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Vitamin D and Sex hormones in female patients with sexual dysfunction: A narrative review

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Abstract

Background: Female sexual dysfunction (FSD) is one of the critical problems that affect many females. Not all patients complain of this problem as it is an embarrassing multifactorial complaint. Herein, we review the etiology, Pathogenesis, and types of FSD and present the available literature to-date regarding a possible relationship between sex hormones and FSD. We conclude that further study is necessary to discern whether there may be a significant relationship between vitamin D and sex hormones and sexual dysfunction in females. Sexual dysfunction affects women's quality of life and relationships. Vitamin D modulates sex hormones and other physiological functions beyond bone health. Vitamin D levels and sex hormones in female sexual dysfunction patients are examined in this narrative review. Evidence shows that vitamin D insufficiency may change sex hormone levels in women, causing sexual dysfunction. Vitamin D regulates estrogen production, androgen levels, and reproductive system processes, which are important for sexual health. Low vitamin D levels are linked to depression, reduced libido, and poor sexual function, highlighting its complicated role in female sexual health. This study summarizes current research on vitamin D, sex hormones, and sexual dysfunction in women, suggesting therapeutic implications. Vitamin D supplementation as an additional therapy for female sexual dysfunction needs more study to determine its causes and effectiveness.

Keywords: Female sexual dysfunction; Female Sexual Functioning Index; Estradiol; Total Testosterone**.**

Introduction

Sexual dysfunction is a major disorder in one's ability to respond to sexual response. These disorders include abnormalities in women's desire, lubrication, orgasm, arousal, satisfaction and pain [1].

Sexual dysfunction can affect the quality of life, among sexually active women. The prevalence of female sexual dysfunction (FSD) varies in the different studies, depending on the criteria applied for its description, the documented rates range between 40 and 60 % [2].

Female sexual response cycle

It is the sequence of physical and emotional changes that occur as a person becomes sexually aroused and participates in sexually stimulating activities.

The circular model described by Basson [3] acknowledges the interplay of the sexual responses of both the mind and the body. Approximately 30% and 50% of women may reach orgasm during vaginal penetration and direct clitoral stimulation, respectively [4].

Female Sexual Dysfunction

Female sexual dysfunction is complex in nature and is clearly distinct from sexual dysfunction in men. Research into FSD has not received as much attention as male sexual dysfunction, because there are no apparent "cures" or current pharmacotherapy for women, unlike for men. Addressing FSD is difficult because sexual function in women is more complex and does not follow the linear male sexual response pattern [5].

One or more breaks in the regular course of sexual functioning occur during the sexual response cycle, which is known as sexual dysfunction. On the other hand, along with on-going distress, a sexual disorder includes both the component of sexual dysfunction [6].

Personal distress

The most important feature of any of these complaints is the element of personal distress. The determination of the primary or secondary nature of these complaints allows a more appropriate analysis of the predisposing, precipitating and maintaining factors and therefore direct interventions. It also allows a more realistic view of the generalist physician's role in treatment. The etiology of these conditions can be organic, psychological, unknown or most likely mixed. The role of urinary incontinence and pelvic organ prolapse on sexual function (or indeed any other chronic gynecological condition) should not be underestimated relative to other factors such as age or menopausal status. However, the importance of sexual 'dysfunction' or inhibition of sexual response as an adaptive mechanism to other dysfunctions should not be dismissed or underestimated. Sexual functioning in a woman should be seen through the window of their relationship, their own sexual history and their physical, pharmacological, and hormonal environment [7].

Prevalence of female sexual dysfunction

The interaction of the female sexual response cycle leads to a frequent overlap of sexual dysfunction disorders. Desire disorders may be a culmination of other precipitating factors and is the most frequent problem among women. The often-cited Laumann study [8] reports 32% desire disorder, 28% orgasmic difficulty, 21% dyspareunia and 27% stating sex was not pleasurable in a North American population. A global study reported 27% with a lack of interest in sex, 21% orgasmic, 17% lubrication problems and 10% pain during sex [9]. The Women's International Survey on Health and Sexuality of European Women used the current DSM-IV categories and found 29% desire disorder, 22% arousal disorder, 19% orgasmic disorder and 14% dyspareunia in over 1,300 women between the ages of 20 and 70 years [10]. A primary-care-based study in the UK [11] corroborated high rates of sexual dysfunction in both women and men according to International Classification of Diseases (ICD)-10 definitions, with 40% of women and 22% of men having at least one ICD-10 diagnosis; increasing age,

unemployment and poorer physical and psychological health were predictors for problems. Women were more likely to seek help (30%), but only 3% to 4% of general practitioners' records contained an entry specifically documenting a sexual discussion. Among postpartum women, up to 25% report adverse sexual changes [12, 13].

Age and female sexual dysfunction

Hayes et al. [14] indicated decreasing sexual activity in older women is not associated with increased distress and is therefore responsible for the stability of sexual dysfunction rates reported in some studies in this group of women. Using combined tools to measure both distress and persistence of symptoms significantly lowers prevalence rates of female sexual dysfunction (FSD) and normalises the intermittent reduction in activity in all women as well as men. Therefore, they report rates which vary from 16% to 75% with desire disorder, 12% to 64% arousal, 16% to 48% orgasm, 7% to 68% with sexual pain, all with considerable overlap [15].

Classification of female sexual dysfunction

Masters and Johnson first characterized the female sexual response in 1966 as consisting of four successive phases: excitement, plateau, orgasmic, and resolution [16].

Kaplan proposed the aspect of "desire," and the three-phase model, consisting of desire, arousal, and orgasm. This three phases model is the basis for the Diagnostic and Statistical Manual of Mental Disorders *(4th edition)* classifications of female sexual dysfunction, as well as the recent reclassification system made by the American Foundation of Urologic Disease (AFUD) Consensus Panel in October 1998 [17]. AFUD consensus panel classifications and definitions of FSD**:**

- Hypoactive sexual desire disorder: persistent or recurring deficiency (or absence) of sexual fantasies/thoughts and/or receptivity to sexual activity, which causes personal distress.
- Sexual arousal disorder: persistent or recurring inability to attain, or maintain, sufficient sexual excitement, causing personal distress. It may be experienced as lack of subjective excitement or lack of genital (lubrication/swelling) or other somatic responses.
- Orgasmic disorder: persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation and arousal, which causes personal distress.
- Sexual pain disorders:

i.Dyspareunia: recurrent or persistent genital pain associated with sexual intercourse.
ii.Vaginismus: recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress.
iii.Other sexual pain disorders: recurrent or persistent genital pain induced by non-coital sexual stimulation.

Categories of female sexual dysfunction

The Diagnostic and Statistical Manual of Mental Disorders (DSM) defines female sexual dysfunction (FSD) as "any sexual complaint or problem resulting from disorders of desire, arousal, orgasm, or sexual pain that causes marked distress or interpersonal difficulty" [18]. To qualify as a dysfunction, the problem must be present more than 75% of the time, for more than 6 months, causing significant distress. In the DSM-5, there were several updates to the classification described in the previous version (DSM-4) [19].

Table (1) DSM classification of FSD

DSM-4 [18]	**DSM-5** [19]
Desire disorders	**Desire/arousal disorders**
-Hypoactive sexual desire disorder	-Merged desire and arousal into single category
-Sexual aversion disorder	-Deleted sexual aversion disorder
Arousal disorders	
Orgasm disorder	**Female orgasm disorder**
Sexual pain disorders	**Genito-pelvic pain/penetration disorder**
-Dyspareunia: pelvic pain with intercourse.	-Merged dyspareunia and vaginismus
-Vaginismus: pelvic floor muscle spasm leading to pain and obstruction with penetration.	

Hypoactive Sexual Desire Disorder

The International Society for the Study of Women's Sexual Health defines HSDD as: Lack of motivation for sexual activity characterized by: decreased or absent spontaneous desire (ie, sexual thoughts or fantasies); decreased or absent responsive desire to erotic cues or stimulation or inability to maintain desire or interest through sexual activity; or loss of desire to initiate or participate in sexual activity including behavioural responses such as avoiding situations that could lead to sexual activity that is not secondary to sexual pain disorders, that is accompanied by clinically significant distress [20].

Sexual Aversion Disorder

DSM-IV TR criteria for sexual aversion include persistent or recurrent aversive response to any genital contact with a sexual partner and emphasize the role of avoidance. The incidence and prevalence of sexual aversion disorders are unknown. Sexual aversion disorder is sometimes conceptualized as sexual phobia, yet aversion implies the element of abhorrence and disgust, while phobia does not. Sexual aversion is routinely characterized by women as including elements of revulsion and disgust in ways that phobias rarely are. The DSM-IV TR criteria, however, do not require the physiologic responses that are often

associated with aversion. While sexual aversion typically encompasses these responses (i.e., nausea, revulsion, shortness of breath), aversion can also be expressed as persistent avoidance of partnered sexual behavior and a situational-specific panic response. For an individual, whatever painful or traumatic event gave rise to the association of sexual behavior with aversion, the disorder can be conceptualized as maintained by ongoing avoidance of sexual behaviour [21].

Sexual Arousal Disorder

Female sexual arousal disorder (FSAD) is defined as the inability to complete sexual activity with adequate lubrication. Absent or impaired genital responsiveness to sexual stimulation is the essential DSM-IV TR diagnostic criterion. These symptoms must cause personal or relationship distress [21].

Orgasmic Disorders

Female orgasmic disorder (FOD) is defined as either "marked delay in, marked infrequency of, absence of orgasm or markedly reduced intensity of orgasmic sensations" The symptoms need to be present for a minimum of about 6 months, cause distress, and not be better explained by another psychological disorder, severe relationship problems, or be due to the effects of a substance/medication or a medical disorder [18].

Dyspareunia

Painful sex (dyspareunia) is a common but neglected female health problem [22].

Vaginismus

Vaginismus involves recurrent or persistent involuntary spasms of the vaginal outer muscles so that her partner cannot penetrate during intercourse [23]. As a clinical phenomenon, it is associated with high levels of distress for those affected and it can have a profound impact on how a woman feels about herself, on her partner, and on their relationship

Physiology and pathophysiology of FSD

Female sexual dysfunction is a complex neurovascular phenomenon that is under the control of psychological, neurovascular, and hormonal factors. During sexual arousal, blood flow to the clitoris and the labia minora increases, leading to engorgement of these organs, which in turn results in protrusion of the glans clitoris and eversion and engorgement of the labia minora. This increase in blood flow to the vagina and uterus leads to increased secretion from the uterus and Bartholin's glands, which lubricates the vagina. Additional lubrication comes from the transudation of plasma from engorged vessels in the vaginal wall. Sexual dysfunction after pelvic surgeries may be due to interruption of the vascular supply and neurologic innervation. Contraction of the pelvic floor muscles (the pelvic diaphragm in particular) intensifies the orgasm. However, a non-voluntary contraction commonly leads to vaginismus. A complete understanding of the physiologic and pathologic aspects of FSD is essential to develop any therapeutic strategies [24].

Table 2. Medications implicated in female sexual dysfunction [25].

Anti-androgens, e.g. cimetidine, spironolactone
Anti-estrogens, e.g. tamoxifen, gonadotrophin-releasing hormone
Anticonvulsants, Anticholinergics, (GnRH) analogues
Antidepressants, e.g. selective serotonin reuptake inhibitors (SSRIs)
Antihistamines, Antihypertensives
Aromatase inhibitors, e.g. letrozole
Hormonal contraception
Sedatives and hypnotics, Sympathomimetic amines
Metoclopramide, Metronidazole, Cyclophosphamide

Vitamin D and female sexual dysfunction

Vitamin D therapy in women with sexual dysfunction and vitamin D deficiency may improve sexual function. Treatment with vitamin D may also improve symptoms of depression in these women. However, the influence of vitamin D treatment on sexual function does not seem to be mediated by the improvement in depression symptoms. An association between vitamin D deficiency and female sexual dysfunction has been reported. Krysiak et al found lower FSFI total scores and higher BDI scores in women with vitamin D deficiency compared to normal controls [26].

Dietary supplements cannot be recommended routinely to patients, but some of them show great promise, including yohimbine in erectile dysfunction patients, vitamin B in patients with hyperhomocysteinemia, L-arginine in patients with endothelial dysfunction nitric oxide related and vitamin D in patients with this deficiency. Also Zinc, Selenium, L-Carnitine, Ginkgo Biloba, Ginseng, Date Palm Pollen, Caterpillar fungus, Puncture vine (Tribulus Terrestris L.) and Horny Goat Weed (Epimedium spp.) [27].

Several mechanisms have been hypothesized to explain the effect of vitamin D on sexual function. Evidence suggests that vitamin D affects endothelial integrity. Low vitamin D levels have been proven to correlate with endothelial dysfunction, and vitamin D may directly protect endothelial cells against oxidative stress [28].

Hormones and FSD

Estradiol

Estradiol is a predominant female sex hormone in women that helps maintain the integrity of vaginal mucosal epithelium and promotes lubrication. Estrogen plays a major role in regulating sexual function and nitric oxide synthesis in the vagina and clitoris. It also has vasoprotective and vasodilator effects on the vagina [29]. After menopause, estrogen decreases, vaginal lubrication and sexual desire and frequency decrease, which may result in vaginal dryness and vaginismus often accompanied by symptoms of vulvovaginal atrophy [30]. These symptoms significantly contribute to the onset of sexual disorders.

Estradiol is also a modulator of serotonergic function, affecting regions of the brain known to regulate mood and desire, which may also have effects on sexual function. The prevalence of SD in postmenopausal women is high, between 68% and 86% [31]. Estrogen replacement therapy in postmenopausal women has been shown to improve vaginal lubrication and sexual desire [32].

Evidence that E plays an important role in human female sexual dysfunction

Vulvovaginal atrophy and dyspareunia have been reported by approximately one fourth of menopausal women, and the symptoms often lead to decreased sexual interest, arousal, and response [33]. Sexual pain is the primary issue that causes aversive conditioning. Moreover, sensitivity of genital and non-genital skin is linked to estrogen status and can affect the sexual response. Unlike VMSs, which generally improve with time, urogenital atrophy does not improve and can worsen with time since menopause [34].

Testosterone (T)

Testosterone is the predominant androgen in women. The adrenal glands and ovaries are the major source for T synthesis. Circulating androstenedione, which is also a major source of T, is derived from the ovaries and adrenal glands. Testosterone levels tend to decrease with age. The levels of T and DHEAS levels decline considerably in women who undergo bilateral oophorectomy [35].

Endogenous T and sexuality

In large population studies,T, calculated free T, dehydroepiandrosterone (DHEAS), and androstenedione have been shown to fall progressively in the premenopausal years from the age of 20 years to menopause, reflecting declining ovarian and adrenal androgen production [36].

T therapy for sexual dysfunction in the premenopausal years

Low levels of T are associated with decreased sexual arousal, libido, sexual response, genital sensation and orgasm. Testosterone acts on the central nervous system and affects sexual behavior. Testosterone might enhance nitric oxide synthase activity, which produces vascular smooth muscle relaxation [37]. Testosterone has also been shown to improve sexual desire in women who are postmenopausal secondary to oophorectomy. However, androgen replacement is associated with virilization, acne, and hirsutism [38].

In women, a large, cross-sectional Australian study has demonstrated that no single androgen level is predictive of low female sexual function. In this study, androgens were measured with RIA [39]. Recently, the association between androgens and sexual desire was investigated in 560 healthy Danish women 19 to 65 years old [40].

Management

A multidisciplinary approach is often required when managing FSD. For example, a patient suffering from genito-pelvic pain disorder (vaginismus) may benefit from cognitive behavioural therapy (CBT), vaginal dilator use, lubricants, pelvic floor physiotherapy and relaxation techniques. Even after treatment of an underlying medical/gynaecological cause, the history of FSD may have longer lasting psychological effects and the patient may still benefit from psychosexual counselling/ psychological interventions [41].

General principles

Educating the patient (and partner, where relevant) about normal physiological response and anatomy may be necessary. It is important to explain age-related physiological changes and associated medical disorders. When the aetiology is not physical, non-pharmacological therapy, lifestyle adjustments, and psychosexual counselling may be the initial line of treatment. Examine your prescriptions and, with your doctor or prescriber, think about switching to a different drug or lowering the dosage of one that may be linked to FSD [25].

Life style modifications

Weight reduction, quitting smoking, abstaining from alcohol, keeping a healthy diet and a regular exercise regime are all valuable interventions for improving FSD and health. Women's sexual lives can also be made better by setting aside particular time for their partners [42].

Conclusion

The data regarding the association between se hormones, vitamin D and FSD are overall inconsistent and conflicting. Smaller studies suggest that there may be an association. Further study to verify or reject this association is warranted as uncovering the relationship could lead to the discovery of common mechanisms that could be of substantial value in the diagnosis and management of FSD.

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