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Large divergence in testosterone concentrations between men and women: Frame of reference for elite athletes in sex-specific competition in sports, a narrative review

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Summary

Objective: The purpose of this narrative review was to summarize available data on testosterone levels in normal, healthy adult males and females, to provide a physiologic reference framework to evaluate testosterone levels reported in males and females with conditions that elevate androgens, such as disorders of sex development (DSD), and to determine the separation or overlap of testosterone levels between normal and affected males and females.

Methods: A literature review was conducted for published papers, from peer reviewed journals, reporting testosterone levels in healthy males and females, males with 46XY DSD, and females with hyperandrogenism due to polycystic ovary syndrome (PCOS). Papers were selected that had adequate characterization of participants, and description of the methodology for measurement of serum testosterone and reporting of results.

Results: In the healthy, normal males and females, there was a clear bimodal distribution of testosterone levels, with the lower end of the male range being four- to five-fold higher than the upper end of the female range (males 8.8–30.9 nmol/L, females 0.4–2.0 nmol/L). Individuals with 46XY DSD, specifically those with 5-alpha reductase deficiency, type 2 and androgen insensitivity syndrome testosterone levels that were within normal male range. Females with PCOS or congenital adrenal hyperplasia were above the normal female range but still below the normal male range.

Conclusions: Existing studies strongly support a bimodal distribution of serum testosterone levels in females compared to males. These data should be considered in the discussion of female competition eligibility in individuals with possible DSD or hyperandrogenism.

KEYWORDS

ambiguous genitalia, androgen insensitivity, disorders of sexual development, hyperandrogenism, polycystic ovary syndrome, testosterone

1 | INTRODUCTION

Anabolic steroids, especially testosterone, have a long history of abuse in sports for performance enhancement and competitive advantage in both male and female athletes.¹⁻⁴ Because of the known anabolic effect of hormones on muscle, the use of anabolic agents such as testosterone, other androgenic steroids, and growth hormone that might enhance athletic performance have been prohibited by the World Anti-Doping Agency and other sports organizations. In addition to these exogenous sources of anabolic agents, there is recognition that endogenous androgenic steroids may also be elevated in certain clinical conditions. This review aims to compare the testosterone levels associated with such conditions with reference to the normal testosterone levels in healthy men and women. As this review is solely concerned with biologic characteristics, especially testosterone levels, we have used the terms "male" and "female" in their biologic sense. Individuals' legal or gender identity may not conform to that biology. We have used the term "normal" in its scientific or statistical sense.

Recently, a few athletes competing in events classified for women have been found to have a male genotype with variable degrees of androgenization, that can vary from a nearly normal female to male phenotype, with testosterone levels in the adult male range. This can occur in genetic males with a disorder of sex development (46XY DSD). These are rare conditions in which a genetic mutation affects cellular enzymes involved in the production of testosterone and the more potent androgen, dihydrotestosterone (DHT) or impairs androgen receptors that control cellular and tissue responses to androgens. There are two notable conditions: 5-alpha reductase deficiency, type 2 (5ARD2) which impairs the conversion of DHT from testosterone^{5,6} and androgen insensitivity syndrome (AIS) caused by mutations of the androgen receptors for testosterone and DHT in tissues.⁷ Because genetic males with DSD may show female phenotypic features, especially in the case of AIS, the question has been raised as to whether male athletes who have a 46XY DSD should compete in sports as men or women.

Polycystic ovary syndrome (PCOS) is another notable condition in genetic (XX) females, which is characterized by excessive ovarian production of androgens.^{8,9} This condition is included for comparison with DSD, as the affected females with PCOS are genetic and phenotypic females. The elevated levels of testosterone in these females can lead to hyperandrogenism, a clinical disorder characterized variably by hirsutism, acne, male-pattern balding, metabolic disturbances, impaired ovulation and infertility. PCOS is a common condition, affecting 7%-10% of premenopausal women.⁹ Females with PCOS demonstrate a range of clinical presentation from mild hyperandrogenism and irregular menses to severe hirsutism and acne with marked oligomenorrhea and failure to ovulate, but seldom exhibit full virilization (eg, clitoromegaly).

Another form of DSD in genetic females (46XX DSD) is 21-hydroxylase deficiency (21OHD), the most common form of congenital adrenal hyperplasia (CAH).^{10,11} Males and females with 21OHD have enzymatic defects in cortisol production by

the adrenal gland, which can lead to deficiencies of cortisol and aldosterone, resulting in increased adrenocorticotrophic hormone (ACTH) stimulation of the adrenal gland, adrenal hyperplasia and excessive secretion of precursor steroids, in particular, adrenal androgens. Individuals with 21OHD may have a severe, life-threatening, salt-wasting, classic form, or a milder nonclassic form in which some cortisol is produced. Excess adrenal androgens can cause short stature due to accelerated long bone growth but early maturation and closure of epiphyseal growth plate. Females with classic 21OHD may be born with varying degrees of virilization and ambiguous genitalia, while those with nonclassic forms may present as female adults with hyperandrogenism, similar phenotypically to PCOS.

The purpose of this commentary was to summarize the well-established reference range of serum testosterone levels in normal, healthy adult males and females, to provide a physiological reference framework against which testosterone levels reported in males with 46 XY DSD (5ARD2 and AIS), females with 46 XX DSD (21OHD), and females with hyperandrogenism due to PCOS or non-classical CAH can be compared. This information provides important context and can inform the discussion of possible benefits on athletic performance that elevated endogenous testosterone levels might have. Furthermore, this summary provides useful background reference values that are based on peer reviewed, published ranges for serum testosterone levels in males and females. Together with the phenotype of these conditions, this information can provide the scientific rationale for developing evidence-based guidelines for adjudicating whether athletes with the above conditions should appropriately compete in contests classified as men's or women's events.

2 | METHODS AND RESULTS

A literature review was conducted for published papers, from peer reviewed journals, reporting testosterone levels in healthy males and females, males with DSD, 5ARD2 and AIS, and females with PCOS or CAH (Data S1). Papers were selected that had adequate characterization of participants, description of the methodology for measurement of serum testosterone, and reporting of results. Papers not included did not provide subject numbers for specific subgroups,¹² used a broad population sample which included unhealthy participants,¹³ or did not provide a full normal range with values for 2.5th to 97.5th percentiles.^{14,15} Studies using liquid chromatography tandem mass spectrometry (LC-MS/MS)-based testosterone assays that are more sensitive, specific and accurate than immunoassays for testosterone were selected and used exclusively for the reference ranges in normal males and females, and for females with PCOS or CAH. The studies reporting testosterone levels in genetic males with 5ARD2 and AIS only reported values obtained by use of immunoassays.

The testosterone levels in normal, healthy males and females as reported are shown in Table 1.¹⁶⁻²³ The weighted average values

TABLE 1 Testosterone levels—Normal, healthy males and females^a. (95% confidence intervals and weighted average values)

Source	Age range (years)	Number of subjects	Testosterone ^a median*/mean [^] (nmol/L)	Lower 2.5th %ile (nmol/L)	Upper 97.5th %ile (nmol/L)
Normal males					
Travison (2017) ²³	19-39	1185	18.4*/19.1 [^]	9.2	31.8
Hart (2015) ¹⁹	19-22	382	16.3*/16.6 [^]	7.4	28.0
Neale (2013) ²¹	20-40	67	NA ^d	10.6	31.9
Kushnir (2010) ²⁰	18-40	70	NA ^d	7.2	24.2
Sikaris (2005) ²²	21-35	124	18.2 ± 4.9 [^]	9.7	34.3
			Weighted average	8.8	30.9
Normal females ^e					
Bui (2013) ^{16,c}	19-39	25	NA ^d	0.3	1.7
Fanelli (2013) ^{17,b}	16-19	159	NA ^d	0.5	1.8
Haring (2012) ¹⁸	20-29	86	NA ^d	0.4	2.1
	30-39	177	NA ^d	0.4	2.1
Kushnir (2010) ²⁰	15-18	323	0.9*	0.4	2.2
	>18	104	0.9*	0.3	1.9
			Weighted average	0.4	2.0

^aAll testosterone measurements by LC-MS/MS; ^bNot on oral contraceptives; ^cTaking oral contraceptives; ^dNA—Not available, ^eAll premenopausal. “*” signifies median and “^” signifies mean values

TABLE 2 Testosterone levels—46 XY individuals with 5ARD2 (absolute ranges)

Source	Age range (years)	Number of subjects	Testosterone ^a median*/mean [^] (nmol/L)	Range ^b (nmol/L)
46 XY individuals with 5ARD2 ^a				
Shabir (2015) ²⁷	12-20	12	10.6 ± 5.2*	3.6-18.4
	>20	4	12.5 ± 3.1	7.6-14.7
Zhu (2014) ²⁹	12-23	8	24.4*	17.2-36.4
Fenichel (2013) ²⁴	18-21	4	20.9 [^]	18.0-22.2
Veiga-Junior (2012) ²⁸	14-18	4	13.4*	9.7-47.2
Maimoun (2011) ²⁶	14-23	17	17.5 [^]	NA
Imperato-McGinley (1979) ²⁵	19-40	12	31.2 ± 7.3 [^]	18.2-38.8

^aAll testosterone measurements by immunoassay; ^bAbsolute ranges. “*” signifies median and “^” signifies mean values

for range (2.5%-97.5%) are: males 8.8-30.9 nmol/L (254-890 ng/dL; ng/dL = nmol/L multiplied by 28.82), and females, 0.4-2.0 nmol/L (12-58 ng/dL). The low value for testosterone in males was four- to fivefold greater than the high value in females based on a normal range of 2.5%-97.5%. The age range varied among the studies, and the overall range for males was 18-40 years, and for females, 15-40 years. All females were postpubertal and premenopausal.

The testosterone levels in the genetic males with 5ARD2 and AIS are shown in Table 2.^{7,24-34} These values are from individuals with a range of phenotypes and varying degrees of virilization. Most of these males showed virilization with apparent male external genitalia. However, some do show a more female phenotype, with testosterone in the normal male range.²⁶ The mean/medians for males with 5ARD2 ranged from 13.4 to 31.2 nmol/L

(386-899 ng/dL), and the absolute range of individual values was 3.6-47.2 nmol/L (104-1360 ng/dL). Males with AIS had mean/medians ranging from 11.9 to 55.7 nmol/L (343-1605 ng/dL), and the overall absolute range was 4.8-68.3 nmol/L (138-1968 ng/dL) (Table 3).^{7,28,30-34} Testosterone levels were similar in males with partial AIS (PAIS) and complete AIS (CAIS). Some of the reports included pubertal males for both 5ARD2 and AIS, and their ranges overlapped with the postpubertal males.

Testosterone levels in women with PCOS (Table 4) were higher than those in normal women.³⁵⁻³⁸ The mean/median range was 1.22-1.71 nmol/L (35-49 ng/dL), and the absolute range was 0.34-5.5 nmol/L (10-159 ng/dL) (Table 4). Some females with marked PCOS can have testosterone levels approaching the low end of male values.³⁶ All studies included control values from normal females,

TABLE 3 Testosterone levels—46XY individuals with PAIS/CAIS (absolute ranges)

Source	Age range (years)	Number of subjects	Testosterone ^a median*/mean [^] (nmol/L)	Range ^b (nmol/L)
46XY individuals with PAIS ^a				
Lucas-Herald (2016) ³³	16-52	23	18.7*	4.8-68.3
Veiga-Junior (2012) ²⁸	18-29	3	40.0*	33.3-52.0
Hellmann (2012) ³²	19-20	4	55.7*	46.0-67.8
Bouvattier (2006) ³⁰	16-43	15	27.4 ± 3.4 [^]	21.5-37.8
Melo (2003) ³⁴	14-30	8	11.9*	6.4-35.8
46XY individuals with CAIS ^a				
Doehnert (2015) ³¹	14-50	42	20*	6.2-52.1
Melo (2003) ³⁴	14-30	9	35.8*	5.4-55.2
Imperato-McGinley (1993) ⁷	15-78	6	31.3 ± 15.2 [^]	16.9-60.5

^aAll testosterone measurements by immunoassay, ^bAbsolute ranges.

“*” signifies median and “[^]” signifies mean values

TABLE 4 Testosterone levels—Females with PCOS(absolute, or percentile groups)

Source	Age range (years)	Number of subjects	Testosterone ^a median*/mean [^] (nmol/L)	Range (nmol/L) ^b
Females with PCOS ^a				
Tosi (2016) ³⁸ PCOS	20-27	204	1.22*	0.90-1.6 ^c
Control				<1.4
Bui (2015) ³⁵ PCOS	18-35	44	1.5*	0.6-3.2
Control	18-39	25	—	0.3-1.6
Keefe (2014) ³⁷ PCOS	18-30	52	1.71 [^]	0.56-4.4 ^d
Control	19-40	42	0.84 [^]	0.35-2.0
Janse (2011) ³⁶ PCOS	18-41	200	1.55*	0.34-5.5
Control	20-38	45	0.87*	0.31-2.8

^aAll testosterone measurements by LC-MS/MS, ^bAbsolute range, ^c25th to 75th percentile, ^d2.5th to 97.5th percentile.

“*” signifies median and “[^]” signifies mean values

for which the upper end of the female range was 1.6-2.8 nmol/L (46-81 ng/dL).³⁵⁻³⁸

Testosterone levels are not shown for females with 21OHD, as adrenal androgens, such as dehydroepiandrosterone (DHEA) and its sulphate form (DHEAS), are the more abundant androgens in these females and comparison of testosterone levels with other conditions is difficult. Data from a mixed population of subjects with classic 21OHD showed a median serum testosterone of 2.78 nmol/L (80 ng/dL) and interquartile range of 1.32-5.62 nmol/L (39-162 ng/dL) which overlap with the testosterone levels in females with PCOS. Testosterone levels in affected females were 3.5-fold higher than controls.³⁹

These results are shown in a forest plot, Figure 1. The ranges of testosterone levels in genetic males with 5ARD2 and PAIS and CAIS are mostly within the normal male range, and well beyond the range for normal females. The range of testosterone levels in females with PCOS extends beyond that of the normal female range, but not into the normal male range, the lower limit of which averaged 8.8 nmol/L

(254 ng/dL), about twofold higher than that of the upper end of the range for PCOS (5.5 nmol/L (159 ng/dL).

3 | DISCUSSION

The results from published studies reviewed show clearly that the range for testosterone levels in healthy males is distinct from that for healthy females. This is highlighted in the forest plot (Figure 1), which shows a marked, bimodal distribution of testosterone levels between males and females without any overlap. The weighted average lower limit of testosterone level in healthy males is 8.8 nmol/L (254 ng/dL), roughly four- to fivefold higher than the average upper limit of the testosterone level in healthy females, 2.0 nmol/L (58 ng/dL). There is no continuum of testosterone levels from normal females to normal males.

Individuals with 46XY DSD due to 5ARD2 are genetic males who as adults typically have serum testosterone levels within the normal

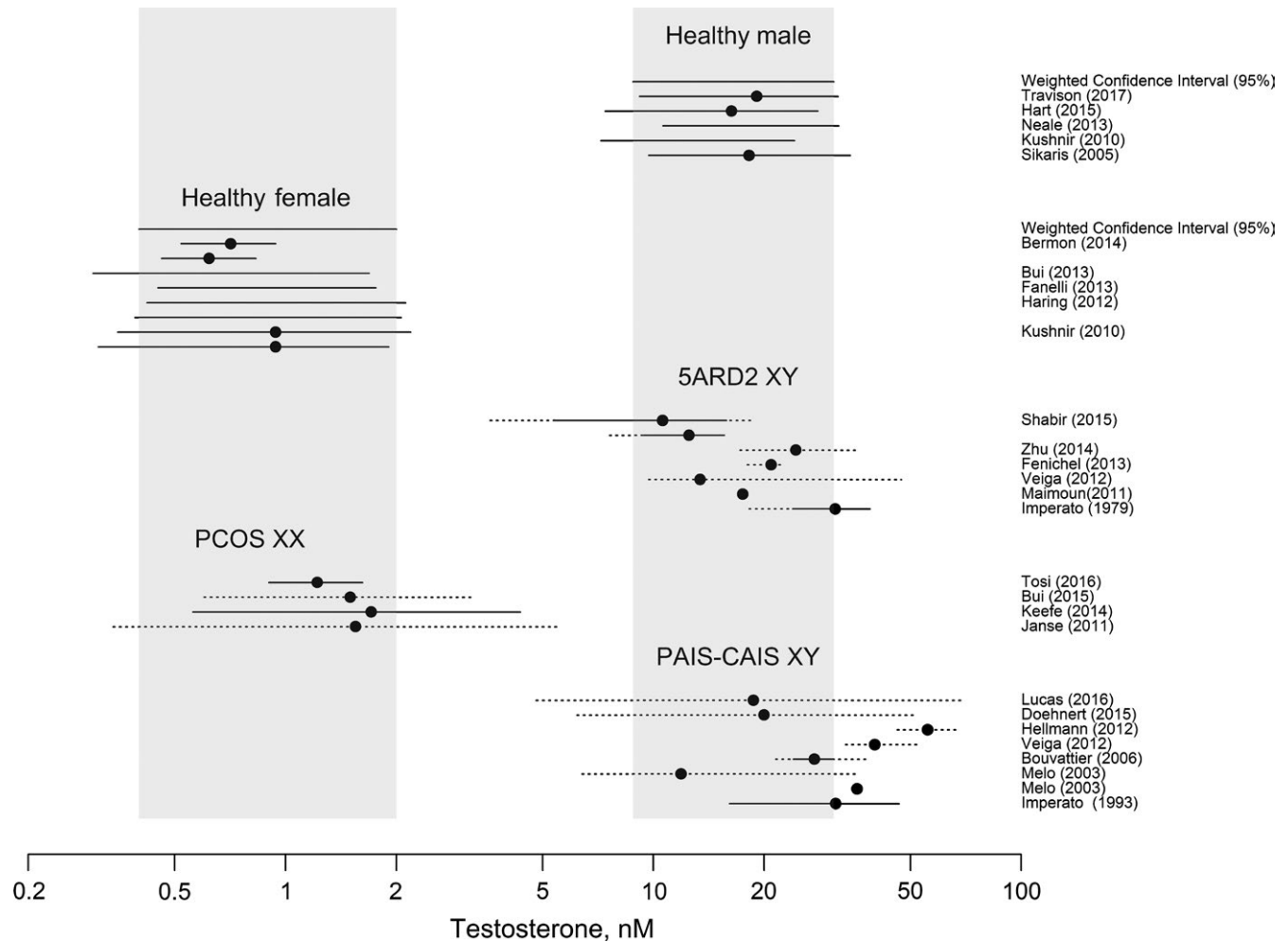


FIGURE 1 Forest plot of testosterone ranges for women and men from reference articles. X axis Log scale for testosterone values in nmol/L (ng/dL = nmol/L multiplied by 28.82), Y axis ranges of testosterone levels for each group of women or men, top solid line for each column is the weighted 95% confidence interval for normal men and women, solid line for each study is 95% confidence interval, dotted line is absolute range. Blank spacer line below a study reference indicates an additional subset for that study

adult male range, as shown in Figure 1 and Table 2.^{5,6,26} During foetal life, 5ARD2 causes impaired conversion of testosterone to DHT resulting in incomplete masculinization of the external genitalia in utero. Male internal genitalia, epididymides and vas deferens, and testes are present. Males with 5ARD2 are born with ambiguous genitalia, such as a bifid scrotum, hypospadias, micropenis, and undescended testes. Typically, they are raised as girls during childhood. At puberty, testosterone production increases, usually into the normal male range, and serum DHT may also increase slightly, due to residual 5 alpha-reductase type 1 activity. The increased androgens result in virilization, penile growth, further descent of the testes, male hair growth, and recognizable male behaviour. The testes can make sperm, and males with 5ARD2 may be fertile. These individuals do not develop gynecomastia, and they usually develop a near-normal male phenotype, some with well-developed male musculature. Thus, individuals with 5ARD2 are genetic males and exhibit phenotypic male features at puberty and during adulthood. Some individuals with 5ARD2 raised as girls, who have fewer male phenotypic characteristics, may choose to retain their female gender identity as adults.

Genetic males with CAIS have a blind vagina, no cervix or uterus, and undescended testes which are usually located in the abdomen.^{28,34,40,41} They have normal foetal male testosterone levels in utero, but ambiguous genitalia, as the impaired androgen receptors do not activate appropriate cellular responses and tissue action. At puberty, testosterone levels increase into the normal adult male range, but there is no tissue response to testosterone and no masculinization. However, the pubertal increase in testosterone causes an increase in estradiol, by aromatization of the testosterone, leading to feminization, with breast development and a near-normal female phenotype. The testes usually remain in the abdomen. Because males with CAIS lack ovaries, they often present for primary amenorrhea with anovulation and lack of menses. Men with PAIS show a range of phenotypes with progressive masculinization depending on the degree of androgen insensitivity.⁴⁰ As children, males with 5ARD2 and PAIS may be raised either as girls or boys, depending upon whether female or male phenotype predominates, and depending upon parental, social, religious and ethnocultural considerations.

In females with PCOS, who have known hyperandrogenism, the upper limit of testosterone levels is 5.5 nmol/L (159 ng/dL), about half the lower limit in normal males.^{8,9} Females who have serum testosterone levels greater than threefold higher than the upper limit of the normal range usually have clinical evidence of virilization, such as clitoromegaly, deepening of the voice and male-pattern balding, and should undergo evaluation for androgen-secreting tumours, as adrenal or ovarian tumours, or other causes of androgen excess, as hypothyroidism, glucocorticoid resistance, and hyperprolactinemia. Females with 21OHD (CAH) may have elevated testosterone levels in the same range as for PCOS, and they should be evaluated for other possible hormonal imbalances, such especially cortisol deficiency.^{10,39}

A key issue for adult, elite athletic performance is whether testosterone levels in genetic males with 5ARD2 or AIS provide a competitive advantage if an individual with either of these 46XY DSD participates in events classified for women. This is a fair consideration in individuals with 5ARD2, where endogenous testosterone levels can be within the normal adult male range and induce normal androgenic, anabolic effects. This is less of a concern in males with AIS, where male range testosterone levels have reduced androgenic anabolic effect due to androgen receptor mutations resulting in impaired androgen action.

There have been recent cases in elite athletic events including major international championships and the Olympics, in which genetic males with 46XY DSD competed as females in women's events. They have been challenged as having a competitive advantage due to elevated testosterone levels in the normal male range. Earlier cases have been addressed by sex change, including surgery and hormonal replacement.²⁴ In response to these cases, the International Olympic Committee (IOC) and International Association of Athletics Federations (IAAF) established an upper limit of serum testosterone level for female athletes of 10.4 nmol/L (300 ng/dL) which is within or near the lower end of the normal range for adult males. This limit suggests a continuum of serum testosterone values, from those in females to those in males.

However, as shown in the forest plot (Figure 1), there is a large, categorical difference in the distribution of testosterone levels between normal, healthy females and males, that is there is no continuum of testosterone levels. From published literature (Table 1 and Figure 1), the normal range of testosterone levels in premenopausal healthy adult females (<45 years old) averages 0.4–2.0 nmol/L (12–58 ng/dL). The lower limit of the normal adult male range, 8.8 nmol/L (254 ng/dL) determined in this review, is approximately 4–5 times higher than the upper limit of the normal adult female range. As described, these normal ranges are supported by several recent publications using accurate, sensitive and reproducible LC-MS/MS measurements (Table 1).^{16–23}

The validity and use of the 10.4 nmol/L (300 ng/dL) cut-off value separating female and male athletes was recently challenged as being inappropriate, and it has been proposed that the cut-off should be higher (ie, >10.4 nmol/L) or there should be no cut-off between male and female athletes.⁴² The rationale for this is unclear,

and establishment of any firm cut-off has been suspended pending further data and discussion, regarding acceptable levels of testosterone in female athletes.^{42–44} The distinct ranges of serum testosterone levels presented in these studies should inform the discussion of cut-offs between males and females.

The relatively small number of women who have serum testosterone levels within or near the adult male range, may be genetic males with 46XY DSD, specifically males with 5ARD2 or AIS. Females with hyperandrogenism due to PCOS or CAH usually have testosterone levels within the normal adult female range, but levels above the normal female range are observed and can approach the lower limit of the normal male range, which is about four- to fivefold higher the upper limit in normal females. Reliable tests are available that can provide useful diagnostic information regarding underlying conditions in individuals with a female phenotype who have a testosterone level above the upper limit for females and approaching or within the male range. How best to apply such information in competitive athletes is yet to be determined.

Consideration of testosterone levels is important as recent data support the divergence in athletic performance between males and females as due in part to the different levels of testosterone. The divergence in athletic performance between men and women at puberty when serum testosterone levels diverge, has been well demonstrated,⁴⁵ and is a natural and well recognized progression to adulthood. Also, recent studies of androgen levels in elite athletes have suggested that female athletes with high testosterone levels, free or total, may have a significant competitive advantage over those with low testosterone levels.^{15,46} Further controlled studies in both males⁴⁷ and females⁴⁸ have shown significant increases in muscle mass and strength, and a clear dose–response effect with administration of increasing amounts of exogenous testosterone.

4 | CONCLUSION

Based on the data summarized from published reports, it is clear that the normal adult female and male testosterone range differ markedly with a bimodal distribution, the lower limit of the male range being approximately four- to fivefold higher than the upper limit of the female range. These results do not support an acceptable upper testosterone limit in female athletes of 10.4 nmol/L (300 ng/dL) or higher. Genetic males with 5ARD2, CAIS and PAIS, whose phenotype at birth was ambiguous or female, have testosterone levels within or near the normal male range. In adult genetic males with 5ARD2, elevated endogenous testosterone levels are likely associated with enhanced athletic performance relative to genetic females. In genetic males with PAIS, tissues do not respond normally to male range endogenous testosterone levels so these levels may not be associated with enhanced athletic performance. Males with CAIS are typically phenotypic females.

In conclusion, existing studies strongly support a clear bimodal distribution of serum testosterone levels in females compared to males. These data should be considered in the discussion of female

competition eligibility and classification of genetic males with possible DSD (5ARD2, PAIS, and CAIS) or genetic females with hyperandrogenism (PCOS and CAH).

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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