Chapter

# Sexual Dysfunction in Patients with Systemic Sclerosis

*Barbora Heřmánková*

## Abstract

Systemic sclerosis (SSc) may affect all aspects of life including sexual function. Although sexual dysfunction is a neglected area of quality of life in patients with SSc, it turns out that it is an important issue for both men and women characterized by high prevalence. The etiology of sexual dysfunction in systemic sclerosis is multifactorial and includes factors associated with both physical and emotional (psychological) status. The most common physical problems in women are vaginal dryness, dyspareunia, and vaginal tightness. Erectile dysfunction is not only a frequent but also often underestimated clinical symptom in men with SSc. The incidence of erectile dysfunction in patients with SSc ranged from 12 to 81% in different studies. The main psychological factors that may affect sexuality are depression, fear, and changes in the appearance of the face and body that usually leads to impaired self-esteem. This chapter is a review about the impact of systemic sclerosis on sexual functioning.

**Keywords:** systemic sclerosis, sexual functioning, female sexual dysfunction, erectile dysfunction

## 1. Introduction

Systemic sclerosis is a chronic rheumatic autoimmune disease characterized by abnormal fibrotic processes, microvascular damage, and excessive deposition of collagen into connective tissues. The vascular alterations and immunological activation lead to progressive fibrosis of multiple organ systems including the skin, the gastrointestinal tract, kidneys, and the lungs. Disease-associated changes can have a negative impact on sexual functioning [1, 2]. Generally, sexuality in systemic sclerosis has been a neglected area so far, especially female sexual dysfunction. Impaired sexual functioning in women was probably less studied due to the complexity and multifactorial nature of female sexual response. A little bit more attention was paid to erectile dysfunction, where etiology is more pronounced even though women are affected by this disease more often [3–5]. The etiology of sexual dysfunctions in systemic sclerosis is not well known; the causes are multifactorial and are related to both the disease symptoms and the therapy. The most common physical problems associated with female sexual dysfunction include vaginal dryness, dyspareunia, vaginal tightness, Raynaud's phenomenon, fatigue, generalized pain, muscle weakness, joint contractures, heartburn, and dyspnea. Presence of depression, fear, changes in face and body appearance, and lack of self-esteem are the psychological aspects, which can play a key role in the pathogenesis of sexual dysfunction in systemic sclerosis patients [6]. The etiology of erectile dysfunction

is a little bit more understood. It is considered to be a result of microangiopathic changes. Due to corporal fibrosis and myointimal proliferation, the blood flow in the penile arteries is reduced.

Several studies have suggested that sexual dysfunction is a widespread problem in both men and women with SSc. It is more prevalent than in general population and other chronic diseases [7]. The most common symptoms of female sexual dysfunction are vaginal tightness, dryness, and dyspareunia [7, 8]. More severe sexual dysfunction is usually associated with depression symptoms, aging, and functional impairment [2, 9, 10]. The prevalence of erectile dysfunction is about 80% [11–13]. In women, more than half of the SSc patients experience some sexual problems [7, 8]. The management of erectile dysfunction has been more studied compared to female sexual dysfunction treatment. However, the number of publications regarding the efficacy of erectile dysfunction treatment in SSc patients is still very limited and further research is needed. The treatment of female sexual dysfunction in SSc women has not been paid much attention so far. There are only general recommendations available.

## 2. Definition and classification of sexual dysfunction

In order to better understand why and how systemic sclerosis may affect sexual functioning, there is an overview of sexual response models, developed over the past few years, which led to the current diagnostic and classification criteria for sexual dysfunction. The first model of female sexual response was described by Masters and Johnson in 1966. They published that a normal female sexual response consists of four consecutive phases including desire, plateau phase, orgasm, and resolution. It was supposed that in both women and men, the sexual response is commenced by desire which is influenced by the activity of two brain centers—dopamine sensitive excitatory center and serotonin sensitive inhibitory center. These centers send a signal going through the descendent nervous system into the spinal cord from where the genital sexual reaction is triggered. The arousal phase is mediated by the parasympathetic nervous system, which leads to vascular and genital changes such as enlargement of the clitoris, dilatation of perivaginal arterioles, and lubrication and expansion of two-thirds of the vagina. The following level of excitement is referred to the plateau phase that lasts until the orgasm. The orgasm phase is accompanied by contractions of pelvic floor muscles, increased heart rate, respiratory rate, and blood pressure. After reaching orgasm, the body usually calms down and this phase is called the refractory or resolution phase (**Figure 1**) [14].

In 1979, this model was modified by Kaplan into a three-phase model, which consists of desire, arousal, and orgasm [15]. Based on this linear model, the diagnostic and classification system was developed. The World Health Organization International Classifications of Diseases-10 (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) by the American Psychiatric Association were established. The ICD-10 focused on how physical factors influenced sexual response, whereas DSM-IV classification emphasized more emotional and psychological aspects of female sexual dysfunction. Because both approaches followed the linear model of sexual response, which was later criticized for not taking into consideration the complexity of female sexual response, the new classification was needed [16].

In 1998, the Sexual Function Health Council of the American Foundation for Urologic Disease (AFUD) convened an interdisciplinary congress, which was attended by 19 experts on female sexual dysfunction selected from five countries. The aim was to develop a consensual definition and classification based on the

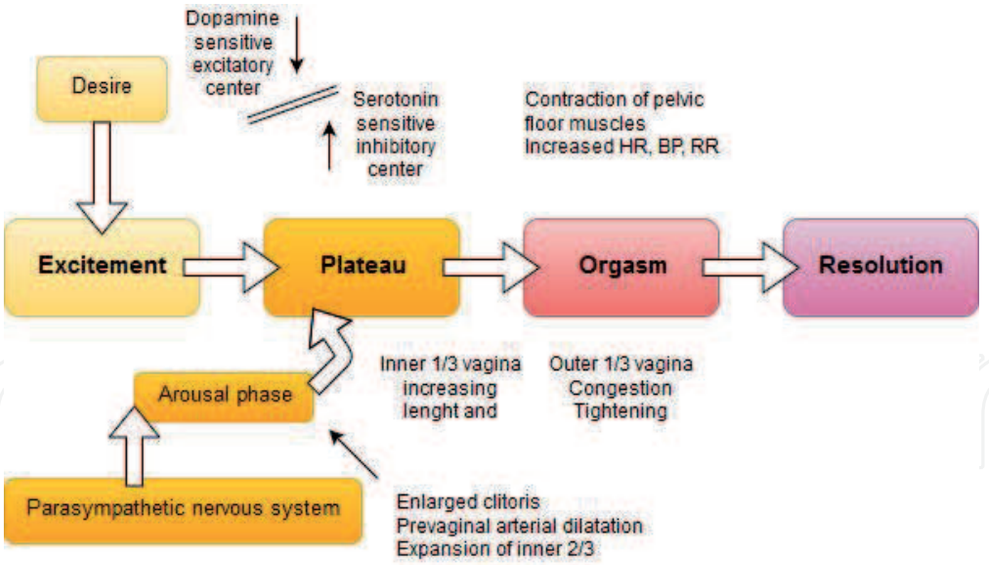


**Figure 1.**
*The four-phase model of female sexual response cycle; BP = blood pressure, HR = heart rate, and RR = respiratory rate. Modified according to [14].*

ICD-10 and DSM-IV. The new developed classification has been extended to include psychogenic and organic causes of desire, arousal, orgasm, and sexual pain disorders. An essential point of this classification is the personal distress criterion considering sexual complaint as a disorder only if it causes a subjective feeling of distress [17].

Further research has shown that the model of female sexual response is still incomplete and that many aspects affecting women's sexual function have been omitted. Studies reported that women often describe overlapping phases of sexual response in variable sequences. For instance, the unfounded assumption that desire always precedes arousal has been mistaken, and based on the women self-report and research data, it was proven that arousal and desire co-occur and reinforce each other. It was also found that motivation for sexual activity is much more complex than the mere presence of sexual desire defined as thinking or fantasizing about sex. Women in different surveys cited that increased desire for sexual activity may be caused by the emotional closeness of a partner or intimacy that increases female well-being and self-image, which may include the sense of feeling attractive, appreciated, loved, or desired. If enough appropriate sexual stimulation is provided, enough time and intimacy are available, the woman's enjoyment and excitement can be intensified. The type of stimulation, time needed, and interpersonal context are highly individual. Moreover, spontaneous desire can be affected by the menstrual cycle, which usually decreases with age and grows with a new relationship. These new findings have surpassed the original hypothesis that women's sexual response must always begin with sexual desire (thoughts and fantasies) and its absence is the result of a disorder. In addition, it was confirmed that, unlike men, there is no correlation between female subjective excitement and genital congestion. Subjective excitement could be influenced by interpersonal relationships, contextual factors, privacy, appropriateness, general emotional status, emotional relationships, biological factors, presence of depression, the influence of hormones (dopamine, testosterone), and others. In 2003, therefore, a revision of the current definition was done. The International Definitions Committee consisting of 13 experts from seven countries convened and proposed new definitions, which take into account new findings in the field of female sexual response [18–20].

Current definition was again revised in 2010 by the International Consensus of Sexual Medicine, where the movement away from the nonoverlapping linear model toward a more circular model depicting the variety of triggers of women's desire was accepted. It was emphasized that innate sexual fantasies and thoughts are not necessary for healthy sexual functioning and that desire is the result of sexual incentive that may be physically or subjectively perceived. Based on the previous findings, the arousal disorder was reclassified into subjective arousal disorder, genital arousal disorder, combined genital and subjective arousal disorder, and persistent genital arousal disorder. In May 2013, DSM-V was released, which also takes the focus away from the four-phase model, removed the sexual aversion disorder and merged vaginismus and dyspareunia into a new genito-pelvic pain/penetration disorder. It was finally noted that sexual dysfunction is a result of both psychological and biological and many other contributing factors [15, 21]. In 2015, the Fourth International Consultation on Sexual Medicine presented the new set of definitions of all forms of sexual dysfunction in women and men, which was based on ICD-10 and DSM-V (**Figure 2**) [22].

The newest changes in nomenclature of female sexual dysfunction came in May 2018, when the World Health Organization developed the eleventh revision of the International Classification of Diseases and Related Health Problems (ICD-11). The ICD-10 classification of sexual dysfunctions was separated to two main groups: "organic" and "nonorganic" conditions. The nonorganic sexual diseases were classified as mental and behavioral disorders and organic belonged to diseases of the genitourinary system chapter. However, since ICD-10 definition, lots of evidences have been accumulated regarding the causes of sexual dysfunction, which often involve a combination of physical and psychological factors. The ICD-10

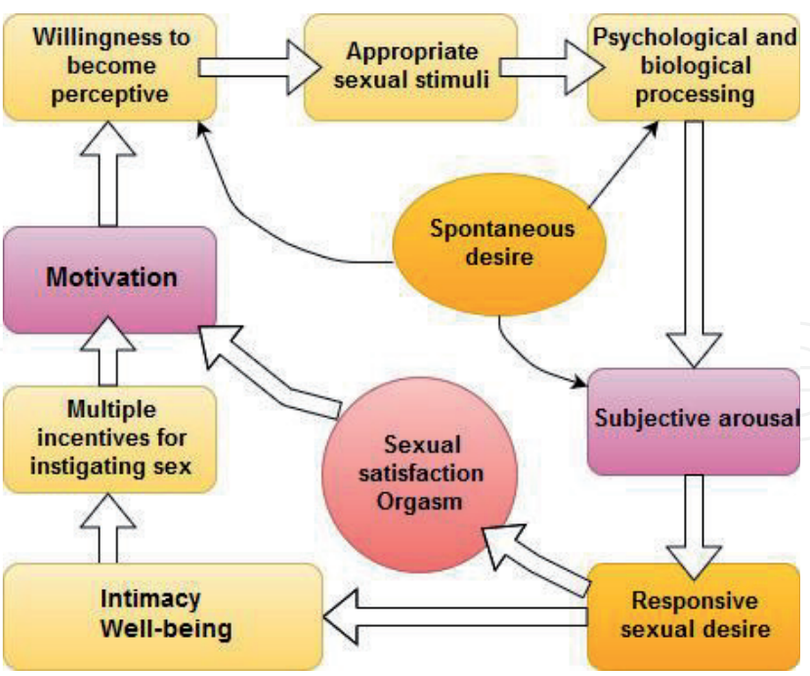


**Figure 2.**
*Nonlinear model of female sexual response cycle. The initial stage of female sexual response is sexual neutrality, but with positive motivation (left). The reasons why a woman is willing to initiate or agree to sexual activity can be that she wants to feel loved, share physical pleasure or be emotionally closer to her partner, please her partner, or she wants to increase her own satisfaction. Stimuli for sexual activity are being processed in the woman's mind, influenced by biological and psychological factors, and result in subjective sexual arousal. If sexual stimuli last sufficiently long, sexual arousal and enjoyment will intensify, and it can trigger a desire for further sexual activity. It is important to note that desire appears at this point, not in the initial phase. When the stimulation continues and no negatives outcomes are involved, the process results in sexual satisfaction (with or without orgasm). Modified according to [23].*

classification was therefore not consistent with clinical approaches in sexual health. ICD-11 diagnostic guidelines organize sexual dysfunctions into four main groups:

1. sexual desire and arousal dysfunctions;

2. orgasmic dysfunctions;

3. ejaculatory dysfunctions; and

4. other specified sexual dysfunctions.

Moreover, a separate grouping of sexual pain disorders has been established. Where possible, categories in this new classification of sexual dysfunctions apply to both men and women even though the differences in sexual response are known. On the other hand, the neural pathways and neurotransmitters mediating sexual response are the same for both men and women. Separate sexual dysfunction categories are provided where clinical manifestations differ [24].

The overview of current diagnostic criteria of sexual dysfunctions is presented below in **Table 1**. The present definition according the WHO ICD-11 is: "Sexual Dysfunctions are syndromes that comprise the various ways in which adult people may have difficulty experiencing personally satisfying, noncoercive sexual activities. Sexual response is a complex interaction of psychological, interpersonal, social, cultural and physiological processes and one or more of these factors may affect any stage of the sexual response. In order to be considered a sexual dysfunction, the dysfunction must: (1) occur frequently, although it may be absent on some occasions; (2) have been present for at least several months; and (3) be associated with clinically significant distress" [25].

| **ICD-11 (2018)** | **DSM-5 (2013)** |
|---|---|
| Chapter: conditions related to sexual health | |
| Grouping: sexual dysfunctions | Grouping: sexual dysfunctions |
| Category: hypoactive sexual desire dysfunction | Category: female sexual interest/arousal disorder; male hypoactive sexual desire disorder |
| Category: sexual arousal dysfunction | Category: female sexual interest/arousal disorder |
| Category: orgasmic dysfunction | Category: female orgasmic disorder |
| Category: ejaculatory dysfunction | Category: erectile disorder |
| Subcategory: male early ejaculation | Category: premature (early) ejaculation |
| Subcategory: male delayed ejaculation | Category: delayed ejaculation |
| Category: other specified sexual dysfunction | Category: other specified sexual dysfunction |
| Category: unspecified sexual dysfunction | Category: unspecified sexual dysfunction |
| Grouping: sexual pain disorders | |
| Category: sexual pain-penetration disorder | Category: genito-pelvic pain/ penetration disorder |

**Table 1.**
*The eleventh revision of the International Classification of Diseases and Related Health Problems (ICD-11) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Adapted from [25, 26].*

## 3. Sexual functioning in women with systemic sclerosis

Persons with systemic sclerosis can experience a variety of symptoms that may affect all aspects of life, including sexual functions. The exact etiopathogenesis of sexual dysfunctions in systemic sclerosis is not well known; the causes are multifactorial and are related to both the disease symptoms and the therapy. Medical, pathophysiological, psychological, and social components may be involved in sexual dysfunction. Both physical and psychological problems arising from disease-related condition contribute to partnership difficulties, less active and less enjoyable sexual life [3, 27, 28].

The most common physical symptom is skin tightness. Due to skin tightness, the fingers becomes fixed in bent position, which could interfere with sexual foreplay, touch, and masturbation. If skin tightening causes the mouth to shrink, kissing or oral sex could become difficult. Sometimes the skin become stiffer around the vaginal introitus, which often leads to painful penetration, and changes in the vaginal mucosae causing lubrication disorder contribute to this [27, 29, 30]. Specifically, 56% of SSc female patients reported painful penetration during the intercourse [31]. The sexual difficulties such as vaginal tightness, dryness, and dyspareunia were reported by more than half of systemic sclerosis female patients [7, 8]. It was also published that vaginal tightness (71%), dyspareunia (56%), and ulceration (23%) were the most common symptoms of sexual dysfunction observed in 60 women with systemic sclerosis [31]. These genital tract abnormalities could be associated with a decrease in number and intensity of orgasm, which are also often observed in SSc individuals [32].

A majority of the systemic sclerosis patients experience Raynaud's phenomenon, which can affect not only fingers and toes but also tongue and nipples. This is another reason, why the cuddling, foreplay, and oral sex could become uncomfortable and unpleasant [27]. In addition, a lot of patients suffer from secondary Sjögren's syndrome characterized by drying of oral, nasal, ocular, and vaginal mucosae. The prevalence of Sjögren's syndrome in systemic sclerosis ranged in different studies from 20 to 69% depending on the criteria used and sample size. In Saad's study, 37% from 83 systemic sclerosis female patients reported Sjögren's syndrome, 56% of them had impaired sexual function, and vaginal dryness was the most presented symptom [29].

Another disease-related problem that impedes sexual activity is the affection of musculoskeletal system. The presence of joint contractures, stiffness, or pain leads to limited range of motion and it could restrict the ability to engage in sexual activities. Other aspects that reduced exercise capacity are muscle weakness and fatigue. It can be difficult to become sexually aroused when extremely tired. The consequence of skin thickening and other physical changes is the impaired body image, self-esteem, and sexuality. However, it has been also reported that body image dissatisfaction does not correlate with reduced sexual function [30]. In a different study, the major reasons for decreased sexual activity in married women with SSc were fatigue, altered body image, and pain [2]. Regarding psychological factors, depression is another often presented symptom that has been significantly associated with a sexual function disorder [8].

There are a few more causes that could lead to less active sexual life in SSc patients. For instance, in rare cases, the fibrotic process of visceral vessels leads to renal impairment that may have an impact on sexual desire and orgasm. It is usually the medication used to treat kidney problems rather than the problems themselves. Also, gastrointestinal problems such as heartburn or chronic diarrhea may disrupt sexual activities [7].

To sum up, existing studies of sexual function among women with SSc have concluded that sexual dysfunction is common in comparison to the general population. It was even showed a significantly greater decrease in orgasm and its intensity in SSc female patients compared to other systemic rheumatic diseases—rheumatoid arthritis and systemic lupus erythematosus [31]. What is more, Knafo et al. [4] published that the prevalence of sexual dysfunction is higher in SSc than in other chronic diseases such as breast cancer, gynecological cancer, or HIV positivity. On the other hand, Impens et al. [33] maintain that SSc women remain sexually active despite the psychological and physical difficulties caused by the disease. In this study, only 17% of women suffered from female sexual dysfunction primarily caused by systemic scleroderma. Other reasons for sexual inactivity were the absence of a partner (37%), personal choice (32%), and the health status of respondents' partners (20%).

## 4. Diagnostic approach of female sexual dysfunction

The first step in the diagnosis of female sexual dysfunction is a detailed personal, sexual, pharmacological, and psychosocial history. Where necessary, further examination by a psychiatrist, gynecologist, or physiotherapist is indicated. There are several objective methods assessing female sexual function, such as laboratory tests including hormonal profile or Doppler ultrasonography. However, laboratory tests in clinical practice are used only as auxiliary diagnostic methods. With duplex Doppler ultrasonography, it is possible to display a blood flow in cavernous tissue vessels, which is performed either under basal conditions or during sexual stimulations (vibrational or audiovisual) and objectified sexual arousal reactions. The most commonly used physiological method for evaluating sexual response is vaginal photoplethysmography, which investigates vascular reactivity during sexual arousal. It is based on the assessment of congestion of the vaginal mucosae. Other methods include electromyography, measurement of changes in vaginal pressure, and measurement of pH [34, 35].

Another widespread screening method is the questionnaire survey. Self-report questionnaires have a long history of use in psychological and sociological studies of sexual behavior. For example, Derogatis Sexual Function Inventory is a 245-item, multidimensional scale that evaluates a wide range of sexual behavior in 10 separate domains. Despite the very strong psychometric properties, this scale is not widely used in clinical trials due to its excessive length and complexity. Instead, several short evaluation scales have been developed [36, 37]. Currently, the female sexual function index (FSFI) is the "gold standard" in assessment of female sexual functioning [38]. FSFI is a widely used tool that has been validated for use across multiple populations including women of various age groups, in various health problems and sexual dysfunctions. It has been developed as a simple multidimensional self-assessment tool for assessing the key domains of female sexual function. The questionnaire consists of 19 items that evaluate sexual function over the last 4 weeks in six domains: sexual desire, sexual arousal, lubrication, orgasm, satisfaction, and pain [39]. Since the first validation study, it has been translated into more than 20 languages and validated in over 30 countries [40, 41].

It has to be noted that both objective methods and questionnaire screenings have their limitations. The main disadvantage of objective methods is the absence of an intimate condition that can play a key role in the female subjective arousal. Basson et al. published that intimacy and desire are essential to women's sexual activity. Raina et al. reported that intimacy leads to emotional arousal of a woman, followed

by sexual desire and physical arousal that result in sexual satisfaction. These findings suggest that the presence of intimacy can be crucial in examining sexual arousal, and its absence can lead to a lack of emotional excitement and consequently to incomplete sexual responses [35, 42, 43]. On the contrary, the questionnaires are filled in private and evaluate women's real sexual experiences. Moreover, this method is not time-consuming and costly. However, as with any brief self-report scale of a complex psychophysiological construct, the questionnaire assessment has notable practical and theoretical limitations. Self-reported screening does not provide objective information but only patient's subjective perception.

In terms of FSFI, its drawback is the assessment of sexual activity in the past 4 weeks. Of course, there are number of reasons why women may be sexually inactive during a 4-week period and it does not necessarily imply significant sexual dysfunction. For example, the absence of sexual partner is a very common reason, why patients are not sexually active. Specifically, the FSFI questionnaire contains 15 questions, which could be answered "No sexual activity" or "Did not attempt intercourse." Both possible responses are scored as zero that could become problematic when lower scores indicate severer sexual dysfunction. In that case, the FSFI could produce biased results. Other inaccurate data may be the result of relatively vague terminology. A problematic issue seems to be to define and measure sexual desire and subjective sexual arousal. Studies suggest that women often have difficulty distinguishing desire and arousal in their sexual experience. Another drawback of the FSFI questionnaire is that questions in orgasm subscale are basically focused on the orgasmic function associated with penile-vaginal contact. In fact, the vagina is primarily a reproductive organ with little sensitivity, and clitoral stimulation is more important for female orgasm. Therefore, achieving orgasm should be judged more in conjunction with masturbation or oral sex than sexual intercourse [38, 44].

## 5. The use of the FSFI questionnaire in systemic sclerosis patients

The FSFI is also the most common questionnaire evaluating sexual function in women with systemic sclerosis. It has been used by an Italian team to evaluate the prevalence of sexual dysfunction in 46 women with SSc. The second purpose of this trial was to investigate the association with sociodemographic, physical, psychological, and disease-related variables. Compared to healthy controls, only the FSFI desire subscale score was significantly lower. The overall score did not substantially differ from healthy controls. The association with health status, functional ability, mouth affection, hand disability, and presence of depression was reported [10]. A very similar study has been conducted in the Netherlands. The FSFI was used to assess the sexual function of 69 SSc women aged 18–60 years. It was that the FSFI total score and the subscale scores for lubrication, orgasm, arousal, and pain were significantly lower in comparison with healthy population in the same age. Impaired sexual functioning and sexual distress were associated with marital distress and depressive symptoms [9]. Levis et al. first detected women with SSc who had engaged in sexual activities with their partner in the past 4 weeks, and then only sexually active patients completed a 9-item version of the FSFI. The aim of this Canadian cross-sectional multicenter study was to evaluate sociodemographic and clinical variables that distinguish sexually active from inactive patients and identify the source of pain during and after sexual activity in sexually active patients. The results showed that in total only 17% of 547 women were sexually active without sexual disorder [45]. The same group of scientists in different project used a shortened version of FSFI to compare sexual activity and impairment rates of women with systemic sclerosis to general population data. Among women with SSc, 296 of

730 (41%) were sexually active and 181 (61%) of sexually active patients reported sexual dysfunction. It means that only 115 of 730 (16%) patients engaged in sexual activities without impairment. It was also confirmed that SSc patients are significantly less likely to be sexually active and more likely to be sexually impaired than the general population of women [46]. Severe sexual dysfunction was also observed in married women with systemic sclerosis. About 8 out of 10 women achieved low scores in the FSFI questionnaire assessed, and all the subscales were affected in this study. The reasons why patients reported decrease in the frequency of intercourse since the onset of their disease and a diminished desire for a sexual relationship were fatigue, altered body image, and pain [2].

## 6. Treatment and recommendation for female sexual dysfunction

The management of female sexual dysfunction in the general population is based on the understanding of the basic physiology of female sexual response. Currently, several approaches of female sexual function treatment are available. It is known that some antidepressants can cause sexual dysfunction as a side effect. Antidepressants, such as SSRIs, are commonly associated with hypoactive sexual desire disorder (HSDD) and they have to be eliminated or dosed at lower levels. In women with major and disabling mood disorders, the adjustment of antidepressants requires a continuous collaboration with the prescribing psychiatrist, because dosage adjustments of antidepressants must be done very gradually [47]. Bupropion, buspirone, mirtazapine, vortioxetine, and vilazodone have been found to have lower rates of antidepressant-induced sexual dysfunction than other antidepressants, and they can be a suitable medication options for the treatment of depression [48–50].

Another option, primarily used in menopausal women, is hormonal therapy. Estrogen therapy may be used to increase clitoral sensitivity and libido and to reduce pain during and after sexual intercourse. In women with menopause-related sexual dysfunction that have estrogen treatment experience improved sexual desire, vaginal atrophy and vaginal dryness [49]. Transdermal estradiol has been found to be a preferred therapy for depleted estrogen. It is considered as the most effective therapy available for reducing vasomotor symptoms and associated menopausal symptoms with minimal adverse effects. Intravaginal estrogens combined with mechanical dilatations are also highly effective for treatment of vaginal atrophy [47]. Testosterone replacement therapy may also be considered to increase sexual desire and libido. Several high-quality sources documenting that transdermal testosterone is effective in restoring sexual desire are available [47]. Intramuscular testosterone combined with estradiol in postmenopausal women had a positive impact on sexual desire, arousal, and frequency of sexual fantasies compared with women without testosterone treatment [51].

Flibanserin is the first nonhormonal treatment for female sexual dysfunction to be approved by the Food and Drug Administration (FDA). The approval, in August 2015, occurred fully 18 years after the approval of sildenafil, the first treatment for erectile dysfunction. Flibanserin is a 5-HT 1A agonist and 5-HT 2A antagonist and is indicated for acquired hypo-active sexual desire disorder in premenopausal women. It is strongly recommended to avoid consumption of alcohol while using flibanserin treatment, because several serious adverse events were found: dizziness, loss of consciousness, hypotension, and circulatory collapse [49]. Another drug approved by the FDA is ospemifene, which is indicated in treatment of dyspareunia in postmenopausal women. It is a selective estrogen receptor modulator that can be prescribed when hormone replacement therapies fail. The daily dose of 60 mg

of ospemifene has been found to be effective and tolerable for postmenopausal women with vaginal dryness and atrophy [52, 53]. To improve sexual functioning in domains of arousal, orgasm, and satisfaction, bupropion can be used, whose efficacy is based on the influence of dopamine and norepinephrine reuptake [54]. Although phosphodiesterase type 5 (PDE-5) inhibitors are mostly used in erectile dysfunction treatment, they can be used in women as well. Sildenafil has been found to significantly improve arousal, orgasm, and enjoyment in women without sexual dysfunction. In women with antidepressant-associated sexual dysfunction, sildenafil (in dose ranges of 50–100 mg) has also shown good efficacy [49].

Rehabilitation treatment can be useful in patients suffering from vaginism, dyspareunia, and anorgasmia due to pelvic muscle spasms. Adequate exercises can lead to normalization of muscle tension and relaxation [55]. Psychotherapy is recommended where the pathogenesis of sexual dysfunction has a psychological nature. Because recent studies have suggested that more severe sexual dysfunctions in patients with SSc are significantly associated with the presence of depression [2, 9, 10], the psychotherapy should be an integral part of the treatment of sexual dysfunction in SSc patients. In terms of sexual pain disorder, psychotherapy seems to be immediately helpful although objective research on the long-term efficacy of psychotherapy for sexual pain disorder is limited and difficult to evaluate [47].

There are some general recommendations for women with systemic sclerosis that may help to continue enjoying an active, fulfilling sexual life. If sexual activity is reduced due to pain, it can be alleviated by use of pain medication. The sexual activity can be scheduled for a time the pain will be at a minimum. A warm bath or shower before sexual activity often eases arthritic stiffness. The range of motion exercises before sex may help to reduce the stiffness. If the range of motion is limited and do not allow comfortable position, then it seems to be a good solution to experiment with sexual positions and try to find those that are the most suitable [3, 56]. If sclerosis has caused the mouth to shrink, physical therapist or occupational therapist can teach patients how to do the exercises to stretch the mouth. The regular stretching can improve the range of motion of the mouth and make kissing and oral sex more enjoyable. When fingers become fixed in a bent position, its possible to integrate stretching exercises as well and use the other part of hands (thumbs, wrists, or backs of the hands) to touch yourself or partner. An auxiliary material such as vibrators, creams, and lotions can also be used to enhance sexual activity. In order to avoid fatigue, patients with SSc may schedule their sexual activity for that part of the day when they still have enough energy, because becoming sexually aroused, when tired, is difficult. To prevent a Raynaud episode, it is necessary to keep entire body warm. It is possible to turn up the thermostat, leave some clothes on, or use extra blankets. When vaginal dryness and dyspareunia occur, the use of vaginal moisturizers on a regular basis along with lubricants as needed for sexual activity is the initial step in managing these symptoms. Women can choose from a number of commercially available lubricants that are either water based, mineral or plant oil based, or silicone based [47, 55]. Dilator therapy is an another option that can be useful in treatment of vaginal tightness. This method offers a nonsurgical approach to restore vaginal capacity and elasticity and alleviate sexual discomfort. If the penetration is still painful, there are alternative sexual activities like clitoral stimulation that can be sometimes more enjoyable than intercourse. If there is no interest in sex, still it is possible to stay physically close by holding or caressing one another [3, 56].

Several options for the treatment of female sexual dysfunction in normal population are available. The management of impaired sexuality in women with systemic sclerosis was less studied and the further research is strongly needed. What is essential and beneficial for the patients is the team-based model of care for management

of sexual dysfunction including a medical provider, physical therapist, occupational therapist, psychotherapist, and sex therapist [57].

## 7. Sexual functioning in male with systemic sclerosis

Systemic sclerosis is an autoimmune connective tissue disorder characterized by following typical findings: endothelial changes, microangiopathic damages, and progressive fibrosis. These pathological processes may affect various organs including penile arteries leading to erectile dysfunction (ED). Male erectile dysfunction is defined as the consistent inability to reach and maintain an erection sufficient to permit satisfactory sexual performance. It is a widespread issue in men with systemic sclerosis. Sexual dysfunction in men has been given more attention than female sexual dysfunction, and the etiology is more obvious compared to women. Erectile dysfunction is a result of microangiopathic changes, when the blood flow is reduced in the small penile arteries due to corporal fibrosis and myointimal proliferation [5]. It was proven that damage of the penile cavernous arteries occurs in almost all SSc patients regardless of clinical symptoms. They are characterized by the presence of hyperechoic spots, suggesting fibrotic changes and low peak systolic velocities that are signs for vascular alterations [58].

The prevalence of erectile dysfunction in SSc patients ranged from 12 to 81% in different studies [28]. However, most studies agree that about 80% of SSc men are affected [11–13]. It was also found that ED is more prevalent in systemic sclerosis than other inflammatory rheumatic diseases. In a majority of men with systemic sclerosis, ED started to manifest after the onset of the disease. The mean duration from the onset of the first SSc symptom to erectile dysfunction was around 3 years [12]. Risk factors of erectile dysfunction such as smoking, hypertension, diabetes, and steroid use have been investigated. It was found that only self-reported history of nerve damage and diabetes are significant for predicting the likelihood of ED in systemic sclerosis. There are also risk factors that are presented in non-SSc men as well, like older age or alcohol consumption. The ED association with more severe diseases in terms of worse skin involvement, elevated pulmonary arterial pressures, presence of restrictive lung disease, and muscular and renal involvement in SSc patients was also confirmed [5, 12, 13, 59].

The most likely hypothesis of ED in SSc is a combination of vascular and fibrotic abnormalities. In men with SSc, decreased penile blood pressure, impaired peak systolic and diastolic blood flow in the penile arteries, and the presence of veno-occlusive dysfunction were found. Also, a decreased penile temperature and a slow recovery after cold exposure were reported. A duplex sonography was conducted to reveal the thickening of tunica albuginea and diffuse hyperechogenic spots within the corpora cavernosa. All these findings point to the microangiopathic cause of ED in male SSc patients. This is confirmed by the fact that no carotid artery thickening has been found in SSc, which would predict atherosclerotic macroangiopathy. From a histological point of view, the ED cause in SSc men is the presence of severe corporal fibrosis, increased collagen production by penile smooth muscle cells, and increased accumulation of extracellular matrix. Due to these changes, penile hypoxia arises, which can lead to overexpression of platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β1 and TGF-β1 receptors in the corpora cavernosa, which are important profibrotic regulators of collagen synthesis and production of extracellular matrix. In addition, endothelin (ET-1) is also released by penile smooth muscle cells. Thus, penile hypoxia stimulates penile fibrosis. Therefore, it can be assumed that once ED in patients with SSc is manifested (due to disease), its next mechanisms are similar to those of non-SSc

population. Other causes such as hormonal abnormalities or neurological causes have not been confirmed. No disturbances have been found in follicle-stimulating hormone, luteinizing hormone, serum testosterone, prolactin, estradiol, and thyroid hormones in SSc patients [5, 11, 59, 60].

## 8. Diagnostic approach of erectile dysfunction

The diagnosis of erectile dysfunction in SSc patients is not always easy. We are following the common steps starting with taking a detailed history. Then assessment with appropriate questionnaires and dynamic penile Duplex ultrasound is required. The ambiguity lies in the fact that penile vascular damage occurs in almost all SSc patients, regardless of clinical symptoms and the questionnaire results that often do not match with vascular findings. Thus, it is always better to carry out both investigations: the duplex ultrasound to document the degree of vascular involvement and self-administered questionnaire. The International Index of Erectile Function is the standardized and most widely used tool for evaluating erectile dysfunction. As mentioned above, penile temperature in SSc patients is lower than in healthy individuals. Since cutaneous temperature depends on cutaneous blood flow and thermal exchanges with deeper tissues, these findings could suggest the presence of functional alterations of both tissue properties and blood flow. Therefore, assessing changes in thermal properties and temperature control processes of the penis in SSc patients could provide a potential clue in diagnosis of erectile dysfunction. It has to be noted that with the progression of micro/macrovascular damage in the natural course of the disease, a concomitant penile fibrosis and veno-occlusive dysfunction occur and usually lead to difficult-to-treat ED. We should pay attention in cases where the reduced blood flow is observed, for example, on the hands (Raynaud's phenomenon), because it can suggest that the penile arterial flow will be also altered, and it may be a sign of initial stage of ED in SSc patients [61, 62].

## 9. Treatment and recommendation for erectile dysfunction

It is not a mistake to initiate ED treatment by eliminating general cardiovascular risk factors including lifestyle, psychological, or drug-related factors, but such treatment is often unsatisfactory. This step usually has beneficial effect on erectile function in the general population [63]. Phosphodiesterase-5 (PDE-5) inhibitors are recommended as a first-line option for pharmacotherapy. In non-SSc men, this group of drugs causes the relaxation of smooth muscle cells and temporarily increases arterial blood flow in the penis. However, to achieve an erection, sexual stimulation is required, because this class of drugs is not considered as an initiator of erection. Several types of PDE-5 inhibitors are currently available. The most commonly used are sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra). Except these, newer molecules of PDE-5 inhibitors can be used, for example, mirodenafil, udenafil, and avanafil. All types of PDE-5 inhibitors are effective and safe regarding the treatment of ED in the normal population. The differences are only in their half-lives, when, for instance, tadalafil is effective for up to 36 hours whereas the effectiveness of sildenafil is only 12 hours. The choice of a PDE5-I depends on the frequency of intercourse and the patient's personal experience [64, 65]. However, research on the efficacy of PDE-5 inhibitors is very limited in SSc patients [5]. Proietti et al. reported that once-daily tadalafil improved both erectile function and vascular measures of cavernous arteries in men with SSc-related erectile dysfunction. Also, an increase in frequency of morning erections

and decrease in plasma ET1 levels were found. They suggest that daily tadalafil dose could play a potential role in preventing progression of penile fibrosis and erectile dysfunction in male SSc patients [58]. Furthermore, long-acting PDE-5 may lead to a decrease in the frequency and severity of Raynaud's phenomenon and the promotion of digital ulceration [66].

Patients who do not respond to PDE-5 inhibitors may be offered to try vacuum constriction devices. It was reported that patients who used the vacuum therapy system for a month to increase blood oxygenation in the corpora cavernosa and then employed the vacuum constriction device to maintain penile erection for sexual intercourse significantly improved their erectile function and sexual satisfaction [67]. However, there are no reports about the use of this system in patients with SSc.

Another option for the treatment of erectile dysfunction is prostaglandin analogues, which can be administered via intracavernous injections or intraurethral application. Alprostadil is a stable form of prostaglandin E1 that increases the concentration of cyclic adenosine monophosphate and decreases the intracellular calcium concentration, resulting in the relaxation of smooth muscle cells. Several studies reported the efficiency of alprostadil in the general population, but in terms of SSc patients, it was reported that a substantial percentage of SSc patients did not respond adequately to intracavernous prostaglandin E1 injections [68].

When pharmacotherapy fails and the patient wants a permanent solution, the surgical implantation of a penile prosthesis may be considered as the third-line option. Penile prosthesis improved erectile dysfunction in over 70% of men in the general population. Available prostheses are either malleable (semirigid) or inflatable (two or three pieces), but it should be considered that there are two main complications of penile prosthesis implantation—the mechanical failure and infection [5, 64, 65].

Most of the treatment options described above have not been verified in patients with systemic sclerosis yet. In spite of the fact that erectile dysfunction is common in men with systemic sclerosis, demographics, risk factors, and ED treatments have not been sufficiently investigated. Only a small case series has described unsatisfactory results with on-demand sildenafil (25–50 mg). The higher dose of sildenafil has not been investigated. Tadalafil has been slightly better evaluated in the treatment of SSc-related erectile dysfunction. The efficiency of 20 mg tadalafil on demand and 20 mg tadalafil in a fixed alternate day regimen has been compared. The results showed that flow-mediated dilatation and peak systolic velocities of cavernous arteries at penile duplex ultrasound improved significantly with the alternate day treatment; but no significant changes were observed after the on-demand tadalafil dosing. In addition, the alternate day regimen also reduced the plasma levels of ET-1 and vascular cell adhesion molecule as markers of endothelial function [68]. Therefore, long-term administration of tadalafil and its constant plasma level seems to have a positive effect on the treatment of ED in male SSc patients.

## 10. Conclusion

Sexual dysfunction is a common problem in both men and women with systemic sclerosis. Erectile dysfunction is the dominant issue in males, which seems to be tightly linked to vascular dysfunction. Sexual dysfunction in the female patient is not less prevalent, but it is considerably more complex and it has been less studied. Several diagnostic approaches have been established to assess sexual dysfunction. Also, there are some treatment options available, but most of them have not been sufficiently verified in patients with systemic sclerosis. Further research regarding sexual dysfunction in patients with systemic sclerosis is strongly needed.

## Acknowledgements

This work was supported by grants AZV NV18-01-00161A, 16-33542A, 16-33574A, and institutional support of the Ministry of Health of the Czech Republic for the Institute of Rheumatology number: 023728 and GA UK 1578119.





## Author details

Barbora Heřmánková
Faculty of Physical Education and Sport, Department of Physiotherapy, Charles University, Prague, Czech Republic

*Address all correspondence to: herman.barbora@gmail.com

## References

[1] Heřmánková B. Sexual dysfunction in patients with systemic sclerosis. London: IntechOpen; 2019. DOI: 10.5772/intechopen.86219

[2] Frikha F, Masmoudi J, Saidi N, Bahloul Z. Sexual dysfunction in married women with systemic sclerosis. The Pan African Medical Journal. 2014;**17**:82

[3] Saad SC, Behrendt AE. Scleroderma and sexuality. The Journal of Sex Research. 1996;**33**(3):215-220

[4] Knafo R, Thombs BD, Jewett L, Hudson M, Wigley F, Haythornthwaite JA. (Not) talking about sex: A systematic comparison of sexual impairment in women with systemic sclerosis and other chronic disease samples. Rheumatology. 2009;**48**(10):1300-1303

[5] Jaeger VK, Walker UA. Erectile dysfunction in systemic sclerosis. Current Rheumatology Reports. 2016;**18**(8):49

[6] Carreira PE. A Female Scleroderma Patient with Sexual Dysfunction: Case Studies in Systemic Sclerosis. London: Springer; 2011. pp. 221-228

[7] Knafo R, Haythornthwaite JA, Heinberg L, Wigley FM, Thombs BD. The association of body image dissatisfaction and pain with reduced sexual function in women with systemic sclerosis. Rheumatology. 2011;**50**(6):1125-1130

[8] Sanchez K, Denys P, Giuliano F, Palazzo C, Bérezné A, Abid H, et al. Systemic sclerosis: Sexual dysfunction and lower urinary tract symptoms in 73 patients. La Presse Médicale. 2016;**45**(4):e79-e89

[9] Schouffoer AA, van der Marel J, Ter Kuile MM, Weijenborg PT, Voskuyl A, Vliet Vlieland CW, et al. Impaired sexual function in women with systemic sclerosis: A cross-sectional study. Arthritis and Rheumatism. 2009;**61**(11):1601-1608

[10] Maddali Bongi S, Del Rosso A, Mikhaylova S, Baccini M, Matucci Cerinic M. Sexual function in Italian women with systemic sclerosis is affected by disease-related and psychological concerns. The Journal of Rheumatology. 2013;**40**(10): 1697-1705

[11] Rosato E, Barbano B, Gigante A, Aversa A, Cianci R, Molinaro I, et al. Erectile dysfunction, endothelium dysfunction, and microvascular damage in patients with systemic sclerosis. The Journal of Sexual Medicine. 2013;**10**(5):1380-1388

[12] Hong P, Pope JE, Ouimet JM, Rullan E, Seibold JR. Erectile dysfunction associated with scleroderma: A case-control study of men with scleroderma and rheumatoid arthritis. The Journal of Rheumatology. 2004;**31**(3):508-513

[13] Foocharoen C, Tyndall A, Hachulla E, Rosato E, Allanore Y, Farge-Bancel D, et al. Erectile dysfunction is frequent in systemic sclerosis and associated with severe disease: A study of the EULAR Scleroderma trial and Research group. Arthritis Research and Therapy. 2012;**14**(1):R37

[14] Chen CH, Lin YC, Chiu LH, Chu YH, Ruan FF, Liu WM, et al. Female sexual dysfunction: Definition, classification, and debates. Taiwanese Journal of Obstetrics & Gynecology. 2013;**52**(1):3-7

[15] Latif EZ, Diamond MP. Arriving at the diagnosis of female sexual dysfunction. Fertility and Sterility. 2013;**100**(4):898-904

[16] Mimoun S, Wylie K. Female sexual dysfunctions: Definitions and classification. Maturitas. 2009;**63**(2):116-118

[17] Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, et al. Report of the international consensus development conference on female sexual dysfunction: Definitions and classifications. The Journal of Urology. 2000;**163**(3):888-893

[18] Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Meyer K, et al. Revised definitions of women's sexual dysfunction. The Journal of Sexual Medicine. 2004;**1**(1):40-48

[19] Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Meyer K, et al. Definitions of women's sexual dysfunction reconsidered: Advocating expansion and revision. Journal of Psychosomatic Obstetrics and Gynaecology. 2003;**24**(4):221-229

[20] Basson R. Women's sexual function and dysfunction: current uncertainties, future directions. International Journal of Impotence Research. 2008;**20**(5):466-478

[21] Basson R, Wierman ME, van Lankveld J, Brotto L. Summary of the recommendations on sexual dysfunctions in women. The Journal of Sexual Medicine. 2010;**7**(1 Pt 2):314-326

[22] McCabe MP, Sharlip ID, Atalla E, Balon R, Fisher AD, Laumann E, et al. Definitions of sexual dysfunctions in women and men: A consensus statement from the fourth international consultation on sexual medicine 2015. The Journal of Sexual Medicine. 2016;**13**(2):135-143

[23] Basson R. Women's sexual dysfunction: Revised and expanded definitions. Canadian Medical Association Journal. 2005;**172**(10):1327-1333

[24] Reed GM, Drescher J, Krueger RB, Atalla E, Cochran SD, First MB, et al. Disorders related to sexuality and gender identity in the ICD-11: Revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations. World Psychiatry. 2016;**15**(3):205-221

[25] WHO. World Health Organization [Online]. 2018. Available from: https://icd.who.int/browse11/l-/en#/http://id.who.int/icd/entity/160690465 [Accessed: March 31, 2019]

[26] Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013

[27] Tristano AG. The impact of rheumatic diseases on sexual function. Rheumatology International. 2009;**29**(8):853-860

[28] Impens AJ, Seibold JR. Vascular alterations and sexual function in systemic sclerosis. International Journal of Rheumatology. 2010;**2010**:139020

[29] Saad SC, Pietrzykowski J, Lewis SS, Stepien AM, Latham VA, Messick S, et al. Vaginal lubrication in women with scleroderma and Sjogren's syndrome. Sexuality and Disability. 1999;**17**(2):103-113

[30] Bruni C, Raja J, Denton CP, Matucci-Cerinic M. The clinical relevance of sexual dysfunction in systemic sclerosis. Autoimmunity Reviews. 2015;**14**(12):1111-1115

[31] Bhadauria S, Moser DK, Clements PJ, Singh RR, Lachenbruch PA, Pitkin RM, et al. Genital tract abnormalities and female sexual function impairment in systemic sclerosis. American Journal of Obstetrics and Gynecology. 1995;**172**(2 Pt 1):580-587

[32] Sampaio-Barros PD, Samara AM, Marques Neto JF. Gynaecologic history in systemic sclerosis. Clinical Rheumatology. 2000;**19**(3):184-187

[33] Impens A, Rothman J, Schiopu E, Cole J, Dang J, Gendrano N, et al. Sexual activity and functioning in female scleroderma patients. Clinical and Experimental Rheumatology. 2009;**27**(3):S38

[34] Wylie K, Daines B, Jannini EA, Hallam-Jones R, Boul L, Wilson L, et al. Loss of sexual desire in the postmenopausal woman. The Journal of Sexual Medicine. 2007;**4**(2):395-405

[35] Basson R. Women's sexual desire—Disordered or misunderstood? Journal of Sex and Marital Therapy. 2002;**28**(1):17-28

[36] Rosen RC. Assessment of female sexual dysfunction: Review of validated methods. Fertility and Sterility. 2002;**77**(Suppl 4):S89-S93

[37] Brotto L, Atallah S, Johnson-Agbakwu C, Rosenbaum T, Abdo C, Byers ES, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. The Journal of Sexual Medicine. 2016;**13**(4):538-571

[38] Stephenson KR, Toorabally N, Lyons L, Meston CM. Further validation of the female sexual function index: Specificity and associations with clinical interview data. Journal of Sex and Marital Therapy. 2016;**42**(5):448-461

[39] Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): Cross-validation and development of clinical cutoff scores. Journal of Sex and Marital Therapy. 2005;**31**(1):1-20

[40] Rosen RC, Revicki DA, Sand M. Commentary on "critical flaws in the FSFI and IIEF". The Journal of Sex Research. 2014;**51**(5):492-497

[41] Nowosielski K, Wróbel B, Sioma-Markowska U, Poręba R. Development and validation of the polish version of the female sexual function index in the polish population of females. The Journal of Sexual Medicine. 2013;**10**(2):386-395

[42] Raina R, Pahlajani G, Khan S, Gupta S, Agarwal A, Zippe CD. Female sexual dysfunction: Classification, pathophysiology, and management. Fertility and Sterility. 2007;**88**(5):1273-1284

[43] Basson R. Rethinking low sexual desire in women. BJOG: An International Journal of Obstetrics and Gynaecology. 2002;**109**(4):357-363

[44] Puppo V. Female sexual function index (FSFI) does not assess female sexual function. Acta Obstetricia et Gynecologica Scandinavica. 2012;**91**(6):759

[45] Levis B, Hudson M, Knafo R, Baron M, Nielson WR, Hill M, et al. Rates and correlates of sexual activity and impairment among women with systemic sclerosis. Arthritis Care and Research. 2012;**64**(3):340-350

[46] Levis B, Burri A, Hudson M, Baron M, Thombs BD, Canadian Scleroderma Research G. Sexual activity and impairment in women with systemic sclerosis compared to women from a general population sample. PLoS One. 2012;**7**(12):e52129

[47] Buster JE. Managing female sexual dysfunction. Fertility and Sterility. 2013;**100**(4):905-915

[48] Jacobsen PL, Mahableshwarkar AR, Palo WA, Chen Y, Dragheim M, Clayton AH. Treatment-emergent sexual dysfunction in randomized trials of vortioxetine for major depressive disorder or generalized anxiety disorder: A pooled analysis. CNS Spectrums. 2016;**21**(5):367-378

[49] Harsh V, Clayton AH. Sex differences in the treatment of sexual dysfunction. Current Psychiatry Reports. 2018;**20**(3):18

[50] Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, et al. Prevalence of sexual dysfunction among newer antidepressants. The Journal of Clinical Psychiatry. 2002;**63**(4):357-366

[51] Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: A prospective, crossover study of sex steroid administration in the surgical menopause. Psychosomatic Medicine. 1985;**47**(4):339-351

[52] Portman DJ, Bachmann GA, Simon JA, Ospemifene Study G. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause. 2013;**20**(6):623-630

[53] Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: A randomised, placebo-controlled, phase III trial. Maturitas. 2014;**78**(2):91-98

[54] Segraves RT, Clayton A, Croft H, Wolf A, Warnock J. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. Journal of Clinical Psychopharmacology. 2004;**24**(3):339-342

[55] Vegunta S, Kling JM, Faubion SS. Sexual health matters: Management of female sexual dysfunction. Journal of Women's Health. 2016;**25**(9):952-954

[56] Kocher A, Adler S, Spichiger E. Skin and mucosa care in systemic sclerosis–patients' and family caregivers' experiences and expectations of a specific education programme: A qualitative study. Musculoskeletal Care. 2013;**11**(3):168-178

[57] Rullo J, Faubion SS, Hartzell R, Goldstein S, Cohen D, Frohmader K, et al. Biopsychosocial management of female sexual dysfunction: A pilot study of patient perceptions from 2 multi-disciplinary clinics. Sexual Medicine. 2018;**6**(3):217-223

[58] Proietti M, Aversa A, Letizia C, Rossi C, Menghi G, Bruzziches R, et al. Erectile dysfunction in systemic sclerosis: Effects of longterm inhibition of phosphodiesterase type-5 on erectile function and plasma endothelin-1 levels. The Journal of Rheumatology. 2007;**34**(8):1712-1717

[59] Aversa A, Proietti M, Bruzziches R, Salsano F, Spera G. The penile vasculature in systemic sclerosis: A duplex ultrasound study. The Journal of Sexual Medicine. 2006;**3**(3):554-558

[60] Lally EV, Jimenez SA. Erectile failure in systemic sclerosis. The New England Journal of Medicine. 1990;**322**(19):1398-1399

[61] Merla A, Romani G, Tangherlini A, Di Romualdo S, Proiettii M, Rosato E, et al. Penile cutaneous temperature in systemic sclerosis: A thermal imaging study. International Journal of Immunopathology and Pharmacology. 2007;**20**(1):139-144

[62] Aversa A, Bruzziches R, Francomano D, Rosato E, Salsano F, Spera G. Penile involvement in systemic sclerosis: New diagnostic and therapeutic aspects. International Journal of Rheumatology. 2010;**2010**:706087

[63] Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor

reduction on erectile dysfunction: A systematic review and meta-analysis. Archives of Internal Medicine. 2011;**171**(20):1797-1803

[64] Wespes E, Eardley I, Giuliano F, Hatzichristou D, Hatzimouraditis K. Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. European Association of Urology. 2013;**2013**:1-54

[65] Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, et al. Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. European Urology. 2010;**57**(5):804-814

[66] Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: A double-blind randomized cross-over trial. Rheumatology. 2010;**49**(12):2420-2428

[67] Li P, Shen YJ, Liu TQ, Ma M, Zhang SJ, Wang YX, et al. Vacuum therapy for erectile dysfunction that fails to respond to PDE-5i: Report of 70 cases. Zhonghua nan ke xue = National Journal of Andrology. 2013;**19**(3):236-240

[68] Walker UA, Tyndall A, Ruszat R. Erectile dysfunction in systemic sclerosis. Annals of the Rheumatic Diseases. 2009;**68**(7):1083-1085