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Review

Androgens in women☆

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Abstract

The role of androgen treatment in women remains controversial. The proposed "Female Androgen Insufficiency Syndrome" (Fertility and Sterility, April 2002) describes a number of non-specific symptoms including unexplained fatigue, decreased well being/dysphoric mood and/or blunted motivation and diminished sexual function. An estimated 40% of women experience sexual dysfunction, highlighting the need for ongoing research into this field in order to fully define the possible contribution of androgen insufficiency. The increasing availability of products, such as dehydroepiandrosterone (DHEA) supplements also points to the need for controlled studies to assess the safety of these and other preparations.

Measurement of androgens in women requires sensitive assays with the ability to detect low levels and a narrow range with precision. Normal ranges of androgens for women of reproductive and post-reproductive age remain poorly defined. Debate exists as per importance of measurement of free versus total testosterone, with the 'free androgen index' offering an alternative method of assessment of testosterone availability.

Testosterone treatment is being developed for women in the form of transdermal patches, gels or cream, with percutaneous implants in common usage in some countries. Recent research has highlighted alternative means of administration, such as oral inhalation or buccal lozenge. DHEA is widely available in some countries. Research to date has demonstrated improvements in libido and sexual function, mood and well being. Evidence points to other potential benefits of androgen treatment, including preservation of bone mass, a possible protective role in breast cancer and beneficial effects on cognition.

Adverse effects of androgen treatment in women are dose-dependent and include virilisation, mood disturbance and acne. These are uncommon if appropriate doses are administered and highlight the need for treatment to be closely monitored clinically and biochemically. Beneficial effects of testosterone treatment in post-menopausal women with lowered androgen levels have been well documented, and preliminary evidence suggests a role for treatment in pre-menopausal women with symptoms and lowered testosterone levels.

The level of interest in the role of androgens in men and women remains high, both in the scientific community and the general public. The increasingly ageing population in developed nations has been associated with emphasis on preservation of youth, memory and sexual function. As such a number of different androgen preparations have been marketed for men and women, with varying levels of evidence to support their use. The scientific literature to date has focused on defining the physiological roles of androgens in men, whilst the actions of androgens in women remain less well understood. There is increasing evidence for widespread anatomical distribution of androgen receptors in women, in areas as diverse as breast, bone and brain. This widespread distribution of receptors indicates that androgens and their metabolites may have important roles in pathologies as diverse as breast cancer, osteoporosis or even cognitive decline. As such the further definition of the role of androgens in both men and women, beyond the areas of growth and sexual differentiation, remains a research priority.

Androgen production in women is ovarian and adrenal based. The principle androgens, in order of increasing potency, include dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione and testosterone. The ovaries and adrenal glands vary in terms of their absolute contributions to the total androgen pool. Evidence suggests that the ovaries and adrenals contribute 50% each to the total testosterone and androstenedione levels [1] whereas more than 90% of DHEAS has been estimated to originate from the adrenals [2]. Our current understanding of androgen metabolism is based on measuring serum levels of these hormones and their metabolites, however the less well understood intracellular actions of these hormones are likely to be of fundamental importance to their end-organ effects. Much remains to be delineated in terms of the physiological role of each androgen or metabolite. For example,

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we still do not know to what degree androgen action occurs via aromatisation to estrogen. Clinical studies currently in progress aim to specifically address this area.

Debate currently exists over which method is best for analysing female testosterone levels, and also the importance of measurement of free versus total testosterone. Given that 66% of testosterone is bound to SHBG in women, and that only 1–2% of testosterone is estimated to be free or biologically available, any factor influencing SHBG levels will consequently affect testosterone levels [3]. Oral estrogen and thyroxine are known to increase SHBG, whereas obesity, growth hormone, hyperinsulinemia and glucocorticoids all decrease SHBG. Free testosterone reflects biologically available testosterone, yet the accuracy of analogue assays for free testosterone has been questioned [4]. A ratio of total testosterone to SHBG, namely the "free androgen index" has been proposed as one means of calculating bioavailable testosterone in females, however this has not been adequately studied in women to date.

Inherent to the lack of understanding of the role of androgens in women is the difficulty with current biochemical methods of androgen estimation. Assays for estimation of testosterone, for example, are generally designed to accurately estimate the much higher levels of testosterone present in males. Testosterone levels in women have been estimated to be approximately one tenth of the levels in men [1] and lie within a narrow range. Research over recent years has attempted to more accurately estimate female levels, using various assays. The gold-standard for free testosterone estimation is considered to be via equilibrium dialysis [4]. Sinha-Hikim et al. estimated circulating free testosterone levels over the normal menstrual cycle for 34 healthy women using equilibrium dialysis, reporting means of 1.2 ± 0.7 nmol/l for total, and 12.8 ± 5.5 pmol/l for free testosterone [5]. A 20–30% pre-ovulatory increase prior to the LH peak was seen for both total and free testosterone. This means of measuring testosterone is costly and time-consuming, and as such is not widely available. The challenge therefore is to determine which alternative assay can accurately and precisely measure female testosterone levels, in the least time and for the least monetary cost.

The pursuit of accurately characterising female levels of androgens is central to defining the controversial "Female Androgen Insufficiency Syndrome". Described by a team of international investigators with an interest in this area, the 'Princeton Consensus Statement' outlines a number of non-specific symptoms thought to characterise this proposed syndrome [6]. These include: decreased well being/dysphoric mood and/or blunted motivation; persistent, unexplained fatigue, and sexual dysfunction including lowered libido, sexual receptivity or pleasure. In addition, a number of potential clinical features are outlined, including decreased bone mineral density, decreased muscle strength, and changes in cognition and memory. The consequences of androgen deficiency in men are well-characterised, and include osteopenia, changes in body composition and lowered mood or well being. The body of evidence for these consequences, and indeed the existence of a clinically relevant androgen deficient state in women, is limited, and current studies aim to determine if there is a link between lowered androgen levels in women and these clinical and psychological features.

The known causes of androgen deficiency in women can be broadly grouped as being those due to ageing versus those due to pathological/iatrogenic processes. In terms of changes with ageing, we currently lack normative data for androgen levels from the early reproductive to the post-menopausal years. This area is currently being examined by members of our group. Some debate exists as to the timing of the decline in androgen levels with age in women, with the current evidence suggesting that the fall in androgens is not as clearly defined as the sharp fall in oestradiol at menopause, as perhaps may be expected with the decline in general ovarian function at this time. In terms of testosterone, recent evidence suggests that the fall begins as early as the third decade in women [7,8] with a gradual decline thereafter. Others have reported a lack of change in testosterone levels across the menopausal transition [9]. There is evidence that there is no further decline in testosterone after menopause, with a suggestion that there is a slight increase postmenopausally, possibly due to ongoing stimulation of the ovary by relatively high levels of luteinizing hormone [10]. This finding has recently been challenged by Couzinet et al. who conversely described a lack of evidence for ongoing androgen production by the post-menopausal ovary [11]. Evidence for an age-related decline in dihydrotestosterone (DHT), DHEAS and androstenedione is such that the most recent evidence suggests a fall from the third decade, as reported for testosterone [7]. Age related falls in DHEAS have been previously reported in both men and women, with the slope of decline being steeper in women as compared to men [12,13].

Pathological or iatrogenic causes of androgen deficiency in women include: hypopituitarism, adrenal insufficiency, ovarian insufficiency or removal, medications, HIV infection, and hypothalamic "stress". Miller et al. reported decreased levels of testosterone, DHEAS and androstenedione in hypopituitary women compared to healthy controls. In addition, a lack of the mid-cycle increase in free testosterone was seen in pre-menopausal women with hypopituitarism compared to controls [14].

Others have reported a 50% or greater fall in testosterone and androstenedione following removal of both ovaries, suggesting the ovaries and adrenal glands equally share production of these androgens, at least premenopausally [15]. Levels of both total and free testosterone have been found to be lower in women infected with HIV versus healthy women [5]. Medications in widespread use which can cause a reduction in androgen levels include oral oestrogen and glucocorticoids [2].

Although the proposed syndrome of female androgen insufficiency remains controversial, various authors

have reported on the benefits of androgen treatment in women, with the bulk of studies having been performed in post-menopausal women. Debate exists as to whether the benefits seen from treatment with testosterone represent a physiological versus a pharmacological effect, with some studies using supraphysiological doses of various androgens. In terms of sexuality, benefits have been reported for testosterone administered sublingually [16], via subcutaneous pellet [17], injection [18] and transdermal patch [19], and also for DHEA at physiological doses in women with adrenal insufficiency [20].

Recently benefits in terms of sexual function have been reported for pre-menopausal women, using transdermal testosterone cream [21]. Positive changes in mood and well being have been reported for oral DHEA use in women with adrenal insufficiency [20] and the transdermal testosterone patch [19].

In combination with estrogen, testosterone has been found to improve bone mineral density, when administered orally as methyltestosterone [22], or via subcutaneous testosterone pellet [17]. Similarly, intramuscular nandrolone use has been associated with increases in bone mineral density [23,24]. Body composition changes following administration of androgens are such that members of our group reported an increase in fat-free mass with concomitant use of subcutaneous estradiol and testosterone pellets [25], with another study reporting increased lean weight following nandrolone treatment [26]. In terms of absolute cardiovascular risk, only surrogate markers have been studied in relation to androgen treatment in women, in the form of lipid profile and endothelial dilatation. A reduction in HDL has been reported with oral use of DHEA [20] and methyltestosterone [27]. In direct contrast with these findings, transdermal or subcutaneous deliveries of testosterone have both been associated with no blunting of the positive effects of estradiol on the lipid profile [19,25].

Oral androgens administered to women include DHEA, testosterone undecanoate and methyltestosterone. The agent tibolone, although primarily a progesterone, has weakly androgenic effects. Non-oral forms of androgens include nandrolone, intramuscular testosterone esters and subcutaneous testosterone pellets. Transdermal testosterone cream, gel and patch are currently the subject of clinical studies. The ideal androgen preparation for use in women will combine safety, clinical efficacy, and will reliably maintain androgen levels within the female normal range. Adverse effects from androgen use in females have included excess hair growth, acne, virilisation and alterations in voice. These have been reported mostly with administration of supraphysiological doses of androgens.

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