Testosterone Substitution Therapy and the Sexual Health of Women

a report by

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Testosterone therapy is of growing interest because of its increasingly recognised role in sexual and mental health, bone and muscle trophism and vitality.[1–4] An expanding body of evidence supports the influence of testosterone on sexuality, with the focus on desire and central (mental) arousal. This is more evident in women who have undergone oophorectomy and, therefore, have a complex symptomatology (sexual and non-sexual), secondary to the loss of ovarian androgens.

The objective of this article is to evaluate testosterone physiology in women, differences in sexuality between women and men, definition and epidemiology of hypoactive sexual desire disorder (HSDD) and characteristics of testosterone patches and clinical indications.

Physiology of Testosterone

The neurobiology of sexual desire and central arousal and the peripheral neurovascular response are substantially modulated by sexual hormones. Androgens have a leading role in the initiation and modulation of sexual function, in women as well as in men.[1,2] In men, testosterone is 10 times higher than in women, contributing to the stronger intensity of the male sex drive. Multiple neurotransmitter systems in the brain, especially the areas known to regulate mood and desire (including the amygdala, hippocampus and hypothalamus), are heavily influenced by sex hormones. The serum levels of testosterone and of proandrogens exceed those of oestradiol, even during the peak reproductive years (see *Table 1*).[3]

In women, about half of the circulating testosterone is secreted directly by the ovarian stroma and adrenal zona fasciculata in roughly equal quantities; the other half is derived from conversion of the proandrogen androstenedione, which is secreted by the same tissues. The proandrogen dehydroepiandrosterone sulphate (DHEAS) is produced entirely in the adrenal zona reticularis, and conversion of DHEAS accounts for about 30% of the circulating DHEA, with the remaining DHEA secreted by the adrenal zona reticularis and the ovarian theca. Androgen levels tend to peak when women are in their 20s and gradually drop with age. At 40 years of age, androgen levels are on average half those at 20 years of age; typical serum levels of testosterone and androstenedione at 60 years of age are about half those at 40 years of age. Therefore, at 60 years of age the biological fuel of the sexual drive is reduced to one-quarter of its level at 20 years of age.

Hypoandrogenic Situations

A decline in testosterone levels can be physiological with ageing; idiopathic; iatrogenic, as a reversible side effect of oestro-progestinic therapy, antiandrogenic therapy, gonadotropin-releasing hormone (Gnrh) analogues or glucocorticoid therapy, as an irreversible effect of radio- and chemotherapy (which may destroy Leydig's cells) or after bilateral oophorectomy; or due to hypothalamic–pituitary abnormalities or adrenal insufficiency.

Impact of Testosterone on the Health of Women

Androgens have a complex impact on the body and functions of women. Evidence suggests a significant impact on the following factors.

The Sexuality of Women (see Table 2*)*

Sexual Function

Desire and central arousal ('I feel mentally excited') is heavily influenced by testosterone in both genders through the dopaminergic system. Its impact is also strong on central arousal, which is difficult to separate from desire itself. Testosterone modulates the action of nitric oxide on the clitoris and on the bulb cavernous bodies, promoting genital arousal ('I feel wet') through vasodilatation and vasocongestion. It also facilitates orgasm, possibly with central and peripheral arousal.

Emotional Aspects of Sexual Function in Women

Sexuality is usually considered as a 'purely' erotic mechanism; however, it is intensely modulated by emotions, feelings and a need for intimacy, especially in women. Animal research suggests that four basic emotion–command systems interact at the neurobiological level with the brain system underlying sexual desire and central arousal. According to Panksepp, the four basic emotion–command systems, i.e. seeking–appetitite–lust, anger–rage, fear–anxiety and panic–separation–distress, represent the biological correlates of the instinctive sexual drive and appetite urges present in both genders.[5,6] The emotional system is primed by sexual hormones, with a prominent role of androgens on seeking–appetite–lust and anger–rage and of oestrogens on fear–anxiety and panic–separation–distress. Sexual desire is the perceptive correlate of the seeking–appetite–lust system.

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Table 1: Medium Hormonal Levels in Women

Hormone	Reproductive Years	Natural Menopause	Iatrogenic Menopause
Oestradiol	100–150	10–15	10
Testosterone	400	290	110
Androstenedione	1,900	1,000	700
Dehydroepiandrosterone	5,000	2,000	1,800
Dehydroepiandrosterone sulphate	3,000,000	1,000,000	1,000,000

Converted in pg/ml. Adapted from Lobo, 1999.[3]

Table 2: Biological Actions of Testosterone on the Sexuality of Women

Increases physical and mental energy, assertiveness and lucidity
Stimulates mental and genital sexual arousal, erotic dreams, voluntary and spontaneous sexual fantasies
Increases nipple and genital excitability, particularly of the clitoris and cavernous bodies
Reduces the time between the beginning of foreplay and the achievement of orgasm
Increases the intensity and pleasure of orgasm and facilitates the achievement of multiple orgasms
Contributes to maintaining a healthy and juvenile shape as abdominal and waist fat increase in their absence
In synergy with oestrogens, testosterone stimulates the production of pheromones by sweat and sebaceous glands

Modified from Graziottin and Serafini, 2008.[4]

'Seeking' describes a positive feeling that is mediated by the neurotransmitter dopamine in both sexes.[7,8] This system is responsible for curiosity, interest and expectancy, and it has long been regarded as the mechanism for reward-orientated behaviour. 'Lust' is associated with the feeling of gratification that occurs when the consummation of the appetites is realised. The command neuropeptide of this gratification system is endorphin. The clinical implications of biological gender variations in the construction of seeking systems are that men tend to express their sexual desires more in the lust domain, articulating stronger sexual drives that are more biologically driven and genitally focused, while women more commonly express their sexual desires as passion, emphasising the aspects of relationship intimacy.[9] Sexual desire is modulated by the interaction among different emotions: anger can excite desire in men, but usually reduces it in women; anxiety (particularly performance anxiety) inhibits desire in both genders; panic may induce men to avoid sex and women to accept it for fear of losing their partner. The panic system, similar to the fear–anxiety system, seems to be more active in women than in men, most likely due to the typically stronger social bonding and parenting patterns exhibited in and socially expected of females. The biological correlates of both the need for intimacy and the dynamics of attachment in women may be important in determining their ability to access arousal states. Menopausal changes of sexual hormones may impact on the basic emotions command system, which represent the emotional scenario where sexuality is acted.

Central Nervous System

The brain is a major target of testosterone. All brain functions are modulated by androgens.[10,14] Specifically, loss of sexual hormone is implicated in a number of disorders, as follows.

Mood

The menopausal transition is a time of risk of mood change, ranging from distress to minor depression to major depressive disorder in a vulnerable subpopulation of women. Somatic symptoms have been implicated as a risk factor for mood problems, although these mood problems have also been shown to occur independently of somatic symptoms. Oestrogen and add-back testosterone have both been shown to positively affect mood and wellbeing.[10]

Cognition and Memory

Difficulty concentrating is negatively correlated with testosterone.[11] Women who underwent oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared with referent women (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.13–1.90 adjusted for education, type of interview and history of depression). The risk increases with younger age at oophorectomy (test for linear trend; adjusted $p<0.0001$).[12]

Neuromotor System

The risk of parkinsonism increases following oophorectomy (odds ratio [OR] 1.68, 95% CI 1.06–2.67; $p=0.03$). In particular, there are linear trends of increasing risk with younger age at oophorectomy.[13,14]

Skin

At a physiological level, testosterone is synergic with oestrogens in promoting fibroblastic synthetic activity, thus contributing to skin texture and trophism, modulating the secretion of pheromones by sweating and (mainly) sebaceous glands, which contributes to the sexually attractive 'scent of woman'. At supraphysiological levels, such as in polycystic ovary syndrome, or in iatrogenic conditions it causes acne, hirsutism, alopecia, increased muscle mass and, in extreme cases, voice deepening.

The Motor System of Women

Muscles

Muscle mass and strength are increased by inducing hypertrophy of type 1 and type 2 muscle fibres and increasing myonuclear and satellite cell numbers.[15,16] For example, development of the perineal striated muscles – bulbocavernosus and levator ani – is sexually dimorphic and developmentally dependent on testosterone.[17]

Bone

Osteoporosis is a leading cause of morbidity and mortality in older women. Low circulating testosterone is correlated with hip fracture and height loss in post-menopausal women.[18] Oestrogen alone has been used to prevent loss of bone mass, but other studies have shown that oral oestrogen–androgen hormone therapy is superior in promoting bone formation.[19]

Definition of Hypoactive Sexual Desire Disorder

Women with HSDD experience absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire, which causes personal distress. By definition, responsive desire is triggered by a sexual partner and/or by positively perceived foreplay when the woman accepts sexual intimacy starting

from a 'neutral' sexual state.[20] Motivations (defined as reasons or incentives) for attempting to have sexual arousal are scarce or absent. The lack of interest is considered to be beyond the normative decrease expected with ageing and relationship duration.[21] Emotional or relational factors that determine 'sexual motivation', as well as physical factors that are modulated by hormones and health-related conditions ('sexual drive'), together contribute to 'sexual interest'. Personal distress (lack of interest in sex that is concerning or distressing to a woman) is recognised as an important component of the last two definitions and must be present before a diagnosis of HSDD can be concluded.

Table 3: Percentage of Women Classified with Low Desire by Country and by Menopausal Status[23]

	Pre-menopause	Surgical Menopause	Natural Menopause
France	11*	39	26
Italy	12*	44	42
Germany	19*	43	59
UK	22*	35	48**

** p<0.05 versus surgical menopause and natural menopause women;*
*** p<0.05 versus surgical menopause women. Base = women with sexual partners.*

Epidemiology of Hypoactive Sexual Desire Disorder

The prevalence of HSDD in menopausal women and the frequency of sexual activity, sexual behaviour and relationship or sexual satisfaction associated with HSDD was assessed with a cross-sectional survey of 2,467 European women 20–70 years of age who were resident in France, Germany, Italy and the UK (see *Table 3*).[22,23] A greater proportion of surgically menopausal women had low sexual desire compared with pre-menopausal or naturally menopausal women (OR 1.4, CI 1.1–1.9; p=0.02). Surgically menopausal women were more likely to have HSDD than pre-menopausal or naturally menopausal women (OR 2.1, CI 1.4–3.4; p=0.001). Sexual desire scores and sexual arousal, orgasm and sexual pleasure were highly correlated (p<0.001), demonstrating that low sexual desire is frequently associated with decreased functioning in other aspects of sexual response. Women with low sexual desire were less likely to engage in sexual activity and more likely to be dissatisfied with their sex life and partner relationship than women with normal desire (p<0.001).[22]

Iatrogenic Menopause

Following bilateral oophorectomy, women develop a significant androgen deficiency that is caused by the sudden decrease of circulating testosterone.[24,25] Androgen insufficiency syndrome (AIS) occurs following a loss of androgens in women. Symptoms that may be correlated to this deficiency are a decrease in sexual desire, arousal and excitement, a lowering of vital energy, a decrease in vital motivation and wellbeing, greater tiredness and mood variations.[25,26] Mazer et al. demonstrated that women who underwent surgical menopause presented a significative reduction (p<0.001) in sexual desire and dreams, excitement, frequency of sexual activity, sexual initiative, orgasm, couple satisfaction and an increase in sexual problems and compared with an age-matched control group. Other studies support these findings.[27–29]

Physiological Menopause – Effects on Sexuality

Physiological menopause is characterised by a decrease in production of oestrogens and progestins while the production of testosterone remains, even if it is markedly reduced. Many organs and systems are influenced by this hormonal lack, which may cause many biological, psychological, sexual and relational consequences. Almost 85% of women experience one or more symptoms during menopause, such as hot flushes, depression or insomnia. The quality of life in one-third of women is significantly worsened because of these symptoms.[30] Hypoactive sexual desire symptoms reported by sufferers include hot flushes and muscular pain (58%), a decrease in vital energy (68%) and insomnia (63%).[31]

Diagnosis of Hypoactive Sexual Desire Disorder

A clinical history is vital. Low sexual desire is usually expressed with simple words – 'I have no more sexual desire', 'I do not feel any more drive for sex' – if the physician opens a discussion with a comprehensive question such as 'How's your sexual life?'. A screening tool to allow a post-menopausal woman to determine whether to seek evaluation for HSDD is the Brief Profile of Female Sexual Function (B-PFSF) (see *Table 4*), which was developed using components from the Profile of Female Sexual Function (PFSF) and the Personal Distress Scale (PDS). This test comprises seven questions and was found to provide good discrimination between post-menopausal women with HSDD and controls and to be a reliable and valid tool. Physical examination is mandatory to diagnose many biological conditions, i.e. vulvar vestibulitis, lichen sclerosus, iatrogenic factors such as poor outcomes of genital/perineal/pelvic surgery, vaginal dystrophy and hyperactive pelvic floor, which may cause/contribute to vaginal dryness, dyspareunia, anorgasmia, thus causing a secondary loss of sexual drive. Blood testing for testosterone level remains controversial.

Testosterone Therapy

Testosterone therapy dates back to the early 1940s, after the action of androgens on the sexual interest of women was observed by Shorr et al.[33] The authors noted that treatment of women with androgens increased sexual desire. In this historic study, it was concluded that: "Libido and sexual response were definitely greater than that experienced with oestradiol alone." Nowadays, the new way to administer testosterone to women is via a patch. In a study reported in 2000, 75 women who had undergone oophorectomy and hysterectomy received conjugated equine oestrogens and, in random order, placebo, 150mcg of testosterone and 300mcg of testosterone per day transdermally for 12 weeks each.[34] In this study, there was a strong placebo response in sexual functioning; however, treatment with 300mcg of testosterone per day was associated with significantly greater sexual improvement, based on the B-PFSF. The placebo response was greater in younger women. More recently, 562 surgically post-menopausal women with HSDD participated in a large multicentre, parallel-group study of 300mcg testosterone per day versus placebo. At 24 weeks, the subjects receiving testosterone displayed an increase from baseline in the frequency of total satisfying sexual activity of 2.10 episodes/four weeks compared with 0.98 episodes/four weeks in the placebo group (p=0.0003). The testosterone group also experienced statistically significant improvements in sexual desire and a decrease in distress.[35]

Testosterone patches are the only approved therapy for women in iatrogenic menopause who suffer from HSDD, which contains bio-identical and bio-equivalent testosterone that is released in a transdermic way. The use of bio-identical testosterone for the treatment of female androgen deficiency is a physiological replacement. This guarantees constant testosterone plasmatic levels, as if the woman's ovaries were still regularly functioning. Each day, 300mcg of

Table 4: Brief Profile of Female Sexual Function Related to the Last Two to Three Months

	Never	Seldom	Sometimes	Often	Very Often	Always
I felt like having sex	0	1	2	3	4	5
I was unhappy about my lack of interest in sex	5	4	3	2	1	0
Getting aroused took forever	5	4	3	2	1	0
I felt sexually numb	5	4	3	2	1	0
I lacked sexual desire	5	4	3	2	1	0
I felt disappointment by my lack of interest in sex	5	4	3	2	1	0
I reached orgasm easily	0	1	2	3	4	5

A total score between 0 and 20 may indicate a hypoactive sexual desire disorder. Adapted with permission from Rust et al., 2007.[32]

testosterone is released. Testosterone patches deliver the bioidentical hormone within the physiological range. The transparent oval-shaped patch is applied onto abdominal skin twice a week. Four to eight weeks are necessary to appreciate its effects. After three to six months, women may notice a 56 and 74% increase in sexual arousal and satisfying sexual activity, respectively, and a 40% reduction in personal distress caused by low arousal. The rebirth of sexual desire also determines a better global physical response. In fact, physical and psychological excitement and the ability to reach orgasm are significantly improved. Furthermore, anxiety is reduced and the sense of femininity is improved.[31] Several women also notice an increase in vital energy, assertiveness, memory and mental lucidity. Indeed, testosterone replacement may promote a 'co-treatment' of co-morbid conditions caused or worsened by the lack of testosterone, besides sexual desire and related sexual disorders, and could have a positive impact on mood disorders, cognitive impairment, osteopoenia and age-related muscle waste. Further studies are needed to support this claim.

Contraindications and Side Effects

The controversy over using testosterone has primarily involved safety concerns. The typical side effects related to oestrogen–testosterone preparations are alopecia, acne and hirsutism, although these are dose- and duration-dependent and are uncommon.[36] Although some retrospective and observational studies provide some long-term safety data, most prospective studies have had a duration of three years or less. In addition, with the exception of female-to-male transsexuals, testosterone was administered in conjunction with oestrogens or oestrogens and progestins, which confounds the interpretation of some of the studies. The major adverse reactions are the androgenic side effects of hirsutism and acne. There does not appear to be an increase in cardiovascular risk factors, with the exception of a lowering of high-density lipoprotein with oral testosterone. Limited data exist on endometrial safety, and most of the experimental data support a neutral or beneficial effect with regard to breast cancer. There does not appear to be an increased risk of hepatotoxicity, neurobehavioural abnormalities, sleep apnoea or foetal virilisation (in pre-menopausal women) with the physiological treatment doses of testosterone.[37] Contraindications are the same as those for oestro-progestinic therapy, i.e. hormone-dependent cancers, increased thrombotic risk and acute hepatitis. The effect of anticoagulant drugs may be increased by testosterone. Therefore, it is important to monitor patients treated by these kinds of medicines.

Future Perspectives

The future goals are to verify testosterone patch effects not only on female sexuality but also on cerebral function, with potential preventative applications in age-related mood disorders, Alzheimer's disease and motor symptoms, muscle and bone trophism and vitality.

Conclusions

Testosterone has a powerful role in the health and sexuality of women. Surgical menopause deprives women of more than 50% of total testosterone, thus contributing to a complex symptomatology, framed as AIS. Recent data suggest that premature menopause may increase the risk of cognitive impairment or dementia by 48% and of parkinsonism by 68%, thus adding further evidence to the critical role of testosterone for the health of the brain and quality of ageing. Testosterone therapy with patches that deliver 300mcg/day replaces testosterone physiological levels. This significantly improves sexual desire, arousal and orgasm and reduces anxiety, concerns and personal distress in women who have undergone surgical menopause and complain of HSDD. New studies suggest the positive impact of testosterone patches in women in natural menopause complaining of HSDD. More studies are needed to support the positive impact of testosterone replacement on different aspects of women's health. ■

Conflict of Interest

Alessandra Graziottin is on the speaker's bureau of Procter & Gamble. Audrey Serafini has nothing to declare.

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