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The therapeutic use of androgens in women ☆

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Abstract

Androgens have significant and varied actions in women and there is now acknowledgment that women may experience symptoms secondary to androgen deficiency. There is also substantial evidence that prudent androgen replacement can be effective in relieving both the physical and psychological symptoms of androgen insufficiency, and is indicated for clinically affected women. Testosterone replacement for women is now available in a variety of formulations. It appears to be safe, with the caveat that doses are restricted to the 'therapeutic' window for androgen replacement in women, such that the beneficial effects on wellbeing and quality of life are achieved without incurring undesirable virilizing side effects.

The predominant symptom of women with androgen deficiency is loss of sexual desire. This is not limited to women experiencing a surgical menopause but may also be a feature of women who have either undergone premature or natural menopause. There is increasing interest in other uses of androgen replacement in women that include premenopausal iatrogenic androgen deficiency states, glucocorticosteroid-induced bone loss, management of wasting syndromes and possibly premenopausal bone loss, premenopausal loss of libido and the treatment of the premenstrual syndrome.

Keywords: Testosterone and menopause; Androgens in women; Hormone replacement therapy

1. Introduction

In women, the adrenal glands and ovaries produce the circulating androgen testosterone (T) androstendine (A) and dehydroepiandrosterone (DHEA). These steroid hormones have important physiological actions in women, either directly via androgen receptors throughout the body, or as important circulating precursor hormones for the synthesis of estrogen in the ovaries and extra gonadal tissues. At menopause there is a sudden drop in circulating estrogen. In contrast the decline in androgens most closely parallels increasing age. The absolute declines in circulating hormone and the adrenal pre-androgens commences in the decade preceding menopause [1,2]. Hence many women experience symptoms of androgen deficiency in the immediate premenopausal years. Androgen deficiency in women may be manifest as impaired sexual function, lessened well being, loss of energy and negative effects on bone mass [3–6]. These symptoms usually develop insidiously and most women are not aware that such symptoms may have a biological basis. Therefore it is important to directly question women about such symptoms when hormone replacement therapy is being considered and again at subsequent consultations. Otherwise many women for whom androgen replacement therapy may be appropriate and beneficial may remain unidentified and untreated.

2. Androgen physiology in the reproductive years

The ovaries and adrenal glands both produce T,A and DHEA, however the adrenals are the main site of production of DHEA-sulphate (DHEA-S). Approximately 50% of total circulating T is derived

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from peripheral conversion of the adrenal preandrogens to T, with A being the main precursor [7]. T is also further metabolised to the potent androgen dihydrotestosterone (DHT). In regularly ovulating women mean circulating levels of both A and T increase in the middle third of the menstrual cycle with a second rise in A production by the corpus luteum occurring during the late luteal phase [8]. It is believed ovarian androgen production by the thecal cells is under the control of LH. The pre-androgens DHEA and DHEA-S are converted peripherally into A and then into the potent androgens T and DHT as well as to oestrogens. Under normal physiological conditions only 1–2% of total circulating T is free or biologically active. The rest is bound by sex hormone binding globulin (SHBG) or albumin with SHGB binding 66% of total circulating testosterone [9]. The binding affinity for steroids bound by SHBG is DHT > T > androstenediol > estradiol > estrone [10]. Increases in estradiol and thyroxine result in increases in SHBG whereas increases in T, glucocorticosteroids, growth hormone and insulin suppress SHBG.

3. Physiological and non-physiological reductions in androgens in women

The mean circulating levels of T decline with increasing age in premenopausal women, such that the levels ofwomen in their 40 s are approximately half of those of women in their 20 s [9]. This is reflected in an absolute decline in free T with age. Circulating levels of DHEA and DHEA-S, an important precursor for ovarian intrafollicular production of T and DHT [7] also fall lineally with age and this partially contributes to the overall age related decline in levels of their main metabolite, T [11,12].

Lessened cyclic ovarian testosterone production has been observed in the premenopausal years and may well be a prodrome to the menopause. Mushayandebvu et al. [12] reported a decline in mid-cycle ovarian androgen production in older reproductive aged women compared to their younger regularly ovulating counterparts. They specifically observed failure of the mid-cycle increase in circulating free T in older women with regular menstrual cycles despite preservation of normal free T levels at other times of the cycle. In other studies, androgen levels have not been found to acutely change in relation to the menopause [9,13]. Longcope et al. reported that the mean concentration of T in women transiting the menopause was significantly less than that of normal youngwomen sampled during the follicular phase of their regular menstrual cycles [13]. This is again consistent with the hypothesis that the decline in circulating T in women precedes the menopause and is most closely coupled with age. Following menopause, direct ovarian production accounts for up to 50% of circulating T, with the adrenal gland being a less important source [14]. However, there is wide variation amongst women in the activity of the ovarian stroma in the postmenopausal years in terms of androgen production [15].

Ovariectomy is the most common cause of iatrogenic androgen insufficiency and on average results in a 50% reduction in both T and A [16]. Other iatrogenic causes of T deficiency include chemical ovariectomy, for example the use of GNRH antagonists, and premature menopause induced by chemotherapy or radiotherapy. The induction of premature menopause by chemotherapy is becoming a major health issue for the survivors of premenopausal breast cancer. Exogenous estrogen administration may also precipitate relative androgen insufficiency. Specifically oral estrogens in the form of the oral contraceptive pill or estrogen given for hormone replacement therapy have been found to suppress circulating free T levels [17–19]. The oral contraceptive pill suppresses ovarian androgen production as well as induces increases in SHBG. Hence on the background of the age related decline in the levels of free T, women in their late reproductive years taking the oral contraceptive pill may report symptoms such as loss of libido and fatigue which are secondary to their suppressed free T levels. Similarly it is not unusual for postmenopausal women to develop androgen deficiency symptoms after commencing hormone replacement therapy. Again, such symptoms may be attributed to an exogenous estrogen-induced increase in SHBG combined with suppression of pituitary LH secretion, leading to lessened stimulus for postmenopausal ovarian thecal T production [20].

The administration of glucocorticosteroids may also induce androgen insufficiency secondary to the suppression of ACTH and therefore suppressed adrenal androgen production [21]. Long term suppression of adrenal pre-androgen production with glucocorticosteroid therapy may partly underlie the pathogenesis of osteopenia and ultimately osteoporosis which is a well known side effect of such chronic treatment in both women and men [22].

4. Clinical sequelae to diminished testosterone levels in the postmenopausal woman and evidence for benefits oftestosterone replacement

The most common complaint of women experiencing androgen deficiency is loss of sexual desire. Other symptomsthat appear to be related to low androgen levels include lessened well being and unexplained, and often subtle, fatigue. The most accepted indication for T replacement in women is low libido coupled with

low blood T levels following surgical menopause or premature menopause induced by chemotherapy or irradiation. Increasingly symptomatic T deficiency following natural menopause is becoming an accepted indication. Women who may also benefit from T replacement include those suffering from premature ovarian failure, including Turner's syndrome, and women with postmenopausal osteoporosis [23,24].

Potential indications for androgen replacement in women unrelated to the menopause include: premenopausal iatrogenic androgen deficiency states, such as the use of GNRH analogues for the treatment of endometriosis; premenopausal bone loss; glucocorticosteroid-induced bone loss; premenopausal loss of libido with diminished circulating free T levels; and possibly management of the premenstrual syndrome.

The symptom that most commonly precipitates consideration of androgen replacement therapy in postmenopausal women is diminished libido despite adequate hormone replacement therapy. Clearly sexuality and libido are determined by many factors including a woman's health status, her physical and social environment, past experiences, expectations and cultural milieu. Satisfactory sexual function is an important part of a woman's health and well being. There is a general misconception that sexuality in women declines with increasing age, however the majority of women who experience natural menopause do not report a decline in sexual desire, erotic pleasure or orgasm [25]. A general age related reduction in sexual frequency has been observed in women as in men. The menopausal transition however has been associated with lessening sexual and coital frequency independent of age [6]. Compared with premenopausal women, women in their postmenopausal years report fewer sexual thoughts and fantasies, have less vaginal lubrication during sex and experience less satisfaction in their sexual relationships, with a low circulating T level being most closely correlated with the reduced coital frequency [26]. In the Melbourne Women's Midlife Health Study, 62% of women aged 45 to 55 years reported no change in sexuality in the preceding year, however 31% reported a decrease [25]. The decline in sexual interest in the study was significantly and adversely associated with menopause rather than with age.

Although estrogen replacement improves vasomotor symptoms, vaginal dryness and probably general well being, this treatment has little effect on libido [27,28]. Oral estrogen replacement improves sexual satisfaction in women with atrophic vaginitis causing this dyspareunia, but women without this symptom benefit little or not at all [29,30]. Not uncommonly women complaining of loss of libido are given increasing doses of estrogen resulting in side effects (mastalgia and weight gain), and further lowering of free T.

Androgens appear to play a key role in female sexuality and diminished androgen levels in the postmenopausal years appear to contribute to the decline in sexual interest experienced by many women. Bachmann & Lieblum studied sexuality in sexagenarian women and reported that of the hormones studied serum free T was positively correlated with increased sexual desire [31]. Several studies have also demonstrated several improvements in the number of parameters of sexuality in postmenopausal women treated with exogenous T over and above the effects achieved with estrogen alone [23,30,32]. As described above, exogenous estrogen at the time of menopause may precipitate relative testosterone deficiency and result in symptoms such as loss of libido [18,19]. The mechanism by which sex steroids influence sexuality is not known. Both estradiol and testosterone are present in the human female brain with the highest concentrations of estradiol in the hypothalamus and the preoptic area and of T in the substantia nigra, the hypothalamus and the preoptic area [33]. The concentration of T is several fold higher than estradiol in each of these regions, with the highest ratio of T to estradiol in the hypothalamus and the preoptic area [33]. Interestingly the distribution of T within the human central nervous system corresponds with areas of high aromatase activity in animal brain [34]. Hence it appears that androgens may act either directly on the brain via the androgen receptor or possibly after conversion to estrogen within the central nervous system. Studies of the effects of cross-sex hormone therapy in transsexuals suppose a direct action of androgens within the central nervous system [35].

Testosterone replacement either as an injection or subcutaneous implant enhances sexual motivation in postmenopausal women [23,29,30,36,37]. Improvements in intensity of sexual drive, arousal, frequency of sexual fantasies, satisfaction, pleasure and relevancy have all been documented. In contrast changes in sexual motivation and improvements in coital frequency and orgasm vary considerably between studies. The failure for T supplementation to improve coital frequency has been attributed to the fact that participants of the studies have been women in long term relationships with established patterns of sexual behaviour.

Androgenic steroids also appear to have an important physiological role in the development and maintenance of bone mass in men and women, although the mechanism of androgen action on bone is still a matter of debate. The skeletal effects of androgens appear to be mediated in part via the estrogen receptor after circulating androgens have been locally aromatised to estrogen within bone [38,39]. However there is evidence that androgens act directly on bone and androgen receptors have been demonstrated in human osteoblast-like cell lines and androgens have been shown to

directly stimulate bone cell proliferation and differentiation [40,41]. Clinical research supports a positive relationship between bone density and androgens in young, premenopausal and perimenopausal women. Premenopausal bone loss is significantly associated with circulating free T levels, but not with circulating estradiol [42,43]. Furthermore low circulating free T is predictive of subsequent height loss (a surrogate measure of vertebral compression fracture) and hip fracture in postmenopausal women [44]. Circulating DHEA and DHEA-S have also been positively correlated with BMD in ageing women and the progressive decline in DHEA with increasing age is believed to contribute to senile osteoporosis [45–47]. It is not clear whether these adrenal pre-androgens directly influence bone metabolism but most likely their effects are mediated indirectly after being converted to estrogen and T. Studies of both oral and parenteral estrogen-plus-T therapy in postmenopausal women have shown beneficial effects of T replacement on bone mineral density (BMD) [23,24,48]. Treatment with a combination of oral esterified estrogen-methyltestosterone resulted in increased spinal BMD over a two year period [24] and with this regimen has been shown to not only suppress biochemical markers of bone reabsorption but to be associated with increases in the markers of bone formation [49]. The treatment of postmenopausal women with nandrolone decanoate has also been shown to result in increased vertebral BMD [50]. Combined estradiol and testosterone replacement with subcutaneous implant pellets also increases bone mass in menopausal women [23,48,51] with the effects in the hip and spine being greater than with estradiol implants alone [23]. Androgens also appear to enhance the mechanical properties of bones as evidenced by studies in female primates [52]. However to date no studies have addressed the impact of androgen replacement on the incidence of fracture in postmenopausal women.

Sex hormones may play a role in the evolution of rheumatoid arthritis (RA): RA is more common in women than in men; RA is associated with low androgen levels in men and women [53] and the direct administration of testosterone replacement has resulted in symptomatic improvement in men [54] and postmenopausal women [22]. There is ongoing research into the effects of androgens on the immune response [55,56] based on the hypothesis that the enhanced susceptibility of females to autoimmune disease in part due to lower testosterone levels in women vs men. Based on the known beneficial effects of testosterone administration in terms of lean body mass, bone density and the adrenal suppressant effects of glucocorticosteroid therapy, testosterone replacement may potentially be beneficial for both women and men with severe RA.

In summary, current data support beneficial effects of androgen replacement in terms restoration of libido and well being in postmenopausal women with low circulating free testosterone levels. Androgen replacement may also potentially be an effective alternative for the prevention of bone loss and the treatment of osteopenia and osteoporosis in postmenopausal women, however recommendations of therapy for the later indications pend the availability of prospective data confirming a reduction in fracture rate with such therapy.

5. Potential risks of testosterone replacement in women

Potentially androgen replacement in women may result in undesirable metabolic side effects particularly with respect to effects on body composition, lipids and lipoprotein, metabolism and vascular function. The clinical data available does not indicate that androgen replacement therapy which results in testosterone levels within the normal physiological range for women has any undesirable metabolic consequences.

In postmenopausal women neither measured nor estimated free T is associated with waist-to-hip ratio measurements nor does there appear to be a direct relationship between androgens and visceral adiposity in this population [57]. Combined estrogen and T replacement with subcutaneous implants is associated with a reduction in total body fat and a modest increase in lean body mass but no change in BMI [23]. With respect to lipids, our research has shown that estrogen replacement results in a decrease in abdominal fat which is associated with a reduction of LDL cholesterol and the LDL to HDL cholesterol ratio. The addition of T replacement to postmenopausal women appears to offset these positive effects ([28] Davis et al. unpublished data). Oral methyltestosterone administration is associated with reductions in HDL cholesterol and apolipoprotein A1 [49,58]. Certainly the incidence of heart disease in postmenopausal women is not associated with circulating androgen levels [59,60] and animal studies have shown that intracoronary T administration induces increases in coronary artery cross-sectional area peak flow velocity which is blocked by pretreatment with an inhibitor of nitric oxide synthesis [61]. Thus evaluating the data to hand, the administration of T to women does not appear to adversely effect the key events in lipid metabolism or coronary artery function.

There have been reports of a positive association between endogenous androgen levels and breast cancer [62,63]. Unfortunately interpretation of available data is limited by the several confounding factors. Androgen receptors are found in up to 50% of breast tumours [64] and are associated with a longer survival

Table 1
Androgen replacement therapy formulations used for women

	Dose range	Frequency	Route
Methyltestosterone[a] (in combination with esterified estrogen)	1.25–2.5 mg	Daily	Oral
Testosterone undecanoate	40–80 mg	Daily or alternate days	Oral
Nandrolone decanoate	25–50 mg	6–12 weekly	Intramuscular
Mixed testosterone esters	50–100 mg	4–6 weekly	Intramuscular
Testosterone implants	50 mg	3–6 monthly	Subcutaneous
Testosterone patch[b]	150 μg	2 × /week	Transdermal

[a] Currently available in USA.
[b] Undergoing clinical trial in USA.

in women with operable breast cancer who manifest a favourable response to hormone treatment withadvanced disease [65]. There is no data regarding the effects of exogenous androgen therapy on the incidence of breast cancer.Despite concerns that androgen replacement may result in undesirable cosmetic side effects, virilization is rare if supraphysiological hormone levels are avoided [23,30,36,37]. Clearly it is inappropriate to treat women troubled by hirsutism, acne or androgenic alopecia with androgen replacement. Although enhanced libido is the most common indication for androgen replacement therapy in postmenopausal women, increased sexual thoughts may in some instances be an undesirable effect and this should be considered when T replacement is considered for prevention or management of bone loss.

6. Testosterone replacement following menopause

Currently few countries have approved the use of testosterone for hormone replacement therapy in women, however it is available as oral methyltestosterone in the US and testosterone implants have been approved for replacement therapy for women in the UK. The currently available therapeutic options are listed in Table 1.

Our clinical experience suggests that in order to achieve a good therapeutic response in terms of enhanced libido testosterone levels often need to be restored to at least the upper end of the normal physiological range for young ovulating women. The doses of testosterone required to achieve such an effect not uncommonly result in an initial post administration peak testosterone level which is supraphysiological regardless of the mode of administration.

Oral testosterone undecanoate is mostly used for replacement therapy in hypogonadal men. Its clinical use in women has been little studied although in some countries this prescription for women is quite widespread. As there is no data pertaining to the safety and efficacy of testosterone undecanoate in women, its use in women cannot be recommended.

Subcutaneous testosterone implants have been used for many years in hormonal replacement regimens in postmenopausal women. These implants are fused crystalline implants 4.5 mm in diameter containing Testosterone BP (British Pharmacopoeia) as the active ingredient. We have found a dose of 50 mg extremely effective without unwanted virilizing side effects [23,36,66]. The implant is inserted under local anaesthesia, subcutaneously, usually into the lower anterior abdominal wall or the lateral thigh using a trochar and cannula. The duration of effect for a 50 mg implant is between 3 and 6 months. However as there is marked individual variation in this period, women treated with testosterone implants should be carefully monitored and serum T levels measured prior to the administration of each subsequent implant. Less commonly T implants of 100 mg are necessary to achieve adequate therapeutic effects. Implants of a greater dose cannot be recommended in women.

Currently other modes of T administration for women are being developed. Transdermal testosterone in the form of patches and gels, and a vaginal ring are currently undergoing therapeutic trial. Nandrolone decanoate is approved in some countries for the treatment of postmenopausal osteoporosis. The dose, given intramuscularly, should not exceed 50 mg and the frequency of treatment is best titrated against the patient's gross build. Thecontraindications to, and side effects of T replacement, are listed in Tables 2 and 3. Once again it is emphasised that with judicious dosing and careful monitoring, side effects of this therapy are rare. In general, all postmenopausal women treated with T replacement should concurrently be prescribed

Table 2
Contraindications to testosterone therapy

- Severe acne
- Moderate—severe hirsutism
- Circumstances in which enhanced libido would be undesirable
- Androgenic alopecia
- Pregnancy or lactation
- Known or suspected androgen-dependent neoplasia

Table 3
Side effects from excessive dosage

- Masculinization—hirsutism, acne, temporal balding, voice deepening, clitoromegaly
- Fluid retention
- Lipids—oral testosterone may adversely affect serum levels of HDL-cholesterol and apolipoprotein A-1
- Drug interactions—C17 substituted derivatives of oral testosterone may decrease anticoagulant requirements. Androgens may elevate serum levels of oxyphenbutazone and in diabetic patients may rarely affect insulin requirements
- Hepatocellular damage has been associated with high dose 17-α-alkylandrogens given orally

estrogen replacement therapy, with the exception being women receiving intramuscular nandrolone decanoate.

7. Conclusions and summary

Together with its metabolite DHT is the most potent physiological androgen in both men and women. Paradoxically T is also the major precursor of estrogen. Whether the actions of T in women are predominantly directly mediated via androgen receptors or secondary to extra gonadal conversion of androgen to estrogen is notknown. However there is increasing evidence that T replacement in addition to standard postmenopausal hormone replacement results in optimal treatment for many women. Anecdotally, younger women with premature ovarian failure appear more likely to require T replacement for restoration of libido and well being. Furthermore, there is preliminary evidence that the addition of an androgen may be extremely important in such women to prevent bone loss. As long as T replacement results in T levels within or close to the normal reproductive range for women, side effects are rare. Unfortunately administration of doses appropriate to women has been limited to date by the lack of availability of preparations specifically developed for treatment of women. The T replacement alternatives currently under development should minimise this therapeutic problem in the future.

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