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ORIGINAL ARTICLE

The presence of symptoms of testosterone deficiency in the exercise-hypogonadal male condition and the role of nutrition

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Abstract
Purpose High volumes of aerobic exercise have been associated with reduced testosterone (T), known as the exercise-hypogonadal male condition (EHMC). Although the presence of low T has been identified, few studies have assessed the presence of androgen-deficient symptoms. The purpose of this investigation is to assess men exhibiting EHMC and evaluate their hypothalamic–pituitary–gonadal axis, the presence of hypogonadal symptoms, and also investigate a possible contribution of inadequate nutrition to the condition.
Methods A cross-sectional design compared 9 long-distance runners exhibiting EHMC to 8 non-active controls. Comparisons included serum T, luteinizing hormone (LH), follicle-stimulating hormone, and cortisol, the Aging Male Symptoms (AMS) questionnaire score, bone mineral density (BMD), and a food frequency questionnaire.
Results Mean T was significantly reduced in the EHMC group (EHMC 9.2 nmol L^{-1} vs. CONT 16.2 nmol L^{-1}). The EHMC group demonstrated significantly higher AMS scores (EHMC 27.1 ± 7.3 vs. CONT 19.7 ± 2.5). There were no differences in bone density, although 3 cases of osteopenia were noted for EHMC in the lumbar spine, 1 in the right femur, and 1 in the radius. Energy availability was significantly reduced in EHMC (EHMC 27.2 ± 12.7 vs. CONT 45.4 ± 18.2 kcal d FFM^{-1}).
Conclusions Men exhibiting EHMC do appear to present with symptoms associated with androgen deficiency. For the most part, these symptoms are limited to those reported on the AMS questionnaire, although there are also some cases of clinically low BMD. It is possible that inadequate energy intake is contributing to this condition.

Keywords Low testosterone · Exercise-hypogonadal male condition · Hypogonadism · Energy balance

Abbreviations

T	Testosterone
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
C	Cortisol
WADA	World Anti-Doping Agency
RED-S	Relative energy deficiency in sport
EHMC	Exercise-hypogonadal male condition
CONT	Control
USG	Urine specific gravity
DEXA	Dual-energy X-ray absorptiometry
FFQ	Food frequency questionnaire
AMS	Aging male symptom questionnaire
EA	Energy availability
ELISA	Enzyme-linked immunosorbent assay

Introduction

The presence of low serum testosterone (T) concentrations in male distance runners was first documented over 30 years ago (Wheeler et al. 1984), a response which was later dubbed the "exercise-hypogonadal male condition"

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(EHMC) (Hackney et al. 2005). This effect of high physical activity leading to reduced T has also been shown in other populations, such as men in the military (Alemany et al. 2008; Santtila et al. 2009). After the initial investigation suggested that serum T concentrations were reduced in men who regularly engage in long-distance running when compared to sedentary controls, it was noted that T concentrations remained within the normal physiological range (Wheeler et al. 1984). However, more recent studies have documented T concentrations well below the normal physiological range, particularly in elite athletic populations participating in ultra-endurance events, such as the 100-mile Western States Ultramarathon (Kupchak et al. 2014), 100-mile Iditarod trail race (Kraemer et al. 2008), and the Ironman World Championships (Hooper et al. 2014). In fact, our data from the Kona Ironman World Championships showed that 13 of the 22 athletes analyzed had T concentrations below what has been described as normal (12 nmol L^{-1}) (Arver and Lehtihet 2009), suggesting a prevalence of over 50% in elite aerobic athletes. This more severe reduction in T concentrations could be due to the increased volume and intensity of aerobic exercise in men competing in such events when compared to the more conservative aerobic exercise regimens of those measured by Wheeler et al. (1984). Also, in military populations, these below-normal T concentrations have been documented following basic training (Santtila et al. 2009).

When these aforementioned cases of severe reductions in T concentrations occur, whether or not these men should be medically treated comes into question. Prior to treatment, typically a follow-up test to an indication of low T would be an assessment of luteinizing hormone (LH), which would offer insight into whether the condition has a primary cause (inadequate response of the testis) or a secondary cause (insufficient stimulus to the testis). In many older men presenting with hypogonadism, a low T occurs with LH concentrations within the normal range (Arver and Lehtihet 2009), which also appears to be the case in the majority of individuals exhibiting EHMC (Hackney 2008). In this case, it can be argued that the pituitary is not adequately responding to reduced T by subsequently increasing LH concentrations. On the other hand, it can also be argued that the stimulus of the testis is adequate through normal LH concentrations, and that therefore there is an inadequate response, suggesting a primary disorder. Thus, such cases may be considered mixed hypogonadism as they appear to have both primary and secondary components (Arver and Lehtihet 2009). Studies have also suggested that high concentrations of cortisol could be playing a role (Hackney et al. 1988), as it had been previously found that hydrocortisone injections can inhibit testosterone secretion without changes in luteinizing hormone (Cumming et al. 1983). Elevated cortisol concentrations could be expected from such populations participating in high volumes of exercise if these individuals fail to provide adequate recovery from prolonged exercise bouts.

Although it does appear that high volumes of aerobic exercise reduces T, the mechanism of the development of the EHMC remains unknown (Hackney 2008). Interestingly, it has also been suggested that this reduced T concentration may not be a concern at all, but rather an adaptation associated with the cardiovascular benefits of aerobic exercise. For example, von Eckardstein et al. pharmacologically induced a reduction in endogenous T concentrations and saw a concomitant increase in high-density lipoprotein (von Eckardstein et al. 1997). In this case, it could certainly be argued that the reduced T exhibited in the EHMC should not be treated at all, as this may be a positive adaptation.

If treatment of this condition is being considered, identifying eligible men for testosterone therapy is typically based not only on a T measurement, but in combination with the clinical assessment of hypogonadal symptoms (Arver and Lehtihet 2009). Despite a substantial number of studies having demonstrated these reduced T concentrations in men performing high volumes of aerobic exercise (Hackney et al. 1988, 1990; MacConnie et al. 1986; McColl et al. 1989; Wheeler et al. 1984, 1991), very few studies have made reference to the presence of symptoms of hypogonadism in these men, which is a surprising oversight considering its importance in diagnosing a person as hypogonadal. Although relatively sparse, there does appear to be some evidence that these men exhibiting the EHMC may very well demonstrate symptoms typically associated with hypogonadism. For example, a case study by Burge et al. (1997) showed that a man regularly running 50-90 miles per week for 14 years demonstrated not only reduced T, but also below-normal LH as well as markedly reduced bone mineral density and a reduction in frequency of erections. This led the authors to declare that exercise-induced hypogonadism exists. Also, Ayers et al. (1985) observed similar evidence of hypogonadal symptoms associated with long-distance runners. In this study, 14 of the 20 subjects showed significantly decreased T, and although 18 of 20 marathon runners had normal semen analyses, the 2 athletes with the lowest T concentrations suffered severe oligospermia. These studies suggest that although it appears to be in the minority of cases of EHMC, it is possible for these men to exhibit pronounced symptoms of hypogonadism.

With the potential for men exhibiting EHMC to indeed suffer from symptoms of hypogonadism, it is clear that more research is required in the area to ascertain whether these men should be treated for this condition. As the EHMC appears to be more severe in athletes participating at a highly competitive level as previously discussed, the presence of hypogonadal symptomology in this

population would lead to an interesting dilemma. Where hypogonadism is often treated with either testosterone, or as others have suggested with clomiphene citrate (Burge et al. 1997), both substances are on the World Anti-Doping Agency (WADA) banned list. Although WADA does allow for therapeutic use exemptions for organic androgen deficiency, such as due to genetic abnormalities, it does not allow for the use of these substances due to a functional deficiency resulting from excessive exercise. Therefore, with EHMC, athletes subject to drug testing under WADA regulations would not be permitted to receive T therapy even if they are suffering from symptoms.

Another factor that could be playing a role in the EHMC is inadequate nutrition. Since the first documentation of reduced T associated with exercise (Wheeler et al. 1984), parallels have been made with the condition now known as the female athlete triad in women (Nattiv et al. 2007). In this condition, women who have a low energy availability (i.e., inadequate energy intake to support high levels of physical activity) demonstrate reduced LH pulsatility (Loucks et al. 1998), which leads to amenorrhea and can eventually lead to osteoporosis. In fact, there has been a recent suggestion that both the male and female versions of this condition should be grouped together and collectively referred to as relative energy deficiency in sport (RED-S) (Mountjoy et al. 2014) although this was met with great concern (De Souza et al. 2014). Nutritional deficiency has been previously highlighted as a factor that should be excluded prior to the prescription of T therapy (Bhasin et al. 2010), which further exemplifies the need to assess nutrition in the EHMC. In the case of the female athlete triad, correcting an energy deficit has been shown to be effective at relieving amenorrhea in women (Cialdella-Kam et al. 2014), and thus could be a potential treatment for men if energy deficit is contributing to the male version of the condition.

With the emergence of this condition in aerobically trained athletes and military populations, low T is a popular concern for many highly active young men, with many individuals considering possible treatments. Yet without proper diagnostics beyond low T for true hypogonadism, mistakes in using an exogenous T treatment as a first option may irreparably impact basic endocrine cybernetics and function. The purpose of this investigation was to assess a group of men that are exhibiting reduced T associated with exercise and evaluate their gonadotropin concentrations, their presence of hypogonadal symptoms, and also investigate a possible contribution of inadequate nutrition to the condition. These assessments would therefore gain greater insight into whether this condition requires treatment, and what possible treatment options there may be.

Materials and methods

Study design

A cross-sectional, between-group design which compared long-distance runners to healthy controls was used. The comparisons that were made included endocrine markers that can identify the underlying cause of the condition, as well as symptoms of hypogonadism, including both physiological (such as follicle-stimulating hormone and bone density) and psychological factors (measured by questionnaires). An assessment of energy availability was also performed to assess whether an energy deficit was potentially contributing to the condition, such as it has in women.

Participants

Nine men (age 36.3 ± 9.2 years; height 180.0 ± 8.8 cm; weight 77.2 ± 6.8 kg) who had ran an average of 81 ± 14 km per week for the past 12 months (EHMC) were compared to 8 men (age 30.8 ± 6.3 years; height 176.9 ± 5.2 cm; weight 77.3 ± 10.7 cm) who had not been participating in any running for the past 12 months (CONT). Height was measured using a stadiometer (Seca, Hamburg, Germany). Weight was measured using a calibrated scale (OHAUS Corp., Florham Park, NJ). All subjects were fully informed of the protocol design and associated risks of this investigation before signing an informed consent document approved by The Ohio State University Institutional Review Board for use of human subjects.

Procedures

Participants arrived at the laboratory at 0730 hours following an overnight fast. Participants were encouraged to drink at least a cup of water the night before, as well as the morning of testing to ensure adequate hydration. Hydration was verified with a urine sample that was measured for urine specific gravity (USG) with a refractometer (Reichert, Depew, NY) and testing would not begin if USG was greater than 1.025. Subjects first underwent a dual-energy x-ray absorptiometry (DEXA) (iDexa, GE Lunar, model: LU44535, Madison, WI) scan. Following the DEXA, an indwelling catheter was inserted by a trained phlebotomist into an antecubital vein which allowed for serial blood draws from the same site. 6 ml of blood was drawn into a serum vacutainer every 15 min beginning at 0800 hours and lasting until 1200 hours for a total of 17 time points. During the blood

draws, participants completed a food frequency questionnaire (FFQ) and the aging male symptom questionnaire (AMS) (Heinemann et al. 2003).

Blood biomarkers

Comparisons included testosterone (T) concentrations, as well gonadotropin concentrations [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] to determine whether the low T was of a primary or secondary nature. In a primary condition, participants would show elevated concentrations of LH and FSH, but testosterone would remain low due to a low functioning testis. In a secondary condition, gonadotropin secretion would be compromised, leading to LH and FSH concentrations being low, and thus LH fails to send an adequate signal to stimulate T secretion. If gonadotropin function is disrupted, FSH could also be compromised which could negatively impact spermatogenesis. Cortisol (C) was also measured as it has been shown to inhibit T secretion and could be another contributing factor to reduced T. LH was measured at all 17 time points, T was measured every 60 min and FSH and C were measured for a single time point at 0800 h.

Questionnaires

Comparisons were also made regarding symptoms of hypogonadism using the Aging Male Symptoms (AMS) questionnaire, which has been previously described (Heinemann et al. 2003). One small modification was made to the questionnaire, where participants were asked if the symptoms pertained to them during the past month, rather than at that specific time, so as to ensure the responses reflected more of a chronic condition, rather than any acute factors that could have impacted them within the previous 24 h. Subjects completed the AMS two times, on separate days, with an average score used for analysis. A food frequency questionnaire which was provided by and analyzed with Nutritionist Pro software (Axxya, Redmond, WA).

DEXA

Body composition and bone density were measured by dual-energy X-ray absorptiometry (DEXA). The scans included anterior–posterior spine, forearm, dual femur, and total body. All scans were performed and analyzed by the same technician using Encore v14.1.

Energy availability

Energy availability (EA) was calculated as (energy intake − energy expenditure)/fat-free mass. Energy intake was determined from the food frequency questionnaire. Energy expenditure was estimated assuming a 10:00 min/mile average pace with caloric expenditure data obtained from Ainsworth et al. (1993) for the EHMC group, and assumed as zero for the non-exercising controls. Fat-free mass values were provided by the total body DEXA scan.

Blood processing and biochemical analyses

Blood was collected in serum vacutainers, which were centrifuged at $1500\times g$ at 4 °C for 15 min. Serum was then aliquoted and stored at −80 °C until it was later analyzed. Samples were thawed once only and analyzed in duplicate. Luteinizing hormone was measured at all 17 time points. Testosterone was measured at five time points (0800, 0900, 1000, 1100, and 1200 hours). Cortisol and follicle-stimulating hormones were measured only at the 0800 hours time point. Testosterone, luteinizing hormone, cortisol and follicle-stimulating hormone were all measured using an ELISA (CALBiotech, Spring Valley, CA) with sensitivities of 0.8 nmol L^{-1}, 3.1 mIU L^{-1}, 11 nmol L^{-1}, and 5 mIU mL^{-1}, respectively. The luteinizing hormone ELISA analyses were conducted on a total of nine plates, with an inter-assay coefficient of variance (CV) of 7.7%, and intra-assay CV of 11.86 ± 2.8%. The testosterone ELISA analyses were conducted on three plates, with an inter-assay CV of 3.0% and an intra-assay CV of 9.3 ± 1.5%. Cortisol and FSH analyses were ran on single plates, with intra-assay CVs of 6.47 and 10.45%, respectively. All sample plates were measured on a Versamax tunable microplate reader (Molecular Devices, Sunnyvale, CA) at a wavelength of 450 nm.

Statistical analyses

Mean T and LH concentrations were calculated, and independent t-tests were used to compare differences between the EHMC and CONT groups. Further, a pulsatile analysis was conducted as previously described by Reame et al. (1984). In brief, a pulse was considered an increase in hormone concentration that was three times greater than the intra-assay CV calculated for the corresponding plate. The frequency of pulses, as well as the amplitude of each pulse was calculated for each subject. For pulse frequency and amplitude as well as all other comparisons, independent *t* tests were used to compare the differences between the two groups. For the comparison of AMS scores, one CONT group subject was greater than two standard deviations from the mean and was removed as an outlier and replaced with the mean. For all other analyses, independent *t* tests were used with a Bonferroni correction factor to control for alpha inflation. Statistical significance in this investigation was set at $P \leq 0.05$. To determine the magnitude of change, a Cohen's d effect size was performed. The criteria used to

interpret the magnitude of the effect size were 0.2 small, 0.5 medium, 0.8 large (Cohen 1988).

Results

Mean T concentration was significantly ($P < 0.001$, 95% CI_{diff} −10.0 to −4.1) lower in the EHMC (9.2 ± 2.3 nmol L^{-1}) group when compared with CONT (16.2 ± 3.4 nmol L^{-1}) (Fig. 1a), with eight of the nine subjects exhibiting T of below 12 nmol L^{-1}. There were no significant ($P = 0.456$, 95% CI_{diff} −165.0 to 76.4) differences between groups for C (EHMC 242.9 ± 84.5 vs. CONT 287.2 ± 144.7 nmol L^{-1}) (Fig. 1b). There were no significant ($P = 0.255$, 95% CI_{diff} −0.7 to 2.5) differences between groups for mean LH concentrations (EHMC 3.76 ± 2.1 vs. CONT 2.9 ± 0.6 mU mL^{-1}). There were no significant ($P = 0.596$, 95% CI_{diff} −1.4 to 2.3) differences between groups for FSH concentrations (EHMC 3.52 ± 2.22 vs. CONT 3.08 ± 0.99 IU L^{-1}).

The EHMC group showed significantly ($P = 0.018$, 95% CI_{diff} 1.5 to 13.1) higher AMS scores than the CONT group (EHMC 27.1 ± 7.3 vs. CONT 19.7 ± 2.5) (Fig. 2).

There were no significant ($P = 1.0$, 95% CI_{diff} −1.0 to 1.0) differences for LH pulse frequency (EHMC 2.0 ± 0.87 vs. CONT 2.0 ± 1.07 No. 4 h^{-1}). There were no significant ($P = 0.817$, 95% CI_{diff} −1.3 to 1.7) differences for LH pulse amplitude (EHMC 2.00 ± 1.07 vs. CONT 2.23 ± 0.99 U L^{-1}). No significant differences were found between groups for any bone mineral density measures (Fig. 3). Two EHMC subjects met criteria for low bone density in the lumbar spine. 1 EHMC subject met criteria for possible osteoporosis in the right femur. 1 EHMC subject met criteria for low bone density in the radius.

There were no significant ($P = 0.783$, 95% CI_{diff} −1032.3 to 792.6) differences measured in energy intake (EHMC 2623.0 ± 796.1 vs. CONT 2742.8 ± 969.0 kcal d^{-1}) (Table 1). There were significant ($P = 0.029$, 95% CI_{diff} −34.3 to −2.2) differences between groups for energy availability (EHMC 27.2 ± 12.7 vs. CONT 45.4 ± 18.2 kcal d FFM^{-1}) (Table 1).

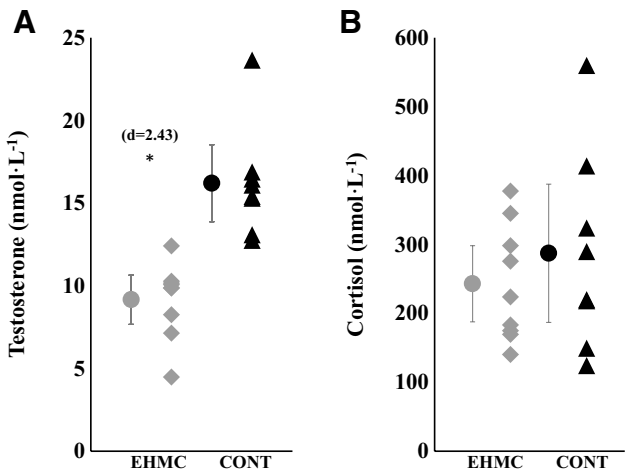

Fig. 1 Individual mean serum testosterone (**a**) and single draw cortisol (**b**) concentrations for EHMC (*gray*) and CONT (*black*) groups. Mean serum testosterone concentrations were significantly ($P \leq 0.05$) different between groups. There were no significant differences between groups for cortisol concentrations. *Circles* indicate mean, *bars* indicate 95% CI. Individual scores are denoted for EHMC with diamonds and for CONT with *triangles*. *EHMC* exercise-hypogonadal male condition, *CONT* healthy, non-running controls

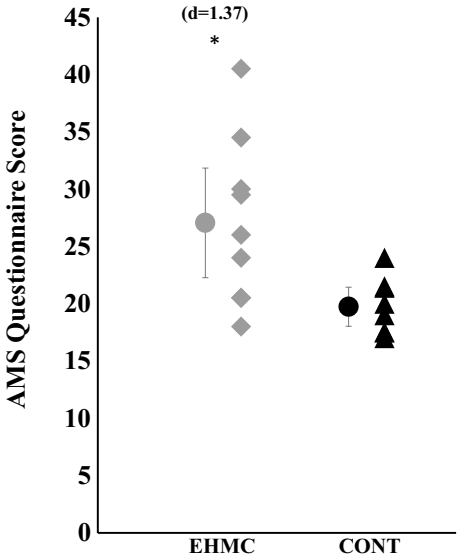

Fig. 2 Individual AMS scores for EHMC (*gray*) and CONT (*black*) groups. AMS scores were significantly different between groups. *Circles* indicate mean, *bars* indicate 95% CI. Individual scores are denoted for EHMC with *diamonds* and for CONT with *triangles*. *AMS* aging male symptom questionnaire, *EHMC* exercise-hypogonadal male condition, *CONT* healthy, non-running controls

Discussion

This study again demonstrated that high volumes of aerobic exercise appears to result in reduced T concentrations when compared to healthy, non-running controls, with a particularly large effect size ($d = 2.43$). However, unlike several prior studies that demonstrated reduced but not clinically low T concentrations (Hackney et al. 1990, 1998; McColl et al. 1989; Wheeler et al. 1984, 1991), 8 of the 9 EHMC subjects in this study demonstrated T concentrations of below 12 nmol L^{-1}, which has previously been suggested to be a threshold for normal (Arver and Lehtihet 2009) (Fig. 1). The reason for such a substantially lower T concentration may have been that the predominance of the

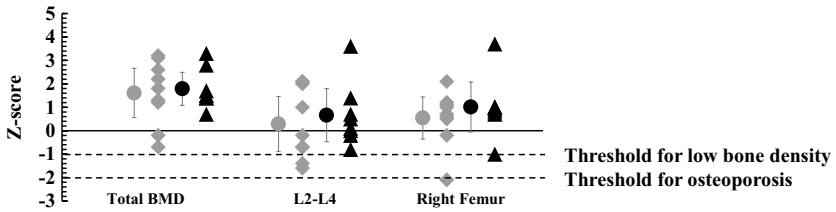

Fig. 3 Individual BMD Z-scores for EHMC (*gray*) and CONT (*black*) groups for total BMD, L2-L4, and Right Femur. There were no significant differences between groups for any variable. A *Z* score of less than −1 is indicative of low bone density. A *Z* score of less than −2 is indicative of osteoporosis if accompanied with secondary risk factors (e.g., undernutrition, prior fractures). Criteria provided by the American College of Sports Medicine for physically active premenopausal women and children (Nattiv et al. 2007). *Circles* indicate mean, *bars* indicate 95% CI. Individual scores are denoted for EHMC with *diamonds* and for CONT with *triangles*. *BMD* bone mineral density, *EHMC* exercise-hypogonadal male condition, *CONT* healthy, non-running controls

Table 1 Energy availability of individuals exhibiting the EHMC condition and healthy, non-exercising controls

Measurement	EHMC ($n = 9$) (mean ± SD)	CONT ($n = 8$) (mean ± SD)	Effect magnitude (d)
Energy expenditure from running (Kcal d^{-1})	914.1 ± 143.5	0	
Energy intake (Kcal d^{-1})	2623.0 ± 796.1	2742.8 ± 969.0	0.13
Total fat-free mass (kg)	63.8 ± 5.1	61.8 ± 8.3	0.28
Energy availability (Kcal kg FFM d^{-1})	27.2 ± 12.7*	45.4 ± 18.2	1.15

EHMC exercise-hypogonadal male condition, *CONT* control

* Significantly ($P \leq 0.05$) different between groups

subjects in this study was competitive ultramarathon runners, which are populations that have previously demonstrated T below-normal physiological range (Hooper et al. 2014; Kraemer et al. 2008; Kupchak et al. 2014), compared to many of the prior studies assessing regular marathon runners. However, although the weekly running mileage in this study (81 km per week average) is higher than some of the prior studies that did not show below-normal T (Wheeler et al. 1984, 1991) (64 km and 56 km), others were comparable or even higher (Hackney et al. 1990; McColl et al. 1989) (123 and 80 km), suggesting that running mileage alone is not enough to predict the severity of low T in these populations. It is also worth noting that even in this study which demonstrated a very high prevalence of clinically low T, that one subject remained within the normal range. This suggests that some men are more prone than others to reduced T in association with high volumes of aerobic exercise and that therefore there could be a genetic component that dictates an individual's susceptibility to the condition.

It is well established that T concentration alone cannot determine whether an individual is hypogonadal, but that the low T must be accompanied by a presence of symptoms for an individual to be a candidate for androgen therapy (Arver and Lehtihet 2009). In this study, men exhibiting EHMC demonstrated significantly higher AMS scores than healthy controls (Fig. 2), with a large effect size ($d = 1.37$). In addition to the use of the AMS, this study also assessed bone mineral density of multiple sites as deficiencies in this area have been associated with androgen deficiency (Bhasin et al. 2006). While no significant between-group differences in bone density were observed at any of the sites, there does appear to be individuals demonstrating low bone density (Fig. 3). Two EHMC subjects showed signs of low bone density in the lumbar spine, with 1 of which also meeting criteria for osteoporosis in the right femur. The presence of changes in bone mineral density associated with low T has been disputed in prior literature. For example, Bennell et al. suggested that bone density and testosterone concentrations in the normal range are not closely related (Bennell et al. 1996). Further, MacDougall et al. (1992) reported no association between running mileage and bone density, but these authors too did not demonstrate any changes in T concentrations, possibly due to the runners only being required to have been at their respective mileage for 3 months. The current study to our knowledge appears to be one of the first to assess athletes with below-normal T concentrations, which could have contributed to this finding. Again, the majority of EHMC subjects had no issues with regards to bone density, but there does appear to be some individuals that are more prone to demonstrate this additional symptom of hypogonadism.

Despite differences in T, there were no between-group differences in C (Fig. 1), LH concentration, or pulse characteristics (see text). Although prior research has hypothesized that high concentrations of cortisol could be playing

a role (Hackney et al. 1988) due to the fact that hydrocortisone injections can inhibit testosterone secretion without changes in luteinizing hormone (Cumming et al. 1983), this study demonstrated differences in T without differences in C. With regards to gonadotropins, although studies have occasionally shown dysfunction at rest (MacConnie et al. 1986), the lack of an increase in LH in response to low T demonstrated in this study are in accordance with what is typically seen in the EHMC literature (Hackney et al. 1988, 1997; McColl et al. 1989). However, when observing each subject individually, again there are cases that do not follow the majority of the group. In this study, there are two subjects that are potentially suffering from a hypogonadotropic hypogonadism, with LH concentrations substantially lower than the means for both the EHMC and CONT groups, and also below-normal physiological range. Interestingly, the two lowest LH concentrations are also the two subjects with the highest AMS scores. Further, while one of these subjects showed normal bone density, the other demonstrated low bone density in the lumbar spine, and potential osteoporosis in the right femur. These findings are very similar to those reported in a case study by Burge et al. (1997), where a hypogonadotropic hypogonadism was associated with markedly decreased bone mineral density. On the other hand, one subject appears to be demonstrating a substantial elevation in LH, indicative of a primary hypogonadism. These results together suggest that while the majority of subjects show normal gonadotropin function, it is essential to carefully consider each case as there remains the possibility for both increases and decreases in LH in the EHMC, which could certainly impact potential treatment strategies.

Findings for follicle-stimulating hormone (FSH) were much the same as LH. Although there were no between-group differences, an observation of individual scores show at least two subjects demonstrating below-normal FSH concentrations. One of these two subjects demonstrated the lowest T concentration, a high AMS score, the lowest LH concentration as well as low density in the lumbar spine and possible osteoporosis in the femur. Thus, this particular case appears to be the most significant demonstration of hypogonadal symptoms in this study. The other subject demonstrating low FSH was also indicative of low bone density in the lumbar spine. In addition to the symptoms documented here, a low FSH concentration for these two individuals could also be indicative of reduced spermatogenesis, although that was not measured in this study.

While pituitary function in this particular study was assessed with the use of concentrations of LH and FSH, prior research has also demonstrated changes in another pituitary hormone, prolactin. The study of prolactin in association with exercise-induced changes in gonadal function dates back to some of the earliest female athlete triad research (Warren 1980), and has also previously been assessed in men with contradictory findings. For example, following an acute intensive aerobic exercise program, after 4 weeks basal T was reduced while prolactin increased (Hackney et al. 1989). However, following chronic endurance exercise, prolactin has also been shown to be reduced along with T when compared to sedentary controls (Wheeler et al. 1984). As this study failed to demonstrate changes in pituitary function with the use of measures of LH and FSH, prolactin perhaps would have been a valuable addition to this study, and warrants further study in future.

It is also worth noting that changes in the concentrations and pulse characteristics of LH and FSH, as well cortisol, could have been masked by our low sample size. Men who perform this volume of exercise are not particularly common and therefore conducting these studies with large samples are inherently challenging. Thus, these lack of differences may not be a product of these outcome measures not changing with the EHMC, but a rather a consequence of inadequate statistical power.

While much of the literature in this area has focused on energy expenditure (i.e., high volumes of aerobic exercise), another potential contributing factor could be a reduced energy intake contributing to low energy availability, much as is the case in the female athlete triad (Nattiv et al. 2007). Surprisingly, despite a substantially higher caloric expenditure in the EHMC group due to the high volumes of aerobic exercise, the two groups demonstrated no differences in energy intake, and thus significant differences were noted with regards to energy availability (Table 1), with a large effect size ($d = 1.15$). This suggests that the EHMC group has significantly less energy available that can contribute to metabolic processes, which could be one potential reason why T, an anabolic hormone synthesized from cholesterol, itself an energetically expensive molecule to produce, could be in reduced concentrations in the blood. It has also been suggested in the Endocrine Society Clinical Practice Guideline that an evaluation for eating disorders and excessive exercise should be made during the diagnosis of suspected androgen deficiency (Bhasin et al. 2006), which this finding offers further support for.

In conclusion, these data suggest that in the majority of cases, a reduced T concentration associated with high volumes of aerobic exercise, even when in the below-normal physiological range, do not demonstrate symptoms typical of androgen deficiency. There are occasional cases, however, where symptoms do appear to be quite pronounced, demonstrated by either elevated AMS questionnaire scores, or clinically low bone density. The pathogenesis of low T in EHMC also appears to be varied between individuals, with some having low gonadotropins, some normal, and some high. Although severe cases may seek treatment in the form of pharmacological intervention, any athlete

obliged to conform to drug testing governed by WADA will not be permitted to do so, and are currently ineligible for therapeutic use exemptions. Furthermore, without properly diagnosed hypogonadal function, use of pharmacological treatment may impact structure and function of the hypopituitary gonadal axis. These athletes may want to consider whether nutritional interventions are more appropriate, as it appears individuals demonstrating EHMC may have inadequate energy intake, which could be contributing to the condition.

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Compliance with ethical standards

Conflict of interest The authors have nothing disclose.

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