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Exercise, Training, and the Hypothalamic-Pituitary-Gonadal Axis in Men and Women

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Abstract

The hypothalamic-pituitary-gonadal (HPG) axis is essential for adequate responses to exercise and training both acutely and chronically. Both testosterone and estrogen play leading roles in neuromuscular adaptation to exercise in males and females. The purpose of this chapter is to illustrate the physiological and pathological changes that occur in the HPG axis secondary to exercise and training. In males, testosterone increases with acute bouts of exercise, but long-term effects are less clear, with evidence of lower testosterone in endurance athletes. Restricted energy availability may negatively affect hormone levels in male endurance athletes, but data regarding low energy availability and its impact on the HPG axis are limited in male athletes. Conversely, in females there is significant evidence that decreased energy availability inhibits the HPG axis, leading to menstrual irregularities and lower bone density. Hormonal changes secondary to acute bouts of exercise are more challenging to interpret in females due to menstrual variability, which traditionally has not been taken into account in many studies. However, some evidence supports an increase in testosterone and estradiol with acute exercise. More work is needed to elucidate the relationships among energy availability, basal hormonal fluctuations, and exercise, and their collective effects on the HPG axis.

An increase in the number of individuals participating in athletics, greater pressure for performance, and sport specialization at a younger age necessitate an understanding of physiological changes that occur in athletes consequent to physical activity. Normal endocrine function is essential for optimal performance, adaptations to exercise, and maintenance of optimal body composition [1, 2]. Effects of long-term training on the reproductive system in female athletes have been widely studied. However, the literature on the endocrine adaptations of male athletes is less robust. This chapter will review changes in the hypothalamic-pituitary-gonadal (HPG) axis noted acutely and chronically with exercise in both males and females.

Normal functioning of the HPG axis is essential for the onset and maintenance of reproductive function, in addition to immune and musculoskeletal function. Neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH), a 10-amino acid neuropeptide. The majority of GnRH neurons are located in the medial basal hypothalamus, the infundibulum and the periventricular region of the hypothalamus. GnRH is released in pulses that vary in amplitude and frequency. The frequency of GnRH secretion modifies the ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) secretion from gonadotropes of the anterior pituitary. Hormones such as prolactin, corticotropin-releasing hormone, glucocorticoids, leptin, adiponectin, ghrelin, insulin, insulin-like growth factor (IGF)-1 and catecholamines, and neurotransmitters such as opiates, modulate the release of GnRH [3].

GnRH receptors are located in pituitary gonadotropes and vary in number depending on gonadotropic secretory capacity. In females, GnRH receptor number varies depending on the phase of the menstrual cycle and is lower during lactation. Certain physiological frequencies of GnRH pulsatility can up-regulate GnRH receptor production, while continuous exposure to GnRH down-regulates its receptors. The GnRH receptor is suppressed by estradiol, progesterone, LH, and FSH, and it is stimulated by calcium, protein kinase C, and a critical level and duration of elevated estradiol [3].

In females, LH is essential for ovulation, androgen production in theca cells, and maintenance of the corpus luteum. FSH stimulates the conversion of androgens to estradiol in granulosa cells and stimulates folliculogenesis. In males, FSH stimulates Sertoli cells to promote spermatogenesis, and LH stimulates Leydig cells to produce testosterone [3].

This chapter will summarize what is known about the short- and long-term effects of training on the reproductive system, focusing on GnRH, gonadotropes, and estradiol and androgen levels, in addition to effects on gametes.

Males

Testosterone

Testosterone is an essential hormone in male athletes both during puberty and adulthood. Changes in androgen levels are of concern because they play an important role in neuromuscular adaptation, muscle maintenance, strength, and aggressiveness in competition [2, 4]. At a cellular level, motor neurons react to testosterone by increasing soma size, dendritic length and synaptic input, and muscle cells respond to testosterone by increasing calcium channels [5]. When given exogenous testosterone, males had an increase in muscle size and/or in performance, both of which increased further if combined with resistance training [6–12].

It has been widely reported that physical activity acutely increases total and free testosterone in men [2, 4, 13]. However, studies of the mid- and long-term effects of exercise on testosterone levels are less clear. Testosterone levels have been shown to be dependent on the time and duration of exercise. Grandys et al. [14] found an increase in serum testosterone after 5 weeks of endurance training on a cycle ergometer in previously untrained healthy

men. In a cross-sectional study by Fitzgerald et al. [15], trained cyclists (cycled 8 h/week) had higher levels of serum total testosterone compared to recreational athletes (< 30 min of exercise most days of the week). In contrast, multiple cross-sectional studies have found either no difference or a decrease in testosterone in trained endurance athletes compared to controls [16–18]. In a small cross-sectional study that compared runners, cyclists, and elite triathletes against controls, there were no significant differences in FSH, LH, and total or free testosterone levels across groups, but there was a *positive* correlation of training volume and testosterone levels [17]. In a prospective study of cyclists, there were no differences in FSH, LH, or testosterone levels before and after a 300-km bike ride [18].

Multiple cross-sectional studies have found lower testosterone levels in endurance athletes [19–23], resistance-trained athletes [23], soccer players [24], and amateur road cyclists [25] compared to controls. In a prospective study evaluating 14 body builders, half the subjects were required to restrict energy in preparation for competition and half continued to train regularly, but were not allowed to restrict energy to achieve competition weight. Testosterone levels were measured at baseline, 10 and 6 weeks, and 4 days (3 days prior to competition). In the energy-restricted group, testosterone levels were significantly lower at the second two time points versus baseline. In the non-energy-restricted group of body builders, testosterone levels were not significantly different at the beginning and end of the study, but there was a slight decrease in testosterone at the 6-week measurement [26]. Similar to this, Grandys et al. [27] found that testosterone levels vary significantly in sprinters along the annual training period, with testosterone levels higher during low-intensity training and lower during high-intensity training.

Effects of exercise training on testosterone levels may also differ according to age. For example, adult males, but not adolescent boys, were found to have increases in testosterone levels with short bouts of resistance training [28–30]. In a small study of young weight lifters, those who had trained for more than 2 years showed an acute increase in testosterone after resistance exercise, while chronologically age-matched weight lifters who were newer to the sport did not have a significant change [31]. Cross-sectional studies evaluating young gymnasts, soccer players, and hockey players versus age-matched controls did not find differences in testosterone levels among the groups [32, 33]. Prospective studies evaluating changes in testosterone levels in pubertal male athletes are needed.

Addressing the other end of the age spectrum, Häkkinen et al. [34] compared middle-aged (mean age 42 years) and elderly males (mean age 72 years) during 6 months of resistance training and did not find changes in basal free or total testosterone levels from the beginning to the end of the study, but did find lower basal free testosterone in the older versus younger males. Additionally, they noted comparable acute increases in free and total testosterone after short bouts of exercise both at the beginning and the end of the study in both age groups. Di Luigi et al. [35] showed a high prevalence of low testosterone levels in exercising men above 50 years of age, which raises the concern of undiagnosed hypogonadism in elderly males.

While transient changes in hormone levels after bouts of exercise are notable, effects of different types of habitual exercise on overall testosterone levels may have more clinical

utility. There is significant variability in basal testosterone levels and overall hormonal profiles among different sports [36]. It is important to note that hormonal changes involved in overtraining and/or decreased energy availability can decrease the production of testosterone. The overtraining syndrome is defined as the combination of excessive overload with inadequate recovery periods that can result in fatigue and decrease in performance [37]. Currently, no ideal biomarker exists to diagnose overtraining, and despite the somewhat frequent use of a testosterone/cortisol ratio, this potential marker has been found to be unreliable [37]. Hackney et al. [22] showed that highly trained or overtrained male athletes had 40–80% lower levels of testosterone compared to controls.

Safarinejad et al. [38] conducted a well-designed, randomized clinical study of the effects of intensive training versus moderate training in males aged 20–40 years. The high-intensity group ($n = 143$) performed at approximately 80% of their maximal oxygen uptake (VO_{2max}) while the moderate-intensity group ($n = 143$) performed at approximately 60% VO_{2max} . Both groups exercised for 2-hour sessions, 5 times a week, for 60 weeks. This was followed by 36 weeks of low-intensity exercise deemed a recovery period. In both groups of exercisers, 60 weeks of exercise resulted in lower free testosterone, FSH, and LH, and higher sex hormone binding globulin (SHBG) and prolactin, with these differences even more pronounced in the high-intensity group. The number of hours of high-intensity exercise significantly correlated negatively with all of the above hormone levels. Moreover, after the administration of exogenous GnRH at the end of the 60 weeks of exercise, both groups had a blunted response of LH and FSH. However, after the recovery phase of 36 weeks of low-intensity exercise, all the parameters returned to normal [38]. This suggests a suppression of the HPG axis, which could be due to a decrease in GnRH production and a reduced response of LH and FSH during habitual exercise.

Leanness and Relative Energy Deficiency in Sport

Participation in sports where leanness is considered a competitive advantage, such as running, cycling, wrestling, lightweight rowing and gymnastics, has been linked to a lower body mass index (BMI) [39], eating disorders [40], and low energy availability [41]. Low energy availability in the context of anorexia nervosa has been associated with low testosterone levels in males [42]. Hagmar et al. [1] evaluated athletes from 26 different sports and divided them into those who participated in leanness sports and those who did not. The leanness sport athletes had lower body fat, higher spinal bone mineral density (BMD), lower serum free testosterone and leptin, and higher IGF-1 binding protein. The authors suggested that the increase in BMD could be because of the increase in mechanical loading in the specific leanness sports, which presumably overcame the effects of lower testosterone and leptin, both of which are bone anabolic hormones.

In female athletes, low energy availability is a component of the female athlete triad (Triad), a term used to describe the interrelationship of decreased energy availability, subsequent HPG inhibition leading to menstrual irregularity, and decreased BMD [41]. Triad was first described by the American College of Sports Medicine in the 1990s. The International Olympic Committee (IOC) has proposed an expansion of the concept of Triad to include males and has coined the term, relative energy deficiency in sport (RED-S) [43]. The

development of the term RED-S had three main purposes: (1) to draw awareness to the fact that energy restriction can have negative consequences in men in addition to women; (2) to highlight other potential negative health and performance consequences of low energy availability in athletes besides bone problems, and (3) to encourage expansive research into the potential myriad effects of low energy availability in various populations, including Paralympic athletes. Multiple studies have not found evidence of decreased BMD in male athletes with decreased testosterone [1, 16, 21], while other studies have shown decreased BMD in male runners [44] and horse-racing jockeys [45].

Additionally, our group studied hormone levels and DXA-derived BMD in collegiate, male runners, wrestlers, and golfers [46]. Wrestlers had significantly greater BMD at all measured sites than runners and golfers, who were not significantly different from each other. Total and free testosterone levels were not significantly different among the groups, nor were they predictors of BMD at the hip or spine. However, total and free estradiol levels were higher in wrestlers than in runners and were important positive determinants of BMD [46]. Perhaps the failure of prior work to show a correlation among energy availability, testosterone, and low BMD may be secondary to the focus on androgens rather than estrogens. Further work is needed to better understand RED-S and possible effects of estradiol and bone in male athletes.

Fertility

Studies evaluating intense training in men have shown that the inhibition of the HPG axis could manifest as changes in fertility. Some studies have found changes in semen from exercise, noting decreases in sperm motility, quality and number [17, 19, 47, 48], while others have not found such alterations [49, 50]. In the previously mentioned study by Safarinejad et al. [38], those participants assigned to high-intensity training had significantly decreased sperm count, concentration, and motility at 24 weeks of exercise, which worsened through the exercise intervention. Similarly, Vaamonde et al. [51] evaluated untrained subjects after 2 weeks of exhaustive endurance exercise and found negative changes in sperm, FSH, and LH that returned to normal 2–3 days after resuming their baseline exercise habits. Additionally, De Souza et al. [19] showed a negative correlation of volume of exercise with sperm motility and density. The above studies, however, did not control for energy availability. Thus, like much of the work in female athletes, research in male athletes will be more easily interpretable in the future if energy availability is accurately quantified and factored into the analysis.

Females

Acute Changes in Testosterone and Estradiol

In females, short-term consequences of training on the HPG axis have not been as widely studied as in males. Differences in hormonal responses between the sexes are believed to be dependent on basal hormone concentrations (i.e. sex differences in basal estradiol and testosterone) [52]. Cumming et al. [53] studied 7 women (aged 18–21 years) and noted increases in total testosterone after an acute bout of resistance training. In a larger study, Nindl et al. [54] studied hormonal changes after acute bouts of resistance exercise in 47

women (mean age 22 ± 3 years), and also found increases in both free and total testosterone. There have been mixed results pertaining to the effects of a few weeks to a few months of resistance training on basal levels of testosterone in women. Kraemer et al. [55] studied 8 women during 8 weeks of heavy resistance exercise and found a small, but significant elevation in testosterone before exercise by week 6 compared to week 1. Studies have also shown an increase in testosterone with acute bouts of endurance exercise [56, 57].

Studies evaluating acute changes in estradiol are challenging given that estradiol levels change widely during a typical menstrual cycle. Estradiol increases during the follicular phase, peaks prior to ovulation, plummets during ovulation, and then experiences a gradual increase and decrease prior to its nadir in early menses. Estradiol levels also experience a diurnal and ultradian rhythm throughout each day that additionally varies throughout the cycle [58]. Nevertheless, multiple studies have found an acute increase in estradiol immediately after exercise [59, 60]. This increase in estradiol seems to be responsible for greater lipid and less carbohydrate oxidation compared to men during exercise [61, 62]. Estradiol also seems to be protective for muscles during the stress of exercise [63, 64]. While the exact mechanisms are poorly understood, the positive effects of exercise may be exerted by estrogen acting as (1) an antioxidant, therefore minimizing oxidative damage; (2) a membrane stabilizer by inserting itself among phospholipids in the cell membrane, and (3) an estrogen receptor substrate, thus affecting downstream gene regulation and other targets [65].

Female Athlete Triad

The long-term impact of exercise and training on hormone levels has been more widely studied in females, particularly in the setting of decreased energy availability. As mentioned briefly above, the Triad is a combination of decreased energy availability, menstrual irregularity (luteal phase defects, anovulation, oligomenorrhea, and hypothalamic amenorrhea), and poor bone health (decreased BMD and higher risk of fracture) [66, 67]. Lower energy availability from increased caloric expenditure and/or relatively decreased caloric intake leads to a suppression of the HPG axis, diverting energy away from the reproductive system to more vital bodily processes, such as cell maintenance and immune function. GnRH pulsatility is disrupted, leading to changes in more downstream hormonal signaling and functional hypothalamic amenorrhea [66]. Functional hypothalamic amenorrhea is defined as the absence of menses secondary to the suppression of the HPG axis where other causes have been excluded [68]. There is evidence of variable susceptibility to functional hypothalamic amenorrhea based on genetic factors [69]. Estradiol and other hormones affected by low energy availability, including IGF-1, cortisol, and leptin, are important for bone metabolism. Therefore, decreases in energy availability can have negative effects on BMD through multiple pathways [70].

Amenorrhea has been reported in up to 66% of athletes, depending on the sports population studied and how screening was performed [66, 71, 72]. GnRH has a direct effect on the pattern of LH release, and LH pulsatility is a direct reflection of GnRH pulsatility. In one study, alterations in LH release were described in 78% of athletes with amenorrhea [73]. When evaluating secretion of LH in amenorrheic athletes, eumenorrheic athletes, and

nonathletic controls aged 14–21 years, overnight secretory LH pulse height, total pulsatile secretion, and area under the concentration time curve (AUC) were lower in athletes with amenorrhea versus nonathletes [74]. In a study examining LH pulsatility in eumenorrheic, sedentary women, subjects were energy restricted from diet alone versus those energy restricted predominantly by increasing exercise. Changes in LH pulse frequency and amplitude were noted in both energy-restricted states, but LH pulse frequency was less decreased when equivalent energy deficiency was achieved mostly from exercise [75]. This suggests that energy restriction, or decreased energy availability, is likely a more important factor in GnRH and LH disruption in Triad, rather than the stress of exercise.

FSH stimulates granulosa cells of the ovaries, which leads to inhibin B secretion and subsequent inhibition of further FSH production, thus allowing only the most advanced (or dominant) follicle to continue to develop and proceed to ovulation. When estradiol levels decrease at the end of the cycle, FSH levels start to rise again and allow for new follicles to be recruited. Although FSH is highly regulated by GnRH, the literature has failed to demonstrate significant differences in FSH levels in athletes with amenorrhea versus eumenorrheic athletes. This may be partially explained by the methods used to study such levels and the significant variability in hormone levels even in eumenorrheic athletes. For example, in a study of daily urinary hormone levels over 3 months in recreational runners who had regular monthly menses, only 45% of the cycles were ovulatory, 43% had luteal phase defects (e.g. shortened luteal phases), and 12% were anovulatory. In this study that involved very careful assessment of gonadotropins and other hormones, FSH elevation during the luteal-follicular transition was lower in athletes with luteal phase defects versus athletes with ovulatory cycles and nonexercising, sedentary controls [76]. Unfortunately, most other studies examining FSH levels in athletes have not gathered samples over multiple times points in one cycle nor have they tested contiguous cycles in subjects.

In a study of 30 women with functional hypothalamic amenorrhea, only 29% had low FSH levels (5th percentile of early follicular phase control values), which was associated with a lower follicular number. However, when 79% of amenorrheic subjects with FSH levels and follicular numbers similar to controls were further studied, some of their functional follicular markers were abnormal. These included higher anti-Müllerian hormone levels, higher anti-Müllerian: 2–5 mm follicular number ratios and lower mean inhibin B levels compared to controls. This suggests that even with ‘normal’ FSH levels, the terminal growth and function of antral follicles may be affected [77].

It is well established that estradiol levels are lower in amenorrheic athletes with functional hypothalamic amenorrhea or Triad compared to eumenorrheic athletes [78, 79]. Urinary estrone-1-glucuronide (E1G) excretion patterns were studied in women who were categorized by exercise (exercisers or sedentary controls) and menstrual status (ovulatory, luteal phase defects, or anovulatory). While there were no significant differences in peak concentrations of E1G among the groups, the day of peak E1G occurred later in exercisers with luteal phase defects versus exercisers who ovulated. Anovulatory exercisers had lower E1G excretion in the follicular phase compared to sedentary and exercising ovulators, and exercisers with luteal phase defects. E1G AUC was lower in anovulatory exercisers versus sedentary and exercising ovulators during the follicular phase, and exercisers with

anovulation or luteal phase defects had lower E1G AUC compared to sedentary ovulators during the luteal phase [80].

Such decreases in estradiol secondary to menstrual irregularity have proven negative effects on BMD, bone microarchitecture, and fracture risk [66, 67, 81]. However, further work has also suggested other negative consequences. Estrogen stimulates the endothelial nitric oxide (NO) synthase signaling system, promoting NO release, which subsequently enhances vascular smooth muscle cell dilation. NO also has anti-atherosclerotic properties [82]. Various researchers have noted endothelial dysfunction in amenorrheic athletes [83–86], with one study noting that estradiol levels correlated positively with vascular function [85] and another noting that the most unfavorable lipid profiles correlated with the most significant menstrual dysfunction in athletes [84]. In the former study, amenorrheic athletes who became eumenorrheic during the follow-up after quitting strenuous athletic activity had improved vascular function that was associated with increased serum estrogen levels [85]. As the IOC's RED-S term suggests, there certainly may be other effects of decreased energy availability on athletes in addition to poor bone health, and more work is needed to explore other potential effects of low estradiol on athletes' health and performance.

Progesterone release is stimulated by LH and has enhanced effects under the influence of estrogens. This is a progestational hormone, because it enhances vascularization of the endometrial cell lining for implantation during the luteal phase of the menstrual cycle and maintains it during pregnancy. Like estradiol, there is evidence that this hormone is also reduced in some female athletes [87]. While the clinical definitions of luteal phase defects have been controversial, they all include low progesterone levels in the luteal phase. Such hormone alterations have negative effects on fertility, secondary to poor follicular development, poor implantation, and pregnancy maintenance (spontaneous abortion) [88].

Energy status is correlated with body fat mass. Adipocytes are responsible for the secretion of leptin and adiponectin, which, as mentioned earlier, have opposing effects on the HPG axis [89–92]. There is consistent evidence that amenorrheic athletes with normal lean body mass and BMI have lower body fat and percent body fat than eumenorrheic athletes and nonathletes [93, 94]. Leptin, an anorexigenic hormone, declines with low energy availability [95, 96] and, as expected, is lower in amenorrheic athletes compared to eumenorrheic athletes and nonathletes [74, 93]. Conversely, there is evidence that adiponectin increases with reduced energy [89, 91]; however, findings in amenorrheic athletes are inconsistent. There were no significant differences in adiponectin levels in adolescent amenorrheic versus eumenorrheic athletes [97], but in another study, adult amenorrheic athletes were found to have higher adiponectin levels than eumenorrheic athletes [98]. Additionally, fat mass plays an important role in the regulation of ghrelin, cortisol, IGF-1, and peptide YY, which in turn affect GnRH regulation [74, 92–94; see also this vol., pp. 1–11, 12–26, 44–57].

Treatment of the Triad should start with modest exercise reduction (10–20%) and an increase in energy availability to at least 30–45 kcal/kg of fat-free mass per day. If the patient is not compliant with treatment, removal from competition may be necessary [41, 66]. Recovery of menstrual cycles and fertility, and improvement in BMD is possible in those athletes who normalize their energy availability. Often BMD cannot improve to a

normal range if the energy depletion occurred during adolescence, a time characterized by significant bone accrual, and/or if the decreased energy availability and menstrual dysfunction were prolonged [66, 99, 100]. Pharmacological therapy with oral contraceptive pills (OCPs) with estrogen and progestin has shown inconclusive results despite their widespread use in amenorrheic athletes and patients with anorexia nervosa [41, 101–103]. Unlike OCPs, estrogen delivered via transdermal patches has minimal suppressive effects on the bone trophic hormone, IGF-1, which may contribute to an increase in BMD in amenorrheic athletes not seen with oral estrogen preparations [104]. Our group found an increase in spine and hip BMD with physiological estrogen replacement using a transdermal patch and cyclic oral micronized progesterone in patients with anorexia nervosa [105]. This treatment is currently being tested in amenorrheic athletes. Additionally, further long-term research is needed to determine the lasting effects on fertility and possible treatment of athletes who have suffered prolonged menstrual dysfunction.

Androgens

Androgen levels have been studied to some extent in female athletes. In a large study of 849 elite female athletes competing in the 2011 International Association of Athletics Federations (IAAF) World Championships, blood samples were drawn to determine karyotype and hormone levels [106]. Five subjects were excluded because of doping and 5 subjects were found to be 46XY with disorders in sex development. The prevalence of the genetic 46XY finding in this population (7.1 per 1,000) was 140 times higher than predicted in the general population, thus suggesting a potential selection bias for these individuals to participate in sport [106]. Two previous studies also found a high prevalence of the 46XY karyotype in phenotypic females in the 1992 (7.5 per 1,000) and 1996 Olympic games (2.67 per 1,000) [106, 107]. Notably, in the 2011 IAAF study and in prior reports, genetic testing was only done in those athletes suspected of hyperandrogenism (HA), and, therefore, the prevalence of Y-chromosomal material may be even higher in elite female athletes. However, after excluding known 46XY and doping subjects, a great variability in the hormonal profile was found in different sports at the IAAF Championships. A higher level of testosterone and dehydroepiandrosterone (DHEA) sulfate was seen in throwers and sprinters compared to long-distance runners [106]. When examined according to menstrual status, oligomenorrheic and amenorrheic athletes had lower testosterone and DHEA sulfate, and higher SHBG concentrations than eumenorrheic athletes [106]. These findings were similar to two prior cross-sectional studies; one in adult and one in adolescent female athletes. Both found decreased testosterone levels in amenorrheic compared with eumenorrheic athletes [87, 93].

Rickenlund et al. [108] found that 8 of 25 endurance athletes with oligo- or amenorrhea had significantly higher serum levels of free and total testosterone, androstenedione and LH:FSH ratio, and lower SHBG compared to eumenorrheic endurance athletes and nonathletes. Subsequently, the same authors compared age- and BMI-matched groups of amenorrheic endurance athletes, oligomenorrheic endurance athletes, eumenorrheic athletes, and sedentary controls, and found that oligomenorrheic (but not amenorrheic) athletes had higher levels of diurnal testosterone [109]. They also noted a positive association between 24-hour testosterone and menarchal age [109]. In a recent, small, retrospective cohort study, Javed et al. [110] examined BMI-matched female athletes diagnosed with functional hypothalamic

amenorrhea from exercise (FHA-EX) plus clinical or biochemical HA (FHA-EX+HA) versus athletes with FHA-EX only versus females with functional hypothalamic amenorrhea from anorexia nervosa (FHA-AN). Based on the Rotterdam criteria, all subjects in the FHA-EX+HA group met criteria for polycystic ovary syndrome. FHA-EX+HA had significantly higher total testosterone levels compared to FHA-EX, but not compared to FHA-AN. FHA-EX+HA had a higher LH:FSH ratio, higher diastolic blood pressure, and fewer stress fractures compared to the other two groups, and higher fasting glucose and lumbar BMD compared to FHA-EX. In a cross-sectional study of Swedish Olympic athletes, of the few with menstrual disturbances not on hormonal contraception, 1 of 5 amenorrheic athletes and 5 of 8 oligomenorrheic athletes were diagnosed with polycystic ovary syndrome instead of hypothalamic inhibition [111]. There seems to be a positive effect of HA on performance in female athletes and, therefore, a positive selection towards sports [108]. The above studies remind us that there may be overt differences in the genetics of some athletes competing as phenotypic females in addition to subtle metabolic differences in those with mild HA features. In studies determining normal ranges of hormones in healthy, nondoping athletes, in addition to studies of the effects of hypothalamic amenorrhea and Triad on health and performance parameters, it is important to remember the wide range of genetic and metabolic differences that may exist.

Effects of the Menstrual Cycle and Oral Contraceptives on Exercise and Training

Multiple studies have examined the effect of the menstrual cycle on VO_{2max} , aerobic endurance, and anaerobic performance, and most have not found significant differences during the different phases of the cycle [112–115]. One exception was a study of 16 eumenorrheic athletes tested in the early follicular and mid-luteal phases of the menstrual cycle. Both absolute and relative VO_{2max} were slightly lower in the luteal versus follicular phase. However, the cycle phase did not significantly affect maximum heart rate, maximum minute ventilation, maximum respiratory exchange ratio, anaerobic performance, endurance time to fatigue, or isokinetic strength [116]. Similarly, in a study of 8 eumenorrheic athletes studied during the follicular and the luteal phase, subjects finished a cycling distance significantly faster during the follicular phase than the luteal phase. Interestingly, when glucose ingestion was allowed during the distance trial, the time to completion was faster compared to both follicular and luteal phases without carbohydrate ingestion, and there was no difference between the menstrual phases. Thus, proper fueling may negate any small performance differences noted between menstrual phases [117].

Progesterone and synthetic progestins are known to have a central thermogenic effect. An increase in body temperature of 0.3–0.5°C has been noted during pregnancy and the luteal phase of the menstrual cycle. There is associated altered skin blood flow and an increased threshold for cutaneous vasodilation and the onset of sweating. A higher core body temperature may reduce the safe margin for heat accumulation when exercising in a hot, humid environment, potentially decreasing the time to fatigue and compromising performance [118–120].

The effect of exogenous estradiol and progesterone administration on performance has now been widely studied. Studies in the 1980s and 1990s did not find any difference in aerobic

performance between OCP users and nonusers [121–124]. More recent studies have found a decrease in $\text{VO}_{2\text{max}}$ with continued OCP use [125, 126]. In 2013, Joyce et al. [127] evaluated the effects of OCP use on endurance performance and found a decrease in $\text{VO}_{2\text{max}}$ in OCP users but no changes in endurance performance. Another similar study in rowers did not find a difference between performance among OCP users and nonusers [128]. Notably, some athletes feel better during specific times of their menstrual cycles, suggesting individual variation in performance based on symptoms. To tease out the effects of menstruation and OCPs on performance, much larger studies are needed with reliable hormonal assays, a variety of OCP formulations, and in-depth questioning about training, mood, menstrual symptoms, and more.

Conclusions

The bulk of the literature regarding hormone levels in male athletes focuses on the effects of short bouts of exercise on transient changes in hormone levels. Testosterone has been the hormone most classically examined, because of its positive effects on muscle and strength, and because it is the primary male sex hormone. Overall, effects of long-term training on hormone levels have been less well studied in males and most prior work has not controlled for energy availability, thus confounding results, particularly in endurance athletes. Decreased energy availability in male athletes and its long-term effects need further evaluation. On the other hand, it is well established that decreased energy availability in female athletes suppresses the HPG axis, manifesting as an alteration in the menstrual cycle and decreased BMD. A better understanding is necessary of possible effects of decreased energy availability on performance and other end points. Effects of short-term bouts of exercise on the HPG axis in females include increases in testosterone and estrogen. Such increases are dependent on the timing of the menstrual cycle, energy availability, and the type of exercise. Further studies over the course of multiple menstrual cycles, appropriately controlled for energy availability, are needed to better understand both acute and long-term hormonal responses to exercise and training.

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