Androgen Co-therapy In Menopause

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Abstract

Menopause is associated with various hormonal changes, including androgen deficiency. This review discusses the place of androgen therapy in the management of menopause, including the pitfalls in diagnosis, the confusion surrounding androgen prescription, and the reasons behind this controversy.

HORMONAL CHANGES IN MENOPAUSE

Menopause is associated with a variety of endocrine changes (1). These lead to a reduction in sexuality and well-being (2). The changes include:

1. Decline in growth hormone. This begins prior to ovarian failure, and is a normal part of life. It is accelerated during peri-menopause, and itself may accelerate ovarian failure.

2. Fibrosis of thyroid gland, and a decline in serum T3 of 25% to 40%, though most post menopausal women remain clinically euthyroid.

3. Reduction in estrogen levels, with the predominant estrogen being the less potent estrone, derived from peripheral conversion of androstenedione in the liver, fat and some hypothalamic nuclei.

4. Fall in serum DHEA and DHEAS levels, which are greater in women than men, and may be due to the relative estrogen deprivation.

5. Decline in androgen production. The production of the predominant androgen, androstenedione, declines from 1500 to 800pg/ml, with only 20% being contributed by the ovary in post menopausal women.

6. Post menopausal testosterone levels are also lower than those in premenopausal women, with the decline beginning around age 30.Testosterone levels at age 40 are half those at age 21. At menopause, a 15% decline occurs in testosterone and androstenedione.

7. Dihydrotestosterone, the most potent of endogenous androgens, decreases by 44% between the third and eighth decade. This decline is associated with reductions in metabolic concentrations.

ANDROGEN DEFICIENCY

Androgen deficiency is associated with failure of formerly useful sexual stimuli to arouse a woman. While the exact definition of androgen deficiency remains controversial, the Princeton Consensus in 2001 (3) tried to create a framework for androgen replacement.

'Female androgen deficiency syndrome' (FADS) may be diagnosed in women who meet all of the following three criteria:

- impaired well-being or libido
- adequate estrogenization (i.e. either normal ovarian function or established estrogen replacement therapy (ERT)
- serum androgen concentrations below or within the lower quartile of the female normal range)

However, this seems to be a rather loose definition, and it is not feasible to consider androgen replacement for every woman with self-perceived impaired well-being or libido.

ANDROGENS AND SEXUAL FUNCTION IN POSTMENOPAUSAL WOMEN

Conflicting evidence is available to correlate testosterone levels with sexual function in postmenopausal women. There

are many studies which report a decline in sexual functioning amongst peri- and post menopausal women. A community- based study of 441 sexually active women aged 45-54 years demonstrated that poor self-reported health and depressive symptoms were associated with dissatisfaction with sexual relations. A statistically significant association was observed between total testosterone and frequency of sexual activity, as well as free testosterone index and frequency of sexual activity (4).

Plasma androstenedione and testosterone concentrations have been shown to be negatively associated with sexual avoidance (r =-0.41) in woman aged 50 to 60 years. Testosterone correlated with sexual initiation (r = 0.53) and responsively (r = 0.47). Androgen concentration also correlated significantly with frequency of intercourse and sexual gratification (5).

A longitudinal study following women from 2 years before, to 2 years after, menopause, has demonstrated a decline in sexual interested and frequency, with the latter correlating directly with plasma testosterone (6). In an Australian study of 1021 women aged 18 to 75 years, low DHEAS level correlated with low scores for sexual response in women aged >45years. However, a majority of woman with low DHEAS did not complain of reduced sexual function (7). No data were provided on circulating levels of biologically active, desulfated DHEA in this cohort. It is well described that circulating DHEAS can be decreased in chronic disease or stress and this may also contribute to the observed decrease in libido in those women.

In 2900 pre and perimenopausal multiethnic women aged 42 to 52 years, enrolled in the SWAN study, there was minimal correlation between total testosterone and free androgen index (FAI), and sexual function (8). The practical implications of these results are that no sweeping generalizations can be made about the need for androgen co-therapy in menopause.

LIMITATIONS IN ANDROGEN ESTIMATION

This problem is compounded by another issue: that of measurement of androgen levels in postmenopausal women. It is difficult to measure androgen levels effectively. Some of the salient issues include (1, 9):

1. Assays for total testosterone are not reliable
2. Assay for free testosterone based on equilibrium dialysis are difficult and time-consuming.
3. RIA-based free testosterone assays underestimate free testosterone concentration.
4. Assays for total, free and bioavailable testosterone are not designed for the female range. Commercial assays are made for men, whose testosterone concentration are 10-20 times those found in young woman, and 20-40 times those seen in post menopausal woman.
5. Normal age-related values are not available for women.
6. Serum levels of testosterone reflect mainly gonadal production, and do not assess cellular availability.
7. Intracellular testosterone produced within the brain needs to be quantified, and assessed for correlation with sexual function.
8. DHEAS, androstenedione and other precursors account for the majority of testosterone activity in menopausal women, and need to be measured.
9. Metabolites of testosterone need to be measured to asses total androgen activity

11. androstane 3, 17-diol glucuronide
12. androstane 3, 17-diol glucuronide
13. androsterone glucuronide.

1. Diurnal variation in androgen levels means that time of collection of samples must be specified.

ANDROGEN SUPPLEMENTATION IN POST MENOPAUSE

Evidence that testosterone supplementation improves health in postmenopausal women with sexual disorder is available.

A double-blind, placebo-controlled, 52-week trial in 814 women with hypoactive sexual desire disorder given a patch delivering 150 or 300 µg of testosterone per day or placebo, evaluated efficacy for 24 weeks and safety for 52 to 104 weeks. At 24 weeks, the increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 µg of testosterone per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, P<0.001) but not in the group receiving 150 µg per day (1.2 episodes, P=0.11). As compared with placebo, both doses of testosterone were associated with significant increases in

desire (300 µg per day, P<0.001; 150 µg per day, P=0.04) and decreases in distress (300 µg per day, P<0.001; 150 µg per day, P=0.04). The rate of androgenic adverse events — primarily unwanted hair growth — was higher in the group receiving 300 µg of testosterone per day than in the placebo group (30.0% vs. 23.1%). Breast cancer was diagnosed in four women who received testosterone (as compared with none who received placebo); one of the four received the diagnosis in the first 4 months of the study period, and one, in retrospect, had symptoms before undergoing randomization (10, 11).

A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial conducted in women (aged 24-70 years) who developed distressful low sexual desire after bilateral salpingo-oophorectomy and hysterectomy, and who were receiving oral estrogen therapy administered placebo (n = 119) or testosterone patches in dosages of 150 µg/d (n = 107), 300 µg/d (n = 110), or 450 µg/d (n = 111) twice weekly for 24 weeks. Of the 447 women randomized, 318 (71%) completed the trial. Compared with placebo, women receiving the 300-µg/d testosterone patch had significantly greater increases from baseline in sexual desire (67% vs. 48%; P = .05) and in frequency of satisfying sexual activity (79% vs. 43%; P = .049). The 150-µg/d group showed no evidence of a treatment effect. The 450-µg/d group also was not statistically different from the 300-µg/d or placebo groups. Marginally significant linear dose-response trends were observed for total satisfying sexual activity and sexual desire at 24 weeks (P = .06 and .06, respectively). Adverse events occurred with similar frequency in both groups; no serious safety concerns were observed (12).

NON-SEXUAL BENEFITS OF ANDROGENS

In undernourished older people, combined treatment with testosterone and nutritional supplementation reduces the number of people hospitalized and the duration of hospital admissions. This, androgen therapy holds promise as an anabolic therapy in both elderly men and women.

Oral testosterone undecanoate (40 mg daily for women, 80 mg twice daily for men) and an oral nutritional supplement (475 kcal/d) were administered, alone or combined, for 1 y to 49 community-dwelling, undernourished people [Mini Nutritional Assessment score <24 and low body weight (body mass index, in kg/m^2: <22) or recent weight loss (>7.5% over 3 mo)] >65 y (mean age: 77 y; 26 women and 23 men). Hospital admissions and other variables were assessed. In subjects receiving combined testosterone and nutritional supplements (n = 11) there were no hospital admissions, whereas there were 9 admissions (2 elective) in 13 subjects in the no-treatment group, 4 in the testosterone-treated group (n = 12), and 5 in the supplement-treated group (n = 13); P = 0.06 with no-treatment compared with combined treatment. When compared with the no-treatment group, the combined-treatment group had significantly fewer subjects admitted to hospital (0 compared with 5, P = 0.03), fewer days in hospital (0 compared with 74, P = 0.041), and a longer time to hospital admission (P = 0.017) (13).

CARDIOVASCULAR BENEFITS

Results from the 180 postmenopausal women studied in the Estrogen in the Prevention of Atherosclerosis Trial indicate that total testosterone and SHBG are inversely related to progression of carotid atherosclerosis. A higher total testosterone level is protective against subclinical atherosclerosis progression at physiological concentrations (in the placebo group) as well as in the total sample, half of whom were on HT. This association was independent of age, BMI, HDL-C, and LDL-C. Total testosterone also showed a beneficial association with HDL-C, whereas free testosterone had a detrimental association with serum cholesterol (14)

A case-control study from the Atherosclerosis Risk in Communities cohort reported that postmenopausal women (not on HT) in the highest quartiles of total testosterone and SHBG had significantly lower odds of atherosclerosis measured by a single CIMT greater than the 95th percentile adjusted for a multitude of cardiovascular risk factors (15)

At physiologic concentrations, total testosterone has been found to be protective against carotid atherosclerosis and cardiovascular disease in postmenopausal women (16, 17).

At least two epidemiological studies in postmenopausal women with established CVD found a positive association between free testosterone and angiographically determined coronary artery disease (18, 19).

ANDROGEN PREPARATIONS

Figure 1

Route	Medication	Dose / Rang	Frequency
Oral	Methyl testosterone	1.25-2.5mg	Daily
	Testosterone undecanoate	40-80mg	2-4 x /dl
	Micronized testosterone	2.5-5mg	Daily
	DHEA	25-50mg	Daily
	Androstenedione	50-100mg	Daily
IM	Mixed testosterone esters	50-100mg	4-6 weeks
	Testosterone emendate	50-100mg	4-6 weeks
	Testosterone ciliolate	50-100mg	4-6 weeks
	Testosterone undecanoate	1000mg	6 weeks
	Nandrolone decanoate	25-50mg	4-6 weeks
Subcutaneous Transdermal	Crystalline testosterone pellets	50-100mg	3-6 weeks
	Gel	1mg	Daily
	Patch	300µg /d	Twice a week
Sublingual	Testosterone cyclodextrin	tbd	tbd
	Testosterone propionate lozenges	1mg	2-4 x / day

The Livensa/Intrinsa Transdermal testosterone patch was granted a license from the European Medicines Agency in July, and is available on Britain's National Health Service from March 2007. It will initially only be available on prescription for post-menopausal women with diagnosed sexual problems.

However, in December 2004 the United States the 14-member FDA advisory committee, plus voting consultants, for Reproductive Health Drugs unanimously rejected Procter and Gamble's fast-track request for Intrinsa citing concerns about off-label use. In Canada, post-menopausal women have been able to obtain government-approved testosterone treatment since 2002. In Australia, post-menopausal women can use Organon testosterone implants which have to be surgically inserted and last from three to six months.

YOHIMBINE

Yohimbine(20) is an Indole alkyl amine alkaloid derived from the bark of tree Pausinystalia yohimbe or root of Rauwolfia. Its structure resembles that of reserpine; and actions are opposite to those of clonidine. It is a competitive selective Alpha-2 adrenergic receptor antagonist, which readily enters CNS, and has peripheral and central actions

It encourages sympathetic outflow and potentiates release of norepinephrine. The drug is said to be a shotgun approach to management of sexual dysfunction, because of its profound effect on sexual behavior. This includes post-synaptic 2 adrenoceptor antagonistic activity, central noradrenergic activity, and serotoninergic potentiation. The average dose is 6 to 10 mg/day. Tolerance occurs, and there is an initial enhanced response followed by decline in effect. It can be prescribed h.s., t.d.s, or p.r.n, as it has a short half-life of 35 minutes.

In a study carried out in female subjects with type 2 diabetes and sexual disorder, aged 18 to 45, (quantified using FSFI questionnaire), 26 were given yohimbine 6 mg h.s. orally for 1 month along with sexual counseling. The control group (n=24) received counseling but no drug therapy. Desire, lubrication, orgasm, satisfaction and total scores rose significantly in the study group, while there was an insignificant rise in pain and arousal scores.

Yohimbine is thus a useful drug for management of sexual desire and orgasm disorder in women with diabetes. It improves lubrication and satisfaction significantly, while contributing to an insignificant improvement in arousal. (21)

DEHYDROEPIANDROSTERONE SULPHATE (DHEAS)

Dehydroepiandrosterone sulphate (DHEAS) (22) is an adrenal androgen which is the most abundant steroid in the human body. It is converted in the body to both estrogens and testosterone, and is used as a safe alternative to HRT.

Its multiple effects include improvements in sexual function, well-being, bone density, endothelial function and cardiovascular health, apart from an association with increased longevity. This has led to its use as a treatment modality for sexual dysfunction in postmenopausal women. This may emerge as a safe, convenient alternative to androgens in management of menopause, once larger studies are done.

ADVERSE EFFECTS OF ANDROGENS

Androgen therapy is safe (23), provided it is given in doses suitable for the female physiology, under regular monitoring, for specific indications, such as sexual disorder. Some of the androgenic side effects to watch for include:

- Hirsutism
- Deepening of voice
- Weight gain
- Acne
- Hepatic effects-not a concern now.

GUIDELINES

ANDROGEN THERAPY IN WOMEN: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE, 2006 (24)

The Task Force set up by the Endocrine Society recommends against making a diagnosis of androgen deficiency in women at present because of the lack of a well defined clinical syndrome and normative data on total or free testosterone levels across the lifespan that can be used to define the disorder. Although there is evidence for short-term efficacy of testosterone in selected populations, such as surgically menopausal women, they recommend against the generalized use of testosterone by women because the indications are inadequate and evidence of safety in long-term studies is lacking.

THE NORTH AMERICAN MENOPAUSE SOCIETY POSITION STATEMENT ON ANDROGEN THERAPY IN WOMEN, 2005 (25)

In contrast, the guidelines from NAMS encourage androgen co-therapy. The authors of the NAMS position state: "Although data are limited, there is consistent evidence that in postmenopausal women with sexual concerns, adding either oral or non-oral testosterone to estrogen therapy results in a positive effect on sexual function, primarily an increase in sexual desire. Data are inadequate to support the therapeutic use of testosterone for any other indication, including bone preservation, menopause symptoms, well-being, body composition or cognition. ... In selecting postmenopausal women for testosterone therapy, clinical factors are generally of much greater importance than serum hormone levels, especially given the relative unreliability of most clinically available testosterone assays for women and the multiple causes of sexual desire disorders."

The discrepancy between these two committees has been thought to be due to (26):

1. The Endocrine Society committee concluded that one cannot make a diagnosis of androgen insufficiency in women because of a lack of a well-defined clinical syndrome and lack of diagnostically low androgen levels that can separate those with from those without the syndrome. In contrast, the NAMS committee keyed in on the data that women receiving estrogen who had undergone oophorectomy and subsequently developed low libido respond to testosterone treatment irrespective of whether one wants to consider it replacement therapy or pharmacotherapy.

2. Whereas both groups acknowledge that at least in the short term (6 months), testosterone therapy is safe, with only androgenic skin side effects being found, there was no systematic collection of long-term, placebo-controlled data available to assess possible concerns about cardiovascular, endometrial, and breast safety. Unlike a therapy for a disorder that may result in severe morbidity or mortality, testosterone therapy is being proposed for a quality-of-life indication. Thus, the benefits must clearly outweigh the risks, which for testosterone, are unknown, but seem unlikely, as recently reviewed (26). The NAMS experts recommended a therapeutic testosterone trial only after a fully informed consent was obtained from the patient:

"Any recommendation for testosterone therapy should be accompanied by a full explanation of the potential benefits and risks of therapy. Women must be informed that none of the commonly used testosterone therapies are government approved for the treatment of symptoms related to female sexual function, and therefore, therapeutic use will be off label. In addition, they should understand that potential risks are associated with a therapy for which safety and efficacy data are limited, including data on long-term use or use without concomitant estrogen therapy. Documentation of this discussion should be recorded in the medical record."

3. All of the participants in the NAMS statement, but not The Endocrine Society group, have a specialty interest in female sexual dysfunction and deal with women suffering from sexual dysfunction and menopausal issues. Thus, they may be more willing to offer a therapy that has been shown to be effective in a subset of such women

4. There is a fear of widespread off-label use of testosterone in women by The Endocrine Society group, who are acutely aware of the longevity clinics that have sprung up and administer GH, testosterone, and other agents for unproven enhancements of quality of life. Condoning testosterone therapy for even a select group of women could potentially lead to greater off-label use of testosterone in women than is found currently. Also, because there is no currently approved testosterone preparation for treating low sexual desire in oophorectomized women, the use of preparations made by compounding pharmacies or the use of testosterone preparations formulated for men is fraught with concern about overtreatment by both committees. The NAMS committee recommends close monitoring of testosterone levels if testosterone is given to women.

The dichotomy between these two position statements means

that the clinician may be free to make her or his own decision regarding androgen co therapy in an individual patient.

CONCLUSION

Androgen concentrations are important, but are not the only component, required to maintain normal female sexual function. Psychosocial issues, concomitant drug use, and other chronic or acute illnesses contribute to the overall sexuality of an individual.

Androgen supplementation is a potentially useful therapy in postmenopausal woman. Androgens should be prescribed preferably when the patient is optimally estrogenized.

Oral DHEAS is a welcome option as it has both estrogenic and androgenic effects, with the parent molecule being converted into estrogen as well as testosterone in the body. Yohimbine is a safe drug which is not being utilized to its full potential.

EMEA-approved testosterone patches should be the drug of choice in women needing testosterone replacement. There is lack of FDA-approved androgens for use in women.

In the Indian scenario, oral DHEAS 25 mg/day or oral testosterone undecanoate 40mg/day can be started for short periods of time, with the dose being reduced once optimal clinical effects are achieved. Using very low doses (5-10% of male replacement doses), with frequent monitoring, will minimize the risk of side effects.

More research is required to answer many of the queries and uncertainties that surround this controversial therapeutic area.

References

1. Braunstein GD. Androgen deficiency in women. In: Carr BR, Blackwell RE, Azziz R, eds. Essential Reproductive Medicine, Mcgraw Hill, New York, 2005.
2. Basson R. Women's Sexuality and Sexual Dysfunction. In: Gibbs RS, Karlan BY, Haney AF, Nygaard IE. Eds. Danforth's Obstetrics and Gynecology, 10th Ed, Lippincott Williams & Williams, Philadelphia, 2008.
3. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril 2002; 77:60–665.
4. Gallichio L, Schilling C, Tomic D et al. Correlates of sexual functioning among mid-life women. Climacteric 2007; 10:132-142
5. Persky H, Dreisbach L, Miller WR, et al. The relation of plasma androgen levels to sexual behaviors and attitudes of woman. Psychosom Med 1982; 44:305-319.
6. McCoy NL, Davidson JM. A longitudinal study of the effects of menopause on sexuality. Maturitas 1985; 7:203-210.
7. Davis SR, Davison SL, Donath S,et al. Circulating androgen levels and self-reported sexual function in women JAMA 2005;294:91-96.
8. Santoro N, Torrens I, Crewford S, et al. Correlates of circulating androgens in mid life women: the study of women's health across the nation. J Clin Endocrinol Metab 2005; 90:4836-45.
9. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H 2007 Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab 92:405–413
10. Davis SR, Studd J, Bouchard C, Kroll R, Moufarage A, Von Schoulz B 2006 The effect of a testosterone transdermal system on hypoactive sexual desire disorder in postmenopausal women not receiving systemic estrogen therapy, the APHRODITE study. Program of the 88th Annual Meeting of The Endocrine Society, Boston, MA, June 24–27, 2006, p 43 (Abstract S38-1)
11. Davis SR, Moreau M, Kroll R, et al. Testosterone for Low Libido in Postmenopausal Women Not Taking Estrogen. N Engl J Med, 2008; 359 (19): 2005-2017.
12. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of surgically menopausal women: a randomized, placebo controlled trial. Arch Intern Med 2005; 165 : 1582-89
13. Chapman IM, Visvanathan R, Hammond AJ, et al.Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. Am J Clin Nutr (January 14, 2009). doi:10.3945/ajcn.2008.26538 (Epub ahead of print), Accessed on 15 March 2009.
14. Karim R, Hodin HN, Stanzyk FZ, Lobo RA, Mack WJ. Relationship between Serum Levels of Sex Hormones and Progression of Subclinical Atherosclerosis in Postmenopausal Women. J Clin Endo Metab, 2008; 93 (1): 131-138.
15. Golden SH, Maguire A, Ding J, Crouse JR, Cauley JA, Zacur H, Szklo M 2002 Endogenous postmenopausal hormones and carotid atherosclerosis: a case-control study of the atherosclerosis risk in communities cohort. Am J Epidemiol 155:437–445
16. Bernini GP, Sgro M, Moretti A, Argenio GF, Barlascini CO, Cristofani R, Salvetti A. Endogenous androgens and carotid intimal-medial thickness in women. J Clin Endocrinol Metab 1999; 84:2008–2012
17. Mantzoros CS, Georgiadis EI, Young R, Evagelopoulou C, Khoury S, Katsilambros N, Sowers JR Relative androgenicity, blood pressure levels, and cardiovascular risk factors in young healthy women. Am J Hypertens 1995; 8:606–614
18. Phillips GB, Pinkernell BH, Jing TY Relationship between serum sex hormones and coronary artery disease in postmenopausal women. Arterioscler Thromb Vasc Biol 1997; 17:695–701
19. Rexrode KM, Manson JE, Lee IM, Ridker PM, Sluss PM, Cook NR, Buring JE Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation 2003; 108:1688–1693
20. Boone and Shields. Dietary supplements for female sexual dysfunction..Am J Health Syst Pharm.2005; 62: 574-580
21. Kalra B. Yohimbine in the management of female sexual dysfunction. Oral presentation at the ASEAN Federation of Endocrine Societies conference, Nov 2007.
22. Panjari M, Davis SR. DHEA therapy for women: effect on sexual function and wellbeing. Human Reproduction Update, 2007; 13(3):239-48.

23. Braunstein GD 2007 Safety of testosterone treatment of postmenopausal women. Fertil Steril 88:1–17
24. Wierman ME, Basson R, Davis SR, Khosla S, Miller KK, Rosner W, Santoro N Androgen therapy in women: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2006; 91:3697–3710
25. Shifren JL, Davis SR, Dennerstein L, Heiman JR, Lobo RA, Simon JA The role of testosterone therapy in postmenopausal women: position statement of the North American Menopause Society. Menopause 2005; 12:497–511
26. Braunstein GD.The Endocrine Society Clinical Practice Guideline and The North American Menopause Society Position Statement on Androgen Therapy in Women: Another One of Yogi's Forks. J Clin Endocrinol Metab 2008; 92 (11) 4091-4093

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