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COMMENTARY

Androgen Replacement in Women: A Commentary

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ABSTRACT

There is increasing evidence to suggest that many postmenopausal women experience symptoms alleviated by androgen therapy and that such symptoms may be secondary to androgen deficiency. Affected women complain of fatigue, low libido, and diminished well-being, symptoms easily and frequently attributed to psychosocial and environmental factors. When such symptoms occur in the setting of low circulating bioavailable testosterone, testosterone replacement results in significant improvement in symptomatology and, hence, quality of life for the majority of women. Whether the apparent therapeutic effects of testosterone replacement are mediated by testosterone and its metabolite 5α- dihydrotestosterone or are a consequence of aromatization to estrogen is not known. Despite the paucity of data regarding its effects, inclusion of testosterone in postmenopausal hormone replacement regimens is not uncommon and is likely to become more widespread with the availability of preparations developed specifically for women.

Other novel and even more controversial potential indications for androgen therapy in women are currently being evaluated. These include use in women with premature ovarian failure, premenopausal androgen deficiency symptoms, postmenopausal and glucocorticosteroid-related bone loss, alleviation of wasting syndrome secondary to human immunodeficiency virus infection, and management of premenstrual syndrome.

The aim of this commentary is to very briefly review the rationale for the use of testosterone in women, create awareness of some of the therapeutic options available in various countries, and stimulate discussion of this important aspect of women's health. (*J Clin Endocrinol Metab* **84:** 1886–1891, 1999)

The therapeutic use of testosterone in women, although controversial, is becoming more widespread. Unfortunately, the data to support this practice are relatively limited, as only a few randomized studies have been conducted. Androgen replacement for women has been previously reviewed in this journal (1) and more recently and more extensively elsewhere (2, 3). This commentary is focused on the evidence to support the use of testosterone therapy in women and potential novel indications, and highlights the need for further research in this area.

Androgens have important physiological actions in women that are poorly understood. Furthermore, there is no consensus on either the clinical or biochemical definition of androgen deficiency in women. The latter has been hampered by the insensitivity of most assays for testosterone at the lower end of the normal reproductive female range. Clearly a working definition of androgen deficiency in women is needed for consistency of ongoing research in this area and as a foundation for clinical guidelines for the use of testosterone in women to prevent its inappropriate use.

It is the cumulative experience of this author and others working in this field (3a) that the clinical profile that characterizes the woman most likely to respond to androgen therapy, and therefore possibly female androgen deficiency, includes persistent inexplicable fatigue, blunted motivation, low libido, and diminished well-being in a woman who is estrogen replete with low circulating bioavailable testosterone (either total testosterone/sex hormone-binding globulin (SHBG) ratio or free testosterone in the lower third of the female reproductive range). Indisputably, the basis of each of these symptoms is potentially multifactorial; therefore, it is essential that the treating physician endeavors to discern the extent to which other factors contribute to these symptoms. Although this may be time consuming and complex, it is essential that the treating physician does so and manages any identifiable factors. This may involve commencement of estrogen therapy for vaginal atrophy or referral to a counselor, psychiatrist or sex therapist. The impact of any intervention should be reviewed before recommending testosterone replacement.

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Causes of hypoandrogenism in women

Circulating androgen levels [total testosterone, free testosterone, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S)] in women fall continuously with age (4, 5). This is a consequence of the age-related decline in adrenal androgen production and loss of the midcycle increase in ovarian testosterone secretion in the late reproductive years (6). After ovariectomy, both testosterone and androstenedione (A) fall acutely by approximately 50% (7). Other causes of suppression of circulating androgen levels include chemical ovariectomy with either chemotherapy or GnRH antagonists, radiotherapy, and the administration of exogenous estrogens and glucocorticosteroids. In general, there is a fall in circulating free testosterone in women using the combined oral contraceptive pill or oral estrogen replacement therapy (8, 9). The latter a result of increased SHBG combined with suppression of LH production by the pituitary, and hence less stimulus for the ovarian stromal production of testos-

terone. These effects are amplified in older women, whose overall androgen production is declining (8, 9). Treatment with oral glucocorticosteroids results in ACTH suppression and therefore reduced adrenal androgen production (10). This appears to contribute in part to the pathogenesis of osteopenia and osteoporosis associated with glucocorticosteroid treatment in both women and men. Hypothalamic amenorrhea and hyperprolactinemia may also be characterized by low testosterone and bone loss. Similarly, women with premature ovarian failure have been reported to suffer significant bone loss despite apparently adequate standard estrogen-progestin therapy (11). Therefore, it may be that some women with either ongoing hypothalamic amenorrhea or premature ovarian failure require testosterone replacement to fully protect their bones.

In women, the mechanisms of androgen action are not well understood. Androgens may act directly via the androgen receptor or as precursor hormones for estrogen production in the ovaries and extragonadal tissues, importantly bone, adipose tissue, and brain. Thus, the maintenance of physiological circulating androgen levels in women ensures an adequate supply of precursor hormone for estrogen biosynthesis in extragonadal sites in which high estrogen tissue concentrations may be required physiologically (for example, maintenance of bone mineralization and prevention of bone loss). Corroborative data for this hypothesis are that total and bioavailable testosterone and DHEA-S are the greatest predictors of bone mineral density (BMD), with low free testosterone being most highly correlated with premenopausal hip bone loss (12, 13); androgen levels are consistently and positively associated with BMD in postmenopausal women (14, 15); and abundant aromatase activity has been reported in fetal osteoblasts and cell lines of osteoclastic origin (16). With respect to the central nervous system, regions of high aromatase activity in animals correlate with regions of the brain in women with the highest concentrations of testosterone (17, 18). However, in these regions, namely the preoptic area, substantia nigra, and hypothalamus, the levels of measurable testosterone greatly exceed those of estradiol in samples from female cadavers taken acutely postmortum (17).

In summary, the extent to which androgens act directly in women or as prehormones for estrogen production, or perhaps by lowering SHBG and increasing free circulating levels of estradiol and other sex steroids, is not known. It is possible that all of these effects are important to varying degrees in different tissues.

Clinical indications for androgen therapy in women

Androgens appear to be important in female sexuality, with reduced androgen levels in the late reproductive years and beyond contributing to the decline in sexual interest experienced by many women. Standard estrogen replacement therapy has little effect on libido in women not troubled by vaginal dryness and dyspareunia (19–21). In a study of sexagenarian women, the only hormone positively correlated with sexual desire was circulating free testosterone (22). We and others have demonstrated improvement in several aspects of sexuality in postmenopausal women treated with testosterone over and above the effects of estrogen replacement alone (19–21, 23–27). Sustained improvement in intensity of sexual drive, arousal, frequency of sexual fantasies, satisfaction, pleasure, and relevancy to daily life were observed in a cohort of postmenopausal women (Fig. 1). Enhancing effects have been reported with both oral methyl testosterone and parenteral testosterone administration. Enhanced sexuality, as observed in these studies, is subtle. Notably increased sexual activity in women is a poor index of response to therapy, as the frequency of intercourse is often dictated by established patterns and interest of the partner. Our results (25) may differ from other reports because we conducted one of the very few blinded randomized studies designed specifically to address the effects of testosterone on sexuality, plus it involved a 2-yr protocol with six monthly evaluations to minimize the confounding effects of a placebo response.

Testosterone replacement should also be considered as part of the management of young women with premature menopause, particularly Turner's syndrome. Women who are sexually active when they develop premature ovarian failure often suffer a great deal as a consequence of their diminished libido. Alternatively, young women who have not become sexually active, who have either primary or secondary premature ovarian failure, should be fully informed about the option of androgen replacement or, perhaps, in some instances offered low dose androgen replacement as a component of their hormone replacement regimen.

Whether premenopausal women who complain of loss of libido who have low bioavailable testosterone levels should be offered androgen replacement is more controversial. In general, management of such women needs to be very open-minded, and therapy completely individualized. It is the

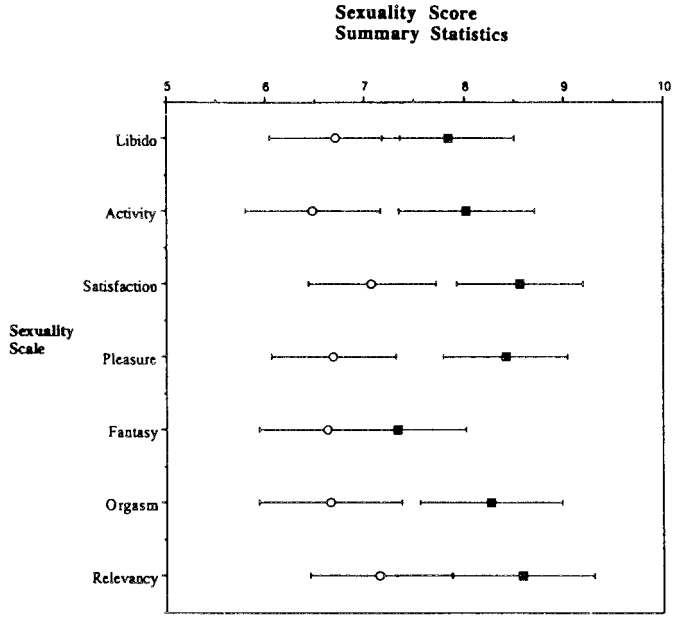

FIG. 1. Summary graph showing the grand mean (*i.e.* means of 6, 12, 18, and 24 months) for each sexuality parameter adjusted for baseline as a covariate. ○, Estradiol implants alone; ■, estradiol plus testosterone implants. *Error bars* represent the SE for each mean. If the error bars do not overlap for a single parameter, the difference is significant at $P < 0.05$ (25).

clinical experience of the author that a subset of premenopausal women with sexual dysfunction and reduced circulating androgen levels significantly benefits from judicious parenteral testosterone replacement. However, testosterone replacement is unlikely to benefit women at any age in whom other factors play a dominant role in their sexual dysfunction. Therefore, a thorough psychosocial and sexual history is essential when evaluating the appropriateness of testosterone therapy in a woman.

Prevention and treatment of bone loss

Studies of both oral and parenteral estrogen plus testosterone therapy in postmenopausal women have shown beneficial effects of testosterone replacement on BMD (25, 28, 29). Oral esterified estrogen in combination with methyltestosterone therapy not only increases spinal BMD, but also suppresses biochemical markers of bone reabsorption, with an increase in markers of bone formation over 2 yr (29, 30). Combined estradiol-testosterone replacement with sc implant pellets increases bone mass in postmenopausal women, with the effects in the hip and spine greater than those with estradiol implants alone (Figs. 2 and 3) (25, 28, 31). Androgen replacement to prevent bone loss should also be considered for women with premature ovarian failure. Despite adequate standard estrogen-progestin therapy, two thirds of such women have significantly reduced BMD to levels associated with increased hip fracture risk. Of these, 47% have reductions in BMD within 18 months of their diagnosis (11).

Effects on body composition

Testosterone levels are frequently lower in human immunodeficiency virus (HIV)-positive premenopausal women, and testosterone replacement is associated with an increase in fat-free mass and body cell mass in HIV-positive men. Augmentation of testosterone levels in HIV-positive premenopausal women using a transdermal patch is associated with overall increased mean body weight and body mass index as well as improved quality of life (32). We have reported an increase in fat-free mass and a reduced fat mass to fat-free mass ratio in postmenopausal women treated with concurrent estrogen-testosterone therapy (25). A gain in fat free mass probably reflects increased muscle mass, and as aging is associated with loss of muscle mass, this is a beneficial effect of testosterone therapy in the older woman. However, administration of testosterone attenuates the reduction in centralized body fat achieved with estrogen replacement alone (25).

Testosterone and the premenstrual syndrome

Recent studies indicate that premenstrual syndrome (PMS) represents individual vulnerability to the effects of circulating steroids. Variations in testosterone levels during the menstrual cycle may influence behavioral changes such as those seen in PMS, and significantly lower levels of testosterone throughout the menstrual cycle have been reported in women who suffer from PMS compared with controls (33, 34). Testosterone replacement is used in the management of PMS in some clinical centers in the United Kingdom and Australia (35). Randomized trials evaluating such therapy are nearing completion, and positive outcomes from these are necessary before testosterone therapy for PMS can be recommended for widespread use.

Testosterone and autoimmune disease

Immunogenetic factors are the major determinants of the development of immune-mediated diseases; however, gender and age also play a role. Androgens appear to suppress both cell-mediated and humeral immune responses, and it

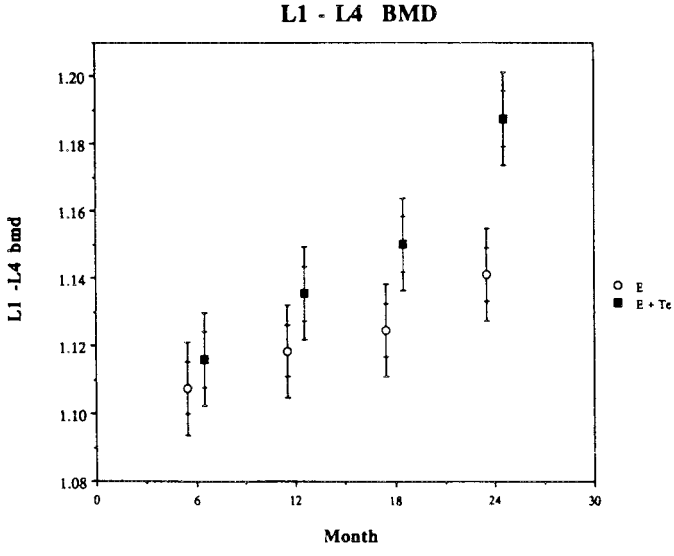

FIG. 2. The effects of hormonal implants on BMD (grams per cm^2), lumbar spine (L1–L4), and femoral trochanter (troc). E, Estradiol; E&T, estradiol plus testosterone. *Error bars* represent the SE. *Inner error bars* are used to compare means between times for the same treatment. The comparison between the treatment groups is made with the outer error bars. If error bars do not overlap, that is differ by more than 2 SE, the means are significantly different by at least $P < 0.05$ (25).

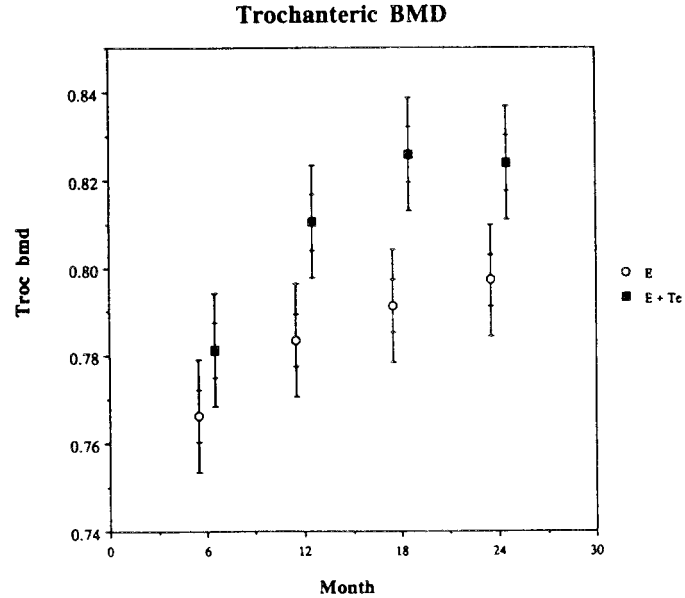

FIG. 3. See Fig. 2 legend.

has been proposed that higher testosterone levels, as seen in men, may be protective against autoimmune disease (36–38). The direct administration of testosterone replacement may result in symptomatic improvement in postmenopausal women with rheumatoid arthritis (39), and reduced disease activity has been reported in both pre- and postmenopausal women treated with DHEA associated with increases in levels of circulating DHEA, DHEA-S, and testosterone (40). Further evaluation of potential beneficial effects of testosterone administration in women with autoimmune arthritis is warranted in view of the favorable preliminary studies, the positive effects of this therapy on lean body mass and bone density, and the adverse effects of glucocorticosteroids on these parameters.

Administering testosterone to women

The majority of available testosterone preparations for human use have been formulated for use in men. Furthermore, few countries have officially approved the use of testosterone for hormone replacement therapy in women, and clinical guidelines for safe use are lacking. Testosterone is available as oral methyltestosterone in the United States, and testosterone implants have been approved for replacement therapy for women in the United Kingdom. It is our clinical experience that even for postmenopausal women, testosterone levels often need to be restored to at least the upper end of the normal physiological range for young ovulating women to achieve a good therapeutic response in terms of improved libido. The dose of testosterone administered, however, should result in circulating levels as close to physiological as possible to avoid adverse side-effects.

Of the available oral preparations, methyltestosterone in combination with esterified estrogen (EE; either 0.625 mg EE plus 1.25 mg methyltestosterone or 1.25 mg EE plus 2.5 mg methyltestosterone) has been the most studied and in the currently available doses in North America offers therapeutic benefits, but has occasional side-effects. Although long term therapy with large doses of this compound has adverse hepatic effects, this has not been seen with lower doses (41). This oral therapy does, however, negate some of the beneficial lipid effects of estrogen, with reductions in high density lipoprotein cholesterol and apolipoprotein A1 with 0.625 mg EE plus 1.25 mg methyltestosterone (41). This combined therapy does not appear to attenuate the favorable effects of EE on vascular reactivity (42) and is associated with reduced concentrations of apolipoprotein B (41, 43) and increased total body low density lipoprotein cholesterol catabolism (43). Physicians should be aware that androgenic side-effects may occur with the EE/methyltestosterone preparations (41) and should warn patients of this possibility and monitor for androgenic side-effects. As this compound cannot be measured in serum in a clinical setting, it is impossible to recommend biochemical treatment guidelines.

Testosterone undecanoate has been less well studied; however, a recent pharmacokinetic study indicates undesirable supraphysiological peaks of circulating testosterone with doses of testosterone undecanoate as low as 20 mg (44). Therefore, with the limited data available, its use in women cannot be recommended.

Subcutaneous testosterone implants have been used for many years in postmenopausal women. These implants are fused crystalline implants 4.5 mm in diameter containing testosterone BP (British Pharmacopoeia) as the active ingredient. Our clinical experience, verified by published data, is that a dose of 50 mg is extremely effective in enhancing libido and improving BMD without unwanted virilizing side-effects (24, 25, 27). The 50-mg implant, which is inserted under local anesthesia, sc, usually in the lower anterior abdominal wall, is effective for between 3–6 months. There is, however, marked individual variation in this period; therefore, testosterone levels should be carefully monitored, and serum testosterone measured before the administration of each subsequent implant. Rarely are testosterone implants of 100 mg necessary to achieve adequate therapeutic effects. Indeed, Buckler and others reported circulating testosterone levels approximately 3 times the upper limit of normal 4 weeks after insertion of a 100-mg testosterone pellet (44). Unfortunately, the impact of these levels on sexuality and other clinical parameters was not reported. In contrast, 6 weeks after insertion of a 50-mg testosterone implant, mean circulating testosterone levels are just above the upper limit of the normal range for ovulating women (27).

Mixed testosterone esters (50–100 mg) are occasionally administered every 4–6 weeks as an im injection to women with androgen deficiency symptoms, although there are no published data to support this practice. Clinically, this therapy results in a more rapid onset of effects, such that women report enhanced libido within 2–3 days of treatment. In contrast, women generally report a delay in restoration of libido 10–14 days after insertion of a testosterone implant. The pharmacokinetics of mixed testosterone esters administered im to women have not been studied; however, many women report increased acne and occasional cliteromegaly with this therapy.

The recent development of a transdermal testosterone matrix patch intended specifically for use in women will provide a new therapeutic option for androgen replacement. The patch, which is now undergoing clinical trials, is designed to deliver 150 μg testosterone/day with a twice a week application. This results in an average increase in circulating testosterone levels of approximately 25 ng/dL (~1 nmol/L). The availability of such a patch will have some obvious advantages over both oral and implant therapy; however, some women may experience skin irritation or simply prefer a less conspicuous mode of therapy. Much higher dose transdermal patches in women have been reported to produce supraphysiological circulating testosterone levels in women, and their use cannot be advocated (44).

Nandrolone decanoate is a very weakly aromatizable androgen that is available in some countries for the treatment of postmenopausal osteoporosis and is administered im. The dose should not exceed 50 mg, and although the recommendation is for this to be give monthly, androgenic side-effects may be encountered but can be avoided with every 8 week administration, or even less frequently in very petite women. In the majority of women, treatment with nandrolone decanoate results in cessation of bone loss over time, and in some women, it produces an absolute increase in BMD (45).

Other alternatives, not currently generally available but

still in widespread use, are transdermal testosterone as a cream or gel, or delivery by a transvaginal ring. Such preparations may be regionally available on specific prescription from compounding pharmacists; however, to date, there are no pharmocokinetic data available or published clinical experience regarding the use of such preparations.

As a general rule, testosterone replacement should not be administered to postmenopausal women who are not receiving concurrent estrogen replacement therapy. In the first instance, estrogen alone may improve other postmenopausal symptoms, alleviate vaginal dryness, and enhance sexuality, obviating the need for androgen therapy. Furthermore, suppression of SHBG with testosterone alone may increase the possibility of adverse side-effects, although this may be less relevant for methyltestosterone, which binds poorly to SHBG (41). The exception to this practice would be the use of nandrolone decanoate in the more elderly woman, hence the need for vigilant monitoring for virilizing side-effects with this preparation used alone.

Relatively strong contraindications to testosterone therapy include moderate to severe acne, clinical hirsutism, androgenic alopecia, and circumstances in which enhanced libido would be undesirable. Absolute contraindications include pregnancy and lactation as well as known or suspected androgen-dependent neoplasia.

Side-effects from excessive dosage include virilization, fluid retention, and potentially adverse lipoprotein-lipid effects, which are more likely with oral administration.

Clinical data indicate that parenteral testosterone therapy that results in testosterone levels close to and within the normal physiological range for women has no undesirable metabolic consequences (25, 31). It is not known whether there is any relationship between exogenous androgen therapy and the incidence of breast cancer, as epidemiological studies have shown both positive and negative associations between endogenous androgen levels and breast cancer risk. Androgen receptors are found in over 50% of breast tumors (46) and are associated with longer survival in women with operable breast cancer and a favorable response to hormone treatment in advanced disease (47). There are also some data to suggest that the mechanism by which high dose medroxyprogesterone acetate has a therapeutic effect on breast cancer is mediated via the androgen receptor (48).

Conclusions

It is increasingly being accepted that androgen deficiency in women underpins a variety of symptoms and pathophysiological conditions and that in certain subsets of women, androgen replacement therapy is of clinical benefit. The inclusion of testosterone therapy in postmenopausal hormone therapy regimens is increasing, but is still limited by the lack of availability of preparations and formulations designed specifically for use in women. Although more controversial, premenopausal women with either spontaneous or iatrogenic androgen deficiency also warrant consideration for androgen replacement, as do women experiencing glucocorticosteroid-induced bone loss and possibly premenopausal bone loss. The role of androgen therapy in the premenstrual syndrome should be further elucidated by results from randomized placebo-controlled studies which are currently underway.

Many women are not comfortable discussing their loss of sexual desire, particularly those who have undergone chemotherapy, and often comment that they feel the issue will be viewed by their physician as trivial relative to their recovery or remission. Also, the symptoms of iatrogenic menopause can easily be attributed to side-effects of chemotherapy or to other psychosocial factors in premenopausal women or in those who have undergone premature menopause. Therefore it is the treating physician's responsibility to facilitate discussion of sexuality in all at risk women, and the possibility of low circulating androgen levels as an underlying cause for those with positive symptomatology should be evaluated.

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