Testosterone insufficiency in women: fact or fiction?

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It has become apparent that androgens play a significant role in women's health. More than the expected level of androgens in a woman's blood stream causes obvious symptoms of androgen excess; less readily apparent are the consequences of female androgen deficiency. The symptoms are subtle, affecting a woman's sexual desire, satisfaction, and mood, and are commonly mistaken as signs of an underlying depression, prompting referral for counseling and psychotherapy, when hormone measurements would be more appropriate and more fruitful. Androgen deficiency in women is a topic that the medical community has been slow to address. This is partially attributed to the fact that the most common symptom is decreased libido, a very common nonspecific complaint that has long been associated with the psychological issues of stress and depression. One of the earliest reports showing an association between decreased sexual desire and decreased testosterone in women was published in 1959, but acceptance of this association has been slow. However, more evidence now shows that many women-pre-menopausal and post-menopausal-do suffer from androgen deficiency. Because the symptoms of such a deficiency resemble those of depression, misdiagnosis and lack of treatment are common. Improved awareness of the symptoms, diagnostic procedures, and appropriate available treatments are needed, to avoid misdiagnosis and unnecessary or inappropriate treatments.

Symptoms of androgen deficiency

The symptoms of androgen deficiency in women may very closely resemble other conditions. The chief complaint of androgen-deficient women is decreased sexual desire, which is often characterized by a decrease in sexual thoughts and fantasies, as well as actions. Muscle weakness is another frequent complaint, especially in athletic patients. It appears that genital arousal and orgasmic response may also be negatively affected, and vaginal lubrication may decrease, even in women who are menstruating regularly. There is some evidence that testosterone, apart from estrogen, may have a direct function in genital arousal and orgasmic physiology .

Female androgen metabolism

In women, testosterone is produced in various locations. One quarter of the hormone is produced in the ovary, a quarter is produced in the adrenal gland, and one half is produced in the peripheral tissues from the various precursors produced in the ovaries and adrenal gland. There is also much interconversion among steroid hormones. The main precursor in the ovary is androstenedione, which is converted primarily to estrone, but which can also be converted to androgens. The main precursors in the adrenal gland are DHEA and DHEA-S. It is, therefore, reasonable to expect the symptoms of testosterone deficiency after menopause, since nearly half of the testosterone is manufactured by the ovary, although the post-menopausal ovary still produces some steroid hormones. The recent finding of decreased testosterone and DHEA-S production in both pre- and post-menopausal women brings up the possibility of an enzyme defect causing decreased DHEA production. DHEA is derived from 17 hydroxypregnenolone through the action of the enzyme 17, 20 lyase. If this enzyme is deficient, the DHEA would be low.

Epidemiology of decreased libido

In 1999, it was reported that the proportion of women in the United States between the ages of 18 and 59 with sexual dysfunction was 43%. However, because little attention has been paid publicly to female sexual dysfunction, this area has remain neglected, and only now is there understanding of such disorders in women. The percentage of women, categorized by age, education, and ethnic background, who complained of decreased sexual desire in the different categories ranged from 22% to 44%, with a mean of 32%. This would put the number of women with decreased libido in the tens of millions in this country alone. How many of these women have decreased androgens is unknown, but the number is estimated to be between 10 and 15 million.

Who may be affected?

Most of the current clinical experience with androgens and androgen deficiency has been in post-menopausal women who complain of decreased sexual desire after cessation of menses, and are not helped by estrogen replacement therapy alone. The question of androgen deficiency has largely been ignored in pre-menopausal women. Testosterone levels have usually been measured in this population only when looking for excess production in women complaining of facial hair, loss of scalp hair, infertility, or acne. A recent presentation at the 2000 Female Sexual Function Forum meeting in Boston revealed that 36 premenopausal and 38 postmenopausal women complaining of decreased libido also had decreased total and free plasma testosterone levels as well as decreased levels of DHEA-S.

Guidelines for assessing androgen deficiency

Assays for plasma total testosterone have been available for over 40 years, and the levels are shown to decrease with age in women, as they do in men. The relatively newer free testosterone assay has been in use for a decade, and whether by equilibrium dialysis or by direct radioimmunoassay, it is felt to be more accurate because it measures the amount of testosterone available for activity in the tissues.

However, very little data are available on normal ranges for these assays. Even the known data, using total testosterone, suffer from the general flaw that none of the women used for the normal ranges were screened for any type of sexual problems, including decreased sexual desire. Until better data exist, a plasma total testosterone level of <25 ng/dL in women under 50 years old, and <20 ng/dL in women aged 50 or older, is indicative of androgen deficiency. For the free testosterone assay by direct radioimmunoassay, the guide is used that in women under the age of 50, a level of <1.5 pg/mL, and in women over the age of 50, a level of <1.0 pg/mL, is indicative of androgen deficiency. If the values are even slightly above the levels mentioned, it should be considered borderline, and a clinical trial of androgen may be in order if the symptoms are suggestive. More accurate and consistent data are available for the measurement of DHEA-S. This hormone also decreases with age. A recent analysis has suggested two age-related curves, one for lean and one for obese women. According to a clinic's experience, in women under the age of 50 with DHEA-S levels of <150 ng/dL a diagnosis of decreased adrenal DHEA production is appropriate. Similarly, the diagnosis of adrenal DHEA production should be considered in women aged 50 or older whose DHEA-S levels are <100 ng/dL.

There are no clear guidelines for evaluating women who might have androgen deficiency. Only recently has there been acknowledgement of the need for clear guidelines for measuring

decreased androgen levels. In reality, women may develop symptoms of androgen deficiency at any age, from their teen years through late adulthood. The chief symptom is often a decrease in sexual interest, which is not often acknowledged. Another common symptom is fatigue, a symptom associated with many clinical conditions and therefore not likely to increase your suspicion of androgen deficiency. Ask female patients about decreased sexual desire and sexual fantasies, as many are reluctant to mention these problems. In many instances physicians have been quick to ascribe sexual problems to anxiety, depression, premenstrual syndrome, or lack of sleep-especially during the child-rearing years. Peri-menopausal women may complain of decreased sexual desire at the onset of their life cycle changes, attributing it to these changes. This may be the time to test for androgen deficiency. Also, in the postmenopausal woman, test the testosterone levels if decreased sexual desire does not improve after 6 months of estrogen replacement or if she declines such therapy.

Androgen therapy

Once a diagnosis of androgen deficiency has been confirmed, or strongly suspect one by borderline testosterone levels, the question of treatment arises. The available medical literature has discussed different options of androgen treatment in post-menopausal women but little is available on premenopausal. The one agent indicated for use in women is a combination of estrogen and methyltestosterone in the form of Estratest, which has been prescribed in post-menopausal women for several decades in this country. However, it is not universally effective, probably because it is a methylated derivative of testosterone, not the natural hormone. In Europe, testosterone pellets have been implanted under the skin, a treatment option that requires a surgical procedure that predisposes the patient to infection or extrusion of the pellets. It has been found to be generally effective in England and in Australia. This treatment is available in this country for men. Intramuscular injection of testosterone esters has been used in men for decades, and very small doses have been used in women. The level of testosterone increases in the blood for a number of days after the injection, and many women reach levels high enough to cause side effects. A current study of testosterone patches suggests that this may be an effective treatment option within a few years. There are limited data on absorption kinetics and consistency of absorption of testosterone. Because levels of testosterone have to be monitored carefully and none of these products are standardized, they are not widely recommended for use. Although not officially approved for use by women in the United States, various pharmacies can compound testosterone in a cream or 1% gel form, as these have been approved for men.

Recently data has been published using an over-the-counter (OTC) oral DHEA for androgen replacement, with the idea that if the patient precursor hormone is provided, it would allow the body to convert it to testosterone. This product is available in pharmacies, supermarkets, and health food stores in the United States. Patients can take it off the shelves (eg, Your Life), as such products do not require a prescription. The dose should begin with a 50-mg dose of OTC oral DHEA each morning, and the patients' total and free testosterone, as well as other androgen values ahould be monitored every 2 to 3 months to verify absorption of the product. If the free testosterone level is between 1.8 ng/mL and 2.2 ng/mL, this regimen is continued. If the measurement is lower, the dosage may be increased to 75-mg DHEA a day. Androgen values should be checked within several months and, if needed, the dose may be further increased to 100-mg DHEA. DHEA treatment is used in premenopausal and postmenopausal women with low androgen levels. A positive response occurs in many women treated with DHEA . Of all

methods of hormone replacement DHEA is preferred although options such as Estratest and testosterone 1% gel are available. DHEA has recently been used to treat women who have adrenal insufficiency, who by definition have markedly decreased DHEA levels. It has been found to improve general energy, well-being and sexuality. DHEA has also been studied in older men and women to aid in muscle strength with variable responses. Used for longer periods of time (ie, 1 year), DHEA has produced some increases on sexual function.

Potential risks and side effects

There is very little clinical research on treating pre-menopausal women. From the small amount of research available, it seems that the androgen levels achieved by treatment, as well as side effects, are the same as those in post-menopausal women. The main untoward effects are acne and facial hair. These occur if the level of testosterone is above normal. However, some sensitive women may have these effects with a level in the normal range. Occasionally fluid retention can occur. If testosterone rises above physiological levels, an abnormal lipid profile may occur. There are no side effects to DHEA itself because there are no receptors in the body for DHEA; all side effects are from the conversion product of DHEA, which is testosterone. Women with a history of breast cancer, severe liver disease, or severe deep vein phlebitis should not take androgens, as a certain amount of testosterone will be converted to estrogen. This treatment is also contraindicated during pregnancy, since testosterones, and even its precursor DHEA, cross the placenta and may cause changes in the genitals of the fetus. Special caution should be used when treating women of childbearing age. When prescribing testosterone treatment to a woman, be sure to prescribe adequate birth control and a warning that the androgen treatment should be stopped immediately if a pregnancy might be even remotely possible, or when considering pregnancy in the near future.

Conclusion

Androgen deficiency is a true medical condition in both pre- and post-menopausal women. The most important recommendation is to listen to the patient and consider androgen deficiency when the symptoms are present, even if they seem non-specific. Making a diagnosis of and subsequently treating androgen deficiency can be tricky because of the scarcity of research on the subject; laboratory determinations do not have very accurate ranges and efforts are being made to try to establish normal ranges at this time. Treatment with androgens has to be monitored carefully because of the possible harmful effects of excessive levels of testosterone. Although it is obvious that more data are necessary to find accurate incidences of androgen deficiency and accurate blood levels of androgens in women of varying ages, it is encouraging that a condition that has long been ignored is now being evaluated and successfully treated.