

Expert Opinion

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The role of androgens in hormone replacement therapy

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In recent years, increased attention to women's sexual health has propelled basic scientific research and clinical trials investigating treatment paradigms for improving sexual well-being. As the prevalence of female sexual dysfunction has become manifest, knowledge of the intricate pathophysiological role of androgens in maintaining sexual function has fostered a clearer understanding of the effect of age on androgen status, the role of androgens in the postmenopausal ovary, and aetiological mechanisms of androgen insufficiency in premenopausal and postmenopausal women. Understanding the long-term safety and efficacy of physiological androgen replacement and the development of sensitive testosterone assays for specific use in women, will better characterise women who are most likely to respond to androgen therapy and, thereby, optimise their quality of life.

Keywords: androgen insufficiency, androgens, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, dihydrotestosterone, female sexual dysfunction, hormone replacement therapy, hypoactive sexual desire disorder, menopause, oestrogen, testosterone

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1. Introduction

Women's sexual health has been the focus of tremendous attention in recent years, particularly among the rapidly growing population of postmenopausal women. Female sexual dysfunction (FSD) has a major psychosocial impact on sexual relationships and quality of life. Androgens play an important role in women's sexual health, and many studies have sought to delineate the role of androgens in maintaining sexual function. There is increasing evidence suggesting that symptoms such as fatigue, low libido and diminished well-being can be relieved by androgen therapy. As the knowledge from clinical trials and basic science research increases, the inclusion of testosterone in hormonal replacement regimens (not only for postmenopausal women, but also for premenopausal androgen insufficiency syndromes such as premature ovarian failure, surgical menopause, hypopituitarism, Addison's Disease, chronic illnesses and medication use) is likely to increase with the availability of preparations specifically designed for women.

1.1 Incidence of female sexual dysfunction

FSD is an age-related, progressive and multi-dimensional condition affecting 30 – 50% of American women. Based on epidemiological data from the National Health and Social Life Survey, where the prevalence of sexual dysfunction in a demographically representative cohort of 1749 women and 1410 men aged 18 – 59 years was examined; 43% of women experienced sexual dysfunction compared with 31% of men. The loss of sexual desire was the most prevalent FSD, occurring in 27 – 32% of women across age groups [1].

1.2 Female sexual response cycle

The traditional model of human sexual response, first characterised by Masters and Johnson in 1966 [2], described four successive phases: excitement, plateau, orgasm

and resolution in which both the clitoris and labia minora become engorged with blood, increasing vaginal and clitoral length and diameter during sexual arousal. In 1979, Kaplan [3] proposed the aspect of 'desire' in a three-phase model consisting of desire, arousal and orgasm. The traditional cycle proposed by Masters, Johnson and Kaplan is an insufficient model of women's sexual response, as women's sexual arousal is complex, comprising more than genital vasocongestion. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association characterised the psychophysiological changes of the female sexual response cycle into: hypoactive sexual desire, sexual aversion, female sexual arousal disorder, female orgasmic disorder, dyspareunia and vaginismus; which cause marked distress and interpersonal difficulty [4]. These phases now incorporate specific medical risk factors and aetiologies of FSD into the pre-existing psychologically-based definitions that have become the basis for the new classification system of the American Foundation of Urologic Disease Consensus Panel [5].

1.3 American Foundation of Urologic Disease Consensus Panel classification and definition of female sexual dysfunction

Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent absence (or deficiency) of sexual fantasies/thoughts, and/or desire or receptiveness for sexual activity, causing personal distress. This may result from physiological conditions such as hormonal deficiencies, medical or surgical conditions/procedures or from psychological and emotional factors.

Sexual aversion disorder is the avoidance or aversion to sexual contact with a sexual partner, which causes personal distress. This is psychologically- or emotionally-based, resulting from physical or sexual abuse and/or childhood trauma.

Sexual arousal disorder is a persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress. This may be expressed as a lack of subjective excitement, or lack of genital lubrication/swelling or other somatic responses. Such disorders may include decreased clitoral/labial sensation and engorgement or absence of vaginal smooth muscle relaxation, which can occur as a result of psychological and medical factors (diminished vaginal/clitoral blood flow, pelvic trauma/surgery or medications).

Orgasmic disorder is the persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress. This may be a primary condition (never achieved orgasm) due to emotional or sexual abuse, or a secondary condition due to surgery, trauma, medications or hormonal deficiencies.

Sexual pain disorders encompass dyspareunia, vaginismus and noncoital sexual pain. Dyspareunia is recurrent or persistent genital pain associated with sexual intercourse, which can develop secondary to medical problems such as vestibulitis, vaginal atrophy and infection. It can be either physiologically and/or psychologically based. Vaginismus is the recurrent or persistent involuntary spasm of the musculature of the outer

third of the vagina that interferes with vaginal penetration and causes personal distress. Vaginismus may develop as a conditioned response to painful penetration, or result from psychological and emotional factors. Noncoital sexual pain disorder is a recurrent or persistent genital pain induced by noncoital sexual stimulation, which includes anatomic and inflammatory conditions such as herpes simplex virus infection, vestibulitis, endometriosis or female genital cutting/female circumcision.

These classifications are subtyped as lifelong versus acquired, generalised versus situational and organic versus psychogenic or mixed. The aetiology of these disorders may be multifactorial and often overlap.

1.4 Androgen biosynthesis pathways in women

Understanding androgen physiology and the pathways by which advancing age and medical conditions can alter androgen production will aid in the comprehension of the impact of androgens on female sexual health. Androgens are important for the development of reproductive function and hormonal homeostasis, and are the precursors for the biosynthesis of oestrogens.

Androgen production in women takes place in three compartments: the ovary, adrenal and peripheral tissues. The major androgen precursors in women, listed in descending order of serum concentration, are: dehydroepiandrosterone sulfate (DHEAS); dehydroepiandrosterone (DHEA); androstenedione; biologically active testosterone; and dihydrotestosterone (DHT). Androgen secretion is regulated by stimulation from adrenocorticotrophic hormone (ACTH) to the adrenal glands and by luteinising hormone (LH) to the ovary, along with other intraglandular autocrine and paracrine mechanisms [6]. Testosterone and DHT have the most potent biological activity of the androgenic steroids, as only they can bind to the androgen receptor. A large proportion of the active sex steroids in women are derived from DHEA and DHEAS, which plays an important role in the synthesis of androgens and oestrogens in peripheral target tissues [7].

Androgen receptors are located in multiple receptor and tissue sites, including the CNS, bone, breast, pilosebaceous unit, skeletal muscle, adipose and genital tissues [8]. Androgens not only have direct effects on target sites, but also their effects on these tissues may be mediated by its conversion to oestrogens.

1.4.1 Dehydroepiandrosterone and dehydroepiandrosterone sulfate

DHEA is among the most abundant of steroids in human serum and is produced at a rate of 6–8 mg/day, with circulating concentrations of 3–35 nmol/l [6]. Of all DHEA, 50% is secreted by the adrenal zona reticularis, 20% by the ovarian theca (20%) and 30% is derived from circulating DHEAS [9]. DHEA can also be produced intracellularly from DHEAS in the course of peripheral androgen synthesis, however levels decrease with age [6].

DHEAS is produced primarily by the zona reticularis of the adrenal cortex at a rate of 3.5–20 mg/day during

reproductive life, with circulating concentrations in the range of 3 – 12 $\mu\text{mol/l}$ [6,10], and is an important source of peripheral androgen production. DHEAS production begins to increase in girls aged 7 – 8 years and is associated with the clinical signs of adrenarche [11]. Circulating concentrations do not change significantly during the menstrual cycle and maximal values of circulating DHEAS are reached between 20 and 30 years of age [12]. Thereafter, serum DHEA and DHEAS levels decrease progressively. The concentrations of DHEA and DHEAS begin to decline between the ages of 30 and 40 years and continue to do so gradually throughout life [13,14]. It has also been reported that 24-hour mean plasma concentrations of DHEA and DHEAS in 37 healthy women in the range of 21 – 75 years of age, demonstrated a linear inverse correlation between concentration and age in both sexes. Menopause, whether natural or surgical, resulted in no additional significant alterations in these adrenal steroids in these women [13,14].

By age 70, serum DHEAS levels have decreased to ~ 20% of their peak values, and they further decrease to 5% by the age of 85 – 90 years [15]. Before the age of 50 – 60 years, $\leq 50\%$ of the age-related decline in serum DHEA and DHEAS concentration takes place [16]. The reduction in the formation of DHEAS (up to 95%) by the adrenals during ageing results in a dramatic reduction in the formation of androgens and oestrogens in the peripheral target tissues, a situation that has been suggested to be associated with age-related diseases, such as insulin resistance [17], cardiovascular disease [18] and obesity [19].

1.4.2 Androstenedione

Androstenedione secretion varies throughout the menstrual cycle, with 50% secreted by the adrenal zona fasciculata and 50% by the ovarian stroma, with a daily production rate of 1.4 – 6.2 mg/day and circulating levels of 2 – 8 nmol/l [6]. Although circulating androstenedione derives from the ovaries and adrenal glands, most of the androstenedione found in androgen-sensitive tissues originates from the intracellular conversion of DHEAS and DHEA to androstenedione [9,20]. Androstenedione serum concentration varies daily, based on circadian changes, and peaks mid-cycle in parallel with the mid-cycle oestrogen peak [21]. Levels of androstenedione decrease only modestly with advancing age. Whereas circulating androstenedione originates in the ovaries and adrenal glands, most of the androstenedione in androgen-sensitive tissues is derived from the intracellular conversion of DHEAS and DHEA to androstenedione [9,20,22].

1.4.3 Testosterone

Testosterone, in contrast with DHEAS, DHEA and androstenedione, is one of the most potent androgens and is biologically active; possessing specific receptors and target tissue activity. Testosterone can also be produced intracellularly from DHEAS. Prior to menopause, 25% of testosterone is secreted by the adrenal zona fasciculata, 25% by the ovarian stroma and

the remaining 50% by circulating androstenedione [9]. The production rate of testosterone is in the order of 0.1 – 0.4 mg/day with circulating levels in the range of 0.6 – 2.5 nmol/l [6]. Sensitive assays reveal that testosterone shows circadian variation, with peak levels seen in the early morning hours. In a menstrual cycle, testosterone is at its lowest concentrations in the early follicular phase of the cycle, and rises to a mid-cycle peak; the luteal phase concentrations are higher than those in the early follicular phase [21]. During the mid-cycle peak in testosterone, an associated enhancement in sexual desire and frequency of sexual intercourse may occur [23,24]. Testosterone levels do not change remarkably during the menopause transition; however, testosterone levels fall slowly with increasing age [25]. Of note, surgical menopause, by either a premenopausal or postmenopausal oophorectomy, results in an ~ 50% decline in circulating testosterone levels [26].

Serum androgens may be either unbound or bound, and it is the unbound androgens that are biologically active to exert their effects on target tissue. Following secretion from the adrenal glands and ovaries, testosterone is strongly bound by sex hormone binding globulin (SHBG) in the peripheral blood such that only ~ 1% of testosterone and DHT circulates freely [27]. SHBG has a low capacity, but high affinity, for testosterone, and has a low affinity for androstenedione, DHEA and DHEAS [27].

1.4.4 Dihydrotestosterone

DHT is also a bioactive androgen, and is considerably more potent than T; binding with greater affinity to receptors in target tissue. Although some DHT is produced by the adrenal zona fasciculata, the majority of DHT is produced by the peripheral conversion of testosterone to DHT in target tissues [21]. Production rates have been calculated at between 4.3 – 12.5 mg/day, circulating in concentrations of ~ 0.02 ng/ml [6]. Levels of both testosterone and DHT have been correlated with increased sexual desire, arousal, initiation and receptivity to sexual activity, as well as frequency of sexual intercourse and gratification [28,29].

1.5 Effect of age on androgen status

Advancing age has a much larger impact on androgen status than menopause. Several studies have examined androgen changes across the menopausal transition. Total testosterone does not change appreciably until women are much older (71 – 95 years of age), whereas androstenedione levels decrease much earlier [30]. Mean 24-hour levels of testosterone decrease in women at 20 – 50 years of age; however, this decline reflects ageing, in that the ratio of DHEAS:testosterone is constant over this time span [25]. DHEA and DHEAS concentrations begin to decline in the second decade of life, and by the age of 80, serum levels are ~ 20 – 30% of peak levels [16]. Data from a large longitudinal study demonstrate a 13% decline in mean DHEAS and a 46% decline in mean testosterone levels between ages 42 and 50 [31]. These data confirm that although ageing affects levels of testosterone,

these levels are not much different before and after the menopause transition, and the small reduction in ovarian production is thought to result from declines in androstenedione [30].

1.6 Androgen function in the postmenopausal ovary

It is currently believed that after menopause, the ovaries are a major site of androgen production [26,32-36]. In the postmenopausal ovary, the loss of ovarian follicles and granulosa cells eliminates its oestrogen-producing ability [37]. However, secondary interstitial cells and hilar cells may persist in the postmenopausal ovary [38], which for many years were thought to remain continuously activated by the high levels of circulating LH, and thus remain steroidogenically active [34]. Furthermore, one of the most convincing data that suggested an important contribution of the postmenopausal ovary to steroidogenesis came from the analysis of ovarian and peripheral vein hormone levels [39]. However, postmenopausal ovaries are atrophic with limited blood flow. Hence, ovarian vein sampling may be difficult and cross-contamination of adrenal venous blood can occur at the sampling site. Thus, herein lies the difficulty in assessing true hormonal activity in the postmenopausal population [40].

The reduction in postmenopausal ovarian androgen production is not precipitous. Instead, ovarian testosterone production decreases slowly over the 5 – 10 years following the last menstrual period, whereas ovarian androstenedione production decreases substantially more at the time of menopause than does testosterone production [41]. Couzinet *et al.* [37] has recently concluded that the commonly held belief of a consistent and significant androgenic capability of the postmenopausal ovary is false. He demonstrated that in the absence of adrenal function, postmenopausal women averaging 12 years after menopause had no detectable circulating androgens and that their postmenopausal ovaries were devoid of gonadotropin receptors and steroidogenic enzymes [37]. These observations suggest that the postmenopausal ovary as early as 5 years after menopause is not a source of androgens. Instead, postmenopausal androgens are derived primarily from an adrenal, rather than ovarian, source [31].

In contrast, Laughlin *et al.* [42] demonstrated that the postmenopausal ovary remains a critical source of androgens throughout the lifespan of older women in a study examining the cross-sectional association of hysterectomy and oophorectomy status, chronological age and years since menopause with plasma levels of total and bioavailable testosterone, oestradiol, androstenedione, oestrone and SHBG in postmenopausal women not using oestrogen replacement therapy. After adjustment for age and body mass index (BMI), both total and bioavailable testosterone levels were reduced by > 40% ($p < 0.001$) in hysterectomised women with bilateral oophorectomy compared with those in intact women, with intermediate levels observed in hysterectomised women with ovarian conservation. Furthermore, androstenedione levels were 10% lower in hysterectomised women with or without

ovarian conservation compared with those in intact women ($p = 0.039$). Total estradiol levels tended to be lower ($p = 0.095$) in bilaterally oophorectomised women. Levels of bioavailable estradiol, estrone and SHBG did not differ by hysterectomy and oophorectomy status [42].

Among intact women, total, but not bioavailable, testosterone levels increased with age ($p = 0.015$), reaching premenopausal levels during 70 – 79 years of age, with relatively stable levels thereafter. Among oophorectomised women, total and bioavailable testosterone levels did not vary with age and were 40 – 50% lower than those in intact women throughout the 50 – 89 years age range. Androstenedione levels decreased by 27% and SHBG levels increased by 30% ($p < 0.001$) with age, in intact, but not oophorectomised, women. Levels of other hormones did not vary with age. Stratification by years since menopause or surgery yielded similar results [42]. Hence, the results of this study seem to demonstrate that the postmenopausal ovary may be a source of androgen throughout the lifespan of older women, and bilateral oophorectomy results in a pronounced and sustained reduction in both total and bioavailable testosterone levels.

Furthermore, it is important to consider that most of the androgens in women, particularly after menopause, are synthesised in peripheral tissues from DHEAS and DHEA [43]. In this fashion, DHEA and DHEAS are converted into more potent androgens or oestrogens in peripheral target tissues, and they exert their action in the same cells in which their synthesis took place without significant diffusion into the circulation; a process defined as intracrine production [40]. Consequently, this process may limit the interpretation of serum levels of active sex steroids, as the sex steroids made in peripheral tissues are then inactivated locally into more water-soluble compounds, which then diffuse into the general circulation where they can be measured [40].

In addition, genetic and ethnic variation has been demonstrated in postmenopausal ovarian androgenic activity as recent studies have shown that DHEAS levels are related to ovarian function in older women, which varies with ethnicity [31,44]. In defining the relationship of adrenal steroid production during declining ovarian function, Lasley *et al.* demonstrated that log circulating DHEAS concentrations were highest among Chinese and Japanese women, and lowest among African-American and Hispanic women in a prospective cohort of 3029 women between the ages of 42 and 54 across five ethnic groups [31]; this pattern persisted after adjustment for age, smoking and log body mass index (BMI).

1.7 Limitation of serum testosterone assays in women

The routine clinical use of testosterone assays began ~ 30 years ago with the development of radioimmunoassays (RIAs) for testosterone [45]. Subsequently, there have been remarkable advancements in assays for T. However, measuring serum testosterone levels in women is difficult because of the varying concentrations of SHBG, the high affinity of SHBG for oestrogen and the large variation in oestrogen

levels among different populations of women. Independent of the source of testosterone production, SHBG levels determine the amount of testosterone that is bioavailable. Therefore, SHBG, free and total testosterone levels are needed to determine the presence of abnormal androgen concentrations. Furthermore, women have lower plasma concentrations of both free and total testosterone than men, and current commercial assays do not possess the sensitivity and reliability to detect testosterone at the lower ranges of measurement. For total testosterone measurements, gas or liquid chromatography with mass spectrometry is considered the gold standard for laboratory assessment. Taieb *et al.* [46] compared serum total testosterone levels measured by several manual and automated platform assays with isotope-dilution gas chromatography-mass spectrometry as a gold standard in men, women and children. Although there were differences in the population studied, immunoassays tested and validation of the isotope-dilution gas chromatography-mass spectrometry method, and some discrepancies in the results obtained with automated immunoassays that were tested, this study came to the conclusion that conventional immunoassays lacked sufficient accuracy and reliability for measurement of total testosterone in women and children.

A number of assays are available to measure free and bioavailable testosterone in blood. Free testosterone concentration, as measured by equilibrium dialysis, is considered the 'gold standard' for laboratory assessment of bioavailable testosterone in women [8]. Alternatively, the non-SHBG-bound, biologically available fraction may be obtained by precipitation of SHBG-bound testosterone with ammonium sulfate. Both of these techniques are time-consuming, expensive and not used by most clinical laboratories, although available from reference laboratories. An indirect parameter of free testosterone can be determined by the free androgen index (FAI). However, this method has been shown to lack reliability [47]. Free testosterone can also be estimated directly by an immunoassay method involving an analogue ligand, which is often considered the easiest and fastest method for measuring free testosterone. However, the values obtained with this analogue ligand immunoassay are substantially lower than values obtained by equilibrium dialysis and has been demonstrated to be an unreliable index of free testosterone [48].

1.8 Female androgen insufficiency

Androgen insufficiency in women may result from a natural age-related decline in adrenal and ovarian androgen production, and in premenopausal women as a result of ovarian, adrenal or central dysfunction. The aetiologic categories of androgen insufficiency encompass: ovarian (premature ovarian failure, oophorectomy, radiation/chemotherapy), adrenal (adrenalectomy, adrenal insufficiency), hypothalamic-pituitary (hypopituitarism), medication-related (corticosteroids, antiandrogenic agents, oral contraceptives, oral oestrogen replacement therapies) and chronic illness [8].

In 2001, the Princeton International Consensus panel proposed three essential criteria in the definition of androgen insufficiency [8]: i) the presence of clinical signs/symptoms including: a diminished sense of well-being or dysphoric mood; persistent, unexplained fatigue; sexual function changes (decreased libido, sexual receptivity, lubrication and pleasure); vasomotor instability, bone loss, decreased muscle strength, and changes in cognition or memory; ii) a diagnosis of androgen insufficiency should only be made in women who are adequately oestrogenised, as oestrogen effects are also strongly linked to mood, psychological well-being, and sexual function in women. This can include normally cycling premenopausal women or postmenopausal women receiving oestrogen replacement therapy; iii) in the absence of a sufficiently sensitive assay or absolute threshold for androgen insufficiency in women, free testosterone values should fall at or below the lowest quartile of the normal range for the reproductive age (20 – 40 years) [8].

1.8.1 Ovarian causes of androgen insufficiency

Bilateral oophorectomy in pre- and postmenopausal women has been shown to result in a 40 – 50% reduction in circulating testosterone [26,49], as these women subsequently experience loss of libidinal interest, fatigue, depression, reduction in muscle mass and strength, immunosenescence and decreased bone strength [30]. Premature ovarian failure accelerates the onset of menopausal symptoms and androgen insufficiency resulting in osteoporosis, fatigue and decreased sexual desire. Potential causes of premature ovarian failure include: cytochrome P450 17 α enzyme deficiency, radiation/chemotherapy, autoimmune disorders and abnormal expression of the X chromosome [26,49,50].

1.8.2 Adrenal causes of androgen insufficiency

Addison's disease, or primary adrenal failure, occurs in 1 in 25,000 individuals and is characterised by chronic glucocorticoid and mineralocorticoid deficiency, which requires lifelong oral replacement [51]. It is caused by a progressive destruction of the adrenal cortex and subsequent loss of androgen-producing cells, resulting in a significant decline in circulating levels of DHEAS and DHEA. A fall in circulating levels of DHEAS results in a state of relative glucocorticoid excess that may adversely influence neural function, with effects on cognition, memory and mood [51]. Lovas *et al.* [52] reported results of an observational study of subjective health status in 79 Norwegian patients with Addison's disease, which found a reduced general health status, vitality perception and increased fatigue compared with the general Norwegian population. Despite optimised therapy with glucocorticoids and mineralocorticoids, patients with adrenal insufficiency suffer from chronic DHEAS deficiency as steroids fail to restore adrenal androgen concentrations [53], and patients with Addison's disease report a reduced quality of life compared with normal individuals, often complaining of persistent fatigue and reduced well-being [54].

1.8.3 Hypothalamic-pituitary causes of androgen insufficiency

Hypopituitarism in women has been shown to be associated with a number of clinical features including osteopenia, obesity, a reduction in lean body mass, decreased libido and a decrease in quality of life [55-57]. Although they are likely to be multifactorial in origin, these signs and symptoms may persist despite conventional hormone replacement therapy [58,59]. Women may acquire hypopituitarism as a result of surgery, radiation therapy, neoplasm or haemorrhage in proximity to the pituitary gland, which diminishes ACTH production and subsequent adrenal androgen production. Furthermore, in the absence of stimulatory LH from the pituitary, ovarian androgen secretion wanes. Panhypopituitarism can cause hypogonadism and hypoadrenalism, thereby affecting two critical sources of androgen production in women [60].

1.8.4 Medications associated with androgen insufficiency

Prolonged corticosteroid therapy inhibits ACTH secretion from the pituitary gland, which results in atrophy of the adrenal cortex and decreased androgen production. In patients with adrenal insufficiency, both the depletion of sex steroids and oversubstitution of glucocorticoid therapy pose the risk of osteopenia. One study has demonstrated low bone mineral density in men, but not in women, with Addison's disease [61], whereas two studies have shown decreased bone mineral density in postmenopausal women, but not in men [62,63]. Likewise, by increasing liver synthesis of SHBG, oral oestrogen therapy decreases the free, bioavailable testosterone for uptake by target tissues [6].

1.8.5 The impact of chronic illness on androgen insufficiency

Although the specific pathophysiological mechanisms are unknown and clinical trials have been inconclusive, it is theorised that patients with severe emotional distress, various immunologic disorders such as rheumatoid arthritis, systemic lupus erythematosus, HIV-AIDS, cytomegalovirus infection, trauma or anorexia may exhibit adrenal gland dysfunction and impaired androgen production [8,64].

1.9 The impact of oestrogen on androgen bioavailability

Oestrogens play an important role in maintaining genital sensation, blood flow and function; vaginal wall thickness, rugae and lubrication have been shown to be oestrogen-dependent [65-69]. Low oestrogen levels are associated with sexual complaints during menopause, particularly vaginal dryness and dyspareunia [70], due to thinning of the vaginal walls, diminished vaginal acidity with resultant vulnerability to infection, trauma and decreased ability to heal [71]. Oestrogens may affect smooth muscle cell growth in the vagina and the clitoris, regulate connective tissue metabolism and

nitric oxide synthesis, and may be important in maintaining the functional integrity of vaginal and clitoral smooth muscle function [68].

In premenopausal women, the ovaries are the principal source of oestrogen, which functions as a circulating hormone to act on distal target tissues [72]. However, in postmenopausal women, the primary source of oestrogen comes from the aromatisation of DHEA, androstenedione and testosterone to oestrone and oestradiol in the peripheral tissues which include: adipose tissues, osteoblasts and chondrocytes of bone, the vascular epithelium and aortic smooth muscle cells and numerous sites in the brain. This circulating oestrogen originates in extragonadal sites where it acts locally, and enters the circulation if it escapes local metabolism [72]; consequently reflecting, instead of directing, oestrogen action in postmenopausal women. The increased aromatase activity following menopause results in the peripheral tissues taking on a greater role in the production of oestrogen compared with this process in younger women [41]. This increased aromatase activity is due to the progressive increase in body fat with ageing, and an increase in aromatase activity per unit of fat with decreased endogenous oestrogen [73]. Increased total body fat has an inverse effect on SHBG – the greater the BMI, the lower the SHBG concentration [74] – with significant implications for the bioavailability of androgens [41].

Oestrogen therapy has been shown to provide significant relief of menopausal somatic symptoms, such as hot flashes, night sweats and vaginal dryness [41]. However, it often does not provide adequate restoration of sexual desire, potentially because of its effect on SHBG and androgens. Oestrogen replacement therapy, particularly at higher doses and when administered orally (as oral contraceptives or hormone replacement therapy), increases the liver's synthesis of SHBG, thereby decreasing the free, bioavailable testosterone for uptake by target tissues due to the strong binding affinity of testosterone to SHBG [75]. Consequently, oral oestrogen therapy may decrease the endogenous production, metabolism and bioavailability of both ovarian and adrenal androgens [41,42,76,77]. However, transdermal oestrogen replacement therapy seems less likely to elevate SHBG except at very high doses [6].

2. History of androgen use in women

Historically, male sexual function and masculinity have been identified with androgens, and this has contributed to the lack of recognition of the effects of androgens in women. One of the earliest descriptions of androgen use in women was reported by Geist and Salmon in 1941, who used testosterone for the treatment of menopausal symptoms, menometrorrhagia, dysmenorrhoea, premenstrual tension, ovulatory pain, endometriosis and mastopathies [78]. The use of methyltestosterone (MT) was reported by Greenblatt in 1950 to improve libido and well-being. Since then, androgen therapy has been

reported in androgen-deficient women for its effects on sexual function, mood, muscle mass and strength, psychological well-being, energy and bone density.

3. Goals of androgen therapy in female sexual dysfunction

Androgens are an important factor in female sexual functioning, particularly sexual desire, as there is increasing evidence that women with androgen insufficiency experience alleviation of their symptoms of fatigue, low libido and diminished well-being with androgen replacement therapy. Although a precipitous drop in androgen production is not seen at the menopause transition, androgen levels slowly and progressively decline over time with age. The impact of this age-related androgen decline and the pharmacological effects of oral oestrogen replacement therapy, reduces the bioavailability of androgens, leading to the clinical manifestations of androgen deficiency.

The goals of androgen replacement therapy are to alleviate the symptomatology of androgen insufficiency and, thereby, improve quality of life while minimising potential adverse reactions and risks. Current androgen replacement therapy is considered 'off-label' as it is not yet FDA-approved for use in women with sexual dysfunction. However, numerous clinical trials are currently underway in several countries to evaluate the safety and efficacy of various therapies in women with androgen insufficiency and clinical signs and symptoms of sexual dysfunction. Long-term, large-scale, randomised, placebo-controlled clinical trials will be necessary along with FDA-approval before full treatment recommendations and algorithms for androgen therapy can be implemented.

4. Availability and efficacy of androgen therapy

The majority of available testosterone preparations for human use have been formulated for use in men. Furthermore, few countries have officially approved the use of testosterone for hormone replacement therapy (HRT) in women, and clinical guidelines for its safe administration are lacking. In addition, there have been a number of limitations in evaluating the role of androgen deficiency in FSD. A major obstacle in the design of clinical trials has been the need for sensitive and reliable measures of outcome. The development of validated instruments as primary end points in clinical trials, as well as for screening and diagnostic purposes, has furthered the understanding of female sexual disorders. However, few validated instruments have been developed to assess secondary end points such as life satisfaction or quality of life changes.

Self-report measures developed for assessing female sexual function across domains of desire, arousal, orgasm and satisfaction have demonstrated a high degree of reliability and validity. However, assessment of sexual function in

women with androgen insufficiency is frequently confounded by the effects of depressed mood or other comorbid medical or psychiatric disorders. Furthermore, premorbid sexual functioning is typically not assessed, and the effects of treatment may be confounded by pharmacological effects of supraphysiological testosterone administration. In addition, inadequate power due to low sample size, as well as lack of distinction of surgically versus naturally menopausal women, and the contribution of placebo effect, all contribute to the overall difficulty in evaluating androgen therapy in women.

A guidance document of FSD, issued by the Center for Drug Evaluation and Research of the FDA, outlines the FDA's recommendation for the conduct of clinical trials in FSD [146]. Clinical trials should entail: essential components of FSD definition and classification; the use of appropriate study populations involving women for whom sexual dysfunction causes personal distress, (i.e., premenopausal women, surgically versus naturally menopausal women, women taking oral contraceptives or hormone replacement therapy); the exclusion of confounding factors (i.e., partner dysfunction, comorbid illness, medications); the use of validated instruments; and placebo-controlled trials.

Intramuscular testosterone has been shown to be efficacious in oophorectomised women [30]. Low doses of oral MT (1.25 – 2.5 mg) along with esterified oestrogens (EEs) have been shown to be beneficial for menopausal symptoms, bone mass and, possibly, improving sexual function and quality of life [30]. Testosterone implants (50 mg pellets) and oral DHEA have been extensively studied in the past [79], and current trials are underway examining the testosterone transdermal patch (150 or 300 µg dose) for use in women [80]. Testosterone gel has been approved for use in men, demonstrating efficacy in sexual function, mood, muscle strength and body composition [81,82]. Sublingual, buccal and vaginal testosterone has been explored along with DHT and androstenedione transdermal gels/creams. Such preparations may be regionally available by specific prescription from compounding pharmacists. However, there are few clinical trials and pharmacokinetic data on the use and safety of these preparations in women and these approaches have not been subjected to efficacy trials in women [30].

Several controlled trials have assessed the effects of oestrogen alone, compared with oestrogen plus testosterone on sexual function [80-95]. Burger *et al.* [88] conducted a single-blind study of a mixed group of 17 surgically and naturally menopausal women, who complained of loss of libido despite treatment with oestrogen, and received subcutaneous implants of estradiol 40 mg and testosterone 100 mg. By the third month following implantation, patients reported a significant increase in libido, enjoyment of sex and in the frequency of orgasm and initiation of sexual activities. In another study by the same authors [90], a double-blind trial demonstrated that additional testosterone was required by postmenopausal women whose lack of libido persisted despite adequate oral

oestrogen and progestin replacement even though symptoms of hot flashes and vaginal dryness were relieved. Patients randomly received a subcutaneous implant containing either oestradiol 40 mg or oestradiol 40 mg and testosterone 50 mg. After 6 weeks, the loss of libido in the oestrogen-only implant group remained, whereas the combined oestrogen-testosterone group demonstrated significant symptomatic relief [88]. Furthermore, Davis *et al.* [89] demonstrated that the addition of testosterone to an oestrogen replacement regimen reversed the loss of libido in postmenopausal women that had not been alleviated with an equivalent dose of oestrogen alone.

Sarrel *et al.* [93] contributed to the accumulating evidence that the addition of testosterone to an oestrogen treatment regimen significantly increases the level and frequency of sexual desire and heightens sexual receptivity in postmenopausal women complaining of hypoactive sexual desire. The authors in this randomised, controlled, multi-centre trial compared the efficacy of oral EEs 0.625 mg plus MT 1.25 mg with that of oral EEs 0.625 mg alone in postmenopausal women who scored in the hypoactive sexual desire range at baseline, despite having been treated with oestrogen-alone. The fact that levels of bioavailable testosterone correlated positively with sexual interest score following 16 weeks of treatment further supports the cause-and-effect relationship between testosterone and aspects of sexual functioning in women [93,94].

Similarly, Lobo *et al.* compared the effects of oral EE 0.625 mg alone, with EE 0.625 mg plus MT 1.25 mg in 218 postmenopausal women over a 4-month treatment period [95]. The combination therapy was associated with significantly greater increases from baseline in scores for sexual desire and frequency of desire than the oestrogen-only therapy ($p < 0.02$) [95]. Furthermore, studies of androgen therapy in premenopausal women who have had an oophorectomy or who have adrenal insufficiency have been shown to demonstrate positive results [91].

Recently, the efficacy of a transdermal testosterone patch has been reported for the treatment of postmenopausal women in a randomised, double-blind cross-over study of 75 healthy women 31 – 56 years of age who had undergone hysterectomy and oophorectomy and reported impaired sexual functioning, despite being on oestrogen replacement therapy. Random assignment of testosterone 150 and 300 $\mu\text{g}/\text{day}$ was administered transdermally for 12 weeks. Outcome measures included scores on the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index and a sexual-function diary. Despite a high placebo response rate, treatment with conjugated equine oestrogens (CEE) and testosterone 300 $\mu\text{g}/\text{day}$ was associated with significant increases in the frequency of sexual activity, as well as pleasure and orgasm ($p = 0.03$), as levels of bioavailable testosterone rose to the upper limit of the normal female range [83].

In addition, Simon *et al.* [80] recently completed a 24 week, randomised, double-blind, Phase III trial of testosterone 300 $\mu\text{g}/\text{day}$ by transdermal patch in 562 surgically menopausal

women with hypoactive sexual desire disorder who were receiving stable doses of oral or transdermal oestrogen. Compared with placebo, treatment with testosterone 300 $\mu\text{g}/\text{day}$ resulted in significant increases in frequency of total satisfying sexual activity ($p = 0.0003$) and sexual desire ($p = 0.0006$).

Tibolone, a synthetic steroid, is used extensively throughout Europe and Asia for the management of climacteric symptoms, as well as the proposed additional benefits of improved libido and mood. Tibolone possesses a 3-keto group with a 7 α -methyl group, which is quickly metabolised upon ingestion in the gastrointestinal tract to two oestrogenic metabolites, 3 α and β , which then circulate predominantly in their inactive sulfated forms [96]. These metabolites become oestrogenically active when desulfated by the sulfatase enzyme in target tissues. Tibolone and its 3 β metabolite may also be converted to a $\Delta 4$ -isomer that binds and transactivates the progesterone receptor and the androgen receptor thus exerting progestogenic effects on the endometrium [96]. Tibolone has also been shown to alleviate postmenopausal vasomotor symptoms without stimulating the endometrium [97]. Consequently, there is neither a requirement for progestin nor induction of cyclical bleeding. Tibolone also significantly lowers SHBG and increases circulating free testosterone, thereby adding to its androgenicity [98].

A placebo-controlled trial was undertaken specifically to measure sexual function in healthy postmenopausal women treated with tibolone versus placebo for 3 months [99]. Tibolone was shown to significantly improve the physiological aspects of sexual function, such as vaginal blood flow and lubrication, as well as subjective measures, such as sexual desire and arousability. However, the frequency of sexual function, initiation and rejection of sexual activity and orgasm were unchanged when compared with placebo. The small sample size in the subgroups ($n = 38$) may have diminished the power to detect statistical differences between the groups. Nathorst-Boos and Hammar [100] compared the effect of tibolone to the combination of estradiol and norethisterone acetate (E2/NETA). A modified McCoy sexual questionnaire was administered to 437 postmenopausal women, and both preparations significantly improved libido ($p < 0.001$). A greater effect was seen with tibolone after 24 and 28 weeks of treatment in terms of overall scores for frequency of sexual activity, satisfaction and enjoyment.

As a result of evidence from randomised and placebo-controlled trials, tibolone may improve libido and other aspects of female sexuality to a greater extent than conventional HRT, most likely because of its combined oestrogenic, androgenic, and SHBG-lowering effects. Further studies are necessary to delineate whether tibolone improves sexual function in postmenopausal women with low libido and androgen insufficiency by increasing free testosterone.

4.1 Dehydroepiandrosterone

Currently, DHEA is considered an over-the-counter dietary supplement for which consistency of grade and quantity in

these preparations has been questioned. In assessing the quality and content of DHEA supplements, 17 DHEA-labelled bottles from various sources were analysed for actual DHEA content. Tablets from three vendors contained no DHEA, whereas most contained 59 – 82% of the expected amount. However, one tablet contained significantly more DHEA than the amount actually stated on the label [101]. DHEA (usually in dose ranges of 25 – 50 mg) has been used in menopausal women for its many purported benefits previously published, which include a decrease in insulin resistance, obesity and beneficial effects on bone density, skin hydration and immune function [102-105]. However, the risk-benefit ratio for breast and cardiovascular protection remains controversial [106-108].

The pharmacology and lowest effective dose of DHEA is unknown. However, in keeping with the findings of previous single-dose pharmacokinetic studies [53,109], Arlt *et al.* [110] found that a single dose of DHEA 50 mg/day given to women with adrenal insufficiency and pronounced androgen insufficiency resulted in significant improvement in well-being and sexuality, as well as no significant effect on body composition, exercise capacity or fasting glucose and insulin levels [110,111]; therefore, this seems to be a suitable, physiological replacement dose for women with adrenal insufficiency. Supraphysiological dosing as high as 1600 mg/day have produced conflicting results in human studies [19,112,113]. Furthermore, higher doses of DHEA have been reserved for the medical management of patients with autoimmune disease, such as lupus [114,115]. Further long-term trials of DHEA in patients with adrenal insufficiency are needed to better elucidate the physiological role of DHEA.

It should be noted that not all studies show a beneficial effect of DHEA on female sexual function. Some have reported an improved sense of well-being, but no improvement in libido or sexual function when high doses of 100 mg/day were given [116]. Others have found neither an improvement in well-being nor sexual function after 6 months of DHEA 50 mg/day treatment [117]. DHEA, however, has been proven to be most effective in improving female sexual function when either a lack of adrenal DHEAS synthesis (adrenal insufficiency) or a loss of ovarian testosterone secretion (natural or surgical menopause) is responsible for the androgen deficit [105].

Premenopausal women with androgen insufficiency may be appropriate candidates for DHEA supplementation as DHEA may be used as an androgen precursor building block to gently allow serum testosterone levels to rise to the normal female range. In premenopausal women, DHEA 50 mg/day has been shown to restore young adult female DHEAS and androgen levels and may improve sexual function [110].

In addition, Johannsson *et al.* [118] evaluated the effect of DHEA on quality of life, well-being and behaviour with secondary end points of evaluating the effects of DHEA treatment on skin, hair, glucose and lipid metabolism, body composition, bone metabolism and safety. In this randomised, placebo-controlled, double-blind study, 38 women,

25 – 65 years of age, with androgen deficiency due to hypopituitarism were treated with oral DHEA; 30 mg/day if < 45 years of age and 20 mg/day if ≥ 45 years of age for 6 months; demonstrating that oral administration of a low dose of DHEA to adult hypopituitary women induced androgen effects on skin and axillary and pubic hair, as well as changes in behaviour, with only minor effects on metabolism. Further research is needed on the role of DHEA in premenopausal as well as postmenopausal women to delineate appropriate dosing and route of administration, and appropriate candidates for DHEA therapy.

4.2 Safety of androgens

Androgen therapy in clinical trials involving postmenopausal women has generally been well tolerated. Theoretical virilisation-related side effects associated with androgen therapy, such as: hirsutism, acne, irreversible voice deepening, weight gain, oily skin, male-pattern balding, emotional changes (i.e., increased anger) and adverse changes in liver and lipid function, are rare in clinical trials involving women undergoing low-dose androgen replacement therapy [119]. These side effects, however, have been commonly encountered in female-to-male transsexuals taking supraphysiological doses of androgens [120]. Androgens also influence mood and behaviour, and anger has been demonstrated to occur in women taking supraphysiologic doses of androgen replacement. Sherwin and Gelfand [121] found an increase in hostility scores among postmenopausal women taking testosterone enanthate 200 mg/month i.m. Studies using low-dose androgens have not reported this adverse effect in women [83,90,95,122-125].

Methyltestosterone use (both 1.25 and 2.5 mg doses) has been shown to result in mild acne and hirsutism, which resolves after discontinuation of the drug [95,122,123]. High-dose parenteral androgens may cause frank virilisation (clitorimegaly, male pattern balding and voice changes) [126]. However, daily transdermal replacement with patches containing testosterone 150 or 300 µg has not been shown to result in higher acne or hirsutism scores, thereby providing the safest option currently available for preventing these adverse effects [83,85].

The tolerability and safety profiles of testosterone therapy depend on the dose and route of administration. For instance, oral administration of testosterone is associated with significant decreases in high-density lipoprotein (HDL) cholesterol, whereas testosterone administered by non-oral routes, such as via a transdermal approach, does not seem to have an impact on lipoprotein lipid levels [84]. Furthermore, high doses of alkylated androgens can result in hepatotoxicity and hepatic adenomas [127]. However, no trial of androgen therapy for women has resulted in elevation of hepatic enzymes or in hepatic failure [83,93,95,122,123].

In addition, the use of testosterone therapy among reproductive-aged women may potentially have virilising effects on the female fetus during pregnancy. However, such effects have not been observed in women who receive substantially lower

doses of androgens for replacement therapy, and avoidance of suprphysiological serum androgen levels will help to minimise these unwanted effects.

The US FDA Advisory Committee for Reproductive Health Drugs has not yet approved the use of the transdermal testosterone patch in women due to the concern of lack of data on the long-term safety of the patch, as well as the small sample size studied so far. Given the paucity of long-term, placebo-controlled trials, female patients should be fully informed of potential risks of off-label use of testosterone in the US and be carefully monitored for potential adverse reactions.

5. Current best practice

Androgen insufficiency underpins a variety of symptoms and pathophysiological conditions that warrant androgen replacement therapy in certain subsets of women. Testosterone therapy in preparations and formulations specifically designed for use in women with sexual dysfunction requires FDA approval, and numerous clinical trials are currently underway evaluating the long-term safety of these various treatment regimens.

Given the lack of sufficient epidemiological data, evidence of long-term safety and accurate and reliable androgen assays for women, appropriate candidates for consideration of androgen replacement therapy should be women with clear clinical symptoms of androgen insufficiency and physiological aetiology for decreased androgen production. Attention should be given to any exogenous form of oestrogen administration (i.e., oral contraceptives or oestrogen replacement therapy), which may lower the bioavailability of testosterone by raising SHBG levels. Efforts should be made to discontinue these regimens, or switch to an alternative non-oral formulation that has less impact on SHBG.

The endogenous oestrogen milieu should be optimised in normally cycling premenopausal women and in postmenopausal women with vasomotor symptoms and vaginal dryness. Vaginal oestrogen (in the form of a tablet, ring or cream) may alleviate vaginal dryness and improve lubrication. Transdermal oestrogen may relieve vasomotor symptoms without the first pass hepatic metabolism effect of raising SHBG levels, as observed with oral oestrogen therapy. The potential risks, benefits, indications and alternatives of hormone replacement therapy should be extensively reviewed and discussed with the patient, including the potential risk of invasive breast cancer, myocardial infarction, stroke, pulmonary emboli and deep vein thromboses; particularly in women with a history of thromboembolic disorders and/or women > 35 years of age who smoke.

In a postmenopausal woman with an intact uterus, progesterone therapy must be administered concurrently with oestrogen replacement to decrease the risk of endometrial hyperplasia, which can proceed to endometrial neoplasia. Because of these risks, oestrogens with or without progestins should be used at the lowest effective dose for the shortest duration, consistent with treatment goals and risks for the individual woman.

Baseline testosterone levels prior to initiation of therapy should be below normal or in the lowest quartile of the normal threshold for women, with goals of achieving normal female physiological levels instead of suprphysiological replacement. Baseline lipid and hepatic panels should be performed initially to identify underlying pathology, and monitored intermittently for adverse effects of androgen therapy on these parameters. Concomitant monitoring of androgen levels and clinical symptoms in response to therapy should be ascertained with the inclusion of free and total testosterone and SHBG levels, and calculation of the free androgen index (FAI) – total testosterone nmol/l \times 0.0347 \times 100/SHBG nmol/l (realising that the FAI is unreliable when SHBG levels are low) [128] – with cognisance of the need for validated testosterone assays with improved sensitivity and specificity to detect the low and normal ranges of testosterone in women. Clinical virilising symptoms should be elicited from the patient during the course of therapy to minimise adverse side effects. Relative contraindications to testosterone therapy include moderate-to-severe acne, clinical hirsutism, androgenic alopecia and circumstances in which enhanced libido would be undesirable [129]. Absolute contraindications to therapy include pregnancy, lactation, as well as known or suspected oestrogen or androgen-dependent neoplasia.

Numerous clinical trials have attempted to delineate the efficacy of various forms of androgen therapy in the form of DHEA, testosterone, DHT or androstenedione; which may be administered orally, via sublingual or buccal absorption, subcutaneous implants, transdermal creams, gels, sprays and patches. The most recent data on the efficacy of the transdermal therapies seem to give the best balance between achieving physiological testosterone levels, without the peaks and troughs seen with the other routes of administration; and with the most favourable safety profile in terms of the lipid and liver effects [83,130].

The further elucidation of the role of androgens in hormone replacement therapy, as well as the long-term safety in both pre- and postmenopausal women, the range of normal values of various androgens throughout different phases of the reproductive life cycle and sensitive androgen assays, awaits the results of randomised, double-blinded, placebo-controlled trials that are currently underway.

6. Other issues

6.1 Use of androgens in breast cancer

Both androgen and oestrogen receptors are expressed in mammary epithelium [131], and experimental evidence suggests that androgens normally inhibit the oestrogenic effects on mammary growth. However, it is unknown at this time whether or not there is any relationship between exogenous androgen therapy and the incidence of breast cancer, as epidemiological studies have shown both positive and negative associations between endogenous androgen levels and breast

cancer risk [129,131]. There is also the theoretical risk of aromatisation of androgens into oestrogens in target tissue, which may have potential deleterious impact on women with a history of breast cancer or any oestrogen-dependent neoplasia. Androgen receptors are found in > 50% of breast tumours and are associated with longer survival in women with operable breast cancer and a favourable response to hormone treatment in advanced disease [132,133]. In fact, clinical observations and experimental data indicate that androgens inhibit mammary growth and have been used with success similar to that of tamoxifen to treat breast cancer [131].

To investigate the potential use of DHEA as a physiological approach for the prevention of breast cancer in women, Li *et al.* [134] treated mice with increasing doses of DHEA delivered constantly by SILASTIC-brand implants of increasing length and number which caused a progressive inhibition of tumour development. This study shed light on the possibility that DHEA and its metabolites could have a preventative effect on the development of mammary carcinoma. Furthermore, treatment with DHEA has been shown to induce androgen-sensitive gene expression in the rat ventral prostate, suggesting that DHEA exerts its inhibition of breast cancer development and growth through its conversion to androgens and activation of the androgen receptor [135,136].

In addition, epidemiological studies have observed a protective effect of DHEA on breast cancer, especially among Western women, as low serum DHEA levels have been found to be associated with breast cancer [137-140]; suggesting that a low secretion rate of DHEA and DHEAS could precede the development of breast cancer [139]. Further studies are needed to evaluate the efficacy of supplementing hormone therapy with androgens and ensuing breast cancer risk, as well as to better understand the role of androgens versus oestrogens on breast tissue.

6.2 Androgens and cardiovascular health

In recent years, there has been a dramatic increase in research into androgen effects on the cardiovascular system. Whereas previously, androgens were considered harmful (and oestrogens protective) for the cardiovascular system, current evidence suggests that androgens have beneficial or neutral cardiovascular effects and that they exert different effects at early (plaque formation) and late (rupture, thrombosis, vasospasm) stages of atherosclerosis [141]. An increasing number of studies demonstrate protective effects of androgens on cardiovascular function. However, these findings derive almost entirely from male patients, and hold undetermined relevance for women's cardiovascular health. Nonetheless, limited human data does suggest that testosterone exposure does not shorten lifespan in either gender, and oral oestrogen treatment increases the risk of cardiovascular death in men as it does in women. Patterns of age-specific cardiovascular death rates provide little support for the gender gap being due to oestrogen protection. Rather, androgen exposure in early life (perinatal androgen imprinting) may predispose males to

earlier onset of atherosclerosis, but the subsequent tempo of atherosclerotic progression is similar in men and women [141].

Coronary artery disease (CAD) is the leading cause of mortality in women, with its incidence increasing after menopause [142]. Low high-density lipoprotein (HDL) levels in elderly postmenopausal women are considered a stronger risk factor for CAD than elevated low-density lipoprotein (LDL) levels [143]. Furthermore, elevated triglyceride (TG) levels are considered a risk factor for cardiovascular disease in women [144]. It has been demonstrated that aromatisable androgen preparations such as transdermal testosterone do not affect lipid profiles [84], in contrast to oral androgens, such as MT which decreases total cholesterol (TC), TG and HDL levels, while having a neutral effect on LDL levels [119]. In terms of the effect of hormones on the vascular system, endothelial dysfunction is considered an early marker of vascular disease and is characterised by a decrease in flow-mediated vasodilation [119]. It has been demonstrated that testosterone replacement in women does not result in endothelial dysfunction and improves both endothelium-dependent and endothelium-independent vasodilation [145]. Increased plasma viscosity, clotting factors, polycythaemia and insulin resistance are all risk factors for cardiovascular disease, and studies have begun to examine the impact of androgen replacement therapy on these factors [83,124,125]. However, future research will aim to better define the role of androgens on cardiovascular factors such as the vasculature, plasma viscosity, coagulation, polycythaemia and insulin resistance, as well as promote a clearer understanding of the effect of lipid changes on women's cardiac outcomes, and the potential effect of androgen replacement on overall cardiovascular mortality.

7. Expert opinion

Increasing evidence suggests that women experience symptoms of androgen insufficiency that can be alleviated by androgen therapy. In an era of longer life expectancies and immense proliferation of studies addressing male sexual function, women have demanded an improvement, not only in their quality of life, but also in the capacity to maintain and enjoy sexual relationships.

In characterising a woman most likely to respond to androgen therapy, it is essential to discriminate the multiple factors that can produce the clinical signs and symptoms of androgen deficiency by identifying concurrent oestrogen therapy use (in the form of oral oestrogen replacement or oral contraceptive use), which may impede testosterone bioavailability; and clinically optimising the oestrogen milieu with either transvaginal oestrogen to treat vaginal thinning and dryness, and/or systemic transdermal oestrogen applications to treat vasomotor symptomatology; bearing in mind the need to utilise concomitant progesterone therapy in women with an intact uterus. Until more sensitive assays are available for detecting low testosterone levels in women, it is advisable to carefully

monitor testosterone levels with free and total testosterone, SHBG and calculation of the FAI, so as to maintain physiological levels of androgen therapy and correlate these levels with clinical improvement and/or side effects. As androgen therapy to treat FSD is considered 'off-label', women should be fully informed of potential risks and adverse effects of treatment.

The choice of androgen therapy should be individualised, based on a woman's clinical history, age, symptomatology and response to therapy, while minimising potential side effects. Future studies will further elucidate the role of androgens in premenopausal women with androgen insufficiency, and identify ethnic variations in postmenopausal ovarian androgenic activity as it may influence a patient's decision to undergo oophorectomy at the time of hysterectomy; as well as future clinical benefits from testosterone

therapy. Furthermore, sensitive and reliable assays for measuring the lower ranges of testosterone in women are necessary to better understand the relationship between laboratory values throughout the lifespan and the establishment of laboratory thresholds for diagnosis of androgen insufficiency, its clinical symptoms and sequela. Future studies will also illuminate the effects of androgen insufficiency and replacement on female sexual function, bone mineral density, muscle strength, energy, mood, cognitive function and breast cancer risk. Lastly, the safety and efficacy of specific androgen replacement therapies will be further defined by long-term, large, randomised, double-blinded, placebo-controlled clinical trials that will characterise specific regimens that will achieve physiological androgen levels while minimising side effects, and optimising clinical response.

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