Androgens and Women at the Menopause and Beyond

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Studies over the last decade have shown that the male hormone, testosterone, declines with age in men (1,2). This decline is associated with a decrease in libido, muscle mass and strength, leptin levels, bone mineral density (BMD), hematocrit, and cognition (3–6). It also has been recognized that total testosterone is a poor measurement of gonadal status because of the increase in sex hormone binding globulin in aging males (7,8).

While there has been a marked increase in studies of the role of testosterone deficiency in aging men, there is a paucity of such studies in women. The small literature is further confounded by the difficulty in accurately measuring the low levels of circulating testosterone in women (9). Besides the difficulty in measuring total testosterone at low levels, often clinically free testosterone is measured by an analog assay or by the free androgen index (testosterone/sex hormone-binding globulin). There is no evidence to support the use of either of these measurements. Free testosterone should be measured by either the dialysis or ultracentrifugal method. Alternatively, bioavailable testosterone can be measured. The available literature suggests that low-dose testosterone treatment in women with androgen deficiency can have positive effects on libido and psychological well-being, and also may retard muscle and bone loss associated with aging (10,11). This article will review the available literature and make recommendations concerning future studies.

Androgen Production Over the Life Cycle

In females, androgens are produced by both the adrenal glands and ovaries. The major androgens are testosterone, androstenedione, and dehydroepiandrosterone (DHEA). Half of the circulating testosterone is produced peripherally from androstenedione and other androgen precursors. DHEA-sulphate is produced predominantly by the adrenals. Dihydrotestosterone is derived from 5α-reduction of testosterone and is a major circulating androgen (Figure 1). Most of the circulating testosterone is bound to sex hormone-binding globulin (SHBG) (~65%). One percent to 2% of testosterone is free, and the rest is loosely bound to albumin and believed to be available to tissues (bioavailable). Estrogens increase the level of circulating SHBG. Testosterone is also aromatized to estradiol intracellularly. Aromatization may increase with age, altering the effects of testosterone in older women.

Testosterone levels decrease markedly from 20 to 40 years of age, such that the levels at 40 years are about 50% of those at 20 years of age (12). The normal midcycle ovarian production, which is partially under the control of luteinizing hormone, also decreases in the premenopausal years (13). As SHBG levels remain constant, there is an even greater decrease in free testosterone during the premenopausal years.

During the menopausal transition there is no further decrease in testosterone, and levels may even increase slightly (14–17). However, these values are still approximately half of those seen in younger women. With the loss of estrogen at the menopause, SHBG levels decrease, resulting in an increase in free testosterone levels. The ovary continues to produce about half of the testosterone following the menopause, though recent studies have suggested this may not be the case with minimal amounts of testosterone coming from the ovary (18). Postmenopausal females with adrenal insufficiency have minimal circulating testosterone and no response to stimulation. Intraovarian testosterone, androstenedione, and P-450 aromatase are at very low levels in the ovary, and gonadotrophin receptors are absent. Postmenopausally, in a study in which hormonal levels were adjusted for body mass index, it appears that testosterone levels may increase, such that an 80-year-old female’s levels will be only approximately 20% lower than those of a 20-year-old female. However, further studies are essential to confirm this concept, which should be considered hypothetical at present (Figure 2) (19). DHEA and DHEA-sulphate levels decrease monotonically throughout the life span.

When a woman has an ovariectomy, there is a 50% decline in both testosterone and androsterone (20). Glucocorticoids suppress adrenocorticotropic hormone (ACTH) production and, therefore, a reduction in adrenal androgen production (21). Deficiency of free testosterone occurs when a postmenopausal woman receives oral estrogen (22). Estrogen increases SHBG resulting in a decline in free testosterone levels. This fall in free testosterone was correlated with total and lean leg mass (22).

Testosterone and Libido

As in males, a decline in sexual enthusiasm is the most commonly associated symptom of testosterone deficiency in women. Libido declines in some but not all women at the time of the menopause (23,24). The relationship of this decline has not been directly related to a fall in testosterone. Other factors affecting libido at the time of the menopause.
include psychosocial factors and menopause symptoms. Dennerstein and colleagues (25) reported that, over the menopausal transition, sexual dysfunction increased from 42% to 88%. This decrease in sexual functioning was more closely related to estradiol than testosterone levels. However, their testosterone assay did not measure levels below 24 ng/dl and, therefore, it cannot be accepted from their data that low testosterone is not associated with low libido in postmenopausal women. On the other hand, a study in older women found that free testosterone was positively correlated with sexual desire (26).

Studd and colleagues (27) reported beneficial effects of estradiol and testosterone implants on psychosexual problems in postmenopausal women in 1977. Dow and colleagues (28) found that, in a small number of postmenopausal women, implants of estradiol alone were as effective as estradiol plus testosterone implants. Studies from Australia demonstrated that combined estradiol (50 mg) plus testosterone (100 mg) enhanced libido (29). In a single blind study, addition of testosterone to estradiol implants increased sexual activity, satisfaction, enjoyment, and frequency of orgasm to a greater extent than estradiol alone (30). Following oophorectomy, testosterone enanthate administered intramuscularly in relatively high doses enhanced sexual desire, fantasies, and arousal more than estrogen by itself or placebo (31).

Seventy-five women who had had an oophorectomy and hysterectomy received placebo and 2 different doses of transdermal testosterone (150 mg or 300 mg per day) for 12 weeks each to determine the effects of testosterone on self-reported sexual function (32). The women ranged in age from 31 to 56 years. They received a constant dose of conjugated equine estrogen throughout the study. Only at the higher dose was there a significant increase in sexual activity and pleasure-orgasm over placebo. Sexual problems decreased with the higher dose of testosterone, but this was not significant. Masturbation at least once a week doubled on both testosterone treatments, and sexual fantasies

![Diagram of sources of circulating androgens in young females. SHBG = sex hormone-binding globulin. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone-sulphate.](image-url)
increased by 8% at the low testosterone dose and 14% at the higher dose (statistical significance not reported in original paper). The higher dose was associated with supraphysiological elevations in total testosterone and dihydrotestosterone levels with a slight decrease in SHBG levels. Clinically important effects on sexual function only occurred at this higher dose.

Studies utilizing Estratest (Solvay Pharmaceuticals, Baudette, MN) (esterified estrogens with methyltestosterone) taken orally are suggestive of improved sexual function (33,34). However, most of these studies have not delineated whether this is due to estrogen or methyltestosterone. Dobs and colleagues (35) controlled for estrogen effect and found that the addition of methyltestosterone enhanced sexual functioning.

**TESTOSTERONE AND PSYCHOLOGICAL WELL-BEING**

Shifren and colleagues (32) found a small but statistically significant increase in the Psychological General Well-Being Index in women receiving testosterone. High-dose testosterone also decreased depressed mood. These effects were confined to older rather than younger women in the study. Dobs and coauthors (35) found that oral methyltestosterone improved psychological well-being and quality of life. Other studies have suggested an improvement in emotional well-being with testosterone, but have not clearly distinguished between the effects of estrogen and testosterone (11,36). Overall, further studies are needed before a definitive statement on the effect of testosterone on psychological well-being in women can be made.

Estratest (Solvay Pharmaceuticals) was shown to improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms (37).

A number of studies have suggested that estrogen may have an effect on cognition, though this is controversial (28,39,40–43). In men, testosterone may modulate cognitive function (4,44). There is a need to examine the effects of testosterone on cognition in older women.

**TESTOSTERONE, BODY COMPOSITION, AND FRAILITY**

Dobs and colleagues (35) reported an increase in lean body mass and an enhancement of lower body muscle strength in women receiving Estratest (Solvay) compared with women receiving esterified estrogen alone. Unfortunately, they utilized bioelectrical impedance to measure body mass, making it difficult to be sure that lean mass truly increased, as increases in body water interfere in this measurement. Davis and colleagues (45) found similar effects of testosterone on lean body mass and a reduction in total body fat.

Sarcopenia (age-associated decline in muscle mass) is an important predictor of frailty in older women (46–50). Frailty is a predictor of further functional decline, hospitalization, institutionalization, and mortality (2,37,51–54). In older males, testosterone deficiency predicts functional decline (55), and testosterone replacement enhances function following hospitalization (56). There is a need to examine the effects of testosterone replacement on muscle mass, strength, and function in older women.

Testosterone has direct effects on bone in addition to the effects produced by aromatization to estrogens. This effect is mainly due to an increase in osteoblastic activity (57), although some studies failed to find a further increase in bone markers of resorption (cross-linked carboxyterminal tetopeptide) or absorption (carboxyterminal propeptide of type I procollagen) after testosterone was added to estrogen (58). Low levels of free testosterone predict height loss and hip fracture in postmenopausal women (59). Testosterone replacement enhances BMD at both the spine and the hip (45). Estratest (Solvay) over a 2-year period increased spinal BMD (34). This combination also increased markers of bone formation and decreased markers of bone resorption.

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**Figure 2. Alterations in testosterone over the life span in women.** Changes postmenopausally are controversial and based on limited data. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone-sulphate; SHBG = sex hormone-binding globulin.
(60). Lumbar spine BMD was increased in postmenopausal women treated with the anabolic hormone, nandrolone decanoate (61). Overall, these studies strongly support a role of androgens in preventing osteoporosis in older females. Studies on the role of androgen replacement in preventing hip fracture are needed.

**Testosterone and Cardiovascular Disease**

There is no epidemiological data on the role of testosterone deficiency in atherosclerotic cardiovascular disease in women. In men, low testosterone levels are associated with increased risk of atherosclerotic disease (62). While testosterone replacement produces a mild decrease in high-density lipoprotein (HDL) cholesterol when given orally, it also increases hepatic lipase, which results in an increase in cholesterol clearance. In women, oral methyltestosterone decreases HDL cholesterol and apolipoprotein A1 (60,62). Testosterone levels are not associated with cardiovascular disease in epidemiological studies (63).

Worboys and colleagues (64) examined the effect of testosterone replacement therapy on arterial reactivity in postmenopausal women. Testosterone resulted in a 42% increase in endothelium-dependent flow-mediated dilation. A further increase was seen when subjects received glycercyl trinitrate. This study suggests that both endothelium-dependent and endothelium-independent brachial artery vasodilation is improved by testosterone in postmenopausal women who are taking estrogen. Penotti and coauthors (65) reported that testosterone undecanoate (40 mg daily) given to women receiving hormone replacement therapy (HRT) decreased vascular reactivity of cerebral arteries but markedly improved sexual desire and satisfaction.

**Rheumatoid Arthritis**

Rheumatoid arthritis is an autoimmune disorder that occurs more commonly in females than in males. Low testosterone levels are common in women with rheumatoid arthritis (66). It is unclear whether the low testosterone levels are a cause of rheumatoid arthritis or precipitated by the disease process or its treatment, e.g., glucocorticoids or cytotoxic drugs. Testosterone therapy in postmenopausal women with rheumatoid arthritis decreases symptoms in these women (67).

**DHEA**

The adrenal androgens (DHEA and DHEA-S) decline over the life span (68). The role of DHEA in physiological function is unknown. DHEA acts as a precursor in the periphery for more potent androgen synthesis (69). DHEA, from the adrenal but not from the ovaries, is regulated partially by ACTH and the gene for the Vitamin D receptor (70). Hormone replacement therapy results in an increase in circulating DHEA-S levels (71).

DHEA-S levels are inversely associated with dysphoria in postmenopausal women (72). Replacement with DHEA cream enhanced spinal BMD and decreased urinary hydroxyproline/creatinine ratio (73). It also increased the vaginal maturation index, but not endometrial proliferation. DHEA increased the insulin-like growth factor (IGF)-1 to IGFBP-3 ratio at 3 months but not 6 months (74). In one study, DHEA improved libido in postmenopausal women, but the minimal change in placebo questions the validity of this effect (75). Their methodology involved directly asking women whether their libido improved without utilizing established scales.

Postmenopausally, DHEA can act as an estrogen to stimulate breast tissue, either directly or by intracellular conversion to estrogen within the breast cells, and thus potentially increase the risk of breast cancer (76–81). The most comprehensive study of DHEA in older women was conducted by Beaulieu and colleagues (82). They examined 288 persons aged 60 to 70 years who received either 50 mg daily of DHEA or placebo for 1 year. Small increases in serum testosterone and estradiol were seen during the course of the study, and DHEA-sulfate increased markedly. Minimal effects were seen. Libido improved only in women over 70 years of age. Skin showed an increase in hydration, epidermal thickness, sebum production, and pigmentation. In women over 70 years, there was a small increase in BMD and a decrease in osteoclastic activity.

Overall, there appears to be no advantage of using DHEA as a replacement androgen in older women compared to testosterone. In addition, a number of DHEA products on the market are not bioavailable when administered to humans.

**Side Effects of Testosterone in Women**

The major side effects of testosterone in women are those related to masculinization, namely acne, deepening of the voice, excessive hair dose, balding, and clitormegaly (83). Testosterone can also cause fluid retention resulting in worsening heart failure and hypertension. In some women, increased libido may be considered a side effect rather than a benefit.

The relationship of testosterone replacement to breast cancer is uncertain. Androgen receptors can be found in about half of breast cancers (84). Studies have suggested that androgen receptor status may increase, decrease, or have no effect on breast cancer (85–89). Further studies are required to establish the role or lack of a role of testosterone in the pathogenesis of breast cancer.

Finally, 17α-alkylated androgens can increase hepatic enzymes, rarely produce severe hepatocellular damage, and decrease the requirements for coumadin (10).

**Androgen Replacement Therapies**

A number of therapeutic options are available for testosterone replacement in postmenopausal women (Table 1). In the United States, Estratest (Solvay) (methyltestosterone in combination with esterified estrogen) is the most commonly administered form. 17α-methyltestosterone is a competitive aromatase inhibitor, which, as such, should reduce endogenous tissue estrogen production (90). In addition, many pharmacies compound testosterone that can be administered intravaginally or transdermally. Shifren and colleagues (32) have demonstrated the efficacy of a testosterone patch.

Testosterone undecanoate is an oral testosterone that is absorbed through the lymphatics, thus avoiding the first pass through the liver (91,92). It should be administered with a fat-containing meal. Maximum absorption occurs 2–4 hours after administration. It also increases dihydrotestosterone and decreases SHBG. It has been widely used in men.
TIBOLONE

Tibolone is a unique pharmacological agent. In tissues, it exhibits estrogenic, progestagenic, and androgenic effects. This makes it theoretically the ideal postmenopausal hormonal replacement. Tibolone decreases hot flashes and other vasomotor symptoms commonly observed at the menopause (101). This is associated with enhanced sexual function (101–103). Tibolone has a direct progestogenic effect on the endometrium (104). Tibolone reduces vaginal dryness and can be used to treat symptomatic atrophic vaginitis (104). Tibolone improves mood and may have positive effects on some aspects of memory (105–107).

Tibolone prevents postmenopausal bone loss (108–111). Tibolone increased handgrip but not isometric knee extension strength in postmenopausal women (112). This is similar to the finding that testosterone therapy improves upper-limb strength in hypogonadal men (113). Tibolone decreased fat-free body mass (114). Tibolone decreased plasma triglycerides, total cholesterol, plasma apolipoprotein E, and very low-density lipoprotein cholesterol (115). Tibolone reduced HDL cholesterol (116). Tibolone decreased the levels of thrombomodulin B-2, a vasoconstrictor (117). Tibolone did not alter endothelial-dependent brachial artery blood flow (118). Again this is similar to findings in hypogonadal older men (119). In rabbits fed an atherogenic diet, tibolone reduced the accumulation of cholesterol in the aortic arch (120). Tibolone increased fibronolysis parameters without altering coagulation parameters (121). Tibolone has small effects on blood pressure (122), possibly secondary to a decrease in endothelin levels (123).

Tibolone is an interesting compound that would appear to be an excellent option for postmenopausal women who are in need of an androgenic effect. There is a need for studies examining the effect of tibolone in frail older women. The effect of tibolone on the pathogenesis of breast cancer is uncertain, but it appears to exert minimal stimulatory effects on breast tissue (124,125).

CONCLUSION

The role of androgen replacement in postmenopausal and older women has been inadequately studied. There is sufficient data to recommend its use in some women with libido problems. Presently available clinical assays make it impossible to recommend a serum testosterone level at which treatment should be undertaken. Testosterone replacement may play an important role in preventing muscle loss in postmenopausal women and, therefore, preventing the development of sarcopenia in old age. Examination of the effects of testosterone in reversing frailty in older women should be a high priority (126). The ideal androgenic replacement in older women needs to be determined. Unfortunately, nearly 20 years after the pioneering study by Burger and colleagues (29), this area remains one in which many more well-controlled studies are required before true evidence-based conclusions about the cost-risk-benefit ratio of testosterone replacement in women can be determined.

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