Testosterone influences libido and well being in women

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There is increasing awareness of the significant and varied actions of endogenous androgens in women, and acknowledgement that women might experience symptoms secondary to androgen deficiency. There is also substantial evidence that prudent testosterone replacement is effective in relieving both the physical and psychological symptoms of androgen insufficiency in clinically affected women. However, our understanding of the actions of testosterone in women is incomplete, with no consensus as to what constitutes either biochemical or clinical testosterone deficiency. The focus of the limited research into testosterone replacement has been on sexuality, primarily sexual desire. However, the influence of testosterone on mood and well being also requires further exploration.

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For decades, physicians worldwide have been giving various androgen preparations to postmenopausal women based on personal clinical observations of improved sexual interest and well being in treated patients. This practice is increasingly widespread, despite the lack of precise clinical or biochemical definitions of androgen deficiency, particularly testosterone deficiency, in women. Such definitions are clearly needed, but will require large prospective clinical studies. In the interim, a framework of how androgens act in women, and clinical therapeutic guidelines, must be derived from cellular and animal studies, as well as from the effects of testosterone replacement in naturally and surgically menopausal women. The therapeutic window for testosterone is small, but the recent availability of preparations designed specifically for use in women is opening the door for clinical research in this field. Although androgen insufficiency might be detrimental to bone and muscle mass, we have limited this review to the physiology of testosterone in women, and the effects of insufficiency and therapy on libido and well being.

Normal females produce testosterone and levels decline with increasing age

The production of androgens in women has been reviewed in detail elsewhere[1]. In summary, the ovaries are a primary site of testosterone synthesis. Whether there is direct secretion of testosterone by the adrenal glands is controversial. The ovaries and adrenals both produce androstenedione (A) and dehydroepiandrosterone (DHEA), with the adrenals also being the main source of DHEA-sulfate (DHEAS). Plasma A and testosterone increase in the middle third of the menstrual cycle, as well as in the luteal phase, and there is a diurnal variation in testosterone, with peak levels in the morning[2]. Testosterone is further metabolized to the potent androgen dihydrotestosterone (DHT) or aromatized to estradiol (E_2) in target organs and peripheral tissues.

Normally, only 1–2% of total testosterone circulates unbound. The rest is bound by sex hormone-binding globulin (SHBG) or albumin, with SHBG binding 66% of total circulating testosterone[3]. In general, it is assumed that the non-SHBG-bound fraction is biologically active. This has not been firmly established and the bioactivity of SHBG-bound testosterone warrants further investigation. E_2 and thyroxine increase SHBG, whereas increases in testosterone, glucocorticosteroids, growth hormone and insulin suppress SHBG.

The mean circulating level of testosterone declines gradually with increasing age, rather than showing a precipitous fall at the menopause transition[4], so that levels in women aged 40 are approximately half those of women in their early 20s. Because the percentage of free testosterone does not vary with age, there is an absolute decline in free testosterone with age. Longcope *et al.* noted that the mean concentration of testosterone in women transiting the menopause was significantly less than that of women sampled between Days 5 and 7 of their regular cycles[4]. Mid-cycle ovarian androgen production in regularly menstruating women in their 40s is low compared with their younger counterparts[6]. After the menopause, peripheral conversion of A becomes the major source of circulating testosterone, although there are varying degrees of ongoing ovarian production[7]. Immediately after bilateral oophorectomy, levels of both testosterone and A decrease by about 50% (Ref. 8), with a lesser reduction after unilateral oophorectomy[9]. DHEA and DHEAS levels fall linearly with age, and this further contributes to the decline in testosterone[10]. Little is known about absolute testosterone levels beyond the menopause because published studies have either included few women or have been extensively manipulated statistically[9]. Other iatrogenic causes of low testosterone include nonsurgical oophorectomy; for example, the use of gonadotropin-releasing hormone (GnRH) antagonists, chemotherapy or radiotherapy. Exogenous oral estrogens in the form of the contraceptive pill or estrogen as hormone replacement therapy (HRT) significantly lower circulating free testosterone levels[11] by increasing SHBG and suppressing pituitary luteinizing hormone (LH) secretion.

Research into the role of testosterone in women has been limited by the insensitivity of current assays for both total and free testosterone within the normal female range. Furthermore, many older studies have

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not taken into account the diurnal or cyclical variation of testosterone in women.

Sexual behavior and androgen action in the brain

Androgens might act directly [via androgen receptors (AR)], as precursor hormones for E_2 production in tissues such as adipose, bone, brain and vascular tissue, or by lowering SHBG and increasing free circulating levels of multiple sex steroids. AR and estrogen receptors (ERs) are both found in the normal female brain[12]. High concentrations of E_2 and testosterone have been demonstrated in the human female hypothalamus and preoptic area, with the concentrations of testosterone being tenfold higher than those of E_2 (Ref. 13). These regions correlate with regions of high aromatase activity in animals[14]. ERα knockout (KO) mice[15] and aromatase KO mice, despite high circulating androgen levels (E. Simpson, pers. commun.), exhibit almost no sexual interest, whereas ERβ KO mice exhibit normal reproductive behaviour[15]. Taken together, the implication is that androgens influence sexual behavior in the rodent brain via conversion to E_2, which then acts through ERα. In animals, visual exposure to sexual intercourse evokes increased aromatization of testosterone to E_2 in the preoptic area[16]. DHEA and DHEAS can be synthesized in the mammalian brain and can act as γ-amino butyric acid inhibitors and potentiators of NMDA receptors[17]. DHEA might have central effects such as increased rapid eye movement, sleep enhancement, positive effects on memory and anxiolytic properties. The extent to which these are direct consequences of DHEA and/or DHEAS, or their metabolism to testosterone or E_2 is unknown.

Androgens influence mood and well being

Androgens, estrogens and progestins each influence mood and sense of well being, and we can only speculate about the complex interplay of these steroids with neurotransmitters. In men, depression scores have been associated significantly and inversely with non-SHBG-bound testosterone and DHT, independent of age, weight change and physical activity[18], and lower testosterone levels correlated with the severity of depression[19–22]. Testosterone replacement restores mood and normalizes depression scores in hypogonadal men[23]. After surgical menopause, the addition of intramuscular testosterone therapy to estrogen replacement results in women feeling more composed, elated and energetic than with estrogen alone[24]. Other studies have demonstrated positive effects of testosterone in peri- and naturally postmenopausal women[25,26].

Transdermal testosterone replacement in surgically menopausal women significantly improves the 'Psychological General Well Being Index' score over placebo, with the greatest change being in improved general well being and less-depressed mood[27]. Treatment with a 50 mg testosterone implant, which results in circulating total testosterone levels just above the upper limit of the normal range for young women at about six weeks[28], is clinically associated with enhancement of well being and diminution of fatigue, with declining well being and increasing fatigue concurrent with the end of the implant activity (cumulative experience of author and colleagues).

DHEA given orally (50 mg day^{-1})[29], or transdermally (by a 10% DHEA cream)[30], is associated with a marked improvement in well being over placebo. Oral DHEA improves well being and depression and anxiety scores in women with adrenal insufficiency[31]. However, not all DHEA trials have been positive[32,33]. Larger prospective trials with this steroid are required before definitive guidelines can be developed for its clinical use.

Low testosterone is associated with diminished libido in women

Multiple factors determine female sexuality and libido. These include the health of the individual, her physical and social environment, education, past experiences, cultural background and her relationship with her partner. Androgens also play a major role, particularly in stimulating sexual motivation behaviors, maintaining optimal levels of sexual desire and possibly contributing to sexual gratification[34–36].

The sharp decline in sexual interest at the time of natural menopause appears to be unrelated to testosterone levels[37], consistent with testosterone levels not falling acutely at this time. Sexual dysfunction, primarily low libido, tends to be more prevalent in women as they age, or following oophorectomy[38]. There is an age-related reduction in coital frequency among women, and a lessening of coital frequency is associated with the menopausal transition, independent of age[39]. A low testosterone level is most closely correlated with reduced coital frequency and loss of sexual desire[40,41]. Anti-androgens have adverse effects on female sexual function[42] and, among lactating women, testosterone and A levels are lowest in those reporting the greatest reduction in sexual interest[43]. These observations are compatible with a decline in female sexuality *pari passu* with a drop in androgenic functions.

Testosterone restores libido in androgen-deficient women

It is generally accepted that estrogen replacement improves vasomotor symptoms, vaginal dryness and general well being, but has a minimal effect on libido[38,39,44]. Women with dyspareunia caused by atrophic vaginitis might experience an improvement in sexual gratification with estrogen replacement[45].

Women treated with intramuscular E_2 and testosterone have improvements in sexual motivational behaviours (desire, fantasy and arousal), and increased rates of coitus and orgasm[35], with the improvements in these sexual parameters

covarying with plasma testosterone, not E_2 (Ref. 35). Sarrel *et al.* investigated the effects of esterified estrogens (EEs) alone versus EE plus methyltestosterone (ET) in postmenopausal women described as being 'dissatisfied' with their HRT regimens[46]. SHBG increased in the EE group and decreased in the ET group. Those taking ET had significant improvements in sexual desire, satisfaction and coital frequency, whereas those treated with EE alone had no improvement[46]. Subcutaneous testosterone implants significantly improve sexual activity, satisfaction, pleasure and orgasm over and above the effect achieved with estrogen alone[28,45,47,48]. Moreover, there are no adverse effects on blood lipids and no virilization effects.

Testosterone therapy results in increased vaginal vasocongestion in response to potent erotic visual stimulation compared with placebo, without increased subjective sexual excitement and lust scores in young hypothalamic amenorrheic women[49]. Hence, testosterone substitution alone is not adequate to restore sexual desire when appropriate cognition and emotions are absent, and impulses are processed as unimportant or even undesirable. Dow *et al.*[50] reported no benefit with testosterone in a study of women presenting with generalized menopausal symptoms rather than low libido.

Potential indications for testosterone therapy in women

The indications for testosterone in women remain empirical, with the most accepted indication being surgical menopause. However, the clinical settings in which we find the use of testosterone acceptable, and potential indications requiring further research, are listed in Box 1.

Testosterone administration

It appears that testosterone levels need to be restored to at least the upper end of the normal reproductive range for young women to be effective; that is, to enhance libido[1]. However, regardless of the mode of administration, the initial post-administration peak is usually supraphysiological. Available preparations are summarized in Table 1. Oral estrogen/androgen therapy is available in the USA in two strengths: EE 0.625 mg plus methyltestosterone 1.25 mg, or EE 1.25 mg plus methyltestosterone 2.5 mg.

Table 1. Testosterone preparations currently available

	Dose range	Frequency	Route
Methyltestosterone[a]	1.25–2.50 mg	Daily	Oral
Mixed esters	50–100 mg	4–6 weekly	Intramuscular
Testosterone implants	50–100 mg	3–6 monthly	Subcutaneous
Transdermal T patches[b]	150–300 mg	Twice weekly	Transdermal
1% T cream[b]	5–10 mg	Daily	Transdermal
Testosterone undecanoate	40–80 mg	Daily	Oral
Nandrolone undecanoate	25–50 mg	6–12 weekly	Intramuscular

[a]Available in the USA.

[b]Currently undergoing clinical trials.

Box 1. Indications for testosterone replacement in women

Clinical indications

- Symptomatic testosterone deficiency following natural menopause
- Symptomatic testosterone deficiency as a result of surgical menopause, chemotherapy or irradiation
- Premature ovarian failure
- Premenopausal loss of libido with diminished serum free testosterone

Potential indications

- Management of premenstrual syndrome
- Glucocorticosteroid-induced bone loss
- Premenopausal/postmenopausal bone loss
- Management of wasting syndromes secondary to human immunodeficiency virus (HIV) infection or malignancy
- Premenopausal iatrogenic androgen deficiency states, including gonadotropin-releasing hormone analog treatment of endometriosis
- Adjunctive therapy for rheumatoid arthritis or systemic lupus erythematosus

Methyltestosterone is not available in some countries because liver damage has been reported with long-term, high-dose therapy[51]; however, recent data do not support any detrimental effects of the above doses on hepatic enzymes or blood pressure over 24 months[51,52].

Testosterone is commonly administered in Australia and the UK as a fused crystalline implant, which contains testosterone BP (British Pharmacopoeia) as the active ingredient. A dose of 50 mg is extremely effective, allows slow release of the hormone over a period of three to six months and does not tend to have virilizing side effects[47]. As there is variability in implant absorption among women, it is essential that testosterone levels should be measured before the administration of each subsequent implant. Doses of 100 mg or more should be avoided to minimize side effects.

A transdermal testosterone matrix patch, designed specifically for use in women, is undergoing clinical trial. As with other hormone patches, some women might experience skin irritation or simply prefer a less conspicuous form of treatment.

Testosterone cream is an alternative available in a few countries. Our experience with a 1% testosterone cream (10 mg day^{-1}) has been generally positive in terms of sexual desire, general well being and energy. Nevertheless, pharmacokinetic data and clinical trials pertaining to its use are required to establish efficacy and therapeutic guidelines.

Mixed testosterone esters are sometimes administered as an intramuscular injection in a dose of 75 to 100 mg every four to six weeks. This dose

Box 2. Possible side effects of testosterone therapy

- Fluid retention
- Breast cancer risk: some studies implicate an association between endogenous androgens and breast cancer risk[a,b], but exogenous testosterone is associated with the inhibition of estrogen-induced mammary epithelial proliferation and suppression of estrogen receptor expression[c]
- Masculinization: hirsutism, acne, temporal balding, voice deepening and clitoromegaly
- Body composition: modest increase in lean body mass, reduction in total body fat and no change in body mass index[d]
- Vascular function: enhanced endothelium-independent and -dependent flow-mediated dilation[e] and preservation of favorable effects of estrogen on coronary artery flow[f,g]
- Lipids: oral testosterone might decrease triglycerides, high-density lipoprotein-cholesterol and apolipoprotein A-1 (Refs h,i). Parenteral therapy does not oppose favorable estrogenic effects[j]
- Drug interactions: C17 substituted derivatives of oral testosterone might decrease anticoagulant requirements
- Hepatocellular damage: such damage has been associated with high-dose oral 17-α-alkylandrogens, but not with standard doses used in women

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regimen is purely empirical and to date no studies have evaluated this therapy in women.

Testosterone undecanoate is an oral androgen used in hypogonadal men. It has been little studied in women, although in some countries its prescription is widespread. Documentation of the safety and efficacy of this agent is required before its use can be recommended.

Nandrolone decanoate, a weakly aromatizable androgen, is approved in some countries for the treatment of postmenopausal osteoporosis. The dose, administered intramuscularly, should not exceed 50 mg, and the frequency of treatment is best titrated against the patient's gross build. It is prudent that treatment should not be given less often than every six weeks, and patients should be monitored very carefully for hirsutism and voice deepening.

Potential adverse effects

Women tend to be anxious regarding the risks associated with the use of androgens – particularly the masculinizing effects of hirsutism, acne and voice deepening. It is vital to identify patients with such conditions to minimize side effects. Judicious dosing and careful patient monitoring further reduce the risk of adverse events.

In general, postmenopausal testosterone replacement should only be prescribed with concurrent estrogen therapy, as there are no data regarding the use of testosterone alone. One would predict that such use would increase the risk of adverse metabolic and cosmetic side effects. The only exception is the administration of nandrolone decanoate.

Concern has been raised that androgen therapy in women might result in undesirable effects on lipids, body composition and vascular function. However, in general, the effects of testosterone in currently prescribed doses on these parameters have been benign or favorable (Box 2).

Conclusion

Androgens have important biological actions in women. Hence, insufficient androgen production can result in adverse female physical and psychological sequelae. Although the phenomenon of 'androgen deficiency' has not been defined, there is substantial evidence from published trials that androgen replacement in 'androgen-deficient' women results in the restoration of libido and well being. Over the decades, the consensus has been to offer testosterone to surgically menopausal women who experience low libido accompanied by lowered testosterone levels. With the emerging evidence that exogenous testosterone not only enhances sexual desire but also increases energy levels, improves general well being, mood and bone and muscle mass, the indications for its clinical use will no doubt expand. It has become increasingly acceptable to add testosterone to HRT for naturally as well as surgically menopausal women. By contrast, there are no current data to support its use in premenopausal women. To date, our experience with testosterone in symptomatic premenopausal patients has been positive, and intervention studies in premenopausal women are currently under way. Other potential indications, beyond the scope of this review, include the prevention and treatment of bone loss, the treatment of premenopausal syndrome and the management of wasting syndromes secondary to human immunodeficiency virus infection and malignancy. As the use of testosterone continues to increase, advances in different routes of administration need to be made.

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