Androgens and athletic performance of elite female athletes

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Purpose of review
During the last decades androgens have been used illicitly by athletes of both genders. Because of some obvious ethical limitations, mechanisms underlying the performance-enhancing effects of these hormone or drugs, as well as the magnitude of their effects, have been poorly addressed. This review aims to combine findings from field and from the laboratory to provide new insights into the ergogenic properties of endogenous or exogenous androgens on female athletes.

Recent findings
Results obtained from recent neuropsychological studies indicated that testosterone, and not the sex chromosomes, is responsible for the sexual differentiation of visuospatial neural activation. These findings could explain how males and hyperandrogenic females benefit from androgens performance-enhancing effects in sports where visuospatial abilities are closely linked to better performance. Another study conducted on elite female athletes showed that, in some athletic events, where muscle power is of critical importance, individuals with the highest free testosterone concentration significantly outperformed competitors with the lowest free testosterone concentration.

Summary
In some sport events, female athletes with high or very high androgen levels (whether it is from endogenous or exogenous origin) have an estimated competitive benefit of 2–5% over those with androgen levels within the normal female range. These findings are to be taken into account in the actual controversy about eligibility of females with hyperandrogenism to compete in women's sports.

Keywords
androgens, disorders of sex development, doping, female, sports

INTRODUCTION

The effects of androgens on the main female, organs, tissues, and physiological functions as well as their theoretical side effects have been extensively described [1]. However, due to obvious ethical and methodological limitations, the performance-enhancing effects of androgens on women during reproductive years have been much less studied than postmenopausal and male counterparts. This article selects new scientific evidence both from the field and the laboratory in order to better describe the relationship between androgens and athletic performance and its roles in doping and fairness in female sports.

Androgens abuse in females athletes

The production of endogenous testosterone (T) is 20–30 times lower in females than males, which results in females having around a 10- fold lower blood T concentration. Hence, it could be suggested that in terms of gains in muscle mass and strength, females have the capacity to gain a greater relative increase from androgens than males. This could explain why T in particular and androgens in general have been widely abused by doped elite female athletes since the 1950s and the first synthesis of nandrolone (19-nortestosterone) by AJ Birch [2]. Indeed, every year the World Anti-Doping Agency (WADA) publishes a list of prohibited substances and prohibited methods. Among these numerous substances, androgens are banned at all times (in and out of competition) because they are known to augment physical performance and facilitate response to training. They are classified under the

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KEY POINTS

- Androgens are still widely abused by female athletes.
- In females, androgens increase lean body mass, oxygen-carrying capacity, visuospatial abilities, and aggressivity, which are decisive factors of sport performance.
- Female athletes with high androgen levels benefit from a 2–5% competitive advantage over other female competitors with normal androgen levels.

class S1 that includes endogenous and exogenous androgens, depending on whether these substances are ordinarily produced by the body naturally or not.

Androgens are synthetic derivatives of the hormone T, which is also included in this category and is the most prevalent androgen. Other commonly used androgens include nandrolone decanoate, methandienone, stanozolol, androsterone, and androstane [3]. Androgens have both anabolic properties, promoting increase in muscle mass and aiding recovery, as well as androgenic properties, promoting masculinization, which has particular health implications when taken by females, because of their virilizing effects.

Androgens are still the most widely used substances by athletes choosing to dope. In its 2015 antidoping testing figures, WADA reported that androgens represented 1728 (50.3%) out of the 3432 adverse analytical findings reported in all sports [4]. Although the use of androgens for nontherapeutic purposes arose in the mid-twentieth century and was primarily restricted to a cadre of adult male, elite athletes, later epidemiological studies and reports from the field showed that these limitations no longer apply, with elite and recreational female athletes becoming regular or occasional users [2]. As far as Athletics is concerned, among the 296 athletes currently (December 19, 2016) serving a period of ineligibility as a result of an International Association of Athletics Federations (IAAF) antidoping rule violation, 116 are females [5]. Sixty-four (55.2%) of these elite female athletes cheated by using androgens. These findings confirm that androgens are the leading substances used by cheating female athletes, in spite of permanently improving analytical techniques and strategies of detection [6].

Do androgens increase sports performance in female athletes?

Because the possible deleterious effects of androgens use at supra-physiological or high doses limit the capacity to conduct controlled trials in healthy women and the illicit use of these drugs limits the quantity of data collated, much of the information that has been gleaned with respect to the effects of androgens on the determinants of athletic performance has come from studies in men [7,8] or animal models. There is however some available data attesting to performance-enhancing effects of androgens in female athletes. An historical source of documentation that clearly illustrates the effect of exogenous androgens on physical performance in female athletes is the documentation (now partially disclosed) from experiments performed by sports scientists in the former German Democratic Republic [1,9]. These scientists concluded after the 1972 Olympic Games in Munich that '*the effects of the treatment with androgenic hormones were so spectacular, particularly in female athletes taking part in strength-dependent events, that few competitors not using the drugs had a chance of winning*.' Later, Cardinale and Stone [10] showed a positive correlation in young female athletes between resting serum T level and explosive strength measured by the countermovement jump performance. These authors speculated that, regardless of the known-effect of T on muscle mass and composition, androgens, through high levels of aggressiveness, could facilitate the neural input during maximal explosive effort. Very recently, Eklund *et al*. [11], studying 106 Swedish female Olympic athletes and 117 age- and body mass index-matched sedentary controls, showed that athletes demonstrated significantly higher levels of DHEA, 5-androstene-3β, 17β-diol (5-DIOL), etiocholanolone glucuronide (Etio-G) ($P < 0.05$), bone mineral density ($P < 0.001$) and more lean mass ($P < 0.001$), and lower levels of estrone ($P < 0.05$), when compared to the sedentary group. Serum levels of DHEA, 5-DIOL, and Etio-G correlated positively to total lean mass in the athletes. Moreover, DHEA concentration and lean mass from the legs explained 66% of the variance in squat jump performance. Very recently, our group has compiled the performance and hormonal data obtained from 1332 females and 795 males taking part to the 2011 and 2013 IAAF World Championships [12▪]. This unique population also included hypoandrogenic males, hyperandrogenic females and doped athletes from both genders. For instance, among female athletes, 44 individuals showed a free T (fT) concentration above 29.4 pmol/L, whereas, 101 males athletes showed a fT value below 0.23 nmol/L. In order to test the influence of serum androgen levels and athletic performance, in each athletic event, athletes were classified in tertiles according to their free T concentration with athletic performances of the highest and lowest fT tertiles being compared.

When compared to the lowest fT tertile, females from the highest fT tertile showed significantly better performance in 400 m, 400 m hurdles, 800 m, hammer throw and pole vault with calculated mean differences of 2.7%, 2.8%, 1.8%, 4.5%, and 2.9%, respectively. In male elite athletes, no significant difference in performance was noted when comparing the lowest and the highest fT tertiles. These results obtained from a large sample of elite athletes confirm that some female athletes with an increased T concentration could derive a significant competitive advantage over their competitors; a phenomenon that is not observed in their male counterparts. Several T supplementation studies conducted on young and old men [7,8,13–15] showed a clear dose–response relationship between T level and change in fat free mass, fat mass, leg press strength, thigh muscle volume, and quadriceps muscle volume. These studies showed that the muscle mass and strength effects of exogenous T are largely unchanged by age. Recently, Huang *et al.* [16] reported that a 24-week T administration in hysterectomized women (mean age 53 years) both with and without oophorectomy was also associated with dose and concentration-dependent gains in lean body mass, chest-press power and loaded stair-climb power. Considering on one hand these experimental results, and on the other the absence of reported difference between male and female muscle cells in their testosterone dose-response curves, it is likely that young women, like young men, show a dose–response relationship between androgen level and functional capacities as initially reported in the GDR state doping program [9,17].

How do androgens improve sports performance?

Muscle. Since the discovery of T and the synthesis of the first androgen, the effects of androgens on body composition and lean body mass have been extensively studied and described [1]. Very briefly, the T-induced increase in skeletal muscle mass is associated with hypertrophy of both type I and type II fibers as well as an increase in the number of myonuclei and satellite cells. T promotes the differentiation of mesenchymal multipotent cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage. T reduces fat mass by inhibiting preadipocyte differentiation into adipocytes. This hormone also increases muscle protein synthesis and improves the reutilization of amino acids by the muscle.

T alters neurotransmission at the neuromuscular junction through a modulation of the choline acetyltransferase [18], and also influences the number of acetylcholine receptors at the neuromuscular junction [19].

Erythropoiesis. When addressing the issue of the ergogenic effects of androgens, the erythropoietic effects of these hormones or drugs are often neglected. One should, however, remember that androgens were largely used in patient with chronic renal failure or bone marrow failure, before the availability of synthetic erythropoietin (EPO). Moreover, increased oxygen-carrying capacity is associated with greater success rate in sports where the performance significantly relies on oxidative metabolisms. Although not fully understood, it is likely that the erythropoietic effect of androgens relies on several explanations; stimulation of the renal secretion of EPO through unknown mechanisms, suppression of hepcidin levels, increase in iron utilization for erythropoiesis, and induction of a rightward shift in the EPO–hemoglobins relationship curve. This last point is of particular importance when the sex-related difference in hemoglobins is considered. Indeed, men and women have similar EPO reference ranges, but different hemoglobins concentrations. Hence, an increased T concentration (endogenous or exogenous) in some female athletes could set a new equilibrium point on the EPO-hemoglobins curve, attesting to an increased EPO sensitivity [20]. In both genders, androgens increase 2,3-diphosphoglycerate in erythrocytes which decreases the hemoglobins-oxygen affinity, thereby facilitating of oxygen release and delivery to the tissues [21]. Recently, Karunasena *et al.* [22▪] demonstrated that androgen levels in women with congenital adrenal hyperplasia are positively associated with hemoglobins and hematocrit levels. According to their calculated linear regressions, increasing circulating T level from 1.5 to 15 nmol/L, by manipulating the glucocorticosteroid treatment, would result in an 11 g/L increase in hemoglobins concentration. A hemoglobins increase of a similar magnitude, associated with a 3% improvement in 10 km running performance, has been reported 4 weeks after administration of 50 IU/kg body mass of recombinant EPO [23].

Central Nervous System. Last but not least, androgens also exert their performance-enhancing effects through the central nervous system. At the spinal cord level, there is growing evidence, mostly from animal studies, that T, like IGF-1, influences the form and function of the motoric system in humans [24]. These reported increased cell excitability, attenuated atrophic changes, and improved regenerative capacity of motor neurons, which could also account for the observed improvement in muscle growth and strength following androgens administration. At the brain level, sex differences have been observed

regarding cognitive abilities, regional brain structures, and functions. There are also sex differences in spatial abilities as measured with the mental rotation task (MRT), where males have an advantage over females. This difference, which is found across the entire life span, is of critical importance since the performance at the MRT is associated with the type of sports practiced and the level of expertise. In a recent study, including nonathletes, orienteers, gymnasts, and endurance runners, Schmidt *et al.* [25], while confirming the known gender difference [26], showed that athletes outperformed nonathletes at the MRT. Interestingly, athletes with high mental rotation demand like gymnasts (egocentric transformation) and orienteers (allocentric transformation) showed the best results at the MRT. Recently, a step has been taken in understanding the sexual differentiation of visuospatial neural activation. By using functional MRI assessment, two research groups [27▪,28] showed a female-like activation pattern in mental rotation-related brain areas in individuals with complete androgen insensitivity syndrome, indicating that the sexual differentiation of visuospatial neural activation is not directly influenced by sex chromosomal composition, but is determined by androgens rather than estrogens exposure. Whilst it appears that long lasting androgens exposure during childhood or adulthood improves spatial abilities, as seen for instance in congenital adrenal hyperplasia female patients [29], the possible facilitating effect of shorter exposure to androgens is still investigated in females [30].

Aggressive behavior and risk taking, which are important determinants of sports performance, are more frequent in individuals exposed to androgens. A recent study [31▪] investigated the structural covariance, that is, the examination of anatomic correlations between the amygdala (a brain area related to augmented aggressive behavior when stimulated) and the prefrontal cortex (a regulating area); two brain areas with the highest density in androgen receptors. Experiments showed that lower T levels were associated with a positive covariance between the amygdala and cortical thickness of this prefrontal region, whereas higher T levels were associated with a negative correlation between these two regions resulting in more aggressive behavior. This work shows how T targets the neural circuits regulating affects and impulses independent from sex, age, estradiol, and pubertal stage, from childhood to adulthood.

The controversy around hyperandrogenic female athletes

The implementation by some major sports-governing bodies of policies governing eligibility of females with hyperandrogenism to compete in women's sports has raised a lot of attention and is still a controversial issue [32–38]. Indeed, regulating women with clinical and biological hyperandrogenism is an invitation to criticism because biological parameters of sex are not neatly divided into two sole categories in the real world. It is, however, the responsibility of the sports-governing bodies to do their best to guarantee a level playing field to all athletes. An Indian athlete, Dutee Chand, challenged the IAAF Regulations governing eligibility of females with hyperandrogenism to compete in women's competition in front of the Court of Arbitration for Sports [39]. The Court of Arbitration for Sports Panel concluded that these IAAF Regulations are discriminatory and that the *'IAAF has not discharged its onus of establishing that the Hyperandrogenism Regulations are necessary and proportionate to pursue the legitimate objective of organizing competitive female athletics to ensure fairness in athletic competition. Specifically, the IAAF has not provided sufficient scientific evidence about the quantitative relationship between enhanced testosterone levels and improved athletic performance in hyperandrogenic athletes.'* Although this point has been discussed in the previous section, some studies on hyperandrogenic females offer the beginning of an answer. Rickenlund *et al.* [40] studying athletes active in endurance sports reported that the hyperandrogenic subgroup (T concentration 1.9 ± 0.2 nmol/L) showed a more anabolic body composition, a higher total bone mineral density, and upper to lower fat mass ratio as well as the highest maximal oxygen uptake and performance values in general than did oligomenorrheic or amenorrheic athletes with normal androgen levels ($1.1–1.2 \pm 0.4$ nmol/L). Hagmar *et al.* [41] reported an overrepresentation of polycystic ovaries in female Olympic athletes (37% vs. 20% in the general population). This polycystic ovary syndrome subgroup showed a higher T concentration and free androgen index than those observed for regularly menstruating or non- polycystic ovary syndrome Olympian athletes. Our group [42] reported, among an elite female athlete population, a prevalence of hyperandrogenic 46 XY DSD individuals, which is approximately 140 times higher than expected in the general population. Lastly, monitoring performances obtained from hyperandrogenic DSD female athletes before and after they had their T levels lowered within the normal female range is a valuable and unique source of information to study the effects of androgens on female athletic performance (Fig. 1). In these individuals, reducing T level from the normal male range to the normal female range led to an average decrease of their best chronometric performance of 5.7% over a 2-year period.

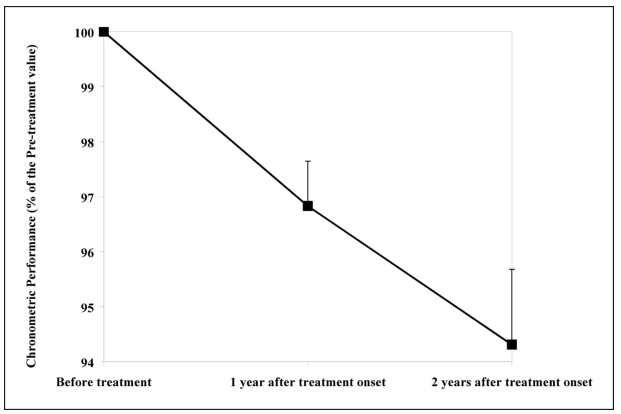

FIGURE 1. Evolution of seasonal best performances in three female distance runners, with a hyperandrogenic disorder of sex developement condition, before and after reducing their serum testosterone level to the normal female range. Results are given as mean and standard error of the mean.

CONCLUSION

Because of their performance-enhancing effects, androgens are still widely used by some female competitors. In addition to their anabolic consequences on lean body mass, androgens also stimulate erythropoiesis and increase physical performance in aerobic sports. When comparing female athletes with high and low T levels, differences in athletic performance from 2% to 5% are observed. Recent findings confirmed that visuospatial abilities are independent from chromosomal sex, but are positively influenced by exposure to androgens, which could also explain a part of the performance enhancing effects of androgens on women.

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Conflicts of interest

Dr S. Bermon has been a member of the IAAF and IOC working groups on hyperandrogenic female athletes and transgender athletes

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