

Androgens in the etiology and treatment of desire disorders in women

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ABSTRACT. *Recent data support an emerging role of androgens in influencing women's health with particular regard to sexual function. Androgens secure libido by acting in the central nervous system throughout genomic and non-genomic mechanisms. In addition, androgens modulate vaginal and clitoral physiology by influencing the muscular tone of erectile tissue and vaginal walls. The production of androgens is dynamic over the menstrual cycle, is influenced by hormonal manipulations, and declines with age. Menopause, especially when induced surgically, may be accompanied by the so-called androgen-insufficiency syndrome, which has a great impact on mental and sexual sense of well-being. Several therapeutic strategies, including the addition of androgens to estrogen replacement preparations and the use of tibolone, have been considered to relieve desire disorders in order to improve postmenopausal women's sexual function and satisfaction.*

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GENERAL VIEW ON WOMEN'S ANDROGENS

The major androgens in women include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T) and dihydrotestosterone (DHT). However, DHEAS, DHEA and A are considered pro-androgens as they require to be converted to T to express their effects. Testosterone (T) is the most potent androgen; it is secreted by the adrenal zona fasciculata (25%) and the ovarian stroma (25%), while the remaining amount (50%) derives from peripheral conversion of circulating A.

Plasma T levels are in the range 0.2-0.7 ng/mL (0.6-2.5 nmol/L), with significant fluctuations related to the phase of the menstrual cycle, being highest at ovulation, lowest during the

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early follicular phase and higher during the luteal phase compared with early follicular phase. In addition, T shows circadian variations, with a peak in the early morning hours. T is converted to DHT, but it can also be aromatizable to E₂ (Estradiol), in target tissues; DHT is the principal ligand to androgen receptors. While estrogen decreases sharply at menopause, plasma T levels fall slowly with age. At physiological menopause, the cessation of follicular activity is characterized by a significant decline of ovarian production of A, more than T, and the progressive fall of plasma T concentrations is the consequence of the reduced peripheral conversion from its major precursor and from DHEA and DHEAS, which decline with age. Indeed, the adrenal production of androgenic precursors declines over time and the final result is that plasma T and A levels at 60's are about half those in women aged 40 years (1).

As far as surgical menopause is concerned, bilateral oophorectomy both premenopausally and postmenopausally leads to a sudden 50% fall in circulating T levels. Low androgens are associated with significant deterioration of sexual desire in premenopausal and postmenopausal women. However, no cut-off level for a normal range of T has been agreed on. The lack of consensus on the definition of low T levels depends on the difficulties with sensitive assays of total and free T in women and on the fluctuations during the menstrual cycle and in different life ages. Therefore, the so-called androgen insufficiency syndrome is a clinical entity comprising specific symptoms, such as low libido, persistent and inexplicable fatigue, blunted motivation and a general reduced sense of well-being. Other signs of androgen insufficiency include reduced pubic hair, bone mass, muscle mass, poor quality of life, and more frequent vasomotor symptoms, insomnia, depression and headache (2, 3). Apart from surgical menopause, other causes of androgen insufficiency include normal aging [physiological

menopause with not enough benefits from conventional hormonal replacement therapy (HRT) and premenopausal women reporting low libido and with circulating free T levels at lower limits of detection], ovarian insufficiency (unilateral oophorectomy, hysterectomy, spontaneous premature ovarian failure or after chemotherapy or radiotherapy, hypothalamic amenorrhea), adrenal insufficiency (adrenal failure or surgery), combined (hypopituitarism, autoimmune adrenal and ovarian failure), iatrogenic (treatment with exogenous oral estrogens, antiandrogen therapy, oral contraceptives, GnRH agonist therapy, chronic exogenous corticosteroid administration) (1).

According to the state of the art, plasma T values at, or below the lowest quartile of the normal range for women in their reproductive years allow the hypothesis of androgen insufficiency (2).

ANDROGENS IN THE ETIOLOGY OF DESIRE DISORDERS

During the entire reproductive life span, sex hormones exert both organization and activation effects, which are relevant to sexual behavior, and their actions are mediated by non-genomic as well as direct and indirect genomic pathways (4, 5). Androgens are essential for the development of reproductive function and the growth and maintenance of secondary sex characteristics directly or throughout their conversion to estrogens. However, they modulate the physiological function of many tissues and organs, including the central nervous system, the cardiovascular system, the muscle-skeletal apparatus, the immune system, etc., in both sexes (1).

The androgen influence over female sexual response has been hypothesized for a long time, but only in recent years basic research in laboratory animals and clinical trials with androgenic compounds are helping to understand the role of androgens on libido and sex-

ual arousal in women (6). Apart from modulating cortical coordinating and controlling centers, interpreting what sensations are to be perceived as sexual, and issuing appropriate commands to the rest of the nervous system, androgens, together with estrogens, affect the sensitivity of both genital organs and hypothalamic-limbic structures where they elicit conscious perception and pleasurable reactions by influencing the release of specific neurotransmitters and neuromodulators. Circulating T levels are aromatized to E_2 or bind to androgen-receptor (AR), following conversion to DHT, within several areas of the central nervous system. A further non-genomic action by T metabolites on sexual receptivity has been described at hypothalamic level (7). At the genital level, androgens modulate vaginal and clitoral physiology by influencing the muscular tone of erectile tissue and vaginal walls. The androgenic facilitation of vaginal smooth muscle relaxation occurs especially in the proximal vagina, producing distinct physiological responses in comparison with estradiol. Androgens down-regulate arginase activity by reducing L-arginine concentrations, a substrate for NOs, a crucial enzyme for vaginal lubrication and genital sensation. Indeed, NO has been identified in clitoral smooth muscle, and the enzyme responsible for cGMP degradation, phosphodiesterase type V, has been isolated in culture from smooth muscle cells of clitoral origin and is inhibited by sildenafil, which causes a dose-dependent relaxation of smooth muscle strips from rabbit clitoris and vagina. In addition, androgens interact with the synthesis and release of nitric oxide synthase (NOs) in the proximal vagina by facilitating vaginal and clitoral smooth muscle relaxation to electric field stimulation. Aging process and surgical castration induce a reduction of vaginal NO and cause the increase of vaginal fibrosis in female rats that are dependent both on estrogens and androgens (1, 8). The recent evidence of phosphodiesterase type V activity in

the anterior wall of human vagina allows the hypothesis that NO system is highly operating even in women at the anatomical site corresponding to the so-called G spot (9).

In clinical practice, the inadequate hormonal-dependent vaginal receptivity is the precipitating factor of dyspareunia, which in turn may cause other sexual symptoms that contribute to amplify pain during coital activity. Indeed, it is extremely common to observe a decline of libido following a history of dyspareunia; the consequent reduction of orgasmic capacity may, then, reduce sexual satisfaction, which negatively influences sexual motivation in a kind of self-sustaining "loop". This model clearly explains the high degree of comorbidity displayed by sexual symptoms in women.

Studies conducted in the fertile age found an increase in establishing interpersonal relationship and in exchanging sexual pleasure during the periovulatory period, corresponding to the plasma androgenic peak, even though no clear correlation has been reported between plasma androgen levels and the entity of sexual response. We should keep in mind that the strong motivation to sexual activity at the time of ovulation may be due to E_2 peak.

Estrogen-progestin use, particularly in monophasic regimen, seems to interfere with the spontaneous expression of sexual desire, but even the effects of the pill on mental well-being may play a role on sexual motivation. There is no doubt that hormonal contraception increases plasma SHBG levels and reduces free and total T, together with the absence of marked endogenous E_2 fluctuations, but how these features relate to sexual function remains to be established (10). Some authors have reported that serum T levels related to genital response and to subjective physical sensation (lubrication and breast sensitivity) in response to visual erotic stimulation both in premenopause and postmenopause. Moreover, antiandrogen administration has

been associated with low libido in females. Further evidences suggest that circulating free T relates to sexual desire and masturbation in young women. Finally, 5α -reductase activity is significantly impaired in target tissues in those women reporting low libido following menopause, while a significant correlation has been found between high levels of circulating T and A and a lower index of vaginal atrophy.

ANDROGENS IN THE TREATMENT OF DESIRE DISORDERS

A recent systematic review including all randomized and placebo-controlled trials of treatment for women's sexual dysfunction in postmenopausal women concluded that many treatments that are used in practice are not supported by adequate evidence (11). The first-line treatment is always represented by estrogen replacement therapy to restore adequate plasma E_2 levels in order to secure the vaginal environment. As a second therapeutic step, after excluding other organic and psycho-relational issues, androgen supplementation may be proposed. Only one trial on estrogen replacement therapy (ERT) was randomized and placebo-controlled, and investigated the effects of estrogen and progestin on sexual desire, arousal and mood in healthy postmenopausal women, without assessing frequency of sexual activity and orgasm. Sherwin concluded that there was a significant improvement of sexual desire and arousal on a short-term basis (12). The most interesting findings on positive sexual effects of sex hormones at menopause come from studies with oral and transdermal combination of estrogens and exogenous T, even though only two trials were randomized and placebo-controlled. The first trial, conducted on a small sample of subjects ($n=20$), reported that sexual desire, satisfaction and frequency in postmenopausal women taking hormonal therapy were improved significantly by combined estrogen-androgen therapy but not by

estrogen or estrogen-progestin therapy. Sexual function improved with estrogen-androgen therapy, even though circulating estrogen levels were lower than those measured during previous estrogen therapy, leading to the conclusion that androgens play a pivotal role in sexual function, with estrogens not having a significant impact on levels of sexual drive and enjoyment. The second trial was conducted in surgical menopause, with two doses of transdermal T (150 and 300 mcg/d) versus placebo, and reported a significant improvement in sexual function with a further increase in scores for frequency of sexual activity and orgasm when women were taking the higher dose. However, there was an extremely strong response in sexual function in women on placebo, and 24% of study participants withdrew from the trial because of androgen-related adverse side-effects. A very recent study demonstrated that the addition of testosterone undecanoate improved specific aspects of sexual function more than treatment with estrogen alone, but suprphysiological levels were achieved in a significant proportion of the women (13). Therefore, the use of androgens in the clinical management of menopause needs a certain degree of caution, even because the long-term effects of such preparations on women's general health are still unknown. In addition, estrogen-androgenic treatments are still unavailable in several countries. In Europe, a long-term experience for the treatment of climacteric symptoms and low mood and libido is available with tibolone, a synthetic steroid with tissue-specific estrogenic, progestagenic and androgenic properties. Apart from direct effects of its metabolites in the vagina and in brain areas relevant to well-being, tibolone lowers SHBG, thus increasing free E_2 , T and DHEA-S levels. In randomized studies versus placebo or E_2 /NETA (norethisterone acetate), tibolone treatment (2.5 mg/d) alleviates vaginal dryness and dyspareunia, ameliorating to a greater extent libido, arousal and sexual satis-

faction in postmenopausal women. Moreover, tibolone shows a positive effect on sexuality which is superimposable to that observed with estro-androgenic preparations. This data, together with recent observation that tibolone significantly increases vaginal pulse amplitude at baseline and following erotic stimulation versus placebo, further supports the notion that such tissue-specific compound is a good therapeutic option to relieve low libido, arousability and lubrication at menopause, because of both its estrogenic and androgenic properties (14). DHEA, as a precursor of E₂ and T, has been proposed in the treatment of low libido both pre- and postmenopausally with encouraging results. Studies conducted in elderly women have shown a positive effect of DHEA on mental well-being and motivational aspects of sexuality, with a mild relief of climacteric symptoms (15).

Further studies are needed to clarify the relevance of androgens to women's sexuality and the impact of hormonal treatments on the clinical expression of sexual symptoms. The role of the clinician in identifying all the possible biological factors leading to low androgen levels is mandatory to design therapeutic strategies tailored on women's need.

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