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Androgens and the Postmenopausal Woman

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THE PREDOMINANT emphasis in the study of hormones in post-menopausal women has been accorded to estrogens and progestins, with lesser attention being given to androgens and the issue of androgen replacement. This is perhaps because androgens are traditionally thought of as male hormones, and the impact of excessive androgen activity in women, for example as in hirsutism, receives more attention than the activity of androgens in normal female physiology and the sequelae of androgen deficiency. There is an increasing awareness of the significant activity of endogenous androgens in women. Women with androgen deficiency may experience a variety of physical symptoms secondary to their androgen depletion as well as psychological changes that affect their quality of life (1).

Androgen physiology in the premenopausal years

Androgens are produced both by the ovaries and the adrenals, which synthesize androstenedione (A), testosterone (T), and dehydroepiandrosterone (DHEA), with the adrenals also producing DHEA sulfate (DHEA-S). At least 50% of circulating T is produced by peripheral conversion of the preandrogens to T, with A being the main precursor (2). In regularly ovulating women, there is a small, but significant, cyclicity of plasma A and T, with increases in the circulating mean levels of both of these hormones during the middle third of the menstrual cycle (3) and a second rise in A production by the corpus luteum occurring in the late luteal phase. Ovarian androgen is secreted by thecal cells under the control of LH.

The adrenals secrete large amounts of the precursor steroids DHEA and DHEA-S, which are converted peripherally into A and then into the potent androgens T and dihydrotestosterone (DHT) as well as into estrogens. The circulating concentration of DHEA-S in adulthood is higher than that of any other steroid except cholesterol. ACTH administered acutely stimulates adrenal DHEA secretion, with prompt increases in DHEA observed in adrenal venous blood (4) and peripheral blood (5). DHEA-S, which has a long plasma half-life (6), does not acutely increase with ACTH administration. However, a dissociation between adrenal androgen production and cortisol secretion occurs in various physiological and pathological conditions. Adrenal androgen levels are normal or suppressed in acute stress (7), severe systemic illness (8), anorexia nervosa (9), and Cushing's syndrome (10), all states characterized by elevated cortisol levels. In contrast, hyperprolactinemia can stimulate adrenal androgen production (5), although most patients with hyperprolactinemia have normal blood androgen levels.

Only 1–2% of total circulating T is free or biologically active; the rest is bound by sex hormone-binding globulin (SHBG) and albumin. The order of binding affinity for the steroids most strongly bound by SHBG is DHT > T > androstenediol > estradiol > estrone (11). SHBG weakly binds DHEA, but not DHEA-S (11). In women, alterations in the level of SHBG have dramatic effects on the free levels in plasma, as SHBG binds 66% of the total circulating T (11). Increased levels of estradiol (E_2) and T_4 increase, whereas T, glucocorticoids, GH excess, and, in particular, insulin (as in obesity) suppress SHBG levels. Thus, high estrogen states such as pregnancy and possibly estrogen replacement therapy may result in decreased free T levels and, in the latter case, exacerbate T deficiency symptoms.

Changes in androgens with menopause

The effect of the menopausal transition on circulating androgen levels has been addressed in several studies with variable results. Longcope *et al.* (12) did not observe any change in T, DHT, or A over 80 months after the final menstrual period (FMP), whereas Rannevik *et al.* (13) documented a small, but significant, decline (~15%) in T and A within the 6-month period encompassing the FMP. SHBG also fell on the order of 15% in association with the FMP; however, the ratio of T to SHBG was not affected (13). In a cross-sectional analysis of a community-based sample of 380 women, aged 46–57 yr, Burger *et al.* (13a) observed no change in the T:SHBG ratio (free androgen index) in relation to menstrual or menopausal status. Longcope *et al.* (12) also noted that the mean concentration of T in all their subjects was significantly less than that in a group of normal young women sampled between days 5 and 7 of their cycles. Consistent with the latter observation, a decline in T with increasing age has been reported in premenopausal women, such that the levels in women in their forties are approximately 50% of those of women in their twenties (14). Although the percentage of free T did not vary with age, an absolute decline in free T with age was observed (14). Circulating T in normal women is derived partly from the adrenal androgen precursors DHEA and DHEA-S. Circulating DHEA-S is also an important prehormone for ovarian intrafollicular production of T and DHT (6). As DHEA-S levels fall linearly with age, independent of the menopausal transition (15, 16), it is logical that circulating levels of T, their main metabolite, decline also. As one would expect, the DHEA to T and DHEA-S to T ratios are age invariant (14).

After ovariectomy, both T and A decrease by about 50% (17). Some individual variation naturally occurs. Direct ovarian secretion can account for up to 50% of postmenopausal T production, with the adrenal gland being a less important

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source (18). After menopause, peripheral conversion of A remains a major source of circulating T (18).

Ovarian stromal hypertrophy and hyperplasia occasionally develop after menopause, probably secondary to elevated LH levels and individual sensitivity, resulting in increased T production (19). In contrast, the ovaries may become fibrotic and a poor source of sex steroids; in such women, the adrenal gland becomes the main androgen source postmenopausally (19).

The decline in total circulating androgens, as described above, results from ovarian failure and the age-related decline in adrenal androgen and preandrogen production. The relative androgen deficiency of women with increasing age and after either natural or surgical menopause may be manifest as impaired sexual function, lessened well-being, loss of energy, and negative effects on bone mass (1, 20–22). As the absolute decline in both circulating T and adrenal DHEA and DHEA-S production generally commences in the decade preceding menopause (8, 12, 14, 15), it is not surprising that many women experience the above symptoms in the immediate premenopausal years. This differs from the sudden drop in estrogen levels observed late in the menopausal transition (13). The failure of various studies to demonstrate an association between the menopause and the symptoms attributable to androgen deficiency is probably due to the gradual nature of the androgen decline. Thus, these symptoms develop insidiously, in contrast to the more abrupt onset of symptoms of estrogen deficiency.

Androgens and postmenopausal sexuality

Undoubtedly, sexuality and libido are determined by many factors. However, a strong and significant association between climacteric phase and declining sexual and coital frequency independent of age has been observed (22). McCoy and Davidson (23) prospectively studied the effect of menopause on the sexual experiences and hormonal parameters of a group of women, commencing in the premenopausal years. Mean weekly rates of sexual intercourse declined over the menopausal transition period. Compared with those before menopause, the women after menopause had significantly fewer sexual thoughts or fantasies, experienced increased lack of vaginal lubrication during sex, and were less satisfied with their partners as lovers. These changes were associated with significant decreases in both E_2 and T, with the decline in T being most closely associated with lessened coital frequency. Clearly, the effect of declining sexual activity with age in men may contribute to the observed decreases in women.

The effect of anticipation of change in sexuality by women entering the menopause has also been examined, and the correlation between the anticipated effect of menopause on sexual well-being and what was actually experienced was weak (20).

There is increasing agreement that androgens play a key role in female sexuality and that androgen deprivation after menopause contributes to the decline in sexual interest experienced by many women. Controlled studies of the effect of estrogen replacement alone show improvement in vasomotor symptoms, vaginal dryness, and general well-being, but little change in libido (24, 25). Oral estrogen therapy improves sexual satisfaction in women with atrophic vaginitis causing their dyspareunia, but women without coital discomfort appear to benefit little or not at all (26, 27). Exogenous androgen replacement in the form of injected T enanthate enhances parameters of sexual motivation, including the intensity of sexual drive, arousal, and frequency of sexual fantasies in hysterectomized and oophorectomized women over and above the effect achieved with estrogen replacement alone (28). In contrast to the effect on sexual motivation, no increase in coital frequency or orgasm has been observed. Several other researchers have reported improved libido in postmenopausal women treated with sc T implants in combination with E_2 implant therapy (26–31). We investigated the effects of sc T implants on several parameters of sexuality in postmenopausal women in a 2-yr single blind randomized study (31). All parameters of sexuality studied improved with both E implants alone and E combined with T implants; however, the inclusion of T resulted in a significantly greater increase in sexual activity, satisfaction, pleasure, orgasm, and relevancy. T administration did not interfere with blood lipids in that total cholesterol and low density lipoprotein (LDL) cholesterol fell equally in both groups. No patients experienced any virilization or other side-effects of T therapy. We concluded that T administration to postmenopausal women enhances sexuality and can be of considerable benefit to women experiencing persistently low libido despite adequate estrogen replacement. It is possible that the effects of androgen replacement on sexuality are mediated by central aromatization of androgens to estrogens. Dow *et al.* (32) found E_2 implants alone to be as effective as E_2 plus T in terms of sexual enhancement; however, their study group consisted of women presenting with generalized menopausal symptoms, not low libido. Sherwin *et al.* (28) observed a greater effect on sexuality with combined estrogen and T replacement despite their estrogen only group being treated with higher doses of estrogen and achieving higher circulating estrone and E_2 levels. Similarly, the supraphysiological circulating E_2 levels achieved with E_2 implants alone do not result in a positive effect on sexuality equivalent to that observed with the addition of T implants (31). Thus, the effects of exogenous androgens on aspects of sexual behavior appear to be mediated by a mechanism other than estrogenic activity.

Although controversial, androgen therapy remains a neglected component of hormone replacement therapy in the management of postmenopausal symptoms. Several studies have now shown parenteral T replacement to be not only efficacious, but well tolerated and relatively safe (1, 26–31). However, there are few data available regarding the long term effects of androgen replacement in women, and clearly, studies involving extended follow-up are required. It is difficult to set out precise guidelines in terms of absolute blood T levels as to when T replacement is indicated. The decision is ultimately clinical. Many women with low normal or even low T concentrations have normal libido, whereas numerous women complaining of hirsutism also have normal to low T levels. This is to some extent explained by the individual variation in the local formation of androgens and estrogens from the adrenal precursors DHEA, DHEA-S, and A. The

enzymes responsible for the metabolic transformation of these prehormones to active androgens and estrogens are expressed in a number of peripheral tissues, including breast, prostate, endometrium, adipose tissue, and skin (33). As T and DHT are synthesized locally in these target tissues, measurement of circulating T, free T, or DHT is of little value apart from excluding rare androgen-producing tumors in women presenting with androgen excess. To achieve a good therapeutic response in terms of enhanced libido with postmenopausal androgen replacement, it appears that T levels often need to be restored to at least the upper end of the normal physiological range for young ovulating females. The doses of androgen replacement required to achieve such levels usually result in an initial postadministration peak T that is supraphysiological regardless of the mode of therapy (28). Our experience indicates that for sc T implant therapy, a dose of 50 mg is extremely effective and does not result in virilizing side-effects (31). These T implants are fused crystalline implants, 4–5 mm in diameter, containing T BP (British Pharmacopoeia) as the active ingredient. The 50-mg dose is obtained by bisecting a 100-mg implant under sterile conditions. The implant is inserted sc usually into the lower anterior abdominal wall using a trocar and cannula. This therapy provides a slow release of the hormone, with an approximate duration of the effect in women treated with 50 mg T of between 3–6 months. Because there is significant individual variation in the duration of the effect of T implantation, women treated with T implants should be carefully monitored, and serum T levels should be measured before the administration of each subsequent implant. It is recommended that additional T implants should not be administered unless total T is within the normal range for young women. T implants greater than 50 mg would prudently be avoided.

The role of androgen replacement in restoring sexuality after the menopause should not be undervalued. Young women who suffer either premature menopause or undergo bilateral ovariectomy early in life frequently experience the greatest distress from their loss of libido. Not only are such women very responsive to androgen replacement in terms of restoration of their sexuality, but they are usually very grateful to the physician who has made this therapeutic option available, as they frequently experience an enhanced general sense of well-being.

Relationship between androgens and bone loss after menopause

Androgenic steroids are known to be important in the maintenance of bone mass in both men and women. Nilas and Christiansen (34) performed a cross-sectional analysis of the sex hormone concentrations and bone mineral densities of women recruited for a prospective study of risk factors for osteoporosis. After controlling for body weight, a significant negative correlation between SHBG and bone mineral density (BMD) and a significant positive correlation between percent free T and BMD, but no relationship between BMD and free E_2 was observed in the premenopausal women (34). In the premenopausal years, BMD is also strongly correlated with body weight (34).

Obesity suppresses SHBG, and thus, the percentage of free T is increased (35). In premenopausal women this may explain the relationship among obesity, free T, and increased BMD, with the increased biologically active free T directly enhancing bone mass.

Human osteoblastic cells have been shown to possess androgen receptors (36), and androgens directly stimulate human bone cell proliferation and differentiation (37). It is not known whether T acts directly on bone cells or only after conversion to DHT. Finasteride, which specifically inhibits 5α-reductase-2 does not result in a reduction in vertebral BMD when administered for 12 months (38). This leaves the possibility that circulating T is converted to DHT in bone by 5α-reductase-1, which is not affected by finasteride. The positive effect of androgens, specifically DHT, on bone cell differentiation appears to be mediated by transforming growth factor-β, and the observed androgen induction of bone cell proliferation is due to an enhanced response of osteoblastic cells to growth factors, namely fibroblast growth factor and insulin-like growth factor II (39).

The antiresorptive effect of androgens on bone may be due to direct androgen action or be mediated by estrogens produced locally from androgen precursors. Aromatase P450 messenger ribonucleic acid is expressed in the bone marrow of postmenopausal women (40). It has been hypothesized that circulating androgens are aromatized in the marrow to estrogens, which then have a direct paracrine antiresorptive effect on bone tissue (40). In postmenopausal women estrogen acts as an antiresorptive agent on bone, thus limiting bone loss.

Ralston *et al.* (41) investigated the effects of sc estrogen implants, either alone or with T, on several parameters of calcium metabolism in postmenopausal women. Significant reductions in serum calcium and phosphate, the renal phosphate threshold, and the urinary calcium/creatinine ratio were observed, with no additional benefit of T on these parameters. The role of T in maintaining bone density has also been seriously questioned by the finding of severe osteoporosis in a male with normal T levels and a defective estrogen receptor (42). This report confirms the critical role of estrogen in skeletal maturation and mineralization in men and women.

There is a body of evidence that supports a direct anabolic effect of T on both protein metabolism and bone, independent of aromatization. Prepubertal hypogonadal girls (with Turner's syndrome) given estrogen replacement as ethinyl estradiol do not have altered whole body protein turnover or increased whole body protein synthesis despite significant increases in insulin-like growth factor I concentrations (43). In contrast, T administration to prepubertal boys exerts an anabolic effect in terms of parameters of protein metabolism (44). Raisz *et al.* (45) compared the effects of estrogen given alone to those of estrogen plus androgen therapy on biochemical markers of bone formation and resorption in postmenopausal women. Urinary excretion of markers of bone resorption decreased equally in both groups. The estrogen only group had a reduction in serum markers of bone formation, whereas in women treated with combined estrogen plus T, all markers of bone formation increased. Treatment with nandrolone decanoate has been shown to increase vertebral BMD in postmenopausal women and has been used for many years to treat postmenopausal osteoporosis (46).

Combined E_2 and T replacement with sc implant pellets increases bone mass in postmenopausal women (47, 48), with the effect being significantly greater than that observed using E_2 implants alone (31). It may be that androgens are only able to exert a direct anabolic effect on bone, as outlined above, when the fundamental estrogen-mediated skeletal maturation and antiresorptive processes are intact. Clearly, the potential therapeutic role for T replacement in the prevention and treatment of osteoporosis in women is controversial and warrants further investigation.

Positive correlations have been observed between DHEA and DHEA-S, and BMD in aging women (49, 50). It is unclear whether this is a direct or indirect effect via E_2, A, or T. The progressive decline in the secretion of these adrenal hormones may contribute to the development of senile osteoporosis (47). Replacement therapy with DHEA in women of advancing age results in restoration of circulating A, T, and DHT to premenopausal levels as well as increases in DHEA and DHEA-S, with no alterations in serum levels of estrone or E_2 (51). In this study, 82% of women experienced enhanced well-being and increased energy during the DHEA phase compared with those during placebo administration. Such improvements are consistent with the increases in androgens documented during DHEA replacement. In contrast, libido measured simply by a visual analog scale did not change with DHEA therapy. Undoubtedly, the effects of DHEA replacement on sexuality in postmenopausal women need to be addressed in future studies. The effects of DHEA therapy on bone metabolism in postmenopausal women are currently being evaluated. The beneficial effects of DHEA therapy in postmenopausal women appear to be mediated by its transformation to androgens and/or estrogens in specific target tissues. It is, therefore, conceivable that DHEA replacement may be an alternate mode of administering combined estrogen and androgen replacement to postmenopausal women in the future.

Potential risks of androgen replacement in women

When considering androgen replacement as a therapeutic option, the possibility of undesirable side-effects must be reviewed. There are concerns that androgen replacement may have an adverse effect on circulating lipids, particularly high density lipoprotein (HDL) cholesterol (52). T replacement may prevent the increase in HDL cholesterol seen in women using estrogen alone (31, 53). When the effects of combined sc E_2 and T implants on plasma lipids in postmenopausal women were evaluated, total cholesterol and LDL cholesterol fell by 11% and 17%, respectively, with no significant variation from baseline for either HDL cholesterol or triglycerides (31). However, the control group receiving only E_2 implants in this study did not have an increase in HDL cholesterol over the study period. Raisz *et al.* (45) reported a 25% reduction in total cholesterol in postmenopausal women treated with E plus T, accompanied by a reduction in HDL_2 and HDL_3 and triglycerides and no change in LDL cholesterol. T replacement should only be recommended to women taking estrogen replacement therapy concurrently, as it is likely that T alone would result in adverse lipid effects. Serum HDL cholesterol has been observed to be reduced in older women by DHEA replacement (51). This effect is most likely mediated by the androgen metabolites of DHEA acting unopposed in an hypoestrogenic milieu.

When the effects of androgen replacement on body composition were addressed, the changes observed included a modest increase in lean body mass and a reduction in total body fat, with no variation in body mass index (31). A slight increase in waist to hip ratio has also been seen after combined sc E_2 and T replacement.

There is conflicting evidence as to whether androgen replacement has an effect on the incidence of breast cancer (54, 55), in contrast to some literature implicating a role for endogenous androgen production in the development of malignant breast disease (56–58). However, the interaction between endogenous androgens and breast cancer remains controversial, with conflicting data suggesting correlations between low circulating androgen levels and breast cancer (59).

Cosmetic side-effects of androgen replacement are rare if supraphysiological hormone levels are avoided (1, 26–31, 45, 46), but the potential virilizing effects, including the development of acne, hirsutism, deepening of the voice, and increased libido, must be borne in mind when androgen replacement is considered. The authors would not recommend androgen replacement for women troubled by existing hirsutism or acne. Enhanced libido may well be a positive outcome of therapy for some; however, increases in sexual thoughts and fantasies may be undesirable for other women.

Conclusion

Androgens are important hormones in women and have diverse actions. The decline in the production of ovarian and adrenal androgens and preandrogens that commences in the decade preceding the average age of naturally occurring menopause may impact significantly on women's health. The clinical sequelae of androgen deficiency in women have only recently been acknowledged, and although still controversial, androgen replacement for symptomatic women is becoming an increasingly available option.

Side-effects are a major concern for many physicians inexperienced in androgen replacement in women. Genuine clinical side-effects are, in fact, rare, when a replacement regimen is used and the patient properly monitored. Androgens, usually in the form of T, should only be administered to women who are concurrently taking estrogen replacement, as without estrogen, the likelihood of an adverse effect on plasma lipids, specifically suppression of HDL cholesterol, is increased.

The option of androgen replacement should be given to postmenopausal women, especially younger women with either premature or surgically induced menopause, who suffer persistent loss of well-being, fatigue, and, most commonly, loss of libido, despite adequate estrogen replacement and after exclusion of other possible underlying pathology. The observed beneficial effects of T replacement on bone mass require further research to define the appropriate clinical indications. Prospective data confirming a reduction in fracture rate with anabolic steroid therapy is lacking. Finally, treatment with DHEA is potentially an alternative means of replacing androgens in older women. Future research should clarify the usefulness and safety of this therapy.

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