

Androgen insufficiency in women: summary of critical issues

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Critical issues concerning the role of androgens in the physical, sexual, and emotional health of women include the following:

1. Which androgens best reflect the androgen status of women?
2. What form of T should be measured and how?
3. Do T levels fall after menopause?
4. What effect does oophorectomy have on T levels?
5. What is the relationship between T and sexual dysfunction?
6. What constitutes androgen insufficiency syndrome?
7. What conditions are associated with androgen insufficiency?
8. How should a patient with suspected androgen insufficiency be evaluated?
9. Does androgen replacement therapy improve sexual dysfunction?
10. Do androgens enhance the quality of life?
11. Is estrogen and androgen therapy superior to estrogen therapy alone for low bone mineral density?
12. What are the indications for androgen replacement therapy?
13. What is the best means for delivery of androgen therapy?
14. How should androgen replacement therapy be monitored?

Based on our current knowledge, it is clear that some women develop symptomatic androgen insufficiency and that androgen replacement therapy has a beneficial effect on libido, sexual satisfaction, quality of life, and bone mineralization. Androgen replacement therapy should be given the same consideration that we give estrogen replacement therapy. (*Fertil Steril*® 2002;77(Suppl 4):S94–9. ©2002 by American Society for Reproductive Medicine.)

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The marked increase in articles appearing in the scientific and lay literature on the subjects of the consequences of androgen insufficiency and the effects of androgen replacement in women attests to the burgeoning interest in this topic. Indeed, during the last decade there have been a number of studies that have better defined androgen production and metabolism in women, the effect of androgens on sexual function, mood, and other parameters of psychological function, bone health, and body composition in women during states of androgen insufficiency and after androgen replacement therapy. The other participants in this symposium have covered these issues in detail, and we have multiple excellent review articles (1–6). This paper will summarize some of the critical, clinically relevant issues concerning androgen insufficiency in women.

CRITICAL ISSUES

1: Which Androgens Best Reflect the Androgen Status of Women?

A variety of androgenic steroids are present in adult women. These include T, androstenedione, dihydrotestosterone, dehydroepiandrosterone and its sulfate, androstenediol, and several other quantitatively minor steroids that exhibit androgenic effects in bioassay systems (7–10). Androgenic action is determined by [1] the quantitative level of the androgen present in the circulation; [2] its degree of binding to various proteins, including sex hormone-binding globulin (SHBG) and albumin, which determines how much of the androgen is free or bioavailable to the target tissues and to some extent its metabolic clearance rate; [3]

the degree of interconversion to other androgens and estrogens; and [4] the biological potency and androgen receptor binding affinity of the androgen. Taking these factors into account, serum T levels best reflect the overall clinical androgen status of women, with low levels being found in women with hypopituitarism or women who have undergone oophorectomy, mildly to moderately elevated levels in women with acne and hirsutism, and markedly elevated concentrations in women with virilization (7, 11–13).

Since over 90% of DHEA-sulfate is of adrenal origin, this hormone reflects adrenal androgen and androgen precursor secretion, and, therefore, measurements of this hormone in serum provides an index of adrenal androgen production. Serum levels of androstenedione and dihydrotestosterone generally correlate with T concentrations and, therefore, do not provide useful additional information in evaluating a woman's androgen status. In addition to the formation of dihydrotestosterone (DHT), T and other androgenic hormones and prohormones are converted to 3α -androstane-3 α -ol-20-one glucuronide, which serves as a final common pathway of androgen metabolism (14). Although measurements of this metabolite have had some utility in the diagnosis and management of androgen excess disorders in which the levels are often elevated, they have not been evaluated and are unlikely to be useful in the assessment of individuals suspected of having androgen insufficiency (7).

2: What Form of T Should Be Measured and How?

Approximately two-thirds to 78% of the circulating T in women is bound to SHBG, while 20%–33% is weakly bound to albumin, leaving an average of 2% of the total T existing in the free or unbound state (7–10). SHBG concentrations are affected by a variety of drugs and clinical conditions. Thus, depressed concentrations are found in patients receiving exogenous glucocorticoids, androgens, or progestogens, as well as in patients with obesity, hyperinsulinemic states, hypothyroidism, acromegaly, Cushing's syndrome, or androgen excess syndromes. Elevated levels are found in women taking exogenous estrogens, especially oral preparations that provide high concentrations of estrogens to the liver, which synthesizes the SHBG; in pregnancy; and in women with endogenous or exogenous hyperthyroidism or cirrhosis (7).

Therefore, either a free T or a Free Testosterone Index should be assessed to accurately evaluate the tissue androgen status. This is especially important in women who have undergone oophorectomy or natural menopause and who are receiving exogenous oral estrogens, as SHBG levels are high and hence the total T levels are often elevated because of its reduced metabolic clearance rate, while the free T levels actually may be normal or low (15–17).

It is generally recognized that equilibrium dialysis is the method of choice for measuring free T levels (18). This requires a measurement of total T by immunoassay and a

percent dialyzable fraction of T. An alternative method involves the direct immunoassay measurement of free T using an analog ligand (19). Although easier and faster to perform than equilibrium dialysis, the results are less reliable than with the dialysis method and cannot be advocated for the assessment of free T levels in presumably hypoandrogenic women (18, 20). T immunoassays have been optimized for measurement of the hormone in men, and the free T levels in women are often at or below the sensitivity of the assays (21). This has resulted in a lack of normative data for free T across the female life cycle, from menarche through the postmenopausal years. Such data, derived from the use of recently developed sensitive equilibrium dialysis methods, which are capable of measuring 2 pmol/L (0.6 pg/mL) of free T (21), are needed to allow a more accurate means for achieving a biochemical diagnosis of androgen insufficiency.

Another means of assessing free T is the use of the Free Testosterone Index (FTI, also referred to as the Free Androgen Index [FAI]) (18). This requires a measurement of SHBG and is derived as a ratio of $100 \times$ total T level/immunoactive SHBG concentration. This value correlates quite well with the free T level measured by equilibrium dialysis and appears to be useful to assess the clinical androgen status in women, except in pregnancy (18).

Another methodological issue to address concerns the timing of drawing the blood sample for androgen measurement. There is a diurnal variation in T secretion, with higher levels in the morning than in the afternoon or evening (22). Therefore, the blood should be drawn in the morning when the T level should be at its peak. In premenopausal, cycling women, there is the additional fact that T levels rise at midcycle (23). Therefore, to avoid this transient increase, the blood sample should be obtained during the first week of the follicular phase.

3: Do T Levels Fall After Menopause?

T levels actually begin to decline before the age of 30 and just before menopause are approximately one-half of the level found in a woman's early 20s (24). In some studies, the levels decline by about 15% after the menopause (8, 10), but this reflects an age-related decline and not a specific menopause-related decline. However, the recent data from the prospective longitudinal study of women during the menopausal transition (the Melbourne Women's Midlife Health Project) showed no change in the serum total T concentrations from 5 years before to 7 years after the menopause, while the FAI actually rose during this time, reflecting the decrease in SHBG levels consequent to the reduction in serum estrogens (25). The lack of a precipitous drop in ovarian T production after the menopause reflects the effect of the elevated LH levels on the ovarian androgen-producing theca cells. Many studies have shown a reduction in DHEA-sulfate levels with age (10, 25, 26), and the late postmenopausal reduction in androgen concentrations found in some

studies probably reflects decreased conversion of adrenal androgens to T.

4: What Effect Does Oophorectomy Have on Serum T Levels?

Since the ovaries in premenopausal women account for approximately half of the direct or indirect T production, and there is no significant decline in ovarian T production after menopause, oophorectomy results in a reduction in serum T concentrations to about 50% of the preoophorectomy level (13). Indeed, this 50% reduction in T (and androstenedione) levels is found in both premenopausal and postmenopausal women undergoing oophorectomy (13). Therefore, it is not surprising that symptomatic androgen deficiency may be precipitated in a woman after oophorectomy, especially if she receives oral estrogens, which raise SHBG and lower free T concentrations even further (15, 16).

5: What Is the Relationship Between T Levels and Sexual Dysfunction?

This remains one of the most vexing issues. Sexual dysfunction is quite prevalent, with recent data indicating that 43% of American women exhibit some dysfunction (27). Sexual function, of course, is dependent on a variety of factors including availability of a partner, expectations, mood, psychological factors, general health of the woman and her partner, medications, and hormonal status. Indeed, the strongest correlates with low libido in the above study were being unmarried, being younger with a less formal education than women with normal libido, poor health, and race (27).

Data supporting the association between T and libido include studies that have found a correlation between the two at the time of the midcycle peak of T (28–30) and overall sex drive, arousability, masturbation, and coital frequency (10). However, it also should be noted that a number of studies have failed to show a relationship between T levels and sexual function (31, 32). The administration of antiandrogens to women has been found to reduce libido (33), which further supports a relationship between T levels and sexual function. Finally, the administration of androgens to hypoandrogenic women has been found to improve a number of parameters of sexual function, including arousability, desire, fantasy, frequency of sexual activity, ability to reach orgasm, sexual satisfaction, and pleasure (17, 34–40). Despite these findings, this area still needs more intense study using better instruments to assess sexual function and improved free T assays.

6: What Constitutes Androgen Insufficiency Syndrome?

Table 1 summarizes the salient components of androgen insufficiency syndrome and is based on the observations and definitions of numerous investigators (34, 41–44). Women often present with a low libido, unexplained, persistent fatigue, and an overall decreased sense of well-being. The

TABLE 1

Components of female androgen insufficiency syndrome.

| |
|--|
| Symptoms |
| Low libido with global decrease in sexual desire or fantasy |
| Persistent unexplained fatigue |
| Decreased sense of well-being |
| Signs |
| Thinning or loss of pubic hair |
| Decreased lean body mass |
| Osteopenia or osteoporosis |
| Other indications |
| Symptoms persist despite having normal estrogen production if premenopausal or being on adequate estrogen replacement therapy if hypogonadal |
| Onset following an event associated with decreased androgen production |
| Other causes of symptoms have been evaluated and ruled out |

Braunstein. Female androgen insufficiency. Fertil Steril 2002.

onset may be traced to an event that is known to be associated with decreased androgen production, such as oophorectomy. Because estrogen deficiency can lead to dry vaginal secretions and dyspareunia, before treatment of androgen insufficiency syndrome, the patient should be adequately estrogenized (45). Thus, premenopausal women should have normal cyclical changes in E₂ levels, while premenopausal and postmenopausal women who are estrogen deficient should receive adequate estrogen replacement therapy. Signs of androgen deficiency may be subtle but include a thinning or loss of pubic hair. Osteopenia or osteoporosis and a decrease in lean body mass also occur with androgen insufficiency but are unlikely to be detected on routine clinical examination.

7: What Conditions Are Associated With Androgen Insufficiency?

Table 2 lists the broad categories of conditions associated with androgen insufficiency. Hypothalamic or pituitary abnormalities, either structural or functional (including the

TABLE 2

Conditions associated with androgen insufficiency in women.

| |
|--------------------------------------|
| Hypothalamic-pituitary abnormalities |
| Premature ovarian failure |
| Adrenal insufficiency |
| Glucocorticoid therapy |
| Exogenous estrogen administration |

Braunstein. Female androgen insufficiency. Fertil Steril 2002.

hypogonadotropic hypogonadism that occurs with acute and chronic illness), are associated with a decrease in gonadotropin secretion with a secondary reduction in gonadal steroid production. In addition, for large structural lesions that impair the secretion of ACTH, there may be an associated loss of adrenal androgen production, reflected in a low DHEA-sulfate level, which can contribute to androgen insufficiency.

Primary ovarian failure also may be associated with low androgen levels, depending on the underlying etiology of the problem. As noted above, bilateral oophorectomy leads to an approximately 50% reduction in androgen production. Patients with Turner's syndrome and other forms of ovarian dysgenesis may have low androgen levels, while patients with the ovarian failure that accompanies normal menopause may have normal or increased androgen levels due to the hyperstimulation of the theca cells by the elevated LH concentrations.

Primary adrenal insufficiency has been clearly shown to be associated with symptomatic androgen insufficiency, which in turn is associated with low levels of DHEA, DHEA-sulfate, androstenedione, and T. These levels rise into the normal range following DHEA replacement (40). Similarly, secondary adrenal insufficiency due to a structural lesion in the hypothalamus or pituitary or secondary to exogenous glucocorticoid administration may result in deficient adrenal androgen production.

Finally, as previously noted, the administration of exogenous estrogens to estrogen-deficient women may unmask an androgen insufficiency by raising the levels of SHBG and thereby lowering the free T concentration (15, 16).

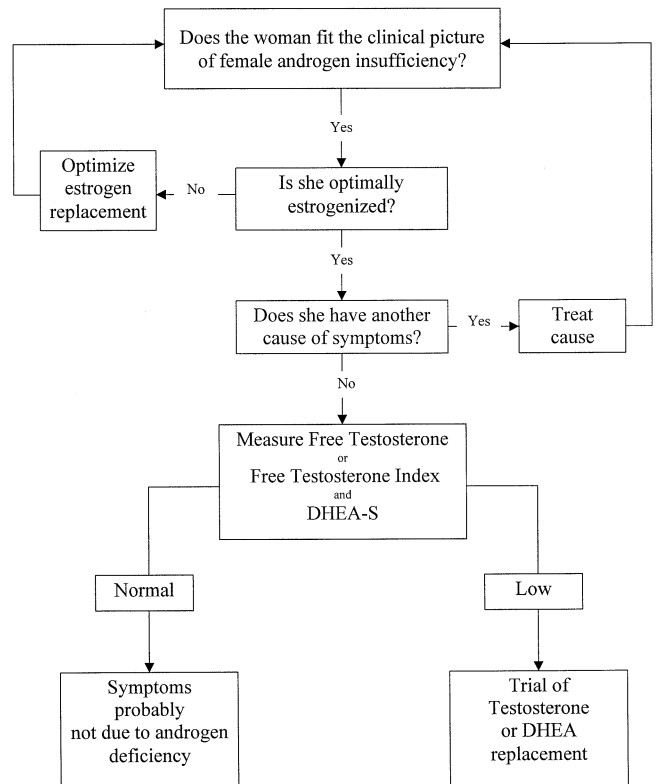
8: How Should a Patient With Suspected Androgen Insufficiency Syndrome Be Evaluated?

Figure 1 outlines an algorithmic approach to the diagnosis and treatment of androgen insufficiency syndrome. If the patient fits the clinical definition of androgen insufficiency syndrome as listed in Table 1, then it is important to assess whether she has adequate quantities of circulating estrogens. If not, then estrogen replacement therapy should be administered. If the symptoms persist despite normal amounts of estrogen in premenopausal women or after estrogen therapy in postmenopausal women or women with estrogen deficiency, then one should rule out other causes of the patient's symptoms, such as depression, anemia, hypothyroidism, or systemic illness. If the symptoms cannot be explained after eliminating these causes from consideration, then a measurement of free T, FTI, and DHEA-sulfate should be taken.

The normative ranges for DHEA-sulfate at various ages have been well defined, and a DHEA-sulfate concentration should be interpreted against the age-matched normal range. However, as noted above, the normal ranges of free T or FTI at different ages carried out with highly sensitive assays have

FIGURE 1

Algorithm for the diagnosis and treatment of androgen insufficiency syndrome.



Braunstein. Female androgen insufficiency. *Fertil Steril* 2002.

not been established. Therefore, until this is accomplished, it is reasonable to use values at or below the lowest quartile of the normal range for women in their reproductive years to support the diagnosis of androgen insufficiency. If the woman exhibits features compatible with the clinical definition and has a low free T (index) level, then a therapeutic trial of androgen replacement therapy may be given. The finding of a low serum concentration of DHEA-sulfate may prompt a trial of DHEA replacement therapy before proceeding to T replacement.

9: Does Androgen Replacement Therapy Improve Sexual Dysfunction?

Several investigators have shown that androgen replacement therapy does improve sexual dysfunction in women who are presumably androgen deficient based on the clinical setting (e.g., after oophorectomy) with or without demonstration of low free T concentrations (17, 34–40). As noted above, together these studies suggest that T replacement improves arousability, sexual desire and fantasy, frequency of sexual activity and orgasm, and satisfaction and pleasure from sexual activity. It should be noted that in some of the

studies, the T levels were superphysiologic, although free T concentrations may remain within the normal range (17).

Also, as clearly shown in the recent study by Shifrin and coworkers (17), there is a large placebo effect in treatment studies and, therefore, it is imperative that studies examining the effects of androgen replacement therapy in women with sexual dysfunction be rigorously controlled through the use of a randomized, double-blind, placebo-controlled methodology.

Also, long washout periods in crossover studies or, ideally, the use of separate groups are important to avoid the carryover effects following T treatment. Additionally, the duration of the studies should be sufficient to adequately assess the effects of therapy on sexual function and to evaluate adverse effects that may not be apparent until several months after the initiation of treatment.

10: Do Androgens Enhance the Quality of Life?

Dr. Susan Davis has made a cogent argument that many of the symptoms of androgen insufficiency reflect an androgen-dependent mood disorder (1). Indeed, low libido, generalized fatigue, and an overall decreased sense of well-being, which is reversed with androgen replacement therapy, certainly suggests that androgens have a profound effect on mood and psychological well-being. A number of studies that have examined this issue have shown that androgens do improve overall energy and sense of well-being, while decreasing somatization and depression (17, 34–37). Androgen treatment also increases hostility (36).

11: Is Estrogen and Androgen Therapy Superior to Estrogen Therapy Alone for Low Bone Mineral Density?

Osteopenia and osteoporosis have been noted in men and women with androgen insufficiency, and androgens clearly have an anabolic effect on the bone. Androgen receptors are present in osteoblasts (47); androgens stimulate proliferation and differentiation of bone cells in vitro (48, 49); and androgens (but not estrogens) stimulate markers of bone formation in vivo (50). Observational studies have shown a positive correlation between androgen levels and bone mass in premenopausal and postmenopausal women (51–54). Treatment trials have demonstrated an increase in bone mineral density in women treated with androgens alone, and the increase in bone density seen in women receiving androgens and estrogens together is greater than that seen in women receiving estrogens alone (34, 55–59).

The serum levels of E₂ do not increase significantly after the administration of pure T (17) and, therefore, it is unlikely that the additive or synergistic effect of the combination of androgens and estrogens together is the result of simple aromatization of androgens to estrogens in the bone, which would have the effect of supplying more estrogens to the bone cells. Indeed, synthetic androgens such as nandrolone decanoate and stanozolol exhibit similar positive effects on bone health (55–57).

12: What Are the Indications for Androgen Replacement Therapy?

The clearest indication for androgen replacement therapy is symptomatic androgen insufficiency associated with pituitary, adrenal, or ovarian failure. A woman who is premenopausal and exhibits symptoms compatible with androgen insufficiency syndrome should also be considered for a trial of androgen replacement if her free T or FTI level is at or below the lower quartile for a young adult woman. Other potential indications that require more data before treatment can be recommended include osteoporosis, glucocorticoid therapy, premenstrual syndrome, HIV wasting syndrome, and autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis (2).

13: What Is the Best Means for the Delivery of Androgen Therapy?

Androgens may be administered orally, through the buccal mucosa, by injection or subcutaneous implants, and transdermally via creams, gels, and patches (60). Each of these methods has advantages and disadvantages, which have been extensively covered elsewhere (1, 2, 5, 6, 9, 60). However, the transdermal therapies appear to give the best balance between achieving physiologic T concentrations, without the peaks and valleys seen with the other routes of administration, and the most favorable safety profile vis-à-vis the lipid profile and liver effects (17, 61).

14: How Should Androgen Replacement Therapy Be Monitored?

The adverse effects of androgen administration include acne, hirsutism, virilization, fluid retention, polycythemia, hepatic injury, sleep apnea, aggressive behavior, and a lowering of the high-density lipoprotein level. Therefore, careful clinical assessment for the presence of acne and hirsutism should be carried out. In this regard, the modified Ferriman-Gallwey Hirsutism Rating Scale is particularly useful for assessing hair growth in the androgen-sensitive regions of the body (62). Measurements of lipids, hemoglobin, and liver enzymes should be performed before and 1–2 months following the initiation of therapy.

In summary, it is clear that some women develop symptomatic androgen insufficiency. In these women, androgen replacement therapy has beneficial effects on libido and sexual satisfaction, quality of life, body composition, and bone mineralization. Therefore, androgen replacement therapy should be given the same consideration that we give to estrogen replacement therapy.

References

1. Davis S. Androgen replacement in women: a commentary. *J Clin Endocrinol Metab* 1999;84:1886–91.
2. Davis SR, Tran J. Testosterone influences libido and well being in women. *Trends Endocrinol Metab* 2001;12:33–7.
3. Arlt W, Allolio B. Dehydroepiandrosterone replacement therapy. *Curr Opin Endocrinol Diabetes* 2001;8:130–9.
4. Cawood EHH, Bancroft J. Steroid hormones, the menopause, sexuality and well-being of women. *Psychol Med* 1996;26:925–36.
5. Guay AT. Advances in the management of androgen deficiency in women. *Med Aspects Hum Sex* 2001;1:32–8.

6. Hoeger KM, Guzick DS. The use of androgens in menopause. *Clin Obstet Gynecol* 1999;42:883–94.
7. Demers LM. Biochemistry and laboratory measurement of androgens in women. In: Redmond GP, ed. *Androgenic disorders*. New York: Raven Press, 1995:21–34.
8. Longcope C. Androgen metabolism and the menopause. *Semin Reprod Endocrinol* 1998;16:111–5.
9. Lobo RA. Androgens in postmenopausal women: production, possible role, and replacement options. *Obstet Gynecol Surv* 2001;56:361–76.
10. Vermeulen A. Plasma androgens in women. *J Reprod Med* 1998;43:725–33.
11. Redmond GP. Interpretation of androgen levels in women. In: Redmond GP, ed. *Androgenic disorders*. New York: Raven Press, 1995:49–57.
12. Miller K, Sesmilo G, Schiller A, Schoenfeld D, Burton S, Klubanski A. Androgen deficiency in women with hypopituitarism. *J Clin Endocrinol Metab* 2001;86:561–7.
13. Hughes CL, Wall LL, Creasman WT. Reproductive hormone levels in gynecologic oncology patients undergoing surgical castration after spontaneous menopause. *Gynecol Oncol* 1991;40:42–5.
14. Moghissi E, Ablan F, Horton R. Origin of plasma androstenediol glucuronide in man. *J Clin Endocrinol Metab* 1984;59:417–21.
15. Casson PR, Elkind-Hirsch KE, Buster JE, Hornsby PJ, Carson SA, Snabes MC. Effect of postmenopausal estrogen replacement on circulating androgens. *Obstet Gynecol* 1997;90:995–8.
16. Simon J, Klaiber E, Wiita B, Bowen A, Yang HM. Differential effects of estrogen-androgen and estrogen-only therapy on vasomotor symptoms, gonadotropin secretion, and endogenous androgen bioavailability in postmenopausal women. *Menopause* 1999;6:138–46.
17. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682–8.
18. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999;84:3666–72.
19. Wilke TJ, Utley DJ. Total testosterone, free androgen index, calculated free testosterone and free testosterone by analog RIA compared in hirsute women and in otherwise normal women with altered binding of sex hormone binding globulin. *Clin Chem* 1987;33:1372–5.
20. Rosner W. An extraordinarily inaccurate assay for free testosterone is still with us [letter]. *J Clin Endocrinol Metab* 2001;86:2903.
21. Sinha-Hikim I, Arver S, Beall G, Shen R, Guerrero M, Sattler F, et al. The use of a sensitive equilibrium dialysis method for the measurement of free testosterone levels in healthy, cycling women and in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab* 1998;83:1312–8.
22. Vermeulen A. The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 1976;42:247–53.
23. Vermeulen A, Verdonck L. Plasma androgen levels during the menstrual cycle. *Am J Obstet Gynecol* 1976;125:491–4.
24. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab* 1995;80:1429–30.
25. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. *J Clin Endocrinol Metab* 2000;85:2832–8.
26. Orentreich N, Brind JL, Rizer RL, Vogelmann JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 1984;59:551–5.
27. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537–44.
28. Persky H, Lief AI, Strauss D, Miller WR, O'Brien CP. Plasma testosterone levels and sexual behavior of couples. *Arch Sex Behav* 1978;7:157–73.
29. Morris NM, Udry JR, Khan-Dawood F, Dawood MY. Marital sex frequency and midcycle female testosterone. *Arch Sex Behav* 1987;16:27–38.
30. Bancroft J, Sanders D, Davidson D, Warner P. Mood, sexuality, hormones, and the menstrual cycle. III. Sexuality and the role of androgens. *Psychosom Med* 1983;45:509–16.
31. Myers LS, Dixen J, Morrissette D, Carmichael M, Davidson JM. Effects of estrogen, androgen, and progesterin on sexual psychophysiology and behavior in postmenopausal women. *J Clin Endocrinol Metab* 1990;70:1124–31.
32. Bachmann GA, Leiblum SR, Kemmann E, Colburn DW, Swartzman L, Shelden R. Sexual expression and its determinants in the post-menopausal woman. *Maturitas* 1984;6:19–29.
33. Appelt H, Strauss B. The psychoendocrinology of female sexuality: a research project. *Ger J Psychol* 1986;10:143–56.
34. Davis SR, McCloud P, Strauss BJG, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227–36.
35. Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. *J Affect Disord* 1988;14:177–87.
36. Sherwin BB, Gelfand MM. Sex steroids and affect in the surgical menopause: a double-blind, cross-over study. *Psychoneuroendocrinology* 1985;10:325–35.
37. Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. *Am J Obstet Gynecol* 1985;151:153–60.
38. Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med* 1987;49:397–409.
39. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. *Psychosom Med* 1985;47:339–51.
40. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999;341:1013–20.
41. Davis SR, Burger HG. Clinical review 82: androgens and the postmenopausal woman. *J Clin Endocrinol Metab* 1996;81:2759–63.
42. Kaplan HS, Owett T. The female androgen deficiency syndrome. *J Sex Marital Ther* 1993;19:3–24.
43. Greenblatt RB. The use of androgens in the menopause and other gynecologic disorders. *Obstet Gynecol Clin North Am* 1987;14:251–68.
44. Warnock JK, Bundren JC, Morris DW. Female hypoactive sexual desire disorder due to androgen deficiency: clinical and psychometric issues. *Psychopharmacol Bull* 1997;33:761–6.
45. Sarrel PM. Broadened spectrum of menopausal symptom relief. *J Reprod Med* 1998;43:734–40.
46. Burger H, Hailes J, Nelson J, Menelaus M. Effect of combined implants of oestradiol and testosterone on libido in postmenopausal women. *Br Med J (Clin Res Ed)* 1987;294:936–7.
47. Liesegang P, Romalo G, Sudmann M, Wolf L, Schweikert HU. Human osteoblast-like cells contain specific, saturable, high-affinity glucocorticoid, androgen, estrogen and 1 α ,25-dihydroxycholecalciferol receptors. *J Androl* 1994;15:194–9.
48. Bodo M, Venti D, Becchetti E, Pezzetti F, Paludetti G, Danti E, et al. Effects of steroids on human normal and otosclerotic osteoblastic cells: influence on thymidine and leucine uptake and incorporation. *Cell Mol Biol* 1991;37:597–606.
49. Kasperk CH, Wergedal JE, Farley JR, Linkhart TA, Turner RT, Baylink DJ. Androgens directly stimulate proliferation of bone cells in vitro. *Endocrinology* 1989;124:1576–8.
50. Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, et al. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab* 1996;81:37–43.
51. Wild RA, Buchanan JR, Myers C, Demers LM. Declining adrenal androgens: an association with bone loss in aging women. *Proc Soc Exp Biol Med* 1987;186:355–60.
52. Brody S, Carlstrom K, Lagrelius A, Lunell NO, Mollerstrom G, Poussette A. Serum sex hormone binding globulin (SHBG), testosterone/SHBG index, endometrial pathology and bone mineral density in postmenopausal women. *Acta Obstet Gynecol Scand* 1987;66:357–60.
53. Buchanan JR, Hospodar P, Myers C, Leuenberger P, Demers LM. Effect of excess endogenous androgens on bone density in young women. *J Clin Endocrinol Metab* 1988;67:937–43.
54. Jassal SK, Barrett-Connor E, Edelstein SL. Low bioavailable testosterone levels predict future height loss in postmenopausal women. *J Bone Miner Res* 1995;10:650–4.
55. Passeri M, Pedrazzoni M, Pioli G, Butturini L, Ruys AH, Cortenraad MG. Effects of nandrolone decanoate on bone mass in established osteoporosis. *Maturitas* 1993;17:211–9.
56. Need AG, Nordin BE, Chatterton BE. Double-blind placebo-controlled trial of treatment of osteoporosis with the anabolic nandrolone decanoate. *Osteoporos Int* 1993;3S:218–22.
57. Chestnut CH 3rd, Ivey JL, Gruber HE, Matthews M, Nelp WB, Sisom K, et al. Stanozolol in postmenopausal osteoporosis: therapeutic efficacy and possible mechanisms of action. *Metabolism* 1983;32:571–80.
58. Savvas M, Studd JWW, Norman S, Leather AT, Garnett TJ, Fogelman I. Increase in bone mass after one year of percutaneous oestradiol and testosterone implants in post-menopausal women who have previously received long-term oral oestrogens. *Br J Obstet Gynaecol* 1992;99:757–60.
59. Barrett-Connor E. Efficacy and safety of estrogen/androgen therapy: menopausal symptoms, bone, and cardiovascular parameters. *J Reprod Med* 1998;43:746–52.
60. Casson PR, Carson SA, Buster JE. Testosterone delivery systems for women: present status and future promise. *Semin Reprod Endocrinol* 1998;16:153–9.
61. Slater CC, Souter I, Zhang C, Guan C, Stanczyk F, Mishell DR. Pharmacokinetics of testosterone after percutaneous gel or buccal administration. *Fertil Steril* 2001;76:32–7.
62. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961;21:1440–7.