CME REVIEW ARTICLE 16

Androgens in Postmenopausal Women: Production, Possible Role, and Replacement Options

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The physiology of normal androgen production in women has not been well understood. Aging, per se, accounts for much of the reduction in both ovarian and adrenal androgen production; and natural menopause does not result in an abrupt decline in testosterone production. Therefore, the definition of an androgen deficiency state in women, in the absence of adrenal suppression and/or bilateral oophorectomy, has been difficult. Nevertheless there are well-documented beneficial effects of androgen on many organ systems, including bone and the brain. This review focuses on the physiology of androgens in postmenopausal women and includes a discussion of the definition of an androgen deficiency state, the anticipated effects of androgen on several parameters of health, and possible ways in which androgens may be administered to women.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to explain the physiology of androgen production in women, outline the risks of androgen replacement, and summarize the treatment options for a women with relative androgen deficiency.

Androgen therapy for women has been proposed more frequently in recent years. Data will be examined critically in this review to assess the role of androgens in women and the potential therapeutical possibilities. The physiology of androgen production and its measurement will be discussed first. This will be followed by the role of androgens in the health of women and what may constitute an indication for androgen therapy. Finally, the efficacy of a variety of treatment options and their potential risks will be discussed and followed by some general recommendations.

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PHYSIOLOGY OF ANDROGEN PRODUCTION IN WOMEN

Androgen production in women takes place in three compartments: the ovary, adrenal, and peripheral tissues. The peripheral compartment involves the interconversion of androgens, as well as the conversion of androgen to estrogen (via aromatase activity). In addition, the pilosebaceous unit is responsible for accentuating androgen action by converting testosterone and androstenedione to more potent androgens such as dihydrotestosterone and androstanedione (1, 2).

The production of androgens produced principally by the ovary and adrenal, and which are interconverted in peripheral tissues, is depicted in Figure 1. Serum DHEA-S signifies adrenal production with more than 90% being derived from this source. Another important circulating marker of adrenal production is 11β-hydroxyandrostenedione (3). However,
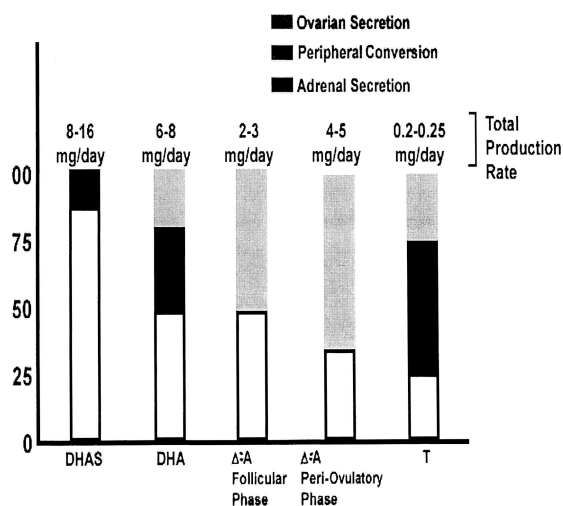
Fig. 1. Ovarian, adrenal, and peripheral androgen secretion. Data adapted from (9), used with permission © The Endocrine Society.

there is little information about this marker in the absence of hyperandrogenism or during the menopausal transition. Serum testosterone is an important marker of ovarian androgen production, although at least one third of circulating levels are derived via precursors from the adrenal. Testosterone levels remain constant during the menstrual cycle, but exhibit a midcycle peak coincident with the LH surge (4).

Levels of the peripherally derived 5α-reduced androgens, such as 3α-androstanediol glucuronide and androsterone glucuronide, reflect enhanced skin 5α-reductase activity in the clinical disorders of hirsutism and acne (5, 6). After menopause, however, these levels decrease (7). This change reflects a decline in androgen substrate from the ovary and adrenal rather than a change in skin activity. The latter (skin 5α-reductase activity) does not decrease significantly after menopause (8).

After menopause, ovarian production of androgens does decrease significantly, but is more marked for

TABLE 1 **Range of ovarian secretion rates of androgens and estrogens in young and postmenopausal women**

	Ovary	
Secreted Hormone	Reproductive Age* (mg/day)	Postmenopausal (mg/day)
Estradiol	40–80	0–20
Estrone	20–50	0–10
Testosterone	50–70	40–50
Androstenedione	1–1.5	0.3–0.6

* Midfollicular phase.

Data extrapolated from Longcope et al., Clin Endocrinol Metab 1986; 15:213–228.

androstenedione than for testosterone (9) (Table 1). There is controversy concerning the decline in testosterone levels after menopause. At least one recent report (10) suggests that testosterone levels increase between the fifth and sixth decades. The majority of studies, however, that will be cited below, point to no major change across the menopausal transition with values decreasing very gradually thereafter. Both testosterone and androstenedione are at least in part LH-dependent after menopause, as reflected by the reduction in levels (30%) after suppression of the postmenopausal levels of LH by a GnRH agonist (11) and antagonists (12, 13).

It is undeniable, however, that unlike estradiol production, the postmenopausal ovary continues to produce testosterone and androstenedione. In postmenopausal women undergoing oophorectomy, testosterone levels decrease by 50% (12) (Fig. 2). Therefore, although it may be difficult to ascertain that testosterone levels are decreased in perimenopausal women who have intact ovaries, all oophorectomized women by definition are androgen deficient. Table 2 depicts serum levels of androgens in postmenopausal women and those who have undergone oophorectomy.

Several studies have examined androgen changes across the menopausal transition, in both cross-sectional and prospective studies (13–15). Total testosterone does not change appreciably until women are very much older (age group: 71–95 years), although androstenedione levels decrease much earlier (Fig. 3A and B). Levels of DHEA-S, however, decline as a function of age (16) and seem to be unaffected by menopausal or estrogen status per se. Mean 24-hour levels of testosterone decrease in women from age 20 to age 50 (17). However, this decline, is thought to reflect aging, in that the ratio of DHEA-S/T is constant over this time span (17) (Fig. 4). These data confirm that although aging affects levels of testosterone, these levels are not much different before and
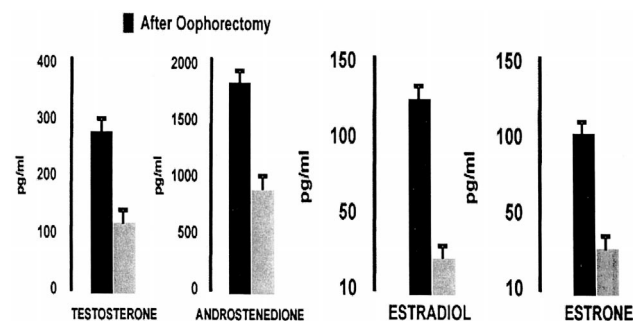

Fig. 2. Serum androgens and estrogens after oophorectomy in postmenopausal women. Adapted from (14).

TABLE 2   **Plasma steroid levels in healthy women**

	Reproductive Age Women	Natural Menopause	Oophorectomized Women
Estrone (pg/ml)	50 ± 15	30 ± 5	20 ± 3
Estradiol (pg/ml)	40 ± 3	15 ± 2	10 ± 2
Testosterone (ng/dl)	40 ± 3	20 ± 2	10 ± 2
DHT (ng/dl)	30 ± 4	10 ± 2	<5
Androstenedione (ng/dl)	140 ± 10	88 ± 11	64 ± 9
DHEA (ng/dl)	420 ± 21	197 ± 43	126 ± 36
DHEA-S (μg/ml)	1.6 ± 0.2	0.8 ± .1	0.6 ± .1

Values are mean ± SEM.

DHT = dihydrotestosterone; DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; DHEA and DHEA-S are age-related.

Adapted from Vermeulen A, J Clin Endocrinol Metab 1976;42:247–253 © The Endocrine Society and Mishell's Textbook of Infertility, Contraception, and Reproductive Endocrinology, 4th Ed. Lobo RA, Mishell DR, Paulson RJ et al., eds. Malden, MA: Blackwell Scientific Publications, 1997.

after menopause, and the small reduction in ovarian production is thought to result from declines in androstenedione.

After menopause, sex hormone-binding globulin (SHBG) levels decline to a small degree, which results in slightly higher levels of unbound, or free, testosterone (also calculated as a free-testosterone index). The reduction in SHBG reflects reductions in E_2 and an increase in body mass index (BMI) (15). However, because of the wide range in values for testosterone and unbound T in perimenopausal women on an individual basis, it may not be possible to predict that a woman may have low levels (Fig. 5*A* and *B*). As a group, however, in women with intact ovaries, perimenopausal women not receiving estrogen have normal or slightly higher free androgen status. Among the steroids, which are most pertinent to this review, the ones that are influenced by SHBG are testosterone (70%) and estradiol (30%). Androstenedione and estrone have no significant binding to SHBG. Variables that increase SHBG levels (such as estrogen and thyroid hormone) would be expected to result in lower levels of unbound or free testosterone.

MEASUREMENTS OF ANDROGENS

Part of the difficulty in determining whether androgens are normal, increased, or decreased is related to the variability in measurements. Although the radioimmunoassay for DHEA-S is reasonably consistent, upper ranges in women vary between laboratories. Values for increased levels have been reported to be as high as 4 μg/ml. The lower part of the normal range also varies because DHEA-S levels decrease with age.

Even greater inconsistency occurs for measurements of testosterone. Methods used vary substan-

tially, and even use of standardized methods such as radioimmunoassay (RIA) are variable depending on whether serum is extracted and/or undergoes chromatography before RIA. Upper normal ranges vary from 50 to 100 ng/dl. This has created difficulty in diagnosing the hyperandrogenism of women with polycystic ovary syndrome and has also challenged the notion of what low levels are in peri- and postmenopausal women. In general, testosterone levels are considered low if they are <20 ng/dl, and values are usually below 10 ng/dl after oophorectomy (Table 2). The most sensitive measurement of testosterone bioavailability is unbound or free testosterone. The commercial assays for "free" testosterone are extremely inconsistent and have been considered to be invalid by some investigators (18). This is the case with the commercial kits currently in use. Dialysis systems are demanding technically and measure that moiety of testosterone not bound to either SHBG or albumin. Assay systems, which include the albumin moiety (unbound or non–SHBG-bound testosterone), are considered to better reflect biological activity, but are not always available. Salivary testosterone measurements are also considered to be highly variable (18). Therefore, many investigators prefer to use the free testosterone index, which is a calculated value, usually the ratio of testosterone to SHBG.

DETERMINATION OF ANDROGEN DEFICIENCY

With these difficulties in measuring androgens, the definition of androgen deficiency has been elusive, and most clinicians must realize that what is being diagnosed is a "relative" deficiency. Only in the setting in which a woman has undergone bilateral oophorectomy can we be certain of androgen defi-
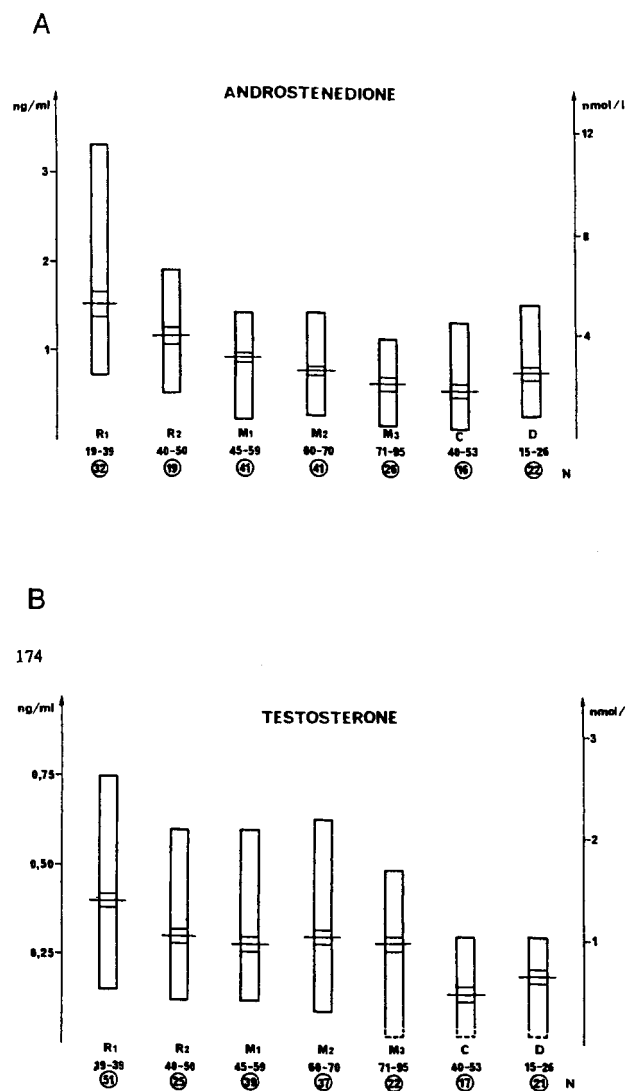
Fig. 3. Mean and range of androstenedione levels (*A*) and testosterone levels (*B*) in age groups of postmenopausal women and in controls. Aging groups are M1–3. *Vertical rectangle* = range. *Horizontal bars* = mean ± standard error of the mean. *N* = number of subjects. Adapted from Roger M, Nahoul K, Scholler R et al. Evolution of ageing of four plasma androgens in postmenopausal women. Maturitas 1980;2:171–177, © 1980, used with permission from Elsevier Science (16).

ciency. Examples of a relative androgen deficiency would be women with androgen values in the low normal range and postmenopausal women receiving oral estrogen replacement, because SHBG levels are increased and unbound testosterone levels are lowered. This may or may not be the case for women receiving thyroid replacement, depending on how SHBG is affected. Additional conditions that may result in relative androgen deficiency are pituitary adrenal insufficiency, corticosteroid therapy, and

chronic illnesses, including muscle-wasting diseases such as AIDS (19–21).

IS THE CONCEPT OF AN ANDROGEN DEFICIENCY SYNDROME VALID?

Some of the difficulty in accepting that androgen deficiency may be a valid entity in women is the confusion surrounding measurements, as described above. Indeed, in most perimenopausal women, testosterone and free testosterone levels are viewed to be normal. In addition, there are women with low levels (e.g., after oophorectomy) who do not complain of the symptoms, which will be discussed here. Finally, because testosterone is efficiently aromatized in many tissues including the brain (22, 23), it has been argued that the effects attributed to testosterone may be because of estrogen and that estrogen replacement alone may be sufficient (24).

Nevertheless, there are several arguments favoring the legitimacy of a clinical syndrome relating to androgen deficiency: 1) it is accepted that symptomatology in women is highly individual; 2) even with estrogen deficiency, there is no direct correlation with blood levels; 3) with aging there is a decrease in testosterone production, although this is a relative decrease; 4) alterations in parameters of mood and well being are difficult to quantify. In many respects, the heterogeneity of the syndrome has been compared with that of PMS and primary dysmenorrhea, both not having a defining measurement and having variable symptomatology. Table 3 lists the symptoms commonly considered in relative androgen deficiency (RAD). A low-energy state in which motivation seems to be blunted has been considered to be a key feature of this symptom complex (25). This may extend to depressive or flat mood, a general decrease in the sense of well being, irritability, and insomnia. Finally, what has been considered to be an important circumstance of RAD is decreased sexual desire and libido.

It is imperative that these presenting symptoms occur in a setting that is not explained by systemic or psychiatric illnesses and that estrogen deficiency has been ruled out. Indeed, these symptoms may only be considered to constitute RAD if they persist or worsen, despite adequate estrogen replacement in a postmenopausal woman. Other causes of chronic fatigue should also be ruled out.

There is a paucity of consistent data linking decreased androgen measurements to the symptoms listed above. Nevertheless, in terms of sexual function, testosterone and free testosterone have been
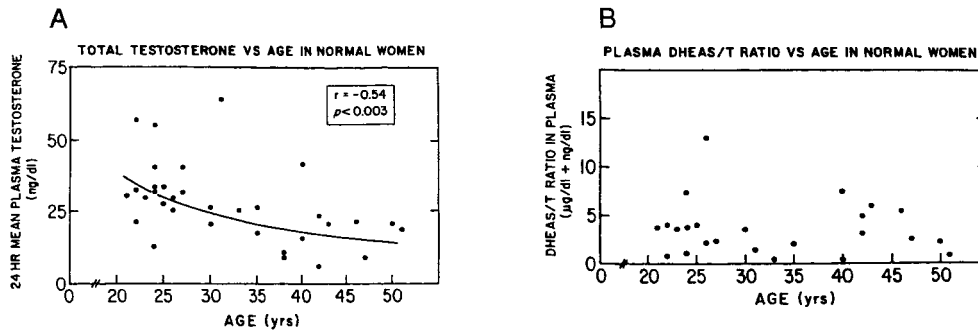
Fig. 4.   *A,* 24-hour mean plasma total testosterone (*T*) versus age in normal women. The regression equation was T (nanomoles per liter) = 37.8 × age (years)$^{-1.12}$ (*r* = 0.54; P < .003); *B*, DHEAS-to-T ratio (moles per liter and nanomoles per liter, respectively) was age invariant, with a mean value of 3.0 ± 2.3. Adapted from (19) used with permission © The Endocrine Society.
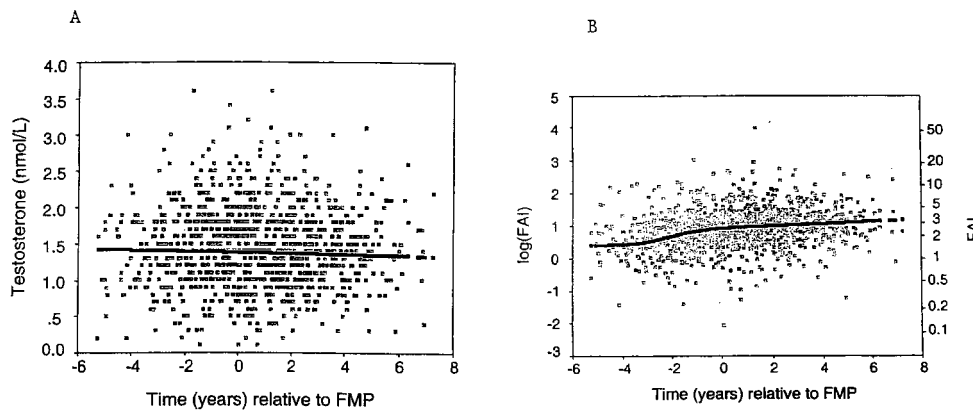

Fig. 5.   *A*, linear regression model: observed testosterone (*T*) and fitted levels of mean T across the menopausal transition. *B*, double logistic model: observed FAI and fitted levels of mean FAI across the menopausal transition. The left and right axes show FAI levels on the log and antilog scales, respectively. The horizontal axis represents time (years) with respect to FMP (○); negative (positive) numbers indicate time before (after) FMP. Adapted from (17) used with permission © The Endocrine Society.

TABLE 3   **Symptoms of relative androgen deficiency (RAD)**

- Decreased energy and blunted motivation.
- Flat mood, diminished well being.
- Irritability, insomnia.
- Decreased sexual desire or libido.

correlated with decreased sexual frequency and desire (25, 26). In a small study, symptoms of decreased sexual arousal and function have also been found to be more prevalent in women with testosterone levels <10 ng/dl compared with those with levels >30 ng/dl (27). In addition, several controlled trials (reviewed below) do show an improvement in parameters of sexual function and well being with testosterone replacement over the use of estrogen alone. There are also potentially important effects of androgen on bone and the musculoskeletal system. Androgen therapy, there-

fore, may enhance the opportunities for treatment of women with osteopenia and/or osteoporosis.

EFFECTS OF ANDROGEN ON BONE

Androgen receptors are present on osteoblasts (28). Bone cells also can metabolize precursors to testosterone and DHT (29). The number of androgen nuclear receptors are quite similar in men and women and also similar (although lower) than the number of estrogen receptors (30) (Fig. 6). Androgens inhibit bone resorption, although this effect may be mediated via estrogen. Aromatase activity is present also in bone cells, and both estrogen receptor deficiency and aromatase deficiency have been implicated in bone loss (31, 32). Nevertheless, more direct effects of androgen on bone also have been shown (33) and these are largely mediated by cytokines such as IL-1 and TGF-β, which play an important role in bone
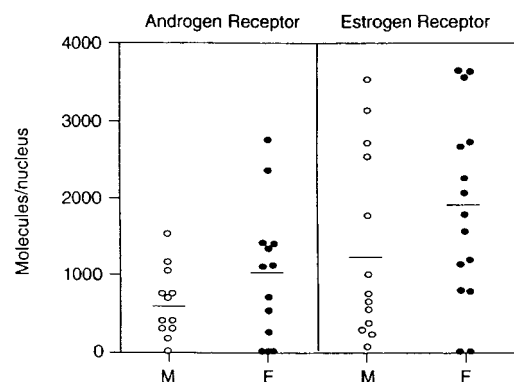
Fig. 6.   Nuclear androgen and estrogen receptor binding in normal human osteoblast-like cells. The number of androgen receptors is only slightly lower than the number of estrogen receptors in bone cells, and the values for women are slightly higher than the values for men. Adapted from Colvard DS, Eriksen EF, Keeting PE, et al. Identification of androgen receptors in normal human osteoblast-like cells. Proc Natl Acad Sci USA 1989;86: 854–857 (32) used with permission.

formation (34). Androgen production has been shown to be decreased in those women who have experienced vertebral crush fractures (35) (Fig. 7). Adrenal androgens have also been correlated with decreased bone mass (36, 37) as have measurements of testosterone and free testosterone (37–39).

In concert with the postulated effect of androgen in enhancing bone formation, several studies have suggested an increase in bone mass in postmenopausal women when androgen has been added to estrogen therapy (40–43). Figure 8A and B depict the increase in bone mass with the addition of testosterone implants. Androgen therapy, when added to estrogen, is associated with increased markers of bone formation (44). When 2.5 mg of methyltestosterone is added to esterified estrogens, there are data to suggest that both spine and hip bone mass is increased more than that of estrogen alone (45) (Fig. 9). A 10% DHEA cream also has been shown to increase hip bone mass in postmenopausal women (46).

Serum testosterone also is lower in the muscle-wasting state of HIV-positive women, and improvements have been noted in muscle mass with the use of transdermal testosterone (47). Fat-free mass in postmenopausal women also is increased (48).

There also may be a role for testosterone for women with autoimmune diseases, although the data are preliminary. Because the male to female ratio is decreased in these diseases this possibility is indicated, and androgen may have a role in inhibiting the immune response (49, 50). Symptomatic improvements in rheumatoid arthritis have been noted with

testosterone (51), as has the course of lupus erythematosus (52).

Although the focus of androgen treatment (as discussed above) should be in peri-or postmenopausal women, there has been some consideration of its use in premenopausal women. One of these conditions is premenstrual syndrome, and clinical trials are ongoing. However, in the absence of a muscle-wasting state (e.g., HIV-positive women) or perhaps in some women with significant osteopenia, there does not seem to be an indication for the use of androgen in hormonally intact premenopausal women. For the sake of completeness, it is important to mention here that young women with premature ovarian failure, or those with gonadal dysgenesis, would be potential candidates for androgen therapy as well.

IS ANDROGEN EFFICACIOUS FOR SYMPTOMS OF RAD?

The concept of using androgen, with or without estrogen, in women to enhance various parameters of well being is not new and dates back to the 1940s (53–59). These studies, which were prospective, mostly used methyltestosterone and were considered to be beneficial for menopausal symptoms and general well being, and for libido, in particular (55, 57, 59). In the 1960s, methyltestosterone was added to esterified estrogens and received class approval from the Food & Drug Administration (FDA) only for the improvement in menopausal symptoms such as hot flushes.

More recent studies have focused on symptoms and well being, in addition to assessing bone mass changes as reviewed above. The studies showing benefit used testosterone as injections or implants as well as transdermal testosterone and oral methyltestosterone (40, 60–68). There is some evidence from these data that the most significant responses are observed in younger women who have undergone bilateral oophorectomy. The instruments used for assessment of well being and sexual function have not been standardized, and thus, some studies not showing a beneficial effect (69) may be criticized on this basis. This is particularly relevant when assessing measures of sexual function, which continue to be an issue for the FDA in approving formulations for use in women. Finally, there is controversy as to whether the improvements, which have been observed in prospective studies, are because of pharmacological rather than physiologic testosterone (T) replacement. Indeed, the data do suggest that levels
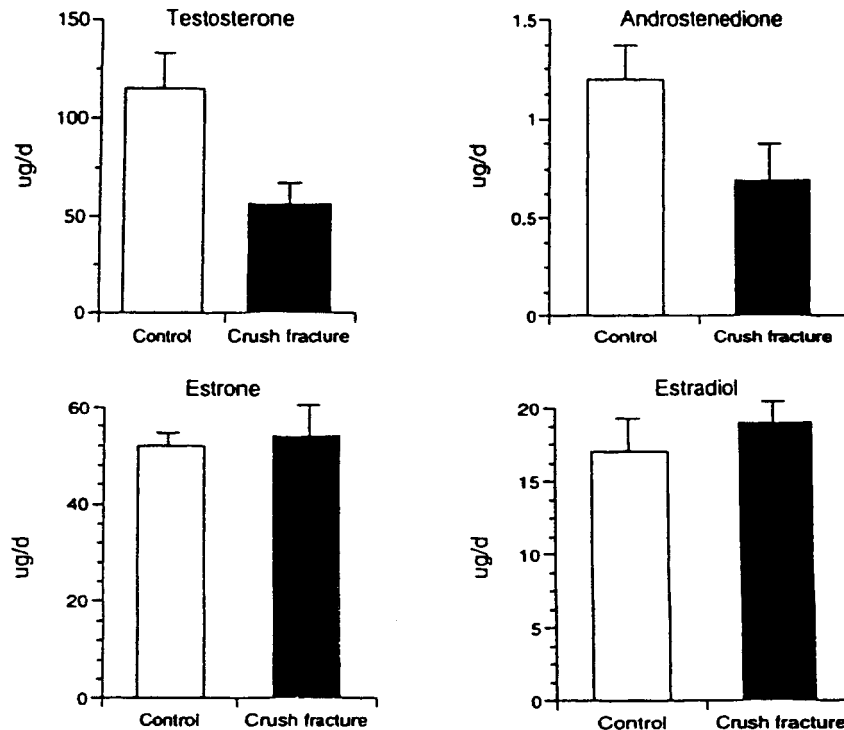
Fig. 7. Sex hormone production in patients with vertebral crush fractures. Using radioactive-labeled hormones, the metabolic clearance rate was determined and used to calculate daily production rates. Note that androgen production is significantly decreased in osteoporotic patients compared with age-matched controls, although there is no difference in estrogen production. Adapted from Maturitas, 6, Longcope G, Baker RS, Hui SL et al., Androgen and estrogen dynamics in women with vertebral crush fractures, pp. 309–318, © 1984, used with permission from Elsevier Science (37).

of T above the physiologic range is necessary for significant improvement.

When women use oral estrogen replacement therapy/hormone replacement therapy (ERT/HRT), the increase in SHBG (approximately 75%) results in a substantial decrease in unbound, or free, testosterone. Several studies have specifically addressed the use of testosterone in estrogen replacement (40, 61, 67). Women who had androgen added had more energy and less problems with sexual function (61) as well as greater sexual frequency, sensitivity, and desire (68) (Fig. 10) as well as various measures of sexual satisfaction (40) (Fig. 11).

Classic studies in the mid-1980s provided evidence of a significant effect of injected testosterone over the effect of estrogen alone in oophorectomized women (63–65). This model provides the most extreme example of androgen deficiency (oophorectomy in premenopausal women). In addition, injected estrogen and testosterone provide a rapid pharmacological peak effect of both sex steroids with values often above 150 ng/dl for testosterone, as well as high levels of estrogen. In addition, this form of

therapy typically results in an accumulation of steroid with even higher levels with repeated dosing. With prolonged therapy, symptoms precipitating the need for another injection precede normalization of testosterone levels. Nevertheless, these studies have shown that testosterone enhances sexual motivation (63) and that this function is maintained (65) (Fig. 12). Apart from sexual function, these studies have also been consistent with the other data reviewed indicating that the addition of androgen (over that of estrogen) enhances the sense of well being and energy level in this cohort of women (64) (Fig. 13A and B).

PHYSIOLOGY VERSUS PHARMACOLOGY

Is there evidence, then, that physiological replacement of androgen results in improvements in sexual function and sense of well being? As stated earlier, the studies showing benefit cited above used regimens that led to pharmacological levels of testosterone. In oophorectomized women, replacement of estradiol and testosterone using 50-mg pellets has been
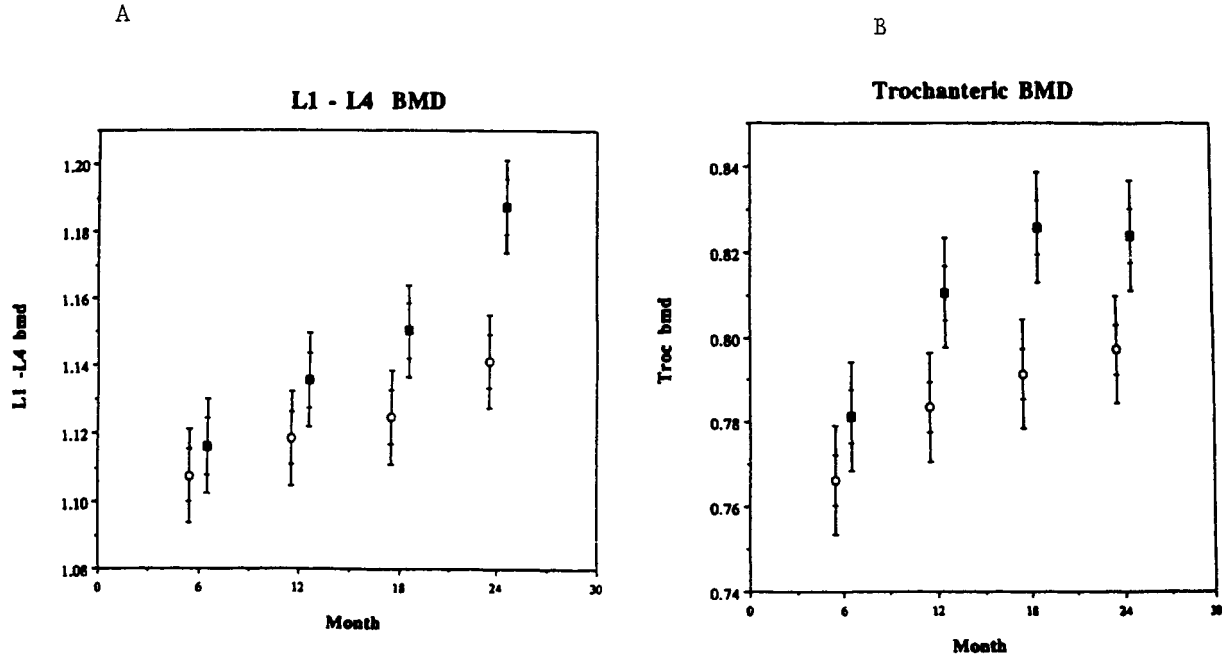
A

B

Fig. 8.   The effect of hormonal implants on bone mineral density (gm/cm^2) in (*A*) the lumbar spine (L1-L4) and (*B*) the femoral trochanter (Troc); estradiol = E, (○); estradiol plus testosterone = E + Te (■). Error bars represent standard error of the differences between means (SED). 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, i.e., differ by more than 2 SED, the means are significantly different by a P value of at least .05. Adapted from Davis SR, McCloud PI, Strauss BJG et al. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995;21:227–236, © 1995, used with permission from Elsevier Science (42).
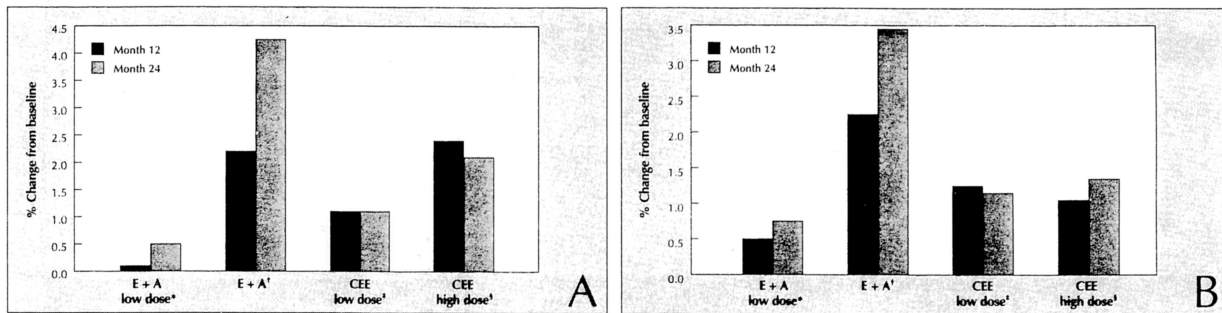

Fig. 9.   Improvement in bone mineral density (BMD): conjugated estrogens versus estrogen + androgen. *A*, BMD (gm/cm^3) of the lumbar spine (L1-L4); *B*, BMD (gm/cm^3) of the hip (total). *E*, esterified estrogens; *A*, androgen; *CEE*, conjugated equine estrogens. *, 0.625 mg of esterified estrogens + 1.25 mg of methyltestosterone; †, 1.25 mg of esterified estrogens + 2.5 mg of methyltestosterone; ‡, 0.625 mg of conjugated estrogens; §, 1.25 mg of conjugated estrogens. Adapted from (47).

shown to improve well being, sexual function, and bone mass (40). Nevertheless, testosterone levels were above the normal range (approximately 90 ng/dl), yet clearly less than those observed with injectable testosterone. In a recent study comparing two doses of transdermal testosterone for 12 weeks in addition to oral estrogen (67), serum testosterone levels averaged 64 and 102 ng/dl with the 150- and 300-μg testosterone patches (normal range 14–54 ng/dl). However, bioavailable testosterone was only in the upper normal range with the 300-μg patch (11.4 ± 9.5 ng/dl; normal range up to 12.7 ng/dl). Here, only the 300-μg dose resulted in statistically beneficial effects on sexual function and well being (67).

Data with the use of esterified estrogen and methyltestosterone are difficult to put into the perspective of physiological versus pharmacological interven-
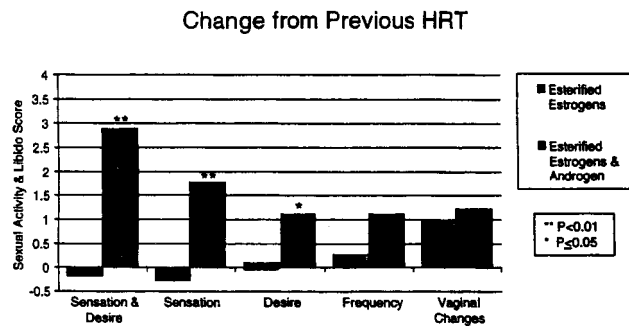
Change from Previous HRT

Fig. 10. Mean sexual activity and libido scale scores after 8 weeks of double-blind treatment. Adapted from (70).

tion. Although there are benefits attributed to the addition of methyltestosterone (not a native androgen) with lower dose of methyltestosterone (1.25 and 2.5 mg/day), the circulating levels of methyltestosterone are relatively low; in the range of 20 to 30 ng/dl (70). Because methyltestosterone is at least as potent as testosterone (71), some andro-

genic biological effect is anticipated. An equally significant androgen effect may be attributable to the increase in unbound T with this therapy. Despite concomitant oral estrogen use, SHBG levels are suppressed by methyltestosterone by approximately 45% (68). Thus, the T/SHBG ratio has been shown to increase by 25% to 50%, which would place reduced unbound T levels into the normal range.

It is concluded, therefore, that although there is some evidence that androgen replacement at near-physiologic levels may be efficacious for symptoms of sexual function and well being, more consistent benefits are achieved with levels that exceed (by some degree) the normal range. This might be even more of a requirement for younger women who have undergone bilateral oophorectomy. There is insufficient information at present to extrapolate the findings in oophorectomized women to the level of androgen needed in older women with intact ovaries.
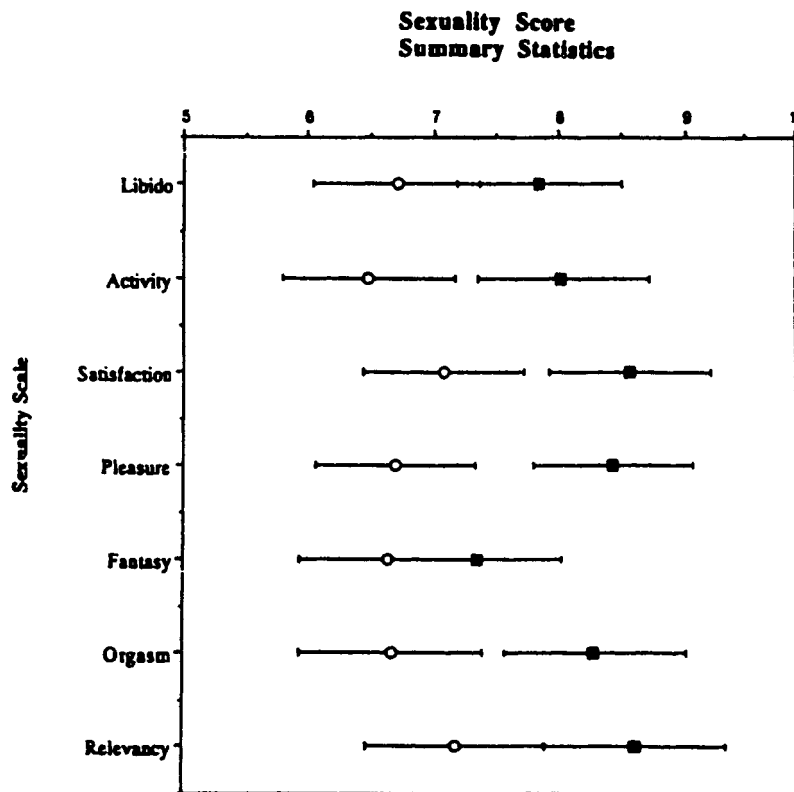

Fig. 11. Summary graph of the effects on sexuality of either three monthly 50-mg estradiol implants alone (○) or 50-mg estradiol plus 50-mg testosterone (■) in postmenopausal women. The grand mean (i.e., means of 6,12,18, and 24 months) for each sexuality parameter is adjusted for baseline as a covariate. Error bars represent standard error of the differences between means. If the error bars do not overlap for a single parameter the difference is significant with a P value < .05. Adapted from Davis SR, McCloud PI, Strauss BJG et al. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995;21:227–236, © 1995, used with permission from Elsevier Science (42).
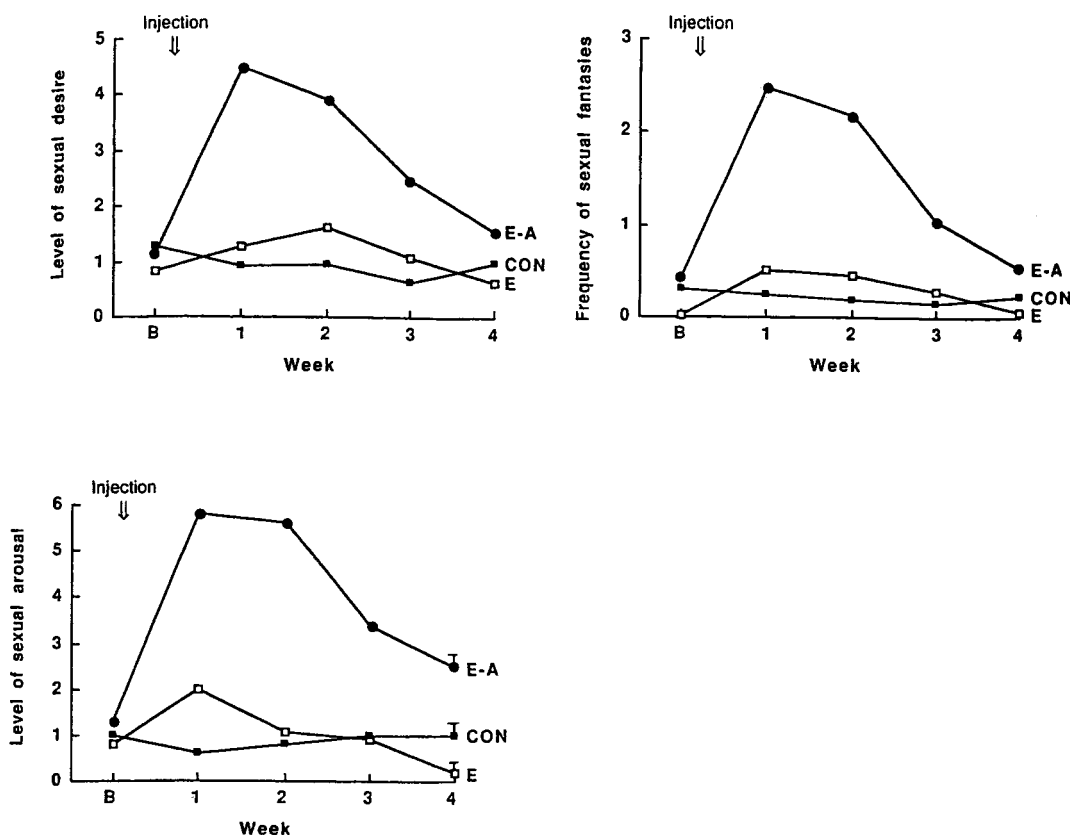
Fig. 12.   Improvement in sexual symptoms with estrogen/androgen therapy. Adapted from Sherwin et al., Psychosom Med 1987;49:397–409 (67). Used with permission.

RISKS OF ANDROGEN REPLACEMENT

The risks of androgen replacement can be divided into those which are masculinizing (acne, hirsutism, alopecia, and clitoromegaly), somatic (fluid retention, bloating) and those which are potentially more serious (hepatocellular, cardiovascular, and cancer risks). There are no large studies quantifying the incidence of the risk of masculinization with injected testosterone. However, this risk does exist and depends on the level of testosterone achieved and the woman's skin sensitivity. With injections of testosterone at 2- to 4-week intervals, there is a risk of levels to accumulate as stated earlier. In a report suggesting that this may lead to iatrogenic hirsutism, values of testosterone as high as 10 ng/dl required 6 months to normalize (R. Lobo, unpublished data, 2000). This effect has also been observed with the use of testosterone implants (pellets) when careful monitoring has not been carried out. However, with lower dose therapy, the overall risk is small. In a safety surveillance study of esterified estrogen and methyltestosterone (73), the risk of hirsutism was less than 5%, and in one other study, the side effects,

with the addition of methyltestosterone, were not different from those of women receiving estrogen alone (74). Similarly, fluid retention (which tends to be more idiosyncratic) and bloating were rare, and there were no reports of hepatic toxicity, changes in liver function, or changes in blood pressure (73).

In terms of cardiovascular disease risk, oral methyltestosterone adversely affects high-density lipoprotein (HDL) cholesterol, with values decreasing by up to 20% from baseline (44, 74). However, low-density lipoprotein (LDL) is lowered to a similar extent as estrogen, as is lipoprotein (a) [Lp(a)]. Triglycerides, which tend to increase with oral estrogen, decrease by approximately 15% with methyltestosterone (44, 74). In terms of direct effects on the vasculature, there are data suggesting that testosterone may be beneficial for dilating coronary arteries, possibly via conversion by aromatase to estrogen (75). In addition, data in the cynomolgus monkey have shown that methyltestosterone does not negatively influence coronary vasodilation (76) (Fig. 14) and decreases coronary arterial LDL uptake (77). Thus, there are no known adverse cardiovascular
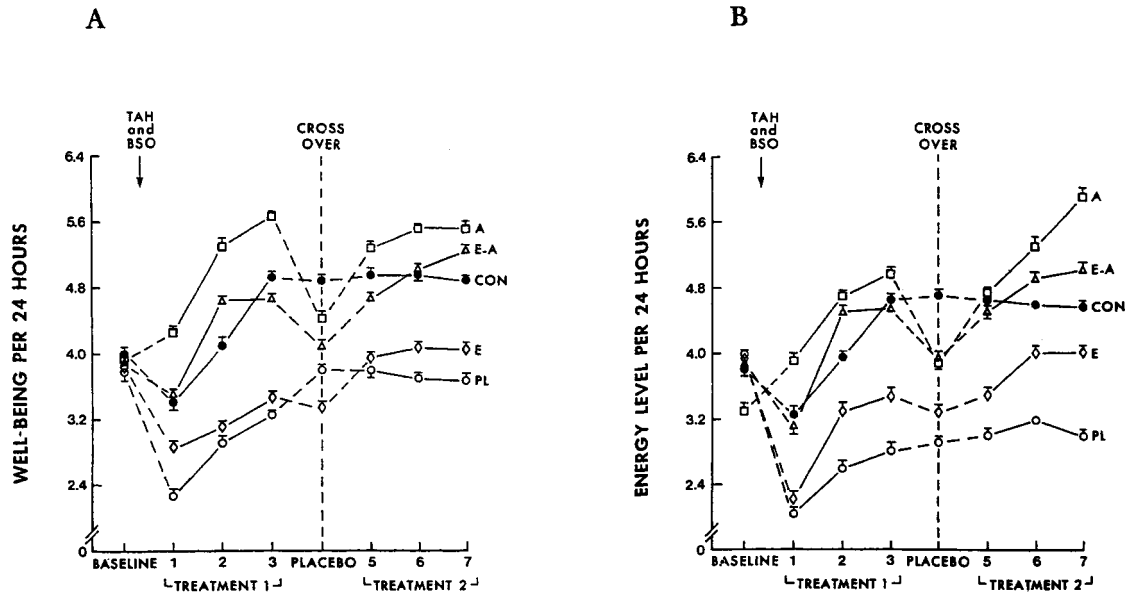
Fig. 13.   *A*, well-being per 24 hours; *B*, energy level for 24 hours. Treatment groups are: estrogen-androgen group (E-A, Δ), estrogen-alone group (E, ◇), androgen-alone group (A, □), placebo group (PL, ○), and control hysterectomy group (CON, ●). Adapted from Sherwin et al., Am J Obstet Gynecol 1985;151:153–160 (66) used with permission from Mosby, Inc.

effects of testosterone replacement, at least using the regimens and doses considered.

Androgen receptors are found frequently in breast cancer tissue and are generally associated with a good prognosis (78, 79). However there are no data suggesting a change in the risk status for developing breast cancer with the addition of androgen. Similarly, there is no difference in the risk of endometrial hyperplasia when comparing estrogen to estrogen-androgen therapy combination (80).

ANDROGEN REPLACEMENT: WHAT IS AVAILABLE?

Various androgen preparations are potentially available for use in women (Table 4). In general, injected testosterone is not recommended because of the pharmacological nature of this approach, the peaks and valleys associated with this therapy, as well as the risk of steroid accumulation. However, as mentioned above, intramuscular testosterone has been shown to be efficacious in oophorectomized women.

Methyl- or fluorinated testosterone in large doses (as used occasionally by men) should not be used. In lower doses, methyltestosterone (1.25–2.5 mg) with esterified estrogens has been shown to be beneficial for menopausal symptoms, bone mass, and possibly sexual function and quality of life variables. The

long-term safety of this product has also been reported (73).

Testosterone undecenoate, an oral form of replacement, is available in Europe and Canada and is believed to be efficacious in that it is absorbed via the lymphatics, particularly if ingested with a fat load (e.g., milk). Because it is marketed for men with hypogonadism, it is unclear what dose should be considered for women. High testosterone levels have been observed with 20 mg/day (81).

Testosterone implants, also known as pellets (50 mg), are inserted at 4- to 6-month intervals with a trocar (the same as used for estradiol pellets), which have been more thoroughly studied (82). Monitoring is mandatory with this therapy and in particular, testosterone levels should be obtained before a repeat insertion. Although values vary considerably among subjects, values remain fairly constant for each individual, which is a characteristic of this method of hormonal replacement (82, 83). As stated earlier, values are usually at the upper level of the normal range 70 to 90 ng/dl.

The transdermal patch (150 μg or 300 μg) has not been approved as yet for use in women. Efficacy in short-term studies has been shown for the higher dose (300 μg), and values are generally in the physiological range with no adverse findings (67). The pharmacokinetics of the 3½-day patch in normal and
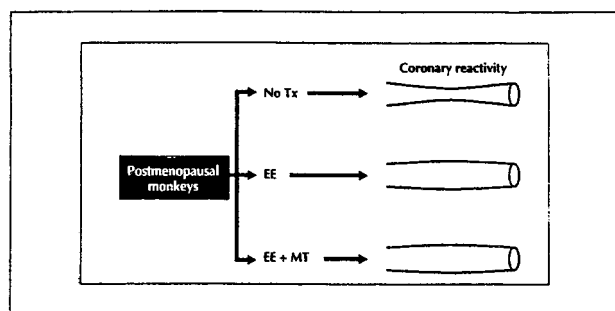
Fig. 14.   Effect on acetylcholine-induced coronary artery dilation of adding methyltestosterone to esterified estrogens. *Tx*, treatment; *EE*, esterified estrogens; *MT*, methyltestosterone. Adapted from (78).

HIV-infected women (with lower T levels) is depicted in Figure 15 (84).

The hydroalcoholic gel of testosterone has been approved for men in whom the pharmacokinetics have been well worked out, and its efficacy has been shown for sexual function, mood, muscle strength, and body composition (85, 86). The 5-gm dose in men provides physiological replacement with steady-state levels of approximately 600 ng/dl (Fig. 16). By extrapolation, the dose required in women would be approximately 1 gm/day or less, although this has not been established.

Oral micronized DHEA has been used in various clinical trials (87–89). Although not the most efficient or efficacious way to deliver testosterone, this approach is an option because levels may be doubled (Fig. 17). A recent study, however, has not confirmed the benefit of 50 mg/day for quality-of-life measures (89). Because DHEA can lower HDL-C levels and

TABLE 4   **Androgen replacement potentially viable for women**

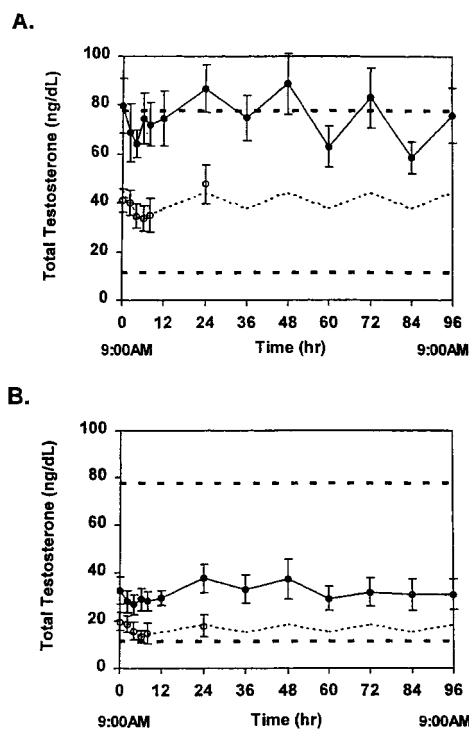| Method	Dose
Injectable (I.M.) approximately every 4 weeks	
Nandrolone decenoate	25–50 mg
Mixed testosterone esters	50–100 mg
Testosterone enanthate	25–50 mg
Testosterone cyprionate	25–50 mg
Oral (daily)	
Methyltestosterone	1.25–2.5 mg
Testosterone undecenoate	40–80 mg
Subcutaneous and transdermal	
Testosterone implant	50 mg every 4–6 months
Transdermal	150–300 μg every 3.5 days
Testosterone gel	1 mg/day
Other options	
DHEA (oral)	25–50 mg/day
Other androgens (androstenedione, DHT)	
Other routes (vaginal, sublingual, and buccal)	

Fig. 15.   Serum total testosterone levels in healthy, menstruating women (*A*) and HIV-infected women (*B*). The normal range in healthy, menstruating women is shown by heavy dotted lines, the baseline circadian-free testosterone levels by light dotted lines, and serum levels during the second TMTDS application period by solid lines. The data are the mean $\pm$ SEM. To convert total testosterone levels from nanograms per deciliters to nonomoles per liter, multiply by 0.03467. Adapted from (86) used with permission © The Endocrine Society.

potentially affect hepatic function, consideration may be given to deliverDHEA vaginally or transdermally.

Other approaches include the administration of testosterone vaginally, buccally, or sublingually. A new sublingual form (T cyclodextrin) has been developed for men. Because cyclodextrin is a carbohydrate, this method is thought to be useful because transport of testosterone occurs across mucous membranes (90). We have also used hydroalcoholic gels of androstenedione and DHT in various trials in women to assess androgen metabolism (91, 92). However, these approaches have not been subjected to efficacy trials in women.

CONCLUSIONS/RECOMMENDATIONS

Although defining androgen deficiency in women is difficult, it is clear that women who have undergone bilateral oophorectomy are androgen deficient because the ovary is a major source of androgen even
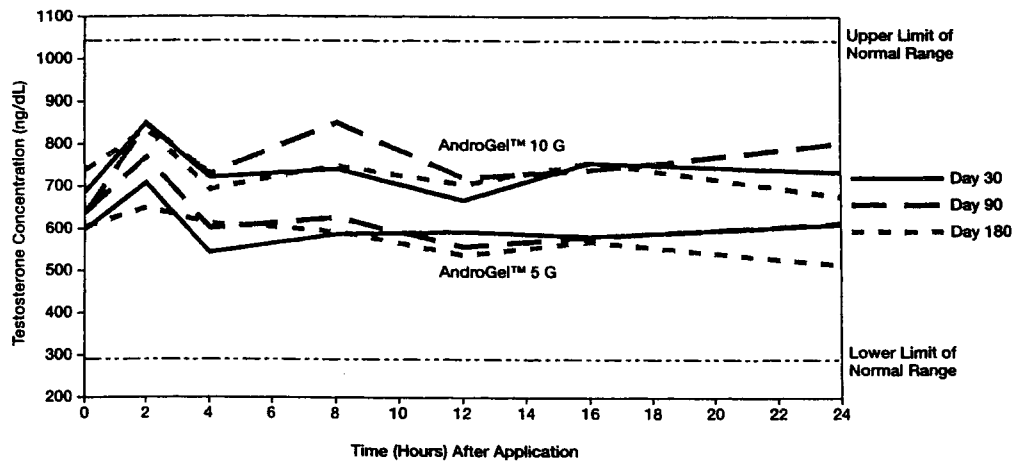
Fig. 16.   Data from product insert: AndroGel, Unimed Pharmaceuticals, Inc., Buffalo Grove, IL, 60089–1684.
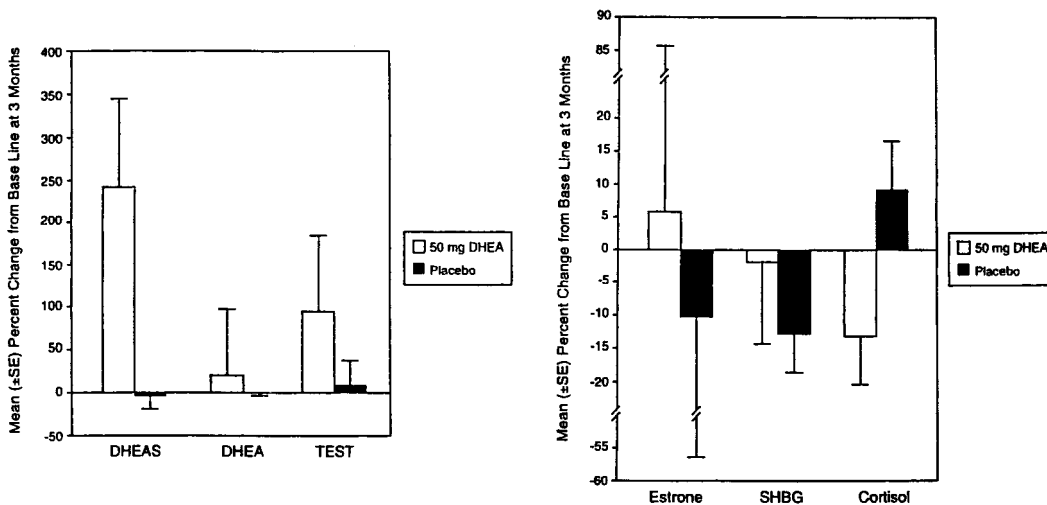

Fig. 17.   Mean percentage change in serum DHEAS, DHEA, testosterone, estrone, SHBG, and cortisol concentration in women treated with 50 mg of DHEA or placebo. Adapted from (91) used with permission © The Endocine Society.

after menopause. A concept of relative androgen deficiency has been proposed to account for individual variability in androgen levels, as well as the biological requirements a woman may have for the effects of androgen. Also, androgen has powerful effects on the brain, musculoskeletal system (specifically bone), and other organ systems as well. Some of these effects, however, may be explained by conversion of androgen to estrogen (93, 94).

Symptoms of androgen deficiency fall into several categories. They include quality-of-life measures such as mood, affect, and energy, but of equal importance are those symptoms involving various aspects of sexual function such as motivation, arousal, and enjoyment. However, it should be realized that not all women will complain of these symptoms and that others will have improvements in various symp-

toms with estrogen therapy alone. That some women who are truly androgen-deficient (status postoophorectomy) feel and function well with estrogen-alone attests to the heterogeneous nature of the concept of androgen deficiency. Indeed, in estrogen-deficient women presenting with any of the symptoms discussed above, it is reasonable to institute estrogen therapy before considering the need for androgen. Because oral estrogen, if anything, causes greater androgen deficiency, at least biochemically (reduction in unbound T), consideration should be given to a nonoral form of estrogen for these complaints.

In considering androgen replacement, the data would suggest that efficacy requires testosterone levels that are at the upper normal range or higher. Given these levels, side effects such as hirsutism and acne are rare in clinical experience, but should still be

considered. The only U.S. FDA-approved product (with androgen) is esterified estrogen in combination with 1.25 or 2.5 mg of methyltestosterone. Although there are some data to suggest safety and efficacy with this regimen, parenteral regimens are attractive alternatives. The testosterone pellets (50 mg) with which this author has personal experience is useful for some women and the transdermal patch and gel offer promise for the future.

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