suggested an energy deficit of ~40,000 kcal over the course of the race. If these three athletes completed the race in the median duration of 6.3 days, this would suggest an energy deficit of 6,349 kcal/day (Berg et al., 2008).

In general, male athletes participating in endurance sports or those in which leanness is emphasized are at increased risk for low or low normal testosterone (Bennell et al., 1996; Hackney et al., 1998; Heikura et al., 2017). This state has been described as the "exercise-hypogonadal male condition (EHMC)," where basal, free, and total testosterone concentrations are reduced without consistent elevations in LH levels (Hackney et al., 2005). However, studies examining testosterone and LH secretion in male endurance athletes at high risk for EHMC are not consistent in testosterone or LH findings. McColl et al. (1989) found lower basal total serum testosterone levels, LH pulse amplitude, and LH AUC (as calculated from frequent sampling over 6 hr) in high-mileage male runners versus controls. MacConnie et al. (1986) reported similar total testosterone levels in male marathon runners versus healthy controls, but lower LH pulse frequency and amplitude over 8 hr. The response of LH to increasing doses of exogenous GnRH was also decreased in the marathoners (MacConnie et al., 1986). In a study using frequent sampling over 4 hr, Hackney et al. (1988) noted lower total and free testosterone levels in endurance-trained men versus untrained men, with a trend toward higher LH concentrations in the athletes, but no difference in LH pulse frequency or amplitude compared with the controls.

Hooper et al. (2017) compared 4-hr hormonal frequent sampling of nine long-distance male runners exhibiting EHMC to eight nonactive controls. As mentioned previously, the runners had a mean EA of 27.2 kcal·kg^{-1} FFM·day^{-1} and the nonathletes had an adequate mean EA of 45.4 kcal·kg^{-1} FFM·day^{-1}. Mean total testosterone was significantly reduced in the EHMC group, with no differences in mean LH concentrations, pulse frequency, or amplitude compared with controls (Hooper et al., 2017). Potential explanations for the inconsistencies in the results of this latter study versus those of the aforementioned studies include differences in EA between the studies; different timing, duration, and frequency of sampling; and different data analysis methods. While it has been

hypothesized that high concentrations of cortisol could suppress testosterone but not LH in EHMC/low EA, the data are inconsistent (Cumming et al., 1983; Hackney et al., 1988; Hooper et al., 2017). If cortisol does indeed suppress testosterone, this suggests a peripheral mechanism for suppression of gonadal hormones in men versus the central dysfunction that occurs in FHA in women.

Lower testosterone levels have also been reported in males participating in nonleanness sports, such as American football and soccer, suggesting male athletes in all sport types are at risk of reduced testosterone and/or EHMC (Grasso et al., 1997; Moore & Fry, 2007; Stone et al., 2017). A study comparing Division 1 male collegiate golfers, runners, and off-season wrestlers found the runners had reduced estradiol levels (Ackerman et al., 2012a). The runners were the only group with pressure to conform to leanness standards during the study. We are unaware of studies showing the effects of EA on progestins in men, which are very low at baseline. Further work is needed to understand the effects of low EA on the hypothalamic–pituitary–gonadal axis in men of various sports types, with a focus on accurate assessment of EA to better understand results.

Bone Health

There are considerable effects of low EA on the health and performance of athletes, which are beyond the scope of this paper. Bone is worth mentioning, however, because of the abundance of literature on this topic and the fact that bone is both an endocrine organ—secreting fibroblast growth factor 23 and osteocalcin—and an endocrine target (Guntur & Rosen, 2012). The majority of the hormones discussed previously are known to impact bone metabolism. Studies of the hormonal changes in females with amenorrhea and in women with AN (hypothalamic–pituitary–gonadal axis suppression; decreased leptin, insulin, and IGF-1; increased PYY and cortisol; and other hormonal alterations) have consistently demonstrated detrimental effects on bone mineral density (BMD), bone microarchitecture, and bone turnover markers in these populations (Ackerman & Misra, 2015; Misra & Klibanski, 2014; Papageorgiou et al., 2017a).

Amenorrheic athletes have been shown to have lower BMD, impaired bone microarchitecture, reduced estimates of bone strength, and higher rates of fracture compared with eumenorrheic athletes and nonathletic controls (Ackerman et al., 2015; Ackerman & Misra, 2011; De Souza et al., 2014). Southmayd et al. (2017) showed that EA and estrogen status exerted combined and independent effects on BMD, bone geometry, and estimates of bone strength. Studies of women in short- and long-term states of low EA (by diet and exercise manipulation) have demonstrated negative effects on markers of bone turnover (Ihle & Loucks, 2004; Papageorgiou 2017b; Zanker & Swaine, 1998).

In contrast, there are fewer studies of the effects of low EA on BMD, bone quality, and bone metabolism in male athletes, and results are less definitive. Male athletes participating in endurance sports and sports emphasizing leanness (including runners, cyclists, and jockeys) have, on average, lower BMD than those in nonleanness sports or sports involving high impact and multidirectional bone loading (Papageorgiou et al., 2017a; Tenforde et al., 2016). Decreased BMD, cortical area, and tibia strength/strain index have been reported in jockeys and have been attributed to chronically low EA (Greene et al., 2013; Warrington et al., 2009). Low EA markers of BMI ≤17.5 kg/m^2 (Tenforde et al., 2015) and expected body weight <85% (Barrack et al., 2017) have been associated with reduced BMD in adolescent male runners. Heikura et al. (2017) reported a greater lifetime history of stress fractures in male athletes with the lowest quartile of testosterone (although within normal) compared with those with testosterone levels above this threshold.

Papageorgiou et al. (2017b) examined the effects of two 5-day protocols of controlled (45 kcal·kg^{-1} FFM·day^{-1}) and restricted (15 kcal·kg^{-1} FFM·day^{-1}) EA in 11 men and 11 eumenorrheic women. EA was achieved by manipulation of diet (either 60 or 30 kcal·kg^{-1} FFM·day^{-1}) and a fixed exercise program of daily treadmill running at 70% of peak aerobic capacity, resulting in an EEE of 15 kcal·kg^{-1} FFM·day^{-1}. The women had significantly higher bone resorption marker AUCs and significantly lower bone formation AUCs in the restricted condition compared with the controlled state. However, markers of bone formation and resorption AUCs were not significantly different between conditions in the men (Papageorgiou et al., 2017b). In contrast, Zanker and Swaine (2000) investigated the effects of 3 days of low EA (50% of estimated energy requirement) compared with an adequate EA condition in eight male distance runners performing 60 min/day of treadmill running. A significant decline in a bone formation marker (N-terminal propeptide of Type 1 collagen) and IGF-1 were noted (15% and 17%, respectively) following 3 days of energy restriction; no change was observed for the adequate energy condition nor in other bone markers in either condition (Zanker & Swaine, 2000).

Interestingly, Ackerman et al. (2012a) reported that estradiol levels, BMI, and resistance training were more important determinants of BMD in male athletes than were testosterone levels. Thus, future research on bone health and low EA in male athletes should investigate the various effects of hormonal interactions on bone in addition to the severity and duration of EA needed to negatively impact bone health parameters.

Summary and Conclusions

Low EA is known to affect the reproductive system and other interrelated hormonal pathways. Lower BMI, fat mass, and RMR values have been reported in both male and female athletes with low EA compared to adequate EA.

In both sexes, anorexigenic leptin is lower in low EA states. In contrast, anorexigenic adiponectin has been shown to increase in some women during low EA. Changes in adiponectin in exercising men have been more inconsistent, and no studies have measured changes in relation to EA. Orexigenic ghrelin is elevated in women and remains normal in men with low EA. Anorexigenic PYY has been shown to increase in both sexes with low EA. Oxytocin levels are lower in athletes of both sexes compared with nonathletic controls, but more research is needed in athletes to better understand its role in modifying eating behaviors in the context of low EA.

Levels of the important glucose-regulating hormone insulin are lower in both male and female energy deficient athletes, while its cosecreted hormone, amylin, has not been investigated in athletes with reduced EA. Total IGF-1 and/or bioavailable IGF-1 have been shown to be lower in low EA states in male and female athletes. T3 has consistently been shown to be lower in women with low EA, but more work is needed in male athletes. Males with low EA have demonstrated a lower TSH:T3 ratio. Determining thyroid profile patterns with changes in EA could prove helpful in monitoring athletes at risk for RED-S.

Cortisol is typically elevated in low EA states, but is also elevated in other stress states, such as during exercise. Thus, not all

athletes with low EA have demonstrated significantly higher cortisol levels in comparison to athletes with adequate EA.

Low female sex hormones, estradiol and progesterone, have been consistently reported in states of low EA, supporting the FHA model. In contrast, some, but not all, studies document reduced testosterone levels in populations of energy-restricted male athletes; differences in sampling and chronicity of energy deficiency may explain variable measures in testosterone levels.

Low BMD has been reported in female and male athletes at higher risk for low EA, though much more work has been done in females with energy deficiency. The influence of low EA on mechanisms underlying impaired bone health are better described in female athletes; further studies in men with low EA may clarify differences in bone turnover markers in men compared to women.

As the prevalence and consequences of RED-S become more understood and such knowledge is applied to optimize the treatment of athletes throughout the international sports and sports science communities, the need to further our understanding of hormonal pathways leading to certain health and performance consequences is amplified. This paper attempts to summarize what is currently known about various hormonal changes in low EA states. It is important to emphasize that the majority of the studies discussed did not directly measure EA, but instead made assumptions about EA based on BMI, menstrual status, type of sport, or duration of activity. Measuring EA with food/training logs might not reflect the athlete's true physiological state, as these logs only provide a snapshot of recent and current behavior, and accurate measurement of EI and EEE is difficult with self-reported methods. Literature related to low EA and RED-S in male populations is sparse and often uses surrogate markers of EA. Endocrinology is an integral component of sports medicine and RED-S, and the endocrine and metabolic effects of low EA should be further investigated using direct measurements, diverse populations, and both short- and long-term study designs. A specific focus of future research should be placed on the hormonal changes occurring in chronic low EA states rather than acute changes, such as those that occur during a training session or competition. With a more rigorous, prospective study of hormonal interactions during changes in EA in athletic populations, we may discover hormonal ranges specific to athletes compared to nonathletes. We may also find that optimizing certain hormonal patterns through diet and training should be individualized based on repeated testing. Such work will improve our care of athletes at risk of RED-S and better inform their training and nutritional planning for optimal health and performance.

Acknowledgments

Thank you to Anisa Haque for her research and editorial assistance. This work was not funded by an external source. The authors have no conflicts of interest to disclose.

References

Ackerman, K.E., Cano Sokoloff, N.G., De Nardo Maffazioli, G., Clarke, H.M., Lee, H., & Misra, M. (2015). Fractures in relation to menstrual status and bone parameters in young athletes. *Medicine & Science in Sports and Exercise, 47*(8), 1577–1586. PubMed ID: 25397605 doi:10.1249/MSS.0000000000000574

Ackerman, K.E., & Misra, M. (2011). Bone health and the female athlete triad in adolescent athletes. *Physician and Sportsmedicine, 39*(1), 131–141. PubMed ID: 21378496 doi:10.3810/psm.2011.02.1871

Ackerman, K.E., & Misra, M. (2015). Neuroendocrine abnormalities in female athletes. In C.M. Gordon & M. LeBoff (Eds.), *The female athlete triad–A clinical guide* (pp. 85–109). Boston, MA: Springer.

Ackerman, K.E., Patel, K.T., Guereca, G., Pierce, L., Herzog, D.B., & Misra, M. (2013). Cortisol secretory parameters in young exercisers in relation to LH secretion and bone parameters. *Clinical Endocrinology, 78*(1), 114–119. doi:10.1111/j.1365-2265.2012.04458.x

Ackerman, K.E., Skrinar, G.S., Medvedova, E., Misra, M., & Miller, K.K. (2012a). Estradiol levels predict bone mineral density in male collegiate athletes: A pilot study. *Clinical Endocrinology, 76*(3), 339–345. doi:10.1111/j.1365-2265.2011.04212.x

Ackerman, K.E., Slusarz, K., Guereca, G., Pierce, L., Slattery, M., Mendes, N., ... Misra, M. (2012b). Higher ghrelin and lower leptin secretion are associated with lower LH secretion in young amenorrheic athletes compared with eumenorrheic athletes and controls. *American Journal of Physiology-Endocrinology and Metabolism, 302*(7), E800–E806. PubMed ID: 22252944 doi:10.1152/ajpendo.00598.2011

Afinogenova, Y., Schmelkin, C., Plessow, F., Thomas, J.J., Pulumo, R., Micali, N., ... Lawson, E.A. (2016). Low fasting oxytocin levels are associated with psychopathology in anorexia nervosa in partial recovery. *The Journal of Clinical Psychiatry, 77*(11), e1483–e1490. PubMed ID: 28076675 doi:10.4088/JCP.15m10217

Barrack, M.T., Fredericson, M., Tenforde, A.S., & Nattiv, A. (2017). Evidence of a cumulative effect for risk factors predicting lower bone mass among male adolescent athletes. *British Journal of Sports Medicine, 51*(3), 200–205. PubMed ID: 29461218 doi:10.1136/bjsports-2016-096698

Bennell, K.L., Brukner, P.D., & Malcolm, S.A. (1996). Effect of altered reproductive function and lowered testosterone levels on bone density in male endurance athletes. *British Journal of Sports Medicine, 30*(3), 205–208. PubMed ID: 8889111 doi:10.1136/bjsm.30.3.205

Berg, U., Enqvist, J.K., Mattsson, C.M., Carlsson-Skwirut, C., Sundberg, C.J., Ekblom, B., & Bang, P. (2008). Lack of sex differences in the IGF-IGFBP response to ultra endurance exercise. *Scandinavian Journal of Medicine & Science in Sports, 18*(6), 706–714. PubMed ID: 18248538 doi:10.1111/j.1600-0838.2007.00758.x

Berga, S.L., Mortola, J.F., Girton, L., Suh, B., Laughlin, G., Pham, P., & Yen, S.S. (1989). Neuroendocrine aberrations in women with functional hypothalamic amenorrhea. *The Journal of Clinical Endocrinology and Metabolism, 68*(2), 301–308. PubMed ID: 2493024 doi:10.1210/jcem-68-2-301

Chan, J.L., Heist, K., DePaoli, A.M., Veldhuis, J.D., & Mantzoros, C.S. (2003). The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. *Journal of Clinical Investigation, 111*(9), 1409–1421. PubMed ID: 12727933 doi:10.1172/JCI17490

Chicharro, J.L., Hoyos, J., Bandres, F., Gomez Gallego, F., Perez, M., & Lucia, A. (2001). Plasma oxytocin during intense exercise in professional cyclists. *Hormone Research, 55*(3), 155–159. PubMed ID: 11549878 doi:10.1159/000049988

Chou, S.H., Chamberland, J.P., Liu, X., Matarese, G., Gao, C., Stefanakis, R., ... Mantzoros, C.S. (2011). Leptin is an effective treatment for hypothalamic amenorrhea. *Proceedings of the National Academy of Sciences of the United States of America, 108*(16), 6585–6590. PubMed ID: 21464293 doi:10.1073/pnas.1015674108

Christo, K., Cord, J., Mendes, N., Miller, K.K., Goldstein, M.A., Klibanski, A., & Misra, M. (2008). Acylated ghrelin and leptin in adolescent athletes with amenorrhea, eumenorrheic athletes and controls: A cross-sectional study. *Clinical Endocrinology, 69*(4), 628–633. doi:10.1111/j.1365-2265.2008.03237.x

Corr, M., De Souza, M.J., Toombs, R.J., & Williams, N.I. (2011). Circulating leptin concentrations do not distinguish menstrual status in exercising women. *Human Reproduction, 26*(3), 685–694. PubMed ID: 21227945 doi:10.1093/humrep/deq375

Counts, D.R., Gwirtsman, H., Carlsson, L.M., Lesem, M., & Cutler, G.B., Jr. (1992). The effect of anorexia nervosa and refeeding on growth hormone-binding protein, the insulin-like growth factors (IGFs), and the IGF-binding proteins. *The Journal of Clinical Endocrinology and Metabolism, 75*(3), 762–767. PubMed ID: 1381372 doi:10.1210/jcem.75.3.1381372

Cumming, D.C., Quigley, M.E., & Yen, S.S. (1983). Acute suppression of circulating testosterone levels by cortisol in men. *The Journal of Clinical Endocrinology and Metabolism, 57*(3), 671–673. PubMed ID: 6348068 doi:10.1210/jcem-57-3-671

De Souza, M.J., Lee, D.K., VanHeest, J.L., Scheid, J.L., West, S.L., & Williams, N.I. (2007). Severity of energy-related menstrual disturbances increases in proportion to indices of energy conservation in exercising women. *Fertility and Sterility, 88*(4), 971–975. PubMed ID: 17418159 doi:10.1016/j.fertnstert.2006.11.171

De Souza, M.J., Leidy, H.J., O'Donnell, E., Lasley, B., & Williams, N.I. (2004). Fasting ghrelin levels in physically active women: Relationship with menstrual disturbances and metabolic hormones. *The Journal of Clinical Endocrinology and Metabolism, 89*(7), 3536–3542. PubMed ID: 15240643 doi:10.1210/jc.2003-032007

De Souza, M.J., Luciano, A.A., Arce, J.C., Demers, L.M., & Loucks, A.B. (1994). Clinical tests explain blunted cortisol responsiveness but not mild hypercortisolism in amenorrheic runners. *Journal of Applied Physiology, 76*(3), 1302–1309. doi:10.1152/jappl.1994.76.3.1302

De Souza, M.J., Nattiv, A., Joy, E., Misra, M., Williams, N.I., Mallinson, R.J., … Expert Panel. (2014). 2014 female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad: 1st international conference held in San Francisco, California, May 2012 and 2nd international conference held in Indianapolis, Indiana, May 2013. *British Journal of Sports Medicine, 48*(4), 289. PubMed ID: 24463911 doi:10.1136/bjsports-2013-093218

De Souza, M.J., Van Heest, J., Demers, L.M., & Lasley, B.L. (2003). Luteal phase deficiency in recreational runners: Evidence for a hypometabolic state. *The Journal of Clinical Endocrinology and Metabolism, 88*(1), 337–346. PubMed ID: 12519874 doi:10.1210/jc.2002-020958

Donoso, M.A., Munoz-Calvo, M.T., Barrios, V., Garrido, G., Hawkins, F., & Argente, J. (2010). Increased circulating adiponectin levels and decreased leptin/soluble leptin receptor ratio throughout puberty in female ballet dancers: Association with body composition and the delay in puberty. *European Journal of Endocrinology, 162*(5), 905–911. PubMed ID: 20145046 doi:10.1530/EJE-09-0874

Druce, M.R., Wren, A.M., Park, A.J., Milton, J.E., Patterson, M., Frost, G., … Bloom, S.R. (2005). Ghrelin increases food intake in obese as well as lean subjects. *International Journal of Obesity, 29*(9), 1130–1136. doi:10.1038/sj.ijo.0803001

Dufour, D.L., & Sauther, M.L. (2002). Comparative and evolutionary dimensions of the energetics of human pregnancy and lactation. *American Journal of Human Biology, 14*(5), 584–602. PubMed ID: 12203813 doi:10.1002/ajhb.10071

Estour, B., Germain, N., Diconne, E., Frere, D., Cottet-Emard, J.M., Carrot, G., … Galusca, B. (2010). Hormonal profile heterogeneity and short-term physical risk in restrictive anorexia nervosa. *The Journal of Clinical Endocrinology and Metabolism, 95*(5), 2203–2210. PubMed ID: 20305007 doi:10.1210/jc.2009-2608

Fazeli, P.K., Lawson, E.A., Prabhakaran, R., Miller, K.K., Donoho, D.A., Clemmons, D.R., … Klibanski, A. (2010). Effects of recombinant human growth hormone in anorexia nervosa: A randomized, placebo-controlled study. *The Journal of Clinical Endocrinology and Metabolism, 95*(11), 4889–4897. PubMed ID: 20668047 doi:10.1210/jc.2010-0493

Fernandez-Fernandez, R., Aguilar, E., Tena-Sempere, M., & Pinilla, L. (2005). Effects of polypeptide YY(3-36) upon luteinizing hormone-releasing hormone and gonadotropin secretion in prepubertal rats: In vivo and in vitro studies. *Endocrinology, 146*(3), 1403–1410. PubMed ID: 15564330 doi:10.1210/en.2004-0858

Geesmann, B., Gibbs, J.C., Mester, J., & Koehler, K. (2016). Association between energy balance and metabolic hormone suppression during ultra-endurance exercise. *International Journal of Sports Physiology and Performance, 12*(7), 1–20. doi:10.1123/ijspp.2016-0061

Gomez-Merino, D., Chennaoui, M., Drogou, C., Bonneau, D., & Guezennec, C.Y. (2002). Decrease in serum leptin after prolonged physical activity in men. *Medicine & Science in Sports and Exercise, 34*(10), 1594–1599. PubMed ID: 12370560 doi:10.1249/01.MSS.0000031097.37179.42

Gordon, C.M. (2010). Clinical practice. Functional hypothalamic amenorrhea. *The New England Journal of Medicine, 363*(4), 365–371. PubMed ID: 20660404 doi:10.1056/NEJMcp0912024

Gordon, C.M., Ackerman, K.E., Berga, S.L., Kaplan, J.R., Mastorakos, G., Misra, M., … Warren, M.P. (2017). Functional hypothalamic amenorrhea: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism, 102*(5), 1413–1439. PubMed ID: 28368518 doi:10.1210/jc.2017-00131

Grasso, G., Lodi, L., Lupo, C., & Muscettola, M. (1997). Glucocorticoid receptors in human peripheral blood mononuclear cells in relation to age and to sport activity. *Life Sciences, 61*(3), 301–308. PubMed ID: 9217290 doi:10.1016/S0024-3205(97)00386-X

Greene, D.A., Naughton, G.A., Jander, C.B., & Cullen, S.J. (2013). Bone health of apprentice jockeys using peripheral quantitative computed tomography. *International Journal of Sports Medicine, 34*(8), 688–694. PubMed ID: 23371826 doi:10.1055/s-0032-1333213

Griffiths, M.D., Szabo, A., & Terry, A. (2005). The exercise addiction inventory: A quick and easy screening tool for health practitioners. *British Journal of Sports Medicine, 39*(6), e30. PubMed ID: 15911594 doi:10.1136/bjsm.2004.017020

Grinspoon, S., Gulick, T., Askari, H., Landt, M., Lee, K., Anderson, E., … Klibanski, A. (1996). Serum leptin levels in women with anorexia nervosa. *The Journal of Clinical Endocrinology and Metabolism, 81*(11), 3861–3863. PubMed ID: 8923829 doi:10.1210/jcem.81.11.8923829

Guntur, A.R., & Rosen, C.J. (2012). Bone as an endocrine organ. *Endocrine Practice, 18*(5), 758–762. PubMed ID: 22784851 doi:10.4158/EP12141.RA

Hackney, A.C., Fahrner, C.L., & Gulledge, T.P. (1998). Basal reproductive hormonal profiles are altered in endurance trained men. *The Journal of Sports Medicine and Physical Fitness, 38*(2), 138–141. PubMed ID: 9763799

Hackney, A.C., Moore, A.W., & Brownlee, K.K. (2005). Testosterone and endurance exercise: Development of the "exercise-hypogonadal male condition". *Acta Physiologica Hungarica, 92*(2), 121–137. PubMed ID: 16268050 doi:10.1556/APhysiol.92.2005.2.3

Hackney, A.C., Sinning, W.E., & Bruot, B.C. (1988). Reproductive hormonal profiles of endurance-trained and untrained males. *Medicine & Science in Sports and Exercise, 20*(1), 60–65. PubMed ID: 3343919 doi:10.1249/00005768-198802000-00009

Hagmar, M., Berglund, B., Brismar, K., & Hirschberg, A.L. (2013). Body composition and endocrine profile of male Olympic athletes striving for leanness. *Clinical Journal of Sport Medicine, 23*(3), 197–201. PubMed ID: 23275346 doi:10.1097/JSM.0b013e31827a8809

Harber, V.J., Petersen, S.R., & Chilibeck, P.D. (1998). Thyroid hormone concentrations and muscle metabolism in amenorrheic and eumenorrheic athletes. *Canadian Journal of Applied Physiology, 23*(3), 293–306. PubMed ID: 9615871 doi:10.1139/h98-017

Heikura, I.A., Uusitalo, A.L.T., Stellingwerff, T., Bergland, D., Mero, A.A., & Burke, L.M. (2017). Low energy availability is difficult to assess but outcomes have large impact on bone injury rates in elite distance athletes. *International Journal of Sport Nutrition and Exercise Metabolism, 28*(4). doi:10.1123/ijsnem.2017-0313

Hilton, L.K., & Loucks, A.B. (2000). Low energy availability, not exercise stress, suppresses the diurnal rhythm of leptin in healthy young women. *American Journal of Physiology-Endocrinology and Metabolism, 278*(1), E43–E49. PubMed ID: 10644535 doi:10.1152/ajpendo.2000.278.1.E43

Hooper, D.R., Kraemer, W.J., Saenz, C., Schill, K.E., Focht, B.C., Volek, J.S., & Maresh, C.M. (2017). The presence of symptoms of testosterone deficiency in the exercise-hypogonadal male condition and the role of nutrition. *European Journal of Applied Physiology, 117*(7), 1349–1357. PubMed ID: 28470410 doi:10.1007/s00421-017-3623-z

Ihle, R., & Loucks, A.B. (2004). Dose-response relationships between energy availability and bone turnover in young exercising women. *Journal of Bone and Mineral Research, 19*(8), 1231–1240. PubMed ID: 15231009 doi:10.1359/JBMR.040410

Jasienska, G. (2003). Energy metabolism and the evolution of reproductive suppression in the human female. *Acta Biotheoretica, 51*(1), 1–18. PubMed ID: 12765249 doi:10.1023/A:1023035321162

Jurimae, J., Jurimae, T., & Purge, P. (2007). Plasma ghrelin is altered after maximal exercise in elite male rowers. *Experimental Biology and Medicine, 232*(7), 904–909.

Kaiserauer, S., Snyder, A.C., Sleeper, M., & Zierath, J. (1989). Nutritional, physiological, and menstrual status of distance runners. *Medicine & Science in Sports and Exercise, 21*(2), 120–125. PubMed ID: 2709975 doi:10.1249/00005768-198904000-00002

Karamouzis, I., Karamouzis, M., Vrabas, I.S., Christoulas, K., Kyriazis, N., Giannoulis, E., & Mandroukas, K. (2002). The effects of marathon swimming on serum leptin and plasma neuropeptide Y levels. *Clinical Chemistry and Laboratory Medicine, 40*(2), 132–136. PubMed ID: 11939485 doi:10.1515/CCLM.2002.023

Koehler, K., Achtzehn, S., Braun, H., Mester, J., & Schaenzer, W. (2013). Comparison of self-reported energy availability and metabolic hormones to assess adequacy of dietary energy intake in young elite athletes. *Applied Physiology, Nutrition, and Metabolism, 38*(7), 725–733. PubMed ID: 23980730 doi:10.1139/apnm-2012-0373

Koehler, K., Hoerner, N.R., Gibbs, J.C., Zinner, C., Braun, H., De Souza, M.J., & Schaenzer, W. (2016). Low energy availability in exercising men is associated with reduced leptin and insulin but not with changes in other metabolic hormones. *Journal of Sports Sciences, 34*(20), 1921–1929. PubMed ID: 26852783 doi:0.1080/02640414.2016.1142109

Kopp-Woodroffe, S.A., Manore, M.M., Dueck, C.A., Skinner, J.S., & Matt, K.S. (1999). Energy and nutrient status of amenorrheic athletes participating in a diet and exercise training intervention program. *International Journal of Sport Nutrition, 9*(1), 70–88. PubMed ID: 10200061 doi:10.1123/ijsn.9.1.70

Lagowska, K., & Kapczuk, K. (2016). Testosterone concentrations in female athletes and ballet dancers with menstrual disorders. *European Journal of Sport Science, 16*(4), 490–497. PubMed ID: 25951882 doi:10.1080/17461391.2015.1034786

Laughlin, G.A., & Yen, S.S. (1996). Nutritional and endocrine-metabolic aberrations in amenorrheic athletes. *The Journal of Clinical Endocrinology and Metabolism, 81*(12), 4301–4309. PubMed ID: 8954031 doi:10.1210/jcem.81.12.8954031

Lawson, E.A. (2017). The effects of oxytocin on eating behaviour and metabolism in humans. *Nature Reviews Endocrinology, 13*(12), 700–709. PubMed ID: 28960210 doi:10.1038/nrendo.2017.115

Lawson, E.A., Ackerman, K.E., Estella, N.M., Guereca, G., Pierce, L., Sluss, P.M., ... Misra, M. (2013). Nocturnal oxytocin secretion is lower in amenorrheic athletes than nonathletes and associated with bone microarchitecture and finite element analysis parameters. *European Journal of Endocrinology, 168*(3), 457–464. PubMed ID: 23258269 doi:10.1530/EJE-12-0869

Lawson, E.A., Ackerman, K.E., Slattery, M., Marengi, D.A., Clarke, H., & Misra, M. (2014). Oxytocin secretion is related to measures of energy homeostasis in young amenorrheic athletes. *The Journal of Clinical Endocrinology and Metabolism, 99*(5), E881–E885. PubMed ID: 24606095 doi:10.1210/jc.2013-4136

Lawson, E.A., Donoho, D.A., Blum, J.I., Meenaghan, E.M., Misra, M., Herzog, D.B., ... Klibanski, A. (2011). Decreased nocturnal oxytocin levels in anorexia nervosa are associated with low bone mineral density and fat mass. *The Journal of Clinical Psychiatry, 72*(11), 1546–1551. PubMed ID: 21903023 doi:10.4088/JCP.10m06617

Leal-Cerro, A., Garcia-Luna, P.P., Astorga, R., Parejo, J., Peino, R., Dieguez, C., & Casanueva, F.F. (1998). Serum leptin levels in male marathon athletes before and after the marathon run. *The Journal of Clinical Endocrinology and Metabolism, 83*(7), 2376–2379. PubMed ID: 9661612 doi:10.1210/jcem.83.7.4959

Lichtenstein, M.B., Andries, A., Hansen, S., Frystyk, J., & Stoving, R.K. (2015). Exercise addiction in men is associated with lower fat-adjusted leptin levels. *Clinical Journal of Sport Medicine, 25*(2), 138–143. PubMed ID: 24926913 doi:10.1097/JSM.0000000000000110

Lieberman, J.L., De Souza, M.J., Wagstaff, D.A., & Williams, N.I. (2018). Menstrual disruption with exercise is not linked to an energy availability threshold. *Medicine & Science in Sports and Exercise, 50*(3), 551–561. PubMed ID: 29023359 doi:10.1249/MSS.0000000000001451

Logue, D., Madigan, S.M., Delahunt, E., Heinen, M., Mc Donnell, S.J., & Corish, C.A. (2018). Low energy availability in athletes: A review of prevalence, dietary patterns, physiological health, and sports performance. *Sports Medicine, 48*(1), 73–96. PubMed ID: 28983802 doi:10.1007/s40279-017-0790-3

Loucks, A.B. (2007). Low energy availability in the marathon and other endurance sports. *Sports Medicine, 37*(4–5), 348–352. doi:10.2165/00007256-200737040-00019

Loucks, A.B., & Callister, R. (1993). Induction and prevention of low-T3 syndrome in exercising women. *American Journal of Physiology, 264*(5, Pt. 2), R924–R930. PubMed ID: 8498602 doi:10.1152/ajpregu.1993.264.5.R924

Loucks, A.B., & Heath, E.M. (1994). Induction of low-T3 syndrome in exercising women occurs at a threshold of energy availability. *American Journal of Physiology, 266*(3, Pt. 2), R817–R823. PubMed ID: 8160876 doi:10.1152/ajpregu.1994.266.3.R817

Loucks, A.B., Laughlin, G.A., Mortola, J.F., Girton, L., Nelson, J.C., & Yen, S.S. (1992). Hypothalamic-pituitary-thyroidal function in eumenorrheic and amenorrheic athletes. *The Journal of Clinical Endocrinology and Metabolism, 75*(2), 514–518. PubMed ID: 1639953 doi:10.1210/jcem.75.2.1639953

Loucks, A.B., Mortola, J.F., Girton, L., & Yen, S.S. (1989). Alterations in the hypothalamic-pituitary-ovarian and the hypothalamic-pituitary-adrenal axes in athletic women. *The Journal of Clinical Endocrinology and Metabolism, 68*(2), 402–411. PubMed ID: 2537332 doi:10.1210/jcem-68-2-402

Loucks, A.B., & Thuma, J.R. (2003). Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly

menstruating women. *The Journal of Clinical Endocrinology and Metabolism, 88*(1), 297–311. PubMed ID: 12519869 doi:10.1210/jc.2002-020369

Loucks, A.B., Verdun, M., & Heath, E.M. (1998). Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. *Journal of Applied Physiology, 84*(1), 37–46. doi:10.1152/jappl.1998.84.1.37

MacConnie, S.E., Barkan, A., Lampman, R.M., Schork, M.A., & Beitins, I.Z. (1986). Decreased hypothalamic gonadotropin-releasing hormone secretion in male marathon runners. *The New England Journal of Medicine, 315*(7), 411–417. PubMed ID: 3090437 doi:10.1056/NEJM198608143150702

Maestu, J., Eliakim, A., Jurimae, J., Valter, I., & Jurimae, T. (2010). Anabolic and catabolic hormones and energy balance of the male bodybuilders during the preparation for the competition. *The Journal of Strength and Conditioning Research, 24*(4), 1074–1081. PubMed ID: 20300017 doi:10.1519/JSC.0b013e3181cb6fd3

Martin, B., Golden, E., Carlson, O.D., Egan, J.M., Mattson, M.P., & Maudsley, S. (2008). Caloric restriction: Impact upon pituitary function and reproduction. *Ageing Research Reviews, 7*(3), 209–224. PubMed ID: 18329344 doi:10.1016/j.arr.2008.01.002

McColl, E.M., Wheeler, G.D., Gomes, P., Bhambhani, Y., & Cumming, D.C. (1989). The effects of acute exercise on pulsatile LH release in high-mileage male runners. *Clinical Endocrinology, 31*(5), 617–621. doi:10.1111/j.1365-2265.1989.tb01286.x

Melin, A., Tornberg, A.B., Skouby, S., Moller, S.S., Sundgot-Borgen, J., Faber, J., … Sjodin, A. (2015). Energy availability and the female athlete triad in elite endurance athletes. *Scandinavian Journal of Medicine & Science in Sports, 25*(5), 610–622. PubMed ID: 24888644 doi:10.1111/sms.12261

Michopoulos, V., Mancini, F., Loucks, T.L., & Berga, S.L. (2013). Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: A randomized, controlled trial. *Fertility and Sterility, 99*(7), 2084–2091.e1. PubMed ID: 23507474 doi:10.1016/j.fertnstert.2013.02.036

Miljic, D., Pekic, S., Djurovic, M., Doknic, M., Milic, N., Casanueva, F.F., … Popovic, V. (2006). Ghrelin has partial or no effect on appetite, growth hormone, prolactin, and cortisol release in patients with anorexia nervosa. *The Journal of Clinical Endocrinology and Metabolism, 91*(4), 1491–1495. PubMed ID: 16449333 doi:10.1210/jc.2005-2304

Miller, K.K., Lawson, E.A., Mathur, V., Wexler, T.L., Meenaghan, E., Misra, M., … Klibanski, A. (2007). Androgens in women with anorexia nervosa and normal-weight women with hypothalamic amenorrhea. *The Journal of Clinical Endocrinology and Metabolism, 92*(4), 1334–1339. PubMed ID: 17284620 doi:10.1210/jc.2006-2501

Misra, M. (2014). Neuroendocrine mechanisms in athletes. *Handbook of Clinical Neurology, 124*, 373–386. PubMed ID: 25248600 doi:10.1016/B978-0-444-59602-4.00025-3

Misra, M., Katzman, D.K., Cord, J., Manning, S.J., Mendes, N., Herzog, D.B., … Klibanski, A. (2008). Bone metabolism in adolescent boys with anorexia nervosa. *The Journal of Clinical Endocrinology and Metabolism, 93*(8), 3029–3036. PubMed ID: 18544623 doi:10.1210/jc.2008-0170

Misra, M., & Klibanski, A. (2014). Endocrine consequences of anorexia nervosa. *Lancet Diabetes Endocrinol, 2*(7), 581–592. PubMed ID: 24731664 doi:10.1016/S2213-8587(13)70180-3

Misra, M., Miller, K.K., Bjornson, J., Hackman, A., Aggarwal, A., Chung, J., … Klibanski, A. (2003). Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. *The Journal of Clinical Endocrinology and Metabolism, 88*(12), 5615–5623. PubMed ID: 14671143 doi:10.1210/jc.2003-030532

Misra, M., Miller, K.K., Herzog, D.B., Ramaswamy, K., Aggarwal, A., Almazan, C., … Klibanski, A. (2004). Growth hormone and ghrelin responses to an oral glucose load in adolescent girls with anorexia nervosa and controls. *The Journal of Clinical Endocrinology and Metabolism, 89*(4), 1605–1612. PubMed ID: 15070919 doi:10.1210/jc.2003-031861

Misra, M., Miller, K.K., Kuo, K., Griffin, K., Stewart, V., Hunter, E., … Klibanski, A. (2005). Secretory dynamics of ghrelin in adolescent girls with anorexia nervosa and healthy adolescents. *American Journal of Physiology-Endocrinology and Metabolism, 289*(2), E347–356. PubMed ID: 15755766 doi:10.1152/ajpendo.00615.2004

Misra, M., Miller, K.K., Tsai, P., Gallagher, K., Lin, A., Lee, N., … Klibanski, A. (2006). Elevated peptide YY levels in adolescent girls with anorexia nervosa. *The Journal of Clinical Endocrinology and Metabolism, 91*(3), 1027–1033. PubMed ID: 16278259 doi:10.1210/jc.2005-1878

Moore, C.A., & Fry, A.C. (2007). Nonfunctional overreaching during off-season training for skill position players in collegiate American football. *The Journal of Strength and Conditioning Research, 21*(3), 793–800. PubMed ID: 17685717 doi:10.1519/R-20906.1

Mountjoy, M., Sundgot-Borgen, J., Burke, L., Carter, S., Constantini, N., Lebrun, C., … Ljungqvist, A. (2014). The IOC consensus statement: Beyond the female athlete triad–Relative Energy Deficiency in Sport (RED-S). *British Journal of Sports Medicine, 48*(7), 491–497. PubMed ID: 24620037 doi:10.1136/bjsports-2014-093502

Myerson, M., Gutin, B., Warren, M.P., May, M.T., Contento, I., Lee, M., … Brooks-Gunn, J. (1991). Resting metabolic rate and energy balance in amenorrheic and eumenorrheic runners. *Medicine & Science in Sports and Exercise, 23*(1), 15–22. PubMed ID: 1997808 doi:10.1249/00005768-199101000-00004

Nakamura, Y., Walker, B.R., & Ikuta, T. (2016). Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction. *Stress, 19*(2), 151–157. PubMed ID: 26586092 doi:10.3109/10253890.2015.1121984

Nattiv, A., Loucks, A.B., Manore, M.M., Sanborn, C.F., Sundgot-Borgen, J., Warren, M.P., & American College of Sports Medicine. (2007). American college of sports medicine position stand. The female athlete triad. *Medicine & Science in Sports and Exercise, 39*(10), 1867–1882. PubMed ID: 17909417 doi:10.1249/mss.0b013e318149f111

O'Donnell, E., & De Souza, M.J. (2011). Increased serum adiponectin concentrations in amenorrheic physically active women are associated with impaired bone health but not with estrogen exposure. *Bone, 48*(4), 760–767. doi:10.1016/j.bone.2010.12.018

Ott, V., Finlayson, G., Lehnert, H., Heitmann, B., Heinrichs, M., Born, J., & Hallschmid, M. (2013). Oxytocin reduces reward-driven food intake in humans. *Diabetes, 62*(10), 3418–3425. PubMed ID: 23835346 doi:10.2337/db13-0663

Papageorgiou, M., Dolan, E., Elliott-Sale, K.J., & Sale, C. (2017a). Reduced energy availability: Implications for bone health in physically active populations. *European Journal of Nutrition, 57*(3), 847–859. doi:10.1007/s00394-017-1498-8

Papageorgiou, M., Elliott-Sale, K.J., Parsons, A., Tang, J.C.Y., Greeves, J.P., Fraser, W.D., & Sale, C. (2017b). Effects of reduced energy availability on bone metabolism in women and men. *Bone, 105*, 191–199. PubMed ID: 28847532 doi:10.1016/j.bone.2017.08.019

Perseghin, G., Lattuada, G., Ragogna, F., Alberti, G., La Torre, A., & Luzi, L. (2009). Free leptin index and thyroid function in male highly

trained athletes. *European Journal of Endocrinology, 161*(6), 871–876. PubMed ID: 19773373 doi:10.1530/EJE-09-0569

Reed, J.L., De Souza, M.J., Mallinson, R.J., Scheid, J.L., & Williams, N.I. (2015). Energy availability discriminates clinical menstrual status in exercising women. *Journal of the International Society of Sports Nutrition, 12*, 11. PubMed ID: 25722661 doi:10.1186/s12970-015-0072-0

Reinking, M.F., & Alexander, L.E. (2005). Prevalence of disordered-eating behaviors in undergraduate female collegiate athletes and nonathletes. *Journal of Athletic Training, 40*(1), 47–51. PubMed ID: 15902324

Rickenlund, A., Thoren, M., Carlstrom, K., von Schoultz, B., & Hirschberg, A.L. (2004). Diurnal profiles of testosterone and pituitary hormones suggest different mechanisms for menstrual disturbances in endurance athletes. *The Journal of Clinical Endocrinology and Metabolism, 89*(2), 702–707. PubMed ID: 14764784 doi:10.1210/jc.2003-030306

Riediger, T., Bothe, C., Becskei, C., & Lutz, T.A. (2004). Peptide YY directly inhibits ghrelin-activated neurons of the arcuate nucleus and reverses fasting-induced c-Fos expression. *Neuroendocrinology, 79*(6), 317–326. PubMed ID: 15256809 doi:10.1159/000079842

Rigotti, N.A., Neer, R.M., & Jameson, L. (1986). Osteopenia and bone fractures in a man with anorexia nervosa and hypogonadism. *JAMA, 256*(3), 385–388. PubMed ID: 3723727 doi:10.1001/jama.1986.03380030087034

Roemmich, J.N., & Sinning, W.E. (1997). Weight loss and wrestling training: Effects on growth-related hormones. *Journal of Applied Physiology, 82*(6), 1760–1764. doi:10.1152/jappl.1997.82.6.1760

Roupas, N.D., Mamali, I., Maragkos, S., Leonidou, L., Armeni, A.K., Markantes, G.K., … Georgopoulos, N.A. (2013). The effect of prolonged aerobic exercise on serum adipokine levels during an ultra-marathon endurance race. *Hormones, 12*(2), 275–282. doi:10.14310/horm.2002.1411

Russell, M., & Misra, M. (2010). Influence of ghrelin and adipocytokines on bone mineral density in adolescent female athletes with amenorrhea and eumenorrheic athletes. *Medicine and Sport Science, 55*, 103–113. PubMed ID: 20956863 doi:10.1159/000321975

Russell, M., Stark, J., Nayak, S., Miller, K.K., Herzog, D.B., Klibanski, A., & Misra, M. (2009). Peptide YY in adolescent athletes with amenorrhea, eumenorrheic athletes and non-athletic controls. *Bone, 45*(1), 104–109. PubMed ID: 19344792 doi:10.1016/j.bone.2009.03.668

Schaal, K., Van Loan, M.D., & Casazza, G.A. (2011). Reduced catecholamine response to exercise in amenorrheic athletes. *Medicine & Science in Sports and Exercise, 43*(1), 34–43. PubMed ID: 20508538 doi:10.1249/MSS.0b013e3181e91ece

Scheid, J.L., & De Souza, M.J. (2010). Menstrual irregularities and energy deficiency in physically active women: The role of ghrelin, PYY and adipocytokines. *Medicine and Sport Science, 55*, 82–102. PubMed ID: 20956862 doi:10.1159/000321974

Scheid, J.L., De Souza, M.J., Leidy, H.J., & Williams, N.I. (2011). Ghrelin but not peptide YY is related to change in body weight and energy availability. *Medicine & Science in Sports and Exercise, 43*(11), 2063–2071. PubMed ID: 21502892 doi:10.1249/MSS.0b013e31821e52ab

Scheid, J.L., Williams, N.I., West, S.L., VanHeest, J.L., & De Souza, M.J. (2009). Elevated PYY is associated with energy deficiency and indices of subclinical disordered eating in exercising women with hypothalamic amenorrhea. *Appetite, 52*(1), 184–192. PubMed ID: 18929607 doi:10.1016/j.appet.2008.09.016

Schorr, M., Lawson, E.A., Dichtel, L.E., Klibanski, A., & Miller, K.K. (2015). Cortisol measures across the weight spectrum. *The Journal of Clinical Endocrinology and Metabolism, 100*(9), 3313–3321. PubMed ID: 26171799 doi:10.1210/JC.2015-2078

Shiiya, T., Nakazato, M., Mizuta, M., Date, Y., Mondal, M.S., Tanaka, M., … Matsukura, S. (2002). Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. *The Journal of Clinical Endocrinology and Metabolism, 87*(1), 240–244. PubMed ID: 11788653 doi:10.1210/jcem.87.1.8129

Simpson, K.A., & Singh, M.A. (2008). Effects of exercise on adiponectin: A systematic review. *Obesity, 16*(2), 241–256. doi:10.1038/oby.2007.53

Skolnick, A., Schulman, R.C., Galindo, R.J., & Mechanick, J.I. (2016). The endocrinopathies of male anorexia nervosa: Case series. *AACE Clinical Case Reports, 2*(4), e351–e357. PubMed ID: 28868357 doi:10.4158/EP15945.CR

Southmayd, E.A., Mallinson, R.J., Williams, N.I., Mallinson, D.J., & De Souza, M.J. (2017). Unique effects of energy versus estrogen deficiency on multiple components of bone strength in exercising women. *Osteoporosis International, 28*(4), 1365–1376. PubMed ID: 28032184 doi:10.1007/s00198-016-3887-x

Stone, J.D., Kreutzer, A., Mata, J.D., Nystrom, M.G., Jagim, A.R., Jones, M.T., & Oliver, J.M. (2017). Changes in creatine kinase and hormones over the course of an American football season. *The Journal of Strength and Conditioning Research*. Manuscript submitted for publication. doi:10.1519/JSC.0000000000001920

Stoving, R.K., Veldhuis, J.D., Flyvbjerg, A., Vinten, J., Hangaard, J., Koldkjaer, O.G., … Hagen, C. (1999). Jointly amplified basal and pulsatile growth hormone (GH) secretion and increased process irregularity in women with anorexia nervosa: Indirect evidence for disruption of feedback regulation within the GH-insulin-like growth factor I axis. *The Journal of Clinical Endocrinology and Metabolism, 84*(6), 2056–2063. PubMed ID: 10372710 doi:10.1210/jcem.84.6.5734

Tenforde, A.S., Barrack, M.T., Nattiv, A., & Fredericson, M. (2016). Parallels with the female athlete triad in male athletes. *Sports Medicine, 46*(2), 171–182. PubMed ID: 26497148 doi:10.1007/s40279-015-0411-y

Tenforde, A.S., Sainani, K.L., Sayres, L.C., Cutti, P., & Fredericson, M. (2015). Identifying sex-specific risk factors for low bone mineral density in adolescent runners. *American Journal of Sports Medicine, 43*(6), 1494–1504. PubMed ID: 25748470 doi:10.1177/0363546515572142

Thienpont, E., Bellemans, J., Samson, I., & Fabry, G. (2000). Stress fracture of the inferior and superior pubic ramus in a man with anorexia nervosa and hypogonadism. *Acta Orthopaedica Belgica, 66*(3), 297–301. PubMed ID: 11033923

Thompson, J., Manore, M.M., & Skinner, J.S. (1993). Resting metabolic rate and thermic effect of a meal in low- and adequate-energy intake male endurance athletes. *International Journal of Sport Nutrition, 3*(2), 194–206. PubMed ID: 8508196 doi:10.1123/ijsn.3.2.194

Tolle, V., Kadem, M., Bluet-Pajot, M.T., Frere, D., Foulon, C., Bossu, C., … Estour, B. (2003). Balance in ghrelin and leptin plasma levels in anorexia nervosa patients and constitutionally thin women. *The Journal of Clinical Endocrinology and Metabolism, 88*(1), 109–116. PubMed ID: 12519838 doi:10.1210/jc.2002-020645

Tornberg, A.B., Melin, A., Koivula, F.M., Johansson, A., Skouby, S., Faber, J., & Sjodin, A. (2017). Reduced neuromuscular performance in amenorrheic elite endurance athletes. *Medicine & Science in Sports and Exercise, 49*(12), 2478–2485. PubMed ID: 28723842 doi:10.1249/MSS.0000000000001383

Vanheest, J.L., Rodgers, C.D., Mahoney, C.E., & De Souza, M.J. (2014). Ovarian suppression impairs sport performance in junior elite female

swimmers. *Medicine & Science in Sports and Exercise, 46*(1), 156–166. PubMed ID: 23846160 doi:10.1249/MSS.0b013e3182a32b72

Villanueva, A.L., Schlosser, C., Hopper, B., Liu, J.H., Hoffman, D.I., & Rebar, R.W. (1986). Increased cortisol production in women runners. *The Journal of Clinical Endocrinology and Metabolism, 63*(1), 133–136. PubMed ID: 3011836 doi:10.1210/jcem-63-1-133

Wade, G.N., & Schneider, J.E. (1992). Metabolic fuels and reproduction in female mammals. *Neuroscience & Biobehavioral Reviews, 16*(2), 235–272. PubMed ID: 1630733 doi:10.1016/S0149-7634(05)80183-6

Warrington, G., Dolan, E., McGoldrick, A., McEvoy, J., Macmanus, C., Griffin, M., & Lyons, D. (2009). Chronic weight control impacts on physiological function and bone health in elite jockeys. *Journal of Sports Sciences, 27*(6), 543–550. PubMed ID: 19337879 doi:10.1080/02640410802702863

Welt, C.K., Chan, J.L., Bullen, J., Murphy, R., Smith, P., DePaoli, A.M., . . . Mantzoros, C.S. (2004). Recombinant human leptin in women with hypothalamic amenorrhea. *The New England Journal of Medicine, 351*(10), 987–997. PubMed ID: 15342807 doi:10.1056/NEJMoa040388

Williams, N.I., Leidy, H.J., Hill, B.R., Lieberman, J.L., Legro, R.S., & De Souza, M.J. (2015). Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction. *American Journal of Physiology. Endocrinology and Metabolism, 308*(1), E29–E39. PubMed ID: 25352438 doi:10.1152/ajpendo.00386.2013

Wojcik, M.H., Meenaghan, E., Lawson, E.A., Misra, M., Klibanski, A., & Miller, K.K. (2010). Reduced amylin levels are associated with low bone mineral density in women with anorexia nervosa. *Bone, 46*(3), 796–800. PubMed ID: 19931436 doi:10.1016/j.bone.2009.11.014

Zanker, C.L., & Swaine, I.L. (1998). Bone turnover in amenorrhoeic and eumenorrhoeic women distance runners. *Scandinavian Journal of Medicine & Science in Sports, 8*(1), 20–26. PubMed ID: 9502306 doi:10.1111/j.1600-0838.1998.tb00224.x

Zanker, C.L., & Swaine, I.L. (2000). Responses of bone turnover markers to repeated endurance running in humans under conditions of energy balance or energy restriction. *European Journal of Applied Physiology, 83*(4–5), 434–440. PubMed ID: 11192068 doi:10.1007/s004210000293