Androgen Supplementation in Older Women: Too Much Hype, Not Enough Data

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Abstract:

Androgen supplementation in women has received enormous attention in both the scientific and lay community. That it enhances some aspect of cognitive, sexual function, muscle mass, strength and sense of well-being is not in question. What is not known is whether physiologic testosterone replacement can improve health-related outcome in older women without its virilizing side effects. It is assumed that testosterone dose-response relationship is different in women than in men and that clinically relevant outcomes on the above mentioned effects can be achieved at lower testosterone doses. These assumptions, however, have not been tested rigorously. Androgen deficiency has no clear-cut definition. Clinical features may include impaired sexual function, low energy and depression, and a total testosterone level of <15ng/dL (nanograms/deciliter), the lower end of normal range in our laboratory. Measurement of free testosterone is ideal as it provides a better estimate of the biologically relevant fraction. It is not widely used in clinical practice, as some methods for measuring free testosterone assay is hampered by methodological difficulties. In marked contrast to the abrupt decline in estrogen and progesterone production at menopause, serum testosterone is lower in older women than in menstruating women with the decline becoming apparent a decade prior to menopause. The article reviews testosterone's effects on sexual function, cognitive function, muscle mass, body composition and immune function in postmenopausal women.

I. INTRODUCTION:

That testosterone supplementation might improve some aspects of cognitive and sexual functions, muscle mass and strength, bone mineral density, and sense of well-being is not in question. It is, however, not known whether physiologic testosterone replacement can induce clinically meaningful improvements in health-related outcomes in older women without the limiting, virilizing side effects. It has been assumed that testosterone dose-response relationships are different in women than in men, and that clinically significant effects on psycho-sexual function, body composition, physical function, bone mineral density, and other health-related outcomes can be achieved at testosterone doses and concentrations that are substantially lower than those required to produce similar effects in men. Neither of these assumptions has been tested rigorously. Furthermore, the premise that the organ systems that are the targets of virilizing side effects, such as the skin, hair, vocal cords, and clitoris, differ in their testosterone sensitivity from muscle and bone remains unsubstantiated. The clinical applications of testosterone in women are critically predicated upon the postulate that by appropriate selection of testosterone dose, clinically beneficial effects can be dissociated from virilizing side effects.

There is enormous public interest and media fascination with the issue of androgen supplementation in women. For instance, in the year 2000, the stories related to this topic appeared in many major US newspapers, the Oprah Winfrey show, and other television network programs in the US, Australia, and Europe. The number of stories appearing in the lay press in the last two years far exceeded the number of randomized clinical trials!

In spite of growing media attention, the issue of androgen supplementation in women has remained controversial in the scientific community. Many uncertainties have contributed to a lack of consensus. The commercially available assays for total and free testosterone were developed for the measurements of much higher circulating concentrations in men; these assays have generally

lacked the sensitivity and precision required to accurately measure the lower levels of testosterone in older women[1] There has been a paucity of normative data on testosterone levels in menstruating women, older women, and women with chronic illnesses; this has made it difficult to define androgen deficiency in women in precise quantitative terms. The available formulations for androgen administration were developed for the replacement of much higher doses required for the treatment of hypogonadal men. Very little pharmacokinetic data exist on the bioavailability and clearance of androgens delivered from the available formulations in women. Therefore, it is not surprising that many previous clinical studies in women used pharmacological doses of testosterone in relatively unphysiological experimental paradigms. The objective of physiologic testosterone replacement is to restore serum total and free testosterone concentrations into a range that is mid-to high-normal for healthy, young women. Testosterone regimens that increase serum testosterone levels into the supraphysiological range should be viewed as pharmacologic.

Sexual dysfunction in women, a highly complex, multi-factorial issue, has become synonymous with androgen deficiency in the lay press. Observations that pharmacological doses of testosterone might improve sexual function in subsets of women with sexual dysfunction have been unjustifiably extrapolated to advocate testosterone replacement as a general treatment for sexual dysfunction in older women.

It would be incorrect to assert that testosterone supplementation of older women has no role in clinical practice; on the other hand, the available data do not warrant a general recommendation for testosterone replacement for all post-menopausal women.

IIA. BIOLOGY OF TESTOSTERONE PRODUCTION IN MENSTRUATING, POSTMENOPAUSAL, AND OLDER WOMEN

Table 1 lists the adrenal androgens, their potencies and concentrations in serum for pre-menopausal and post-menopausal women.

Adrenal and ovarian production of androgens in healthy young menstruating women collectively contributes to secretion of approximately 300 μg testosterone daily into the general circulation.[2] Approximately, half of the circulating testosterone is derived from ovarian secretion.[3] The adrenal gland produces testosterone precursors, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione, whose peripheral conversion to testosterone contributes the remaining 50% of circulating testosterone.[4] Although the current dogma assumes approximately equal contribution from the ovaries and the adrenal glands, these assumptions may not be entirely correct. The data from studies in which testosterone production rates were measured after suppression of hypothalamic-pituitary-adrenal axis with dexamethasone administration are suspect because dexamethasone is known to also suppress ovarian steroidogenesis. DHEAS is secreted entirely from the adrenal gland, while DHEA is secreted by both the adrenal glands and the ovaries. The majority of circulating DHEA is derived from peripheral conversion of DHEAS. The metabolism of DHEA(S) into bioactive sex steroids may occur in many tissues, including adipose tissue, bone, muscle, prostate, breast, skin, brain, ovary, testes and the liver. Circulating androstendione is derived equally from secretion by zona fasciculata of the adrenal glands and stromal cells within the ovary.

IIB. Androgen Levels During The Menstrual Period. In regularly ovulating women, the plasma levels of testosterone and androstenedione rise gradually during the follicular phase to reach their highest levels in the pre-ovulatory phase, with a second rise in androstenedione during the late luteal phase.[1,5] Serum testosterone concentrations during the mid-follicular phase are not significantly different from those in mid-luteal phase.[1] Ovariectomy causes a drop in the serum testosterone and androstenedione by about 50% each.[6]

IIC. Changes In Androgen Levels With Menopause And Aging. Serum testosterone levels are lower in older women than young, menstruating women. The decline in DHEAS and testosterone

becomes apparent in the decade prior to menopause, and is gradual and progressive[7] such that the testosterone level of women in their sixties is about 50% that of women in their twenties.[8] This is in contrast to the dramatic decline in estradiol and progesterone production that occurs at menopause. The progressive decline of DHEAS and testosterone with age is independent of the menopausal transition.[8] Although some studies have reported a decrease in androstenedione concentrations during menopause[9], a large cross-sectional, epidemiological study in Australia reported no significant change in serum total testosterone concentrations in the peri-menopausal period, demonstrating that the ovarian androgen secretion is not attenuated in most women at menopause.[10] It has been reported that some ovaries may undergo stromal hyperplasia under the control of elevated gonadotropins,[9] and produce even higher amounts of androgens than they produced prior to menopause. However, on average, testosterone production continues to decrease gradually after the fourth decade.[11]

IID. Testosterone Metabolism. Testosterone serves not only as an androgenic hormone, but also as a prohormone; it is converted in the periphery into two active metabolites, estradiol and dihydrotestosterone (DHT). Testosterone's effects on the skin require its obligatory 5-α-reduction to dihydrotestosterone.[12] In contrast, testosterone's effects on bone resorption, gonadotropin suppression, plasma lipids, brain organization, and some aspects of cognitive function require its aromatization to estradiol.[13] We do not know whether 5-α-reduction of testosterone to DHT is obligatory for mediating its effects on the muscle and cortical bone formation.

DHEA(S) is enzymatically converted to testosterone and then DHT in the adrenals, ovaries and other peripheral tissues.

Labrie et al[14] have suggested that serum concentrations of testosterone and DHT may underestimate the total androgenic activity and that conjugated metabolites of DHT, androsterone glucuronide, androstane-3α,17β-diol-glucuronide, androstane-3β,17β-diol-glucuronide and

androsterone-sulfate, may be more reliable markers of the androgen action at the end organ[15,16] We do not know whether measurement of 3-alpha androstanediol glucoronide would provide a better marker of androgen action than serum levels of total and free testosterone.

III. MEASUREMENT OF TOTAL AND UNBOUND TESTOSTERONE

In healthy women, approximately, 50%-60% of testosterone is bound to sex hormone binding globulin (SHBG), 30%-40% to albumin, and only 0.5%-3% is unbound. The free hormone hypothesis assumes that only the free and loosely bound (testosterone bound to albumin) exerts biologic effects.[17] SHBG is affected by many factors; it is increased by thyroid hormone, estrogen and aging, and decreased by testosterone, glucocorticoids, growth hormone, and insulin.[18] Ideally, measurements of unbound testosterone should provide a better estimate of the biologically relevant fraction, however, in practice, some measurements of free and bioavailable testosterone have been hampered by methodological difficulties, particularly in women. The commercially available assays for the measurement of unbound testosterone include the equilibrium dialysis method, the bioavailable testosterone by the ammonium sulfate precipitation method, free testosterone indices calculated from the measured total testosterone and SHBG concentrations, and tracer analog methods for estimates of free testosterone. Of these methods, the equilibrium dialysis method for the measurement of unbound testosterone, and ammonium sulfate precipitation method for the measurement of albumin-bound and unbound testosterone (bioavailable testosterone) are both acceptable methods that have good clinical correlation, are accurate, independent from the effects of SHBG concentrations, and available at specialized commercial endocrinology laboratories. The estimates of free testosterone, calculated from total testosterone and SHBG concentrations, have also been shown to correlate with free testosterone concentrations measured by dialysis in men. These algorithms have not been extensively tested in women.[19] Tracer analog methods of measuring free testosterone are widely available but are

affected by SHBG concentrations and do not provide an accurate measure of unbound testosterone[19] and are not recommended. A recent commentary by Rosner emphasized that direct radioimmunoassay of free testosterone by the tracer analog method may underestimate its concentration.[20]

IV. ANDROGEN DEFICIENCY STATES IN WOMEN

Currently, there is no consensus on a clinical or biochemical definition of androgen deficiency in women. A physical and behavioral symptom complex termed "female androgen deficiency syndrome" includes impaired sexual function, loss of energy and depression.[21] Based on the distribution of serum total and free testosterone concentrations in healthy, menstruating women, androgen deficiency could be defined by serum total testosterone concentrations less than 15 ng/dl, the lower end of the normal female range in our laboratory.[1]

The causes of androgen deficiency in women can be divided into ovarian, adrenal, central and systemic causes. Ovarian causes include premature ovarian failure, Turner's syndrome, and surgical or chemical ovariectomy. Turner's syndrome is characterized by gonadal dysgenesis, streak gonads, estrogen deficiency, and low circulating levels of androstenedione, testosterone, free testosterone, and SHBG.[22] Most of these women are receiving estrogen and progesterone replacement, which further decreases their free androgen levels by increasing the SHBG concentrations; in addition, LH suppression by the hormone replacement therapy may further decrease the stimulus for ovarian androgen production.[19] It is possible that the reduction in free androgen levels induced by the traditional hormone replacement therapy might adversely affect sexual function in post-menopausal women.

Primary adrenal insufficiency is associated with deficiencies of glucocorticoids as well as adrenal androgens. Central causes of androgen deficiency include disorders affecting the pituitary or the hypothalamus. Panhypopituitarism affects androgen secretion from both adrenal and

ovarian sources; not surprisingly, patients with panhypopituitarism have lower circulating concentrations of total and free testosterone, and androstenedione than those found in patients with either adrenal or ovarian failure alone.[23] GnRH agonist or antagonist analogs, often used for treating endometriosis and other reproductive disorders, suppress gonadotropin secretion. Glucocorticoid therapy suppresses corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) and leads to low levels of cortisol, DHEA, DHEAS, and androstenedione.[24] In addition, pharmacologic doses of glucocorticoids in amounts greater than 10 mg prednisone daily or equivalent doses of other glucocorticoids directly inhibit ovarian steroidogenesis.[25] Human immunodeficiency virus infection and chronic illness are examples of systemic causes of androgen deficiency.

V. TESTOSTERONE AND SEXUAL FUNCTION (Table 2)

The prevalent dogma is that androgens regulate libido in women, although a woman's sexual behavior is greatly affected by environmental, emotional, cultural and hormonal factors.[21] The effects of androgens in the brain are mediated directly through the androgen receptor and through aromatization of testosterone to estradiol. Androgen receptors have been identified in the cortex, pituitary, hypothalamus, pre-optic region, thalamus, amygdala and brainstem.[26] Testosterone supplementation is associated with increased well-being, energy, appetite and improved somatic and psychological scores in surgically menopausal women.[27] For instance, in one study of surgically menopausal women, supraphysiologic doses of testosterone enanthate alone or in combination with estrogen, increased sexual desire, fantasies and arousal more than estrogen alone.[28] In another study, testosterone and estradiol implants increased sexual activity, satisfaction, pleasure and frequency of orgasm more than estrogen implants alone.[29]

In a recent, well-designed, placebo-controlled, randomized clinical trial, women who underwent hysterectomy and oophorectomy and were on estrogen replacement were randomized

to placebo patches or testosterone patches designed to nominally deliver 150 or 300 μg of testosterone daily for 12 weeks each. Although both dose-regimens of testosterone significantly increased serum testosterone levels, only the higher dose that increased mean serum free testosterone levels into the upper end of the normal female range was associated with improvements in frequency of sexual activity, pleasure orgasm, sexual fantasies, masturbation and positive well-being.[30] Tutten et al reported that oral administration of testosterone undecanoate increased vaginal vasocongestion as measured by vaginal plethysmography during exposure to a potent visual stimulus in a small number of women with hypothalamic amenorrhea.[29]

In a placebo-controlled, crossover study, daily administration of 50 mg DHEA daily for 4 months in women with adrenal insufficiency improved several aspects of sexual function and sense of well-being. It is unclear whether these effects were direct effects of DHEA on the brain or indirect effects due to the conversion of DHEA to testosterone.[31] In contrast, a cross-sectional study did not show correlation between sexual function and gonadal steroids.[32]

Thus, it appears likely that supraphysiologic doses of testosterone that increase serum testosterone levels above the physiologic range for healthy, young women may improve some aspects of sexual function in a subset of women with low androgen levels. However, we do not know whether physiologic replacement doses that increase serum testosterone levels into the mid-range for young, menstruating women would produce meaningful improvements in sexual function and activity in healthy older women with low testosterone levels.

VI. EFFECTS OF TESTOSTERONE ADMINISTRATION ON AND BODY COMPOSITION, MUSCLE PERFORMANCE, AND PHYSICAL FUNCTION (Table 2)

There is agreement that testosterone administration to men is associated with a dose- and concentration-dependent increase in fat-free mass, muscle size, and maximal voluntary strength,

and a decrease in fat mass.[33-38] The data on the effects of testosterone administration in women are far more limited.

Total lean mass and lean leg mass is significantly correlated with free, but not total testosterone levels in postmenopausal women aged 46-55 years[39]. One cross-sectional study showed that testosterone level predicted muscle strength in post-menopausal women.[40] Estrogen therapy of post-menopausal women, by lowering free testosterone concentrations, can accelerate the loss of lean body mass.[39]

The data on the anabolic effects of testosterone in women are very limited. Kenyon et al reported significant nitrogen retention with administration of pharmacologic doses of testosterone propionate to healthy, menstruating women.[41] In a more recent study, combined administration of testosterone and estrogen implants increased lean body mass and decreased body fat more than estrogen implants alone.[42] In a placebo-controlled study of HIV-infected women with weight loss, testosterone supplementation by means of transdermal testosterone patches, designed to nominally deliver either 150 or 300 μg testosterone daily, was not associated with significant gains in lean body mass or muscle strength, at either testosterone dose.[43]

DHEA administration has been reported to increase fat-free mass in postmenopausal women.[44,45] However, in another study, DHEA (50 mg/day) given for 4 months in women with adrenal insufficiency did not result in a change in body mass index or waist hip ratio.[46]

Most of the published studies that have examined the effects of androgen supplementation in women have had small sample sizes, few examined the effects on muscle performance and physical function, and none has unequivocally demonstrated improvements in health-related outcomes. Therefore, it remains unclear whether increasing testosterone concentrations of older women with low testosterone levels into the mid- to upper normal range will be associated with clinically significant gains in fat-free mass, muscle performance or physical function.

VII. TESTOSTERONE AND COGNITIVE FUNCTION

Most of the research on the hormonal contribution to cognitive function has focused on estrogens. The neuroprotective and neurotrophic effects of estrogens are well recognized, but the underlying mechanisms are not well understood. Estrogens interact with nerve growth factor, brain derived neurotrophic factor, insulin-like growth factor-1(IGF-1) and fibroblast growth factor.[47-51]Estrogens also act directly at neurotransmitter complexes or ion channels, exhibit anti-oxidant effects in the brain, reduce neuronal death after exposure to pro-oxidant and improve cerebral blood flow.[52-54]

Testosterone is aromatized to estradiol in the brain and some effects of testosterone may be mediated through its conversion to estradiol. However, androgen receptors are expressed in specific regions of the brain,[55] and likely mediate some of testosterone's organizational effects during brain development and some activational effects postnatally.[56,57] There are gender differences in the distribution of androgen receptor in the human hypothalamus.[58] The effects of testosterone on cognitive function are conflicting. Low DHEAS levels in postmenopausal women did not correlate with cognitive decline.[59] It is possible that brain levels rather than plasma hormone levels are important. In another study in older men, there was a positive correlation between testosterone and bioavailable testosterone levels and global cognitive function and mental control but not visual-spatial skills.[60] An investigation of healthy young adults showed that salivary testosterone was negatively correlated with visual-spatial and verbal cognitive scores among right handed males and positively correlated among right-handed females in a curvilinear fashion.[61] This pattern was not evident in left-handed individuals.

The effects of androgens on cognitive function are domain-specific. For instance, observations that men outperform women in a variety of visual-spatial skills suggest that androgens enhance visual-spatial skills.[63] Janowsky et al.[62] tested verbal and visual memory, spatial cognition, motor

speed and cognitive flexibility in a group of older men who received 3 months of testosterone supplementation. Testosterone replacement was associated with a significant improvement in spatial cognition only. Serum testosterone levels were not significantly correlated with spatial performance, but estradiol levels showed a significant inverse relationship with spatial performance suggesting that estradiol might inhibit spatial ability. In San Bushmen,[63] testosterone, but not estradiol, levels correlate with better spatial ability and worse verbal fluency. Circulating levels of dihydrotestosterone, a metabolite of testosterone, are positively correlated with verbal fluency. Barrett-Conner**,** et al[64] found an association between total and bioavailable testosterone levels, and global cognitive functioning and mental control, but not with visual-spatial skills in older women. Other studies[61,65,66] have reported a curvilinear relationship between androgen levels and spatial ability such that women with high testosterone levels and men with low testosterone levels show the best performance. Several small clinical trials on testosterone supplementation and cognition in elderly hypogonadal men have provided conflicting results. Sih et al[67] found no effect, while other studies[68,69] reported an effect. Hypogonadal men performed worse on tests of verbal fluency than eugonadal men, and showed improvement after testosterone replacement.[70] In transsexual males, administration of anti-androgen and estrogen, prior to surgery for gender reassignment, decreased anger and aggression, sexual arousability, spatial skills, and increased verbal fluency. Conversely, testosterone administration to females decreased verbal fluency and increased spatial skills.[71,72]

In summary, the reported literature on testosterone and cognition is equivocal but these inconsistencies should not be interpreted to mean that there is no effect. Prospective, randomized placebo-controlled, trials are needed to determine the effects of physiologic testosterone replacement on cognitive function in older women.

VIII. TESTOSTERONE AND BONE MINERAL DENSITY (Table 3)

Androgens regulate bone mineral density and fracture risk by multiple mechanisms. Testosterone inhibits bone resorption through its conversion to estradiol.[73,74] In addition, androgens also directly stimulate cortical osteoblastic bone formation. Androgen receptors have been reported on osteoblasts and osteocytes. In addition to effects that are mediated through the nuclear androgen receptors, androgens may also exert nongenomic effects on the osteoblasts. Androgens directly stimulate alkaline phosphatase and type-1 alpha collagen synthesis by osteoblasts. In addition, they may indirectly regulate osteoblastic activity by modulating the activity of other bone growth regulators such as insulin-like growth factor-1 (IGF-1), IGF-II, fibroblast growth factor, and transforming growth factor-α. IGF-1 and insulin-like growth factor binding proteins (IGF-BP) have important effects on osteoblast proliferation and differentiation. Androgens increase the expression of IGF-1, IGF-BP2 and IGF-BP3, but decrease inhibitory IGF-BP4, in an androgen responsive human osteoblastic cell line.[75] Testosterone inhibits PTH and interleukin-6 activity; these effects might indirectly result in decreased osteoclastogenesis.[76,77]

In men, androgen deficiency is associated with osteoporosis. Androgen replacement in hypogonadal men decreases markers of bone resorption and increases markers of osteoblastic bone formation, and cortical bone mass.[78] However, the role of androgen deficiency in the pathophysiology of osteoporosis in older women is poorly understood. We do not know whether age-related decline in testosterone contributes to the risk of osteoporosis and fractures in older women. Serum levels of bioavailable testosterone correlate positively with bone mineral density and negatively with N-telopeptide excretion.[79,80] Women with syndromes of androgen excess have higher bone mass than controls.

Raisz et al[81] compared the effects of conjugated equine estrogen (CEE) alone with a combined regimen of CEE plus 2.5 mg methyl testosterone on markers of bone formation and bone resorption. Compared to CEE alone, methyl testosterone plus CEE produced a greater

increase in bone formation markers such as osteocalcin and bone specific alkaline phosphatase; however, the markers of bone resorption, such as hydroxyproline and pyridinoline crosslinks, were not significantly different between the two groups.

Davis et al[42] reported greater increases in BMD in the spine and hip with estrogen plus testosterone implants as compared to estrogen implants alone. In another study of post-menopausal women, Watts et al[82] also found that testosterone plus CEE treatment increased BMD, but CEE alone did not. Both of these important studies[42,82] had small sample sizes and were of relatively short duration. The effects of androgen supplementation on fracture risks in women have not been examined. It is possible that testosterone supplementation might augment muscle mass and quadriceps muscle strength in older women with low testosterone levels. Because quadriceps muscle strength is a major determinant of fall propensity, direct effects of testosterone on the muscle might provide an additional mechanism by which testosterone might reduce fracture risk in older women.

Long-term placebo-controlled studies are needed to determine whether testosterone replacement reduces fracture risk in older women. Because the reference of comparison will likely be women receiving hormone replacement therapy, these studies will likely require very large sample sizes.

IX. TESTOSTERONE AND IMMUNE FUNCTION

Testosterone regulates several important aspects of immune function. The prevalence of autoimmune diseases is generally higher in women than in men.[83] Decreased levels of androgens were observed in women with systemic lupus erythematosus (SLE), with lower levels correlating with higher disease activity.[83,84] In an animal model of lupus, the development of "lupus-like" syndrome and progression of kidney disease is more rapid in females than males.[85,86] In this animal model, castration of males is associated with a more accelerated development of lupus like

syndrome, and testosterone administration to females retards the progression of this syndrome.[87,88] DHEA is noted to inhibit interleukin-6, tumor necrosis factor and other cytokines, by inhibiting nuclear factor-kappa B (NF-kappa B), activation of which is associated with worsened disease activity.[89]

Many patients with autoimmune diseases receive glucocorticoids that might cause loss of muscle and bone mass. Theoretically, testosterone administration, in addition to its immunomodulatory effect, might also prevent or reverse the glucocorticoid induced muscle wasting and osteoporosis in these patients. However, the data on the effects of testosterone administration in patients with autoimmune diseases are not clear. While some trials of androgen administration failed to demonstrate benefits in patients with rheumatoid arthritis or SLE,[90,91] other studies have reported improvements in some intermediate outcomes and disease activity scores.[92-95] In one study, DHEA administration facilitated withdrawal from glucocorticoid therapy in patients with SLE.[94] Whether DHEA can ameliorate the deleterious effects of glucocorticoids on muscles, bones, and endothelium remains to be determined in randomized clinical trials.[96]

X. ADVERSE EFFECTS ASSOCIATED WITH ANDROGEN REPLACEMENT

The potential deleterious effects of androgen supplementation in women include the risks of virilization, hirsutism, acne, voice change, erythrocytosis, alterations in plasma lipids and apolipoproteins, and liver toxicity.[97,98] Abnormalities of liver enzymes have been reported with orally administered, 17-alpha alkylated androgens. Hirsutism is uncommon if supraphysiologic levels are avoided.[42,81,99-101] There is concern regarding the increase in cardiovascular risk through lowering of high-density lipoprotein (HDL) levels in women receiving long-term androgen therapy. Davis et al[42] found no significant change in HDL cholesterol levels in women treated with combined estrogen and testosterone implants, although there was a reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol levels. In another study, combined

administration of estrogen and 17-alpha-methyl testosterone resulted in a 25% reduction in total cholesterol and a modest decrease in HDL2 and HDL3 levels.[81] DHEA treatment in women has been shown to have negative effects on lipids and lipoproteins in some,[102,103] but not all studies.[44,104] We do not know whether these adverse effects on plasma lipid profile is limited to supraphysiologic doses of androgens, and whether physiologic testosterone replacement can be administered without significant adverse effects on cardiovascular risk factors.

Hyperandrogenemia is associated with insulin resistance in adolescent girls and women with polycystic ovary syndrome (PCOS).[105, 106] Endothelial dysfunction, associated with elevated levels of androgens, may lead to increased risk of macrovascular complications.[105] However, consistent correlation between insulin resistance and hyperandrogenemia has not been found in all studies.[106,107] It is unclear if the insulin resistance in patients with PCOS is due to high androgen levels, or is inherited as an independent trait. It has been speculated that androgen effects on insulin sensitivity might be biphasic. Holmang et al [108] demonstrated that in a rat model, physiologic doses of testosterone improve insulin sensitivity, while higher doses induce insulin resistance.[109,110]

A recent epidemiological study found an inverse correlation between serum testosterone concentrations and carotid intima-media thickness, a measure of generalized atherosclerosis. [111,112] In LDL-receptor deficient mice, testosterone administration retards the development of early atherosclerotic lesions. Therefore, it remains unclear whether physiologic testosterone replacement in older women will increase or decrease the risk of atherosclerotic heart disease.

XI. METHODS OF ANDROGEN ADMINISTRATION

17-alpha-methyltestosterone, approved for use in women in the US, is typically administered orally in combination with estrogens in doses between 1.25-2.5 mg daily. It may be associated with liver toxicity.[97,98]

Other formulations that have been empirically used in women include testosterone esters, testosterone pellets, and testosterone undecanoate given orally in oleic acid (not available in the US). Testosterone esters, enanthate and cypionate, and the androgenic steroid, nandrolone decanoate, are used traditionally at doses of 25 to 50 mg every 4 weeks; however, this regimen may provide supraphysiological androgen concentrations within the first few days after the injection and suboptimal levels during the last ten days of the dosing interval. Testosterone implants, administered at a dose of 50-mg every four to six months, have been used widely outside the USA, but because of the need for skin incision and insertion through a trocar, and the small incidence of spontaneous extrusion, the implants have not been popular in the USA. Oral micronized DHEA at a dose of 25-50-mg daily has also been used in clinical trials. However, there is considerable batch-to-batch, and brand-to-brand variability in the amount of DHEA in various formulations sold over-the-counter. In addition, the absorption of DHEA from the gastrointestinal tract is variable, and its efficacy in post-menopausal women in improving health-related outcomes has not been established. It should be emphasized that only limited amount of pharmacokinetic data are available in women about these formulations, and the regimens used in clinical practice have generally not been physiologic.

Two novel testosterone formulations, specifically for use in women, are currently in development. A transdermal testosterone matrix patch has been designed for twice weekly application to the skin. Each transdermal testosterone matrix system (TMTDS) nominally delivers 150 μg of testosterone per day. Thus, two patches when applied twice a week can deliver 300 μg of testosterone daily, approximating the daily production rates of testosterone in healthy, menstruating women. The pharmacokinetics of transdermally administered testosterone have been studied in pre-menopausal women, surgically menopausal women, and HIV-infected women.[30,113]

These studies have demonstrated that a regimen of two TMTDS patches applied twice a week can maintain serum total and free testosterone levels in the upper-normal range, respectively, in pre- and post-menopausal women with low testosterone levels. Application of each TMTDS patch increases serum total testosterone concentrations on average by 20-25 ng/dL.[113] The increments in serum total and free testosterone levels are lower in HIV-infected women treated with TMTDS than healthy women, presumably due to increased plasma clearance or decreased absorption. The skin tolerability of the TMTDS patch has been excellent, with only a very small proportion of treated women experiencing mild erythema at the patch application site.

A 1% hydro-alcoholic testosterone gel is under development for use in women; its potential advantages include ease of delivery, its invisibility after application, and good skin tolerability. We postulate that testosterone patches and gels will be the most widely used forms of androgen replacement for women in the future, leading to high patient satisfaction and the ability to tolerate dosing to achieve testosterone concentrations in the upper-normal range.

XII. CONCLUSION

Because of the limited availability of sensitive and accurate assays for the measurement of total and free testosterone levels in women, and the paucity of normative data, it has been difficult to biochemically define androgen deficiency in women. Although there is tremendous interest in exploring the clinical applications of testosterone supplementation in older women for a number of clinical indications, we do not know whether physiologic testosterone replacement can improve clinically relevant outcomes such as physical function, muscle mass and performance, fracture risk, cognitive function, and sexual function. The long-term risks of virilizing side effects and cardiovascular disease also remain largely unknown. Therefore, it would be premature to make a general recommendation about testosterone replacement of all older women with low testosterone

levels. At this time, testosterone supplementation in women with the symptom complex that has been loosely named “female androgen deficiency syndrome” should be individualized, and preceded by a discussion of the uncertainty about beneficial effects and the potential risks of long-term androgen administration. Further studies are needed to establish testosterone dose-response relationships in women in order to determine whether it is possible to dissociate the clinically beneficial effects from potential adverse effects.

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Table 1: Relative Androgenic Activity and Levels of Adrenal Androgens

Steroid	Androgenic Activity*	Normal serum Levels in Pre-Menopausal Women**	Normal serum Levels in Post-Menopausal Women**
Dihydrotestosterone	300	4-22 ng/dL	3-20 ng/dL
Testosterone	100	10-55 ng/dL	7-40 ng/dL
Androstenedione	10	60-245 ng/dL	30-120 ng/dL
DHEA	5	350-700 ng/dL	150-300 ng/dL
DHEAS	5	20-250 μg/dL	10-150 μg/dL

*Relative Activity based on testosterone=100, ** Representative normal values, actual values will depend on assay and laboratory used. Values expressed in ng/dL (nanograms/deciliter) and μg/dL (micrograms/deciliter)

Table 2: The Effects of Testosterone Administration on Sexual Function

Study	Androgen formulation and dose	Duration	Study Design	Patient group	Effects
Myers, 1990[32]	Conjugated equine estrogen 0.625 mg daily plus methyl-testosterone 5mg daily	4 weeks	Double-blind, placebo-controlled	Naturally menopausal women	Increased pleasure from masturbation, but no improvements in other components of sexual function
Arlt, 2000[31]	DHEA 50 mg daily.	4 months	Double-blind, placebo-controlled, cross-over	Women with adrenal insufficiency	Improvements in sexual function and well-being
Sherwin, 1985[28]	Testosterone enanthate 150 mg IM every 4 weeks.	Monthly injection for 2 months	Prospective placebo-controlled cross-over	Surgical menopause	Increased sexual fantasies, arousal, desire, somatic and psychological scores
Davis 1995[42]	Testosterone implants 50 mg plus estradiol implants 50 mg vs. estradiol	Every 3 months for two years	Prospective, single-blind	Post-menopausal women	Increased sexual fantasies, orgasm, and several other aspects of sexual function

	implants 50 mg alone				
Shifren, 2000[30]	Conjugated equine estrogen 0.625 mg, transdermal testosterone 150 µg daily or 300 µg daily.	12 weeks	Double-blind, placebo-controlled	Surgically menopausal women	Increased sexual activity, pleasure orgasm, increased sexual fantasies, masturbation and positive well-being with 300 µg dose
Tutten 1996[29]	Testosterone undecanoate 40 mg daily	8 weeks	Double blind, placebo-controlled	Women with amenorrhea	Increased vaginal vasocongestion during exposure to potent visual stimulus

Table 3. The Effects of Testosterone Supplementation on Body Composition and Muscle Function

Study	Androgen formulation and dose	Dose/ duration	Study design	Patient Group	Effects
Davis 1995[42]	Estradiol implants (50 mg) plus testosterone implants (50 mg) vs. estradiol implants alone	Every 3 months for 2 years	Single-blind, randomized, placebo controlled	Postmenopausal women	Increased lean body mass, decreased body fat without change in BMI*
Miller 1998[43]	Transdermal testosterone patch 150 μg and 300 μg daily	Twice weekly week for 12 weeks	Randomized, placebo-controlled	Women with AIDS** wasting	No significant change in lean body mass
Diamond 1996[45]	DHEA 10% cream	Daily for 12 months	Single-blind	Older women 60-70 years old	Increased fat-free mass
Morales 1998[44]	DHEA 100 mg daily	Daily for 6 months	Randomized, double-blind, placebo-controlled, cross-over	Older men and women	Increased total body mass

* BMI= body mass index ** AIDS acquired immune deficiency syndrome

Table 4: Effect Of Testosterone On Bone Mineral Density

Study	Androgen formulation/dose	Duration	Study Design	Patient group	Effects
Raisz 1996[81]	Conjugated equine estrogen 1.25 mg plus methyl testosterone 2.5 mg daily vs. conjugated equine estrogen alone	9 weeks	Double-blind, randomized	Post-menopausal women	Greater increase in bone formation markers (osteocalcin and bone specific alkaline phosphatase) with combined treatment than with estrogen alone
Davis 1995[42]	Testosterone implants 50 mg plus estradiol implants vs. estradiol implants alone	Every 3 months for 2 years	Single-blind, randomized, placebo-controlled	Post-menopausal women	Greater increase in bone mineral density in the spine and hip in combined treatment group than with estradiol alone
Watts 1995[82]	Conjugated equine estrogen 1.25 mg plus methyl testosterone 2.5 mg daily vs. conjugated	Once daily for 2 years	Double-blind, randomized, parallel group	Post-menopausal women	Greater increase in bone mineral density with combined treatment than with estrogen alone

	equine estrogen alone				

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