Journal of Endocrinology and Diabetes Research
2024 Volume 2, Issue 1
DOI: 10.59657/2996-3095.brs.24.010

BRS BioRes Scientia
Value your Research

Short Communication

Open Access

Testosterone and Gender in Health and Disease

Adel A A Ismail

Consultant in Clinical Biochemistry and Chemical Endocrinology; (RTD) Mid-Yorkshire and Leeds hospital trusts, West Yorkshire; UK.

Keywords: disorders of sexual development; testosterone; homosexuality; heterosexuals; gender; genetic; steroidogenesis; foetal hormones; foetal development

Introduction

Discord between body-sex and gender occurs in two settings, in healthy homosexuals and in disorders of sexual development (DSD). In both cases, lesser consideration was given to biophysiological role of testosterone on gender discord.

Early in the first trimester of pregnancy, body sex is determined by a functional *SRY* gene on the Y-chromosome [1]. which if present directs foetal ambisexual genital tubercle to male with testicular Leydig cells producing testosterone. Testosterone is a substrate for the enzyme 5α-reductase which converts 5-10% of testosterone to dihydrotestosterone (DHT), also a potent androgen. Testosterone and DHT act on numerous targets. For example, masculinization of external genitalia, prostate and penile growths are DHT dependent (not testosterone per se). Other androgenic targets are essentially testosterone dependent. Testosterone and DHT actions are mediated (a) by their concentrations (b) binding to appropriate androgen receptors (AR) with different binding affinities and (c) two intracellular biophysiological processes; a post-translational pathway ultimately resulting in interaction with nucleus DNA (genomic) and another pathway directly involves proteins in the cytoplasm which regulate signal transduction without interaction with nucleus DNA [2] (non-genomic). Efficacies of these multiple molecular testosterone processes must also be timely, synchronized with concurrent and pertinent developments such as the brain which are growing rapidly by ~215,000 neurons per minute[3] including neuroendocrine brain region responsible for postnatal male hypothalamic-pituitary-gonadal axis (HPG-axis) and gender. The outcome of these sequential and highly coordinated several independent biophysiological actions ultimately determines testosterone and DHT manifestations at each target. Development of female body-sex, female HPG-axis and gender is the default option, occurs when *SRY* gene and foetal testicular tissues are absent. After birth, testosterone concentrations initially decline in both sexes. However, it starts to rise in male neonates (not in females) after ~2 weeks reaching a peak at ~3 months of age with testosterone concentrations comparable to fathers and probably higher than grandfathers (referred to by some as mini-puberty with occasional erections). Testosterone levels decline thereafter to very low levels by 6 months of age [4-6]. Despite quiescent gonads during childhood in both sexes, children generally exhibit sexual awareness of their gender around the age of 3 years and gravitate towards preferential toys, sports and other activities associated with their gender. In a longitudinal study on 81 male neonates, the magnitude of postpartum testosterone surge at 3 months of age was found to predict masculine behavior at 4 yrs of age [7].

Puberty is initiated by the activation of HPG-axis and the secretion of pulsatile gonadotrophin releasing hormone (GnRH) and feedback by sex-hormones in both sexes. Many additional hormonal modifiers modulate HPG-axis e.g., activin (stimulate GnRH), inhibin (inhibit activin) as well as others e.g., follistatin, leptin, insulin, ghrelin and kisspeptin [8]. Gender identity at puberty is innate, powerful, driven, enduring and indelible, enforcing gender orientation irrespective of the body's physical attributes even when dissonant as in homosexuals. All pubertal manifestations in healthy homosexuals and heterosexuals including fertility and fecundity are similar apart from gender discord.

Animal experiments had limitations because animals cannot report, as humans can, on their gender. However, data from eight different DSD entities [9, 10] in males highlighted an etiological role of testosterone on external genitalia and gender. For example, severe deficiencies in testosterone

production in utero caused by steroidogenic aberrations affecting foetal testosterone synthesis or impediments to its biological action in males' results in newborn with female external genitalia and female gender identity e.g., androgen insensitivity syndrome (androgen receptor mutation), Swyer syndrome (*SRY* gene mutation), LH/hCG receptor mutation, 17ß-HSD (type 3) deficiency, 17α-hydroxylase deficiency, and 20-22 desmolase deficiency [9, 10].

In the female with syndrome of aromatase deficiency [9-11], the relatively small amount of ovarian testosterone (a substrate for oestradiol) is blocked. A 5-10% of the accumulated testosterone is converted to DHT in amounts sufficient to cause virilization of external genitalia. Yet, explicit impact on gender was unreported being less visible as dissonance [11].

The prevalence of healthy homosexuals (~5%) is too high for the trait to be maintained by random processes. Data obtained from DSD support a critical role of testosterone on gender**.** Two specific examples further highlight such role; firstly, the clinical course of events of a Canadian baby (Brian) age 7 months whose penis was severed from base during a botched surgery (circumcision). Management advice given by an eminent US pediatrician was to nurture this genetically baby boy as a girl. Such advice was implemented with full corrective surgery to fit future development of the baby as a girl (Brenda). She was regularly assessed and her behavior was tomboyish and troublesome throughout childhood and rebellious at puberty and thereafter. Brenda refused to accept her gender as a female, culminating in eventual suicide [12]. At 7 months of age both prenatal testosterone and neonatal surge have had normally occurred, hence the expression of male gender identity during childhood and adulthood in this case. Secondly, males with severe 5α-reductase deficiency are born with female external genitalia due to the lack of DHT. However, because prenatal and postnatal testosterone production and actions are not affected and normal, these "seeming girls" at birth, the majority acquire male gender orientation/identity in adulthood [9, 10].

It may be important to point out that simple elevation of testosterone and DHT in utero from non-gonadal source e.g. congenital adrenal hyperplasia (CAH) in female appears to be confined to virilisation of external genitalia but without deleterious effect on HPG-axis in whom fertility rate and fecundity is nearly normal (in treated patients). Its impact on gender however remains contentious. For example, a descriptive review suggests that non-heterosexual orientation is more prevalent in CAH patients who had exhibited severe degree of virilization at birth. Yet in a recent meta-analysis of 250 adult's females with CAH, the majority (~95%) retained female gender identity, incidence not dissimilar in non-CAH individuals [13-16].

DSD are clinical entities which highlighted the biophysiological and pathophysiological impact of testosterone on HPG-axis, external genitalia and gender; information which is impossible to attain or replicate by any other means on humans on moral and ethical ground [4-6]. Clinically, diagnosis is simple when severe. However, partial deficiencies/aberrations occur in all DSD with lesser manifestations e.g., milder genital ambiguity or atypical puberty. Thorough biochemical investigations and genomic tastings are paramount prior to sex assignment/re-assignment. Furthermore, potential influence and preponderance of testosterone role in utero (retrospectively) and early neonatal life (prospectively, appropriate in some cases) and its likely impact on gender in neonates with ambiguous genitalia are described elsewhere [9, 10].

Finally, in healthy heterosexuals and homosexuals, there is now a growing sentiment to accept the role of *SRY*-gene in determining binary body-sex, but rejects extending "binaries" concept to gender because ultimate manifestation of gonadal testosterone actions involve numerous independent, sequential and timely coordinated processes. The outcome in any phenomena involving such multiple and independent elements is not and can't be binary; rather a spectrum/continuum depicted as probability distribution density (based on the mean (μ) and standard deviation (σ) of each independent process). This provides a calculable and predictable number of different traits expected in large cohorts fulfilling central limit theorem. Furthermore, such prediction is to be expected in cohorts/generation after generation as shown by the persistent incidences of healthy heterosexuals and homosexuals in all races, ethnicity in ancient and modern cultures.

Conflict of interest: None

References

1. Berta P, Hawkins JB, Sinclair AH, et al. (1990). Genetic evidence equating SRY and the testis-determining factor. *Nature,* 348:448-450.

2. Heinlein CA, Chang C. (2002). "The roles of androgen receptors and androgen-binding proteins in nongenomic androgen actions". *Molecular Endocrinology*, 16:2181-2187.
3. Wang Y, Wu H, Sun Z S. (2019). The biological basis of sexual orientation: How hormonal, genetic, and environmental factors influence to whom we are sexually attracted. *Front Neuroendocrinol*, 55:100798.
4. Ismail AAA, Walker PL, Macfaul R, Gindal B. (1989). Diagnostic Value of Serum Testosterone Measurement in Infancy: Two Case Reports. *Annals of Clin Biochem*, 26:259-261.
5. Bizzarri C, Cappa M. (2020) Ontogeny of Hypothalamus-Pituitary Gonadal Axis and Minipuberty: An Ongoing Debate?. *Front. Endocrinol*, 11.
6. Le Tissier P. Campos P, Lafont C, Romanò N, Hodson D J, Mollard P. (2017). An update view of hypothalamic-vascular-pituitary unit function and plasticity. *Nature Rev Endocrinol*, 13:257-267.
7. Pasterski V. (2017). Fetal androgens and human sexual orientation: searching for the elusive link. *Arch Sex Behav*, 46:1615-1619.
8. Padda j, Khalid K, Moosa A, Syam M, Kakani V, et al. (2021). Role of Kisspeptin on Hypothalamic-Pituitary-Gonadal Pathology and Its Effect on Reproduction. *Cureus*, 13:17600.
9. Acién P, Acién M. (2020). Disorders of Sex Development: Classification, Review, and Impact on Fertility. *J. Clin. Med*, 9:3555.
10. Ismail A A A. (2018). Genes, Hormones, Sex and Gender; Harmony and Disharmony. *Adv Clin Endo Met*, 1:22-31.
11. Marino R, Garrido N P, Costanzo M, Guercio G, Juanes M, Rocco C ET AL. (2015). Five New Cases of 46,XX Aromatase Deficiency: Clinical Follow-Up From Birth to Puberty, a Novel Mutation, and a Founder Effect. *J Clin Endocrinol Metab*, 100:301-307.
12. Diamond M, Sigmundson H K. Sex Reassignment at Birth: Long-term Review and Clinical Implications. *Arch Pediatr Adolesc Med*, 151:298-304.
13. Gondim R, Teles f, Barroso Jr. U. (2018). Sexual orientation of 46, XX patients with congenital adrenal hyperplasia: a descriptive review. *Pediatric Urology*, 14:486-493.
14. Meyer-Bahlburg H F L, Dolezal C, Baker S W, Ehrhardt A A, New M I. (2006). Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Arch sex Behav*, 35:667-684.
15. Rosenthal S M. (2021). Challenges in the care of transgender and gender-diverse youth: an endocrinologist's view. *Nature Reviews Endocrinology*, 17:581-591.
16. Berenbaum S A, Beltz A M. (2021). Evidence and implications from a natural experiment of prenatal androgen effects on gender behavor. *Curr Dir Psychol Sci*, 30:202-210.

Cite this article: Adel A A Ismail. (2024). Testosterone and Gender in Health and Disease. *Journal of Endocrinology and Diabetes Research*, BioRes Scientia Publishers. 2(1):1-3. DOI: 10.59657/2996-3095.brs.24.010

Article History: **Received:** December 30, 2023 | **Accepted:** January 18, 2024| **Published:** February 24, 2024