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Neuroendocrine mechanisms in athletes

Madhusmita Misra*

Pediatric Endocrine and Neuroendocrine Units, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

INTRODUCTION

Increased athletic activity is characterized by significant energy expenditure. When energy intake is sufficient to allow for a balanced caloric state, the beneficial effects of physical activity are evident. In addition to a positive body image, improved self-esteem, and increased likelihood of academic success, bone health is optimized. However, when energy intake is insufficient to meet individual needs, several adaptive neuroendocrine mechanisms come into play either to conserve energy for the most essential functions, or to allow the body to draw on its reserves to meet energy needs. These adaptive or physiologic neuroendocrine changes then lead to changes in body composition and weight, which can eventually impact bone metabolism. Low bone density is an important pathologic consequence in low energy states, notwithstanding the beneficial effects of exercise and mechanical loading on bone. Subsequent sections will discuss neuroendocrine changes that occur in athletes based on whether or not they are energy-replete, and the effects of these neuroendocrine changes on bone.

NEUROENDOCRINE ALTERATIONS IN ATHLETES

Hypothalamic–pituitary–gonadal axis

Spectrum of menstrual function in the female athlete—The functionality of the hypothalamic–pituitary–gonadal (HPG) axis in athletes depends on their state of energy availability, although a contribution of genetic factors appears likely, based on recent data (Caronia et al., 2011). Low energy availability from excessive energy expenditure (from exercise), and/or a decrease in energy intake, presumably leads to varying degrees of perturbation of the HPG axis, particularly in female athletes (Loucks and Thuma, 2003). There is, in fact, a spectrum of menstrual function reported in the female athlete that ranges from ovulatory eumenorrhea to sub-clinical menstrual dysfunction (luteal phase defects and anovulatory eumenorrhea) to functional hypothalamic oligoamenorrhea (Nattiv et al., 2007).

One study reported that amongst normal cycling (eumenorrheic) recreational runners, 45% of the women have luteal phase defects and 12% have anovulatory cycles, compared to a 90% prevalence of ovulatory cycles amongst sedentary controls in the study (De Souza et

*Correspondence to: Madhusmita Misra, MD, MPH, BUL 457, Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA 02114, USA. Tel: 617-726-3870, Fax: 617-726-5072, mmisra@partners.org.

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al., 1998). Menstrual irregularity occurs in up to 24% of adolescent athletes (Nichols et al., 2006, 2007b) and is variably reported in 3–66% of adult athletes. The prevalence of oligoamenorrhea (the most extreme form of menstrual dysfunction in the female athlete) depends on several factors, which include the nature of exercise, the intensity of training, and the nutritional status of the athlete. A higher prevalence of oligoamenorrhea is reported in endurance sports (such as running, cycling, and swimming), gymnastics and in ballet dancers, and the prevalence increases with increasing intensity of training, and with decreasing nutritional status of the athlete (Sanborn et al., 1982).

Disordered eating behavior is common in the female athlete, and is reported in up to 18–20% of adolescent athletes (Nichols et al., 2006, 2007b), and 25% of college athletes (Beals and Hill, 2006). This contributes to a low energy state from decreased caloric intake, and the triad of low energy availability, menstrual dysfunction, and low bone density is commonly referred to as the “female athlete triad.” Disordered eating is particularly common in sports that emphasize leanness or appearance (such as gymnastics, diving, and figure skating), increases with the level of competition, and is more prevalent in judged compared with refereed sports (Rosen and Hough, 1988). It is also more common in amenorrheic than eumenorrheic athletes, and in one study, 62% of adolescent amenorrheic athletes reported disordered eating behaviors compared with 11% of eumenorrheic athletes (Christo et al., 2008b). Another study reported eating disorders in 68% of amenorrheic compared with 38% of oligomenorrheic girls visiting a youth clinic (Loucks, 2007). Additionally, high school athletes who have a history of disordered eating are more than twice as likely to report oligoamenorrhea as those without this history (Nichols et al., 2007b).

Low energy availability in turn may impact GnRH pulsatility (as reflected by luteinizing hormone (LH) pulsatility). This has been demonstrated in acute settings where energy availability was restricted to varying degrees in eumenorrheic healthy women in a clinical research setting (Loucks and Thuma, 2003). The study reported a change in the pattern of LH pulsatility when energy availability decreased below 30 kcal/kg lean body mass/day (45 kcal/kg lean body mass/day being a state of energy balance), with a decrease in pulse frequency and an increase in pulse amplitude (Loucks and Thuma, 2003). There are, however, limited data regarding net energy availability in chronically exercising women.

One study reported lower net energy balance (standardized for body weight) in normally cycling anovulatory recreational runners compared with runners with luteal phase defects or ovulatory runners (De Souza et al., 1998). However, in chronically exercising women, studies have not been able to demonstrate a clear or consistent cut-off below which women are more likely to become oligoamenorrheic. This may be consequent to other contributory factors that impact the HPG axis, such as genetic factors. Women with hypothalamic amenorrhea are more likely to have heterozygous mutations in genes that impact GnRH neuron migration or function (Caronia et al., 2011). Presence of these mutations may predispose some women to menstrual dysfunction even when energy availability is above 30 kcal/kg lean body mass. Additionally, some women may be more capable than others of implementing adaptive changes that allow them to continue to have normal cycles despite very low energy availability.

Luteinizing hormone and follicle-stimulating hormone secretion in female athletes

Pulsatility patterns of luteinizing hormone and follicle-stimulating hormone in athletes:

Data from adult and adolescent athletes regarding LH pulsatility are limited, but do indicate differences in oligoamenorrheic athletes compared with eumenorrheic athletes and nonathletes. Reported results are not always consistent, possibly because available studies differ with respect to (1) timing of frequent blood sampling in relation to menses (days 1–3 (Loucks et al., 1989), days 1–5 (Rickenlund et al., 2004), days 2–5 (Berga et al., 1989), days 3–6 (Laughlin and Yen, 1996), and days 1–10 (Ackerman et al., 2012c)); (2) the frequency of blood sampling (every 10 minutes during the sleep cycle and every 20 minutes during the wake cycle (Loucks et al., 1989), every 10 minutes for 8 hours overnight (Ackerman et al., 2012c), or every 10 (Laughlin and Yen, 1996), 15 (Berga et al., 1989) or 20 minutes for 24 hours (Rickenlund et al., 2004)); (3) methods used to analyze data from frequent sampling (Cluster (Berga et al., 1989; Loucks et al., 1989; Laughlin and Yen, 1996), Pulsar (Rickenlund et al., 2004) or Deconvolution (Ackerman et al., 2012c)).

Overall, studies in adults report lowest LH pulse frequency in amenorrheic athletes, intermediate pulse frequency in eumenorrheic athletes, and highest pulse frequency in nonathletes (Loucks et al., 1989; Laughlin and Yen, 1996; Rickenlund et al., 2004), particularly during the waking hours (Loucks et al., 1989), with either no differences in pulse amplitude (Laughlin and Yen, 1996; Rickenlund et al., 2004) or higher amplitude in eumenorrheic athletes compared with nonathletes (Loucks et al., 1989). One adolescent study that examined nighttime LH pulsatility reported no differences in LH pulse frequency among groups; however, amenorrheic girls had lower pulse amplitude and total pulsatile secretion than nonathletes (Ackerman et al., 2012c). The 24 h mean LH concentration or area under the curve (AUC) have been variably reported to be low (Loucks et al., 1989; Ackerman et al., 2012c) or unchanged (Laughlin and Yen, 1996; Rickenlund et al., 2004) in amenorrheic athletes compared with eumenorrheic athletes and nonathletes. In contrast, most studies report no differences in mean follicle-stimulating hormone (FSH) or FSH AUC in amenorrheic athletes compared with eumenorrheic athletes and nonathletes (Loucks et al., 1989; Laughlin and Yen, 1996).

Determinants of altered luteinizing hormone pulsatility in athletes: If indeed low energy availability determines why some (but not all athletes) develop oligoamenorrhea (Loucks and Thuma, 2003), there are likely metabolic and presumably hormonal links between decreased energy availability and impaired LH pulsatility. Although studies have not clearly identified low energy availability in chronically exercising women with amenorrhea in an ambulatory setting (Ackerman et al., 2013a), this may relate to inaccuracies inherent in the methodologies used to assess energy intake and expenditure, such as food records, exercise questionnaires, and accelerometers (Trost et al., 2006; Pietilainen et al., 2010). Fat mass and percent body fat are surrogate and objective measures of energy status as fat is a source of fuel in long-standing energy restricted states. Amenorrheic athletes do have lower fat mass and percent body fat than eumenorrheic athletes and nonathletes, even when body mass index (BMI) and lean body mass are in the normal range (Christo et al., 2008a; Ackerman et al., 2013a). Of note, in anorexia nervosa, a severely energy restricted state, increases in fat

mass are the strongest predictor of resumption of menses (Misra et al., 2006). In addition to serving as a measure of energy stores, fat mass may be a link between low energy availability and altered pulsatile GnRH secretion through secretion of adipokines, such as leptin and adiponectin, that have a known impact on the HPG axis (Welt et al., 2004; Lu et al., 2008; Wen et al., 2008). Fat mass is also an important determinant of hormones that are altered in low energy states such as ghrelin, peptide YY (PYY), cortisol, insulin, and insulin-like growth factor 1 (IGF-1) (Misra et al., 2007; Christo et al., 2008a, b; Ackerman et al., 2012c, 2013a), which may in turn impact the HPG axis (Vulliemmoz et al., 2004; Fernandez-Fernandez et al., 2005; Pinilla et al., 2006; Kluge et al., 2007; Sadler et al., 2010). Subsequent sections will discuss alterations in these hormones and hormonal axes in athletes, and their potential to impact GnRH pulsatility.

Genetic factors may also explain why some excessively exercising women are more likely than others to develop hypothalamic amenorrhea. In one study of 55 women with functional hypothalamic amenorrhea, seven women (two of whom were exercisers) had functional heterozygous mutations in the FGFR-1, PROKR2, GnRHR, or KAL-I genes, compared with none of 422 eumenorrheic control women and 47 menstruating exercisers (Caronia et al., 2011). Further studies are necessary to determine whether a genetic predisposition to hypogonadotropic hypogonadism explains which exercisers are more likely to become amenorrheic.

Finally, in girls with anorexia nervosa, one study has implicated coexisting polycystic ovarian syndrome (PCOS) as a predisposing factor for developing amenorrhea at a relatively higher weight (Pinhas-Hamiel et al., 2006). Rickenlund et al. reported higher 24 hour testosterone concentrations in oligomenorrheic athletes compared with both amenorrheic and regularly menstruating athletes and nonathletes (Rickenlund et al., 2004). The same study also reported a positive association between 24 hour testosterone concentration and menarchal age. Other studies have reported either lower levels of testosterone in amenorrheic compared with eumenorrheic athletes (Loucks et al., 1989; Christo et al., 2008a), or no differences among groups (Laughlin and Yen, 1996). More studies are necessary to determine whether an underlying predisposition to PCOS explains early development of amenorrhea in some athletes. Estradiol levels are generally lower in amenorrheic athletes compared with nonathletes (Loucks et al., 1989; Laughlin and Yen, 1996) or eumenorrheic athletes (Christo et al., 2008a).

Kisspeptin in athletes and nonathletes—Kisspeptin is an important driver of normal GnRH pulsatility and gonadotropin secretion (Navarro et al., 2005); however, data are limited regarding kisspeptin levels in athletes versus nonathletes. In prepubertal rats, a 3 day fast leads to decreased Kiss-1 expression in the hypothalamus in both males and females, and LH responses to administered kisspeptin were potentiated in a fasting state (Navarro et al., 2004). These findings suggest that a decrease in Kiss-1 expression in conditions of low energy availability may lead to decreased pulsatile GnRH secretion and decreased levels of gonadotropins. In women with hypothalamic amenorrhea, twice daily kisspeptin administration leads to an acute increase in LH, FSH, and estradiol secretion, although subsequently, desensitization occurs (Jayasena et al., 2009). More studies are necessary to determine the impact of changes in kisspeptin levels on the HPG axis in athletes.

Prolactin and oxytocin in athletes and nonathletes—Levels of prolactin are typically lower in amenorrheic athletes compared with normally cycling women (Laughlin and Yen, 1996; Rickenlund et al., 2004). Similarly, pooled overnight oxytocin levels are lower in amenorrheic athletes compared with normally cycling women, even after controlling for estradiol levels (Lawson et al., 2013).

Appetite regulating and gut peptides that may regulate energy homeostasis and impact the hypothalamic–pituitary–gonadal axis

Leptin: Leptin is an adipokine that correlates very strongly with absolute fat mass, and levels of leptin decrease both acutely and chronically with energy deprivation (Grinspoon et al., 1996, 1997) and in conditions associated with low fat mass (Misra et al., 2005b). Leptin is also anorexigenic, and a decrease in leptin in conditions of low energy availability is an appropriate adaptive response to prevent further suppression of food intake. Both fasting (Christo et al., 2008a) and integrated measures of overnight leptin secretion (Ackerman et al., 2012c) are markedly lower in adolescent and young adult amenorrheic athletes compared with eumenorrheic athletes and nonathletes, subsequent to decreases in pulse amplitude, pulse mass, and total pulsatile secretion. Leptin is also lower in adult ovulatory exercisers, exercisers with luteal phase deficiency, and anovulatory eumenorrheic exercisers compared with sedentary controls (De Souza et al., 2003, 2007), and lower in amenorrheic exercisers compared with ovulating exercisers (Corr et al., 2011).

Leptin has a known impact on the HPG axis. Leptin-deficient mice and humans are hypogonadal, and replacing leptin reverses this state of hypogonadotropic hypogonadism (Chehab et al., 1996; Strobel et al., 1998). Leptin is an important determinant of pulsatile LH secretion, as demonstrated in amenorrheic athletes and in a combined group of athletes and nonathletes, independent of BMI (Ackerman et al., 2012c). Administration of leptin to women with hypothalamic amenorrhea (not specifically athletes) normalizes gonadotropin secretion and induces ovulation in 30–40% of these women (Welt et al., 2004; Chou et al., 2011).

Ghrelin: Ghrelin is an orexigenic hormone and GH secretagogue that also increases secretion of ACTH, FSH and LH (Arvat et al., 2001; Vulliamoz et al., 2004; Kluge et al., 2007). Levels of ghrelin reflect overall energy status, and are inversely associated with fat mass (Ackerman et al., 2012c). High ghrelin levels are common in severely energy-restricted states (Misra et al., 2005a), likely an adaptive response. Adolescent normal-weight amenorrheic athletes have higher fasting acylated ghrelin levels than eumenorrheic athletes and nonathletes (Christo et al., 2008a). Additionally, amenorrheic normal-weight adolescent and young adult athletes have higher overnight total ghrelin secretion than nonathletes subsequent to increased pulse amplitude and pulse mass (Ackerman et al., 2012c). In adult women, fasting ghrelin levels are higher in exercising amenorrheic women compared with exercising eumenorrheic and sedentary women (De Souza et al., 2004, 2007).

Ghrelin administration suppresses LH and FSH pulsatility in animals and humans (Vulliamoz et al., 2004; Kluge et al., 2007), and consistent with these findings, overnight ghrelin secretion is a strong inverse determinant of overnight LH secretion in adolescent and

young adult amenorrheic athletes and in a combined group of athletes and nonathletes (Ackerman et al., 2012c). Interestingly, these effects persist after controlling for fat mass.

Peptide YY: Peptide YY (PYY) is an anorexigenic hormone secreted by the L cells of the gut, and levels of PYY are increased in conditions of energy deficiency (Misra et al., 2005c) and decreased in conditions of energy excess (le Roux et al., 2006). PYY levels correlate inversely with BMI and fat mass (Misra et al., 2005c; Russell et al., 2009). Amenorrheic athletes and exercisers have higher PYY than eumenorrheic athletes and exercisers and sedentary controls (Russell et al., 2009; Scheid et al., 2009). Importantly, PYY has been shown to attenuate GnRH secretion in *in vitro* models and gonadotropin secretion in prepubertal rats. In one study, PYY was an inverse predictor of testosterone levels in adolescent athletes and nonathletes (Russell et al., 2009).

Insulin: Insulin and glucose levels are typically decreased in low energy states, and low insulin may impact the HPG axis. Insulin increases GnRH promoter activity in GnRH neurons (Kim et al., 2005) through the transcription factor Egr-1 (DiVall et al., 2007), and increases aromatase activity in granulosa cells (Paul et al., 2010). Additionally, administration of insulin to healthy women increases LH pulse frequency while also decreasing pulse interval (Moret et al., 2009). Within normally cycling exercisers, those with luteal phase defects have lower insulin levels than ovulatory exercisers with normal luteal phase length and sedentary ovulatory women (De Souza et al., 2003, 2007). Insulin levels are lower in amenorrheic (Laughlin and Yen, 1996) or oligomenorrheic (Rickenlund et al., 2004) athletes compared with eumenorrheic athletes and nonathletes, and insulin AUC is positively correlated with LH pulse frequency (Laughlin and Yen, 1996; Rickenlund et al., 2004).

Adiponectin: Adiponectin levels may be increased in energy restricted states, although this is not a consistent finding. *In vitro* data indicate that adiponectin may suppress GnRH and gonadotropin secretion (Lu et al., 2008; Wen et al., 2008). Although absolute adiponectin levels do not differ in adolescent amenorrheic versus eumenorrheic athletes and nonathletes (Russell et al., 2009), adult amenorrheic athletes have been reported to have higher adiponectin relative to fat mass than eumenorrheic athletes and nonathletes (O'Donnell and De Souza, 2011).

Reproductive function in male athletes—In contrast to female athletes, there are limited data regarding the impact of exercise on the reproductive axis in male athletes. Overall, data suggest that sexual and hormonal maturity during the childhood and adolescent years does not change with increased athletic activity (Moore et al., 2010), and baseline testosterone levels do not differ significantly in sprinters (Grandys et al., 2011) and other athletes (Lucia et al., 1996) compared with untrained subjects. Testosterone levels may decrease with increased intensity of training within sprinters (Grandys et al., 2011) and with energy restriction in bodybuilders (Maestu et al., 2010), although another study reported no change in hormonal profiles over different intensities of training in three groups of athletes (Lucia et al., 1996). One study of elite cyclists reported higher levels of testosterone compared with recreational athletes (Fitzgerald et al., 2012), and another reported lower

sperm mobility in cyclists during the training period (Lucia et al., 1996). More studies are necessary to better understand these findings. Significant energy restriction in young men and boys associated with low weight, as in anorexia nervosa, is associated with lower testosterone levels than in normal-weight controls (Misra et al., 2008).

With respect to other hormones that may impact the HPG axis, IGF-1 and insulin levels decrease with energy restriction in athletes (Maestu et al., 2010). Low baseline leptin levels have been reported in elite gymnasts (Weimann et al., 1999) and marathon runners (Bobbert et al., 2012), and a decrease in leptin and an increase in ghrelin occurs after an acute training session in male rowers (Jurimae et al., 2007, 2011).

Hypothalamic–pituitary–adrenal axis

Data are conflicting regarding the impact of athletic activity on the hypothalamic–pituitary–adrenal (HPA) axis. Loucks et al. reported no differences in ACTH secretory patterns and cortisol secretory pulse frequency in amenorrheic athletes compared with eumenorrheic athletes and nonathletes (Loucks et al., 1989). However, overnight cortisol levels were higher in both groups of athletes compared with nonathletes, and whereas pulse amplitude remained high over the course of the day in amenorrheic athletes, pulse amplitude decreased in eumenorrheic athletes. As a consequence, 24 hour urinary cortisol measurements were higher in amenorrheic athletes than the other two groups. Rickenlund et al. have reported higher baseline cortisol secretion in amenorrheic athletes compared with eumenorrheic athletes and nonathletes (Rickenlund et al., 2004). In contrast, another study reported higher 24 hour serum cortisol in both groups of athletes (amenorrheic and eumenorrheic) than nonathletes (Laughlin and Yen, 1996). In an adolescent and young adult population, Ackerman et al. reported higher cortisol pulse amplitude, mass, half-life, and AUC in amenorrheic athletes than eumenorrheic athletes and nonathletes (Ackerman et al., 2013a). As with studies of LH pulsatility, differences in reports of cortisol pulsatile secretion in athletes and nonathletes may be attributable to differences in sample size, frequency of blood draws, and methods used to assess secretory hormone dynamics. Overall, data suggest higher cortisol levels in athletes who are amenorrheic and presumably in a state of low energy availability, compared with normally menstruating athletes and nonathletes. The diurnal rhythm of cortisol secretion is maintained in athletes.

Cortisol is a gluconeogenic hormone, and one proposed reason for elevated cortisol in conditions of low energy availability (as in heavily exercising athletes) is an adaptive response to maintain euglycemia. This is consistent with an inverse association of cortisol with fat mass (Rickenlund et al., 2004; Ackerman et al., 2013a). However, Laughlin et al. found no association of cortisol with fasting glucose (Laughlin and Yen, 1996).

An inverse relationship exists between integrated measures of cortisol secretion (such as 24 hour mean serum cortisol) and LH pulse parameters. Several studies have reported an inverse association between 24 hour mean serum cortisol or baseline cortisol secretion and LH pulse frequency (Loucks et al., 1989; Laughlin and Yen, 1996; Rickenlund et al., 2004), and between cortisol levels and the number of menses in the preceding year in amenorrheic athletes (Rickenlund et al., 2004). In a study of adolescent and young adult athletes, overnight cortisol AUC correlated inversely with LH AUC even after controlling for fat

mass and other hormones such as ghrelin and leptin (Ackerman et al., 2013a). These data are consistent with stress-like elevations in cortisol causing a decrease in GnRH secretion, and an impaired gonadotrope responsiveness to GnRH in animal models (Breen et al., 2008; Oakley et al., 2009). This effect appears to be mediated by the type II glucocorticoid receptor within the pituitary (Breen et al., 2008). Additionally, a CRH receptor-1 antagonist can mitigate the deleterious effects of stress and cortisol on LH pulse frequency (Herod et al., 2011). Of interest, ghrelin can stimulate ACTH and therefore cortisol secretion (Arvat et al., 2001), and leptin inhibits cortisol secretion (Glasow et al., 1998). This may explain why associations of integrated measures of ghrelin and leptin secretion with LH are lost when cortisol measures are added to the regression model, while inverse associations of cortisol with LH persist (Ackerman et al., 2013a).

Growth hormone–insulin-like growth factor 1 (IGF-1) axis

Rickenlund et al. reported higher baseline GH secretion in amenorrheic (but not oligomenorrheic) athletes compared with regularly menstruating athletes and nonathletes (Rickenlund et al., 2004), with no differences between groups for pulse frequency or amplitude, or for 24 hour AUC. Another study reported higher 24 hour GH concentrations in both amenorrheic and eumenorrheic athletes compared with nonathletes, with higher pulse frequency in the amenorrheic women, and higher pulse amplitude in the eumenorrheic athletes compared with the other groups (Laughlin and Yen, 1996).

In conditions of extreme energy deprivation, as in anorexia nervosa, there is an increase in basal and pulsatile GH secretion and AUC compared with normal-weight women, associated with low systemic IGF-1 levels, suggestive of a nutritionally acquired hepatic resistance to GH (Misra et al., 2003). This is further corroborated by a decrease in GH binding protein (GHBP), the extracellular portion of the GH receptor, in anorexia nervosa (Counts et al., 1992), and a failure to increase IGF-1 levels with administration of supraphysiologic doses of rhGH (Fazeli et al., 2010).

In athletes, who are typically not as severely energy deprived as women with anorexia nervosa, GHBP levels are lower in amenorrheic women compared with eumenorrheic athletes and nonathletes, and correlate inversely with GH levels (Laughlin and Yen, 1996). However, IGF-1 levels are not as low as in anorexia nervosa. A study in adolescent athletes reported lower IGF-1 levels in the amenorrheic exercisers compared with nonathletes (Christo et al., 2008b); however, studies in adult athletes have reported no differences among groups for IGF-1, IGFBP-3 or the ratio of IGF-1/IGFBP-3 (Laughlin and Yen, 1996). In contrast, IGFBP-1 is higher in the amenorrheic group, leading to lower ratios of IGF-1/IGFBP-1 in amenorrheic athletes (Laughlin and Yen, 1996). Within normally cycling exercisers (with normal ovulatory cycles or with luteal phase deficiency), levels of GH, IGF-1, IGFBP3, and ratios of IGF-1/IGFBP-1 and IGF-1/IGFBP-3 do not differ from sedentary controls (De Souza et al., 2003).

GH levels correlate inversely with percent body fat (Laughlin and Yen, 1996; Rickenlund et al., 2004), whereas GHBP levels correlate positively with body fat mass and 24 hour integrated glucose concentrations (Laughlin and Yen, 1996), consistent with net energy status being an important driver of GH secretion.

Importantly, alterations in the GH-IGF-1 axis in athletes have the potential to impact the HPG axis. GnRH neurons express both IGF-1 and the IGF-1 receptor, and central IGF-1 has a direct effect on GnRH neurons (Daftary and Gore, 2005). IGF-1 also stimulates kisspeptin gene expression (Hiney et al., 2010) and therefore GnRH secretion, and potentiates gonadal steroidogenesis and oocyte maturation *in vitro* (Sadler et al., 2010). Additionally, IGF-1 increases aromatase activity in granulosa cells (Paul et al., 2010). Of note, GH and IGFBP-1 levels are inversely associated with LH secretion in athletes and nonathletes (Laughlin and Yen, 1996; Rickenlund et al., 2004), whereas the ratio of IGF-1/ IGFBP-1 is positively associated with 24 hour LH pulse frequency (Laughlin and Yen, 1996). One study reported that IGF-1 levels were a positive determinant of estradiol levels in adolescent athletes and nonathletes after controlling for potential confounders (Russell et al., 2009).

Hypothalamic–pituitary–thyroid axis

There are few data regarding the HPT axis in athletes compared with nonathletes. In thin women with functional hypothalamic amenorrhea (not specifically athletes), the circadian rhythm of TSH secretion is maintained with a nadir between 12:00 and 17:00 hours and a peak between 21:00 and 02:00 hours (Berga et al., 1989). These women, however, have lower total T₃ and T₄ levels than normally cycling controls (Berga et al., 1989), a finding also observed in anorexia nervosa, a condition of amenorrhea and extreme energy deprivation (Misra et al., 2004), although free T₄ levels only trend lower in anorexia nervosa.

No differences were noted in TSH, free T₄ or total T₄ levels among sedentary ovulatory women, exercising ovulatory women, and exercising women with luteal phase deficiency, though total T₃ levels were lower in both groups of exercising women compared with the sedentary group (De Souza et al., 2003). Another study reported lower total T₃ levels in exercising women who were amenorrheic, anovulatory eumenorrheic, or eumenorrheic with short luteal phases compared with sedentary women (De Souza et al., 2007).

IMPACT ON BONE METABOLISM OF ATHLETIC ACTIVITY AND ASSOCIATED NEUROENDOCRINE CHANGES

The various neuroendocrine changes that occur in athletes, particularly in heavy exercisers, are mostly physiologic and in response to a low energy state. These adaptive changes (1) conserve energy for more important and vital functions (by suppression of the HPG axis and thyroid hormones), and (2) increase substrate availability (by increases in cortisol and GH, both of which are gluconeogenic, as well as decreases in leptin and increases in ghrelin, which should stimulate caloric intake). However, if persistent, these physiologic changes can subsequently lead to the major pathologic consequence of energy deficiency, namely poor bone accrual over time in adolescents, and low bone density in adults.

Areal bone density in athletes

The impact of athletic activity on bone depends of various factors. These include the nature of athletic activity, weight-bearing patterns, intensity of training, and associated neuroendocrine hormonal alterations. Bone metabolism is adversely affected in athletes with

restricted energy availability (namely amenorrheic athletes), despite the beneficial effects of physical exercise on bone (Cobb et al., 2003; Christo et al., 2008b; Ackerman et al., 2011).

Impact of physical activity and the nature of the sport—In states of *adequate energy availability and eumenorrhea*, bone density is not only preserved, but may be increased compared with a sedentary population. Thus, eumenorrheic weight-bearing endurance athletes have higher bone density than eumenorrheic nonathletes, particularly at sites of predominantly cortical bone such as the hip (Ackerman et al., 2011). This is attributable to the known beneficial effects of weight-bearing and mechanical loading on bone. Eumenorrhea is protective to bone in exercising women even when subclinical menstrual dysfunction exists, and normally cycling exercising women with luteal phase defects do not differ for bone density at the spine, hip, or femoral neck compared with cycling and ovulatory exercising women (De Souza et al., 1997).

Of importance, the kind of impact experienced with any specific sport determines the direction and nature of mechanical loading on bone, and can differentially affect bone metabolism. Thus, eumenorrheic high school athletes involved in high/odd impact sports such as soccer, softball, volleyball, tennis, lacrosse, sprinting, and jumping have higher bone density at the total hip than eumenorrheic athletes involved in repetitive/nonimpact sports such as cross-country, track, and swimming (Nichols et al., 2007a).

Impact of energy deficiency and/or hypogonadism—Both energy status and gonadal status determine the impact of athletic activity on bone. *Reduced energy intake* in runners, as indicated by increased dietary restraint, is associated with lower bone density (Barrack et al., 2008). In both adult and adolescent amenorrheic athletes, who are presumably *energy deficient and hypoestrogenemic*, bone density is deleteriously affected at the lumbar spine, a site of predominantly trabecular bone, compared with eumenorrheic athletes and nonathletes (Cobb et al., 2003; Christo et al., 2008b; Ackerman et al., 2011), and at the total hip compared with eumenorrheic athletes (Cobb et al., 2003; Ackerman et al., 2011). Similarly, oligo/amenorrheic high school athletes participating in repetitive/nonimpact sports have lower spine bone density than eumenorrheic athletes who participate in high/odd impact sports (Nichols et al., 2007a). In one study, 38% of adolescent amenorrheic weight-bearing endurance athletes had lumbar spine bone density Z-scores of < -1 compared with only 11% each of eumenorrheic athletes and nonathletes (Christo et al., 2008b). In an energy replete state, one study reported that hypogonadism in exercisers was not associated with perturbations in bone formation or resorption (as indicated by surrogate markers of bone turnover); however, bone density Z-scores at the femoral neck were lower in the hypogonadal group (De Souza et al., 2008). In male athletes, lower estradiol levels are associated with lower bone density (Ackerman et al., 2012b).

Modifying effect of the nature of impact—It is interesting to note that even in athletes with estrogen deficiency, bone density may be preserved or be higher than in nonathletes and other athletes, depending on the nature of the sport. Robinson et al. have reported higher bone density at the femoral neck and preservation of bone density at the spine in gymnasts compared with sedentary controls, whereas runners have lower bone density at both sites compared with gymnasts and controls, despite a similar prevalence of amenorrhea in

gymnasts and runners (Robinson et al., 1995). This has been attributed to the impact loading effect of gymnastics versus the repetitive impact associated with running, and higher lean body mass, muscle strength and IGF-1 levels in the gymnasts.

Bone turnover in athletes—Adolescent athletes with amenorrhea have a coupled decrease in bone turnover compared with eumenorrheic athletes and nonathletes (Christo et al., 2008b). This is in contrast to normal adolescence, which is characterized by increased bone turnover in early adolescence, and a decrease in bone turnover to approach adult levels in late adolescence (Mora et al., 1999). Adult exercising amenorrheic women, however, have an uncoupling of bone turnover, with a decrease in bone formation and an increase in bone resorption markers (De Souza et al., 2008).

Determinants of bone density in athletes—As discussed above, important determinants of bone density in athletes are the nature of physical activity, the nutritional status of the athlete (driven by net energy availability) and associated neuroendocrine changes. Nutritional status is reflected by BMI, fat mass, lean (or fat-free) mass, IGF-1, and leptin levels. Although lean mass is preserved in normal-weight athletes, it decreases when weight decreases below 90% of what is ideal for age and height. As indicated earlier, important endocrine alterations occur in low energy states (in addition to low IGF-1 and leptin levels), and include hypothalamic amenorrhea with associated hypogonadism, high ghrelin, PYY and cortisol, and low total T₃. Many of these changes impact bone density in energy-deficient athletes.

In one study, important determinants of bone density in young elite rhythmic gymnasts included BMI, fat-free mass, and levels of gonadal steroids and IGF-1 (Maimoun et al., 2010). These are also important determinants of bone density in young weight-bearing endurance athletes (Christo et al., 2008b). Additionally, relatively higher cortisol and PYY levels and lower leptin contribute to lower bone density (Russell et al., 2009; Scheid et al., 2011). PYY acts primarily through the Y2 receptor, and the Y2 receptor knockout mice have increased bone mass (Baldock et al., 2006), suggesting that high PYY should be associated with lower bone density. Higher PYY levels are associated with lower levels of bone formation markers and lower lumbar bone mineral apparent density Z-scores in adolescent athletes (Russell et al., 2009), and with lower hip and whole body bone density Z-scores in adult exercising women (Scheid et al., 2011). Leptin is a bone anabolic hormone, and low leptin levels in amenorrheic athletes are also associated with lower bone density measures (Christo et al., 2008b; Russell et al., 2009).

Limitations of areal bone density assessment—A limitation of bone density measured by dual energy X-ray absorptiometry (DXA) is that it assesses areal (rather than volumetric) bone density, which is affected by stature and body composition (Bachrach, 2006, 2007). Therefore, adjustment for body size is important at the extremes of stature, and this is particularly important in certain kinds of sports, and inherent to the nature of the sport and its demands. For example, adjustment for height may be important in certain gymnasts and basketball players. Whether or not adjustment for bone age is necessary in adolescents is a matter of controversy, but may need to be factored into the evaluation of bone density in adolescent amenorrheic athletes.

Also, areal bone density cannot provide measures of bone geometry or differentiate between trabecular and cortical bone at different weight-bearing and non-weight-bearing sites (Burrows et al., 2010). High resolution peripheral quantitative tomography (HRpQCT) is a novel technique that allows assessment of bone structure (cortical, trabecular, and total cross-sectional area), cortical and trabecular microarchitecture (cortical porosity, trabecular number, thickness, and separation) and volumetric measures of cortical, trabecular, and total bone density. Using finite element models, HRpQCT data can also be used to derive estimated measures of bone strength (stiffness and failure load). Although studies have shown that bone microarchitecture provides additional estimates of bone strength not provided by DXA measures of bone density (Boutroy et al., 2008; Bredella et al., 2008), there are limited data regarding bone microarchitecture in adolescent and adult athletes.

Bone microarchitecture, volumetric bone density, and estimates of bone strength in athletes

Existing studies have attempted to differentiate changes consequent to mechanical loading (evident in all athletes within a study) from those consequent to energy deficiency and hypogonadism (evident in amenorrheic athletes).

Bone structural changes—In adolescent and young adult weight-bearing endurance athletes, athletic activity is associated with an expansion outwards of weight-bearing bone (distal tibia), as evidenced by an increase in trabecular and total cross-sectional area in both eumenorrheic and amenorrheic athletes. These changes are not evident at the non-weight-bearing distal radius (Ackerman et al., 2011). Amenorrheic normal-weight athletes, however, have lower percent cortical area at weight-bearing bone than nonathletes, attributable to increased endosteal bone resorption in a hypogonadal state.

Cortical and trabecular microarchitectural changes—Adult elite fencers have higher trabecular number and decreased trabecular separation in the femur (assessed using MRI) (Chang et al., 2008). At weight-bearing sites, adolescent amenorrheic normal-weight athletes have lower trabecular number and increased trabecular separation (but no differences in trabecular thickness) compared with eumenorrheic athletes and nonathletes (Ackerman et al., 2011). Cortical pore diameter is highest in amenorrheic athletes (Ackerman et al., 2012a).

Volumetric bone density—Elite fencers have higher trabecular bone density than controls in the femur (Chang et al., 2008). However, cortical density is lower at weight-bearing sites in adolescent athletes (amenorrheic and eumenorrheic) compared with nonathletes, believed to be consequent to delayed mineralization of an outwardly expanding cortex. In addition, total density at weight-bearing bone, and trabecular density at non-weight-bearing bone is lower in amenorrheic compared with eumenorrheic athletes and nonathletes (Ackerman et al., 2011).

Estimated bone strength and fractures—Amenorrheic athletes have lower measures of estimated bone strength (stiffness and failure load) at non-weight-bearing bone compared with nonathletes, and lose the beneficial effect of exercise at weight-bearing sites

(Ackerman et al., 2012a). Similar data have been reported for the hip in adolescent and young adults athletes and nonathletes using hip structural analysis (Ackerman et al., 2013b). A study in adult athletes compared women with a history of lower extremity stress fractures with those without a history of such fractures. This study reported that women with a history of fractures had thinner tibia after adjusting for body size, and a higher load was carried by the cortex in these women. In addition, they had lower trabecular bone mineral density in the posterior region of the tibia and less cortical area (Schnackenburg et al., 2011).

Determinants of bone structure, microarchitecture, volumetric bone density, and estimated strength—Hypogonadism has significant and deleterious effects on bone microarchitecture in athletes. In addition, lean mass has a positive impact, and older age at menarche has a negative impact on bone microarchitecture and strength (Ackerman et al., 2011, 2012a). Interestingly, oxytocin, now known to have bone anabolic effects (Colaizzi et al., 2014), is associated positively with bone microarchitectural parameters in amenorrheic athletes (Lawson et al., 2013).

Strategies to optimize bone health in athletes

It is essential to increase energy availability in amenorrheic athletes. This may be achieved by increasing nutritional intake, reducing the intensity of training, or both (Nattiv et al., 2007). Resumption of menses, an indicator of increasing levels of gonadal steroids, is critical to optimizing bone health in athletes with functional hypothalamic amenorrhea. In addition, normalizing energy balance is likely to cause a normalization of other hormones that impact bone such as IGF-1, leptin, PYY, and cortisol.

Studies in adult amenorrheic women (exercisers or nonexercisers) are conflicting regarding the effect of hormone replacement on bone density. Some report no change (Gibson et al., 1999), others report an increase (Hergenroeder et al., 1997; Castelo-Branco et al., 2001) and some a decrease (Burr et al., 2000; Hartard et al., 2004) in bone density following estrogen administration. Additionally, the studies are usually small (Hergenroeder et al., 1997), often retrospective (Hartard et al., 2004), not randomized (Burr et al., 2000; Castelo-Branco et al., 2001), and do not control for weight changes (Hergenroeder et al., 1997; Castelo-Branco et al., 2001). A study in adolescents with anorexia nervosa, an extreme energy restricted state, has recently reported an increase in bone density and maintenance of bone density Z-scores at the lumbar spine and the hip using the transdermal estrogen patch with cyclic progesterone (Misra et al., 2011). However, catch up of bone density did not occur, and this strategy has not been studied in an exclusively athlete population. Another study in adolescent and young adult women with anorexia nervosa has reported stabilization of lumbar spine bone density Z-scores using a combination of oral estrogen–progesterone with micronized oral dehydroepiandrosterone, but without catch-up (Divasta et al., 2012).

Calcium and vitamin D intake is usually sufficient in most athletes, but should be optimized if not sufficient, with the aim to maintain vitamin D levels between 80 and 125 nmol/L. There are no studies of recombinant human (rh) IGF-1 administration in athletes, although a beneficial effect of rhIGF-1 when given with estrogen has been reported in adult women with anorexia nervosa (Grinspoon et al., 2002). Administration of metreleptin (a commercial

form of leptin) to women with functional hypothalamic amenorrhea (not necessarily exercisers) caused resumption of menses in 60–70% of the women, resumption of ovulatory cycles in 30–40%, and was associated with an increase in bone formation markers and in bone mineral content (Welt et al., 2004; Chou et al., 2011; Sienkiewicz et al., 2011). However, a significant decrease in weight and fat mass occurred with leptin administration. No effective strategies currently exist to reduce cortisol or PYY levels or their effects in this population.

IMPACT ON NEUROCOGNITIVE FUNCTION

Although participation in athletic activities is associated with a positive body image, improved self-esteem and increased likelihood of academic success, there are limited data regarding the impact of amenorrhea on neurocognitive function in athletes. Hypogonadism in other conditions, such as anorexia nervosa and Turner syndrome, is associated with specific changes in neurocognitive parameters that improve with hormone replacement (Collaer et al., 2002; Chui et al., 2008). Additionally, testosterone levels have been associated with mood in women with anorexia nervosa (Miller et al., 2007), while physiologic estrogen replacement causes a reduction in anxiety scores in adolescents with anorexia nervosa, and prevents increases in anxiety and body dissatisfaction following weight gain (Misra et al., 2013). Further investigations are necessary to determine whether amenorrhea leads to a blunting of the beneficial effects of athletic participation on neurocognition and mood.

IMPACT ON FERTILITY

Infertility in athletes with anovulatory cycles and in amenorrheic athletes can be treated with pulsatile GnRH or gonadotropin combinations. In other conditions of hypogonadotropic hypogonadism, ovulatory rates of up to 96% are reported (Martin et al., 1993; Borges et al., 2007). Low-weight women with functional hypothalamic amenorrhea have a higher prevalence of low birth weight offspring than normal-weight women (Gordon, 2010).

CONCLUSION

Athletic activity is characterized by changes in many neuroendocrine axes, and the degree of affectation of these axes depends on the state of energy availability in the athlete, although genetic factors and an underlying predisposition to PCOS may play an important role in determining which athletes become amenorrheic early. Figure 25.1 summarizes adaptive changes in neuroendocrine axes that result from a state of low energy availability. These adaptive changes in neuroendocrine axes in athletes then lead to alterations in bone metabolism, and may affect neurocognition and mood. Figure 25.2 summarizes the impact of energy and menstrual status, and the nature of mechanical loading on bone. The American College of Sports Medicine (ACSM) in its position stand (Nattiv et al., 2007) has emphasized the importance of educating athletes, parents, coaches, trainers, and judges about the consequences of overexercising and the female athlete triad. The ACSM recommends screening for triad components during pre-participation examinations, during the annual health screening examination and as needed. It is critical to discourage unhealthy

weight loss practices amongst athletes. If an athlete develops oligoamenorrhea, a multidisciplinary treatment team needs to be established to include a healthcare professional, a registered dietician, a mental health professional (if eating issues are evident), and additional members (such as a certified athletic trainer, exercise physiologist, athlete's coach, and family members). Nutritional counseling and monitoring may suffice for some athletes, whereas others may require a reduction in exercise activity (a 10–20% decrease in activity per week is recommended). If eating disorders are identified, psychotherapy becomes essential, with clear criteria for continuation of exercise. When necessary, training and competition intensity may need to be modified. The position stand emphasizes that no pharmacologic agent at this time is known to adequately treat functional hypothalamic amenorrhea or low bone density in athletes.

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Fig. 25.1.

Pathways demonstrating physiological and adaptive mechanisms that result from a state of low energy availability, and resulting alterations in various hormonal axes.

Fig. 25.2.

Impact of energy availability, menstrual status, and nature of mechanical loading on bone density.