

Sexual Function and Dysfunction among Patients with Systemic and Auto-Immune Diseases

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1. Summary

Systemic autoimmune diseases affect various organs and they can determine sexual dysfunction in females and males patients particularly with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren syndrome (SS), antiphospholipid syndrome, Behçet's disease and other vasculitis.

Sexual dysfunction among patients with rheumatic diseases is multifactorial due to disease-related factors (chronic disease aspects, disease activity) as well as therapy.

There is little data regarding the impact of these diseases and treatments, mainly with large population, on sexual function. In rheumatoid arthritis patients, sexual dysfunction is principally associated with pain and depression. In patients with SLE, Sjögren's syndrome and systemic sclerosis, vaginal discomfort or pain during intercourse could be the principal factors contributing to sexual dysfunction. Sexual dysfunction is probably associated with psychological status and neurological involvement in patients with BD.

This systematic review synthesizes the current literature concerning sexual function and dysfunction in patients with systemic and auto-immune diseases. Our attention was directed specifically on the sexual function and dysfunction of patients affected by SLE, systemic Sclerosis, primary Sjogren syndrome, antiphospholipid syndrome and Behçet's disease.

2. Introduction

Sexuality is a complex aspect of the human being's life and is closely associated to the quality of life (QoL). Sexuality has been

cited as an important part of the whole person, and sexual expression has been described as a crucial part of personal's self-identity [1]. Normal sexual functioning is important for healthy and all individuals and consists of sexual activity with transition through the phases from arousal to relaxation with no problems, and with a feeling of pleasure, and satisfaction [2,3].

Sexual dysfunction refers to a term that encompasses problems that affect any phase of sexual responses. Sexual dysfunction in females mainly includes desire, arousal, orgasmic, as well as sexual pain disorders whereas males encounter erectile dysfunction, diminished libido, and abnormal ejaculation [4,5].

Systemic autoimmune diseases affect various organs and they can determine sexual dysfunction in patients particularly with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren syndrome (SS), Behçet's disease (BD) and other vasculitis.

Sexual dysfunction among patients with rheumatic or systemic auto-immune diseases is multifactorial due to disease-related factors (chronic disease aspects, disease activity) and drugs. Many factors including pain, stiffness, fatigue, functional impairment, negative body image, reduced libido, hormonal imbalance, depression and anxiety, contribute to reduce an individual's sexual interest and lead to a less active and enjoyable sex life [6].

Because of sexuality may be a taboo subject to many people, sexual health is rarely addressed by health professionals during routine consultations and is rarely proactively reported by patients. In other hand, sexual dysfunction can cause frustration and distress

and can impact both a couple's relationship and sexual satisfaction. In routine clinical practice, the focus is typically on fertility, pregnancy or contraception, whereas sexual function is not addressed. There is little data regarding the impact of these diseases and treatments, mainly with large population, on sexual function.

In rheumatoid arthritis, sexual dysfunction is principally associated with pain and depression. In patients with SLE, Sjögren's syndrome and systemic sclerosis, vaginal discomfort or pain during intercourse could be the principal factors contributing to sexual dysfunction. Moreover, the disturbances of sexual function may also be attributed to psychological and cultural factors [6,7].

To date, little is known about the prevalence and the characteristics of sexual dysfunction among patients with systemic and auto-immune diseases such as SLE, SSc, SS, antiphospholipid syndrome and Behçet's disease. Thus, this paper aimed to investigate the impact of those diseases on patients's sexual function by performing a systematic review of studies available in the literature.

3. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a connective-tissue disorder, chronic inflammatory autoimmune disease of unknown etiology that can affect multiple organs (skin rash, arthritis, serositis, nephritis, pneumonitis, cardiac disease, hematological problems and neurological involvement) [8,9].

Various studies have revealed that SLE can exert detrimental influences on different aspects of patients' life, leading to an impairment of psychological health (depression and low self-esteem), health-related quality of life, and sexual function [10,11,12] in both males and females.

Sexual function is of particular significance for SLE patients because it occurs predominantly in women, especially young women, at a ratio of 9 : 1 (women : men) and plays a vital role in quality of life [13]. The impact of SLE on sexual functioning has been studied in previous studies and more evidence suggests that an important part of QoL, sexual function is affected by SLE. The proportion of SLE patients reporting sexual dysfunction across studies ranged between 15% to 85.9% [10,13-16].

Shen et al. Found that the frequency of self-reported impaired sexual function among patients with SLE was significantly higher than healthy individuals (64.10% vs. 35.7%, $p < 0.001$) [13].

Curry et al. [17] found that patients with SLE, when compared with controls, had a significantly higher rate of abstention, a lower frequency of sexual activity among the sexually active, diminished vaginal lubrication, poorer general sexual adjustment, and more depression. In this study, sexual dysfunction in f SLE patients may be associated with age, relationship status, weight concerns, pre-morbid sexual adjustment, and depression

In a review, the author reported that sexual dysfunction in women

with SLE is apparently most associated to vaginal discomfort or pain during intercourse [3].

In a cross-sectional study, Morales et al [18] found that women with SLE had a lower desire, lubrication, and orgasm. The results of a recent meta-analysis showed that female SLE patients have a lower total FSFI score, compared with healthy controls, which means that SLE had some influence on women's sexual function [8]. Male patients with SLE might be also more vulnerable to sexual dysfunction [10]. In fact, an increased prevalence of impotence has been suggested [19].

However, other studies did not find a negative relationship between SLE and sexual dysfunction. Tseng et al. [20] reported that female patients with SLE were not more inclined to experience impaired sexual function than the control population (52.5% vs. 47.1%, $p = 0.206$).

SLE touches on all aspects of life including sexuality and reproduction. The pathogenesis of sexual problems in SLE patients is still unclear. The reasons for inhibited sexual functioning and inefficient reproduction are multifactorial and comprises of disease-related factors as well as medication [6]. Previous studies have found that sexual function is significantly related to depression in female SLE patients [21] and depression affects about 40% of SLE patients [22]. Recent studies have shown that impairment of the normal structure and function of microglia, caused by autoimmune diseases, can result in depression and associated impairments in neuroplasticity and neurogenesis [23].

3.1. Disease-Related Factors

In SLE patients, two main disease-related factors account for the sexual dysfunction : diminished sexual drive and difficulties in performing sexual intercourse [10].

The impairment of motion, fatigue, stiffness and pain of knee or hip joints also limited sexual activity [10].

It is recognized that the androgenic status could be related with sexual function including sexual desire and satisfaction. Female SLE patients often had a higher level of estrogen but a lower level of testosterone and dehydroepiandrosterone. In addition, vaginal dryness and dyspareunia associated with secondary Sjogren's syndrome are frequently found in women with SLE [6,10].

In males, erectile dysfunction can result from arterial and venous-occlusive insufficiency because of the lupus nephritis [24].

Several studies revealed that an increased prevalence of renal involvement and progressive renal damage among males with SLE compared to females [25]. Furthermore, sexual dysfunction is relatively more common among patients with renal dysfunction and chronic kidney disease [26].

3.2. Psychological Factors

The psychological consequences of chronic disease also play a cri-

tical role in the development of sexual dysfunction and therefore should not be neglected. Patients with SLE often have a higher level of depression and anxiety, a lower quality of life, and more negative attitudes towards their body image. The SLE patients are often encumbered with disfigurement and disabilities caused by skin rashes, hair loss, and joint deformities [27].

Boomsma et al., [28] reported that 14% of SLE patients had suicidal ideation, and half of them described that their disease had a great impact on their daily lifestyles.

Pinto et al. [29] showed that when factors such as a higher dose of steroids and disease activity were disregarded, it becomes apparent that depression, anxiety, and marital satisfaction might impair the sexual function of SLE patients.

All these combined effects of psychological factors might impair patients' sexual desire and function.

3.3. Drugs Factors

Glucocorticoid agents used in the treatment of SLE might also negatively impair sexual function and sexual satisfaction. High doses of glucocorticoids can reduce testosterone levels, which plays a crucial role in sexual dysfunction [30]. Glucocorticoids are known to exert an inhibitory effect on sex hormones, or cause Cushing's Syndrome and other side effects during treatment. The glucocorticoids can also induce hypothalamic-pituitary-adrenal (HPA) axis dysregulation and result in persistently low sexual desire [31].

The use of Non-steroidal anti-inflammatory drugs (NSAID) can increase risk of erectile dysfunction [32]. Cyclophosphamide can interfere with DNA repair mechanisms and lead to gonadal toxicity. This cytotoxic alkylating agent can also lead to decreased sex drive or erectile dysfunction [33].

In summary, most studies suggested that SLE is significantly associated with an increased risk of sexual dysfunction in both female and male patients. However, all conclusions need to be carefully evaluated. In fact, the literature quality of included studies was inadequate and the sample size of the available studies was insufficiently small and limited. Substantial heterogeneity was also found in the published studies. Further studies of a larger population of SLE patients are required to further evaluate the mechanism by which SLE affects sexual function.

4. Systemic Sclerosis

Systemic Sclerosis (SSc) is a chronic multisystemic disease characterized by abnormal fibrotic processes, inflammation and microvascular damage. The disease is most frequently seen at ages between 30 and 50 years and the female/male ratio is 8/1.

The vascular alterations and immunological activation lead to progressive and widespread fibrosis of multiple organ systems including the skin, the lungs, the gastrointestinal tract and the kidneys. Changes associated with SSc such as skin tightening, muscle

weakness, joint pain, deformity and decreased physical function can have a negative impact on sexuality and sexual functioning.

Sexual dysfunction and lower health quality are common problems in female patients with SSc [34,35]. In the literature, the number of female patients with SSc reporting sexual dysfunction is higher than those reported in the general population and also higher than those reported in studies on other chronic diseases [36,37,38].

A study assessed the prevalence of sexual dysfunction in 163 patients with rheumatic diseases including SLE; rheumatoid arthritis; systemic sclerosis; antiphospholipid antibody syndrome; and fibromyalgia. The mean age was 40.4 years. The prevalence of sexual dysfunction was 18.4%, but 24.2% of the patients reported no sexual activity over the past 4 weeks. Patients with fibromyalgia and systemic sclerosis had the highest sexual dysfunction index (33%). Excluding patients with no sexual activity, the sexual dysfunction rate reaches 24.2% [39].

A systematic review found that women with diffuse or limited SSc experienced levels of sexual impairment similar to or higher than women with breast cancer, HIV and gynaecological cancer [36].

Levis et al. [40] investigated sexual dysfunction and related clinical symptoms in an evaluation of both sexually active and inactive patients. The FSFI was applied to 165 sexually active SSc patients. The presence of Reynaud's phenomenon and digital ulcers and evaluation of the modified Rodnan skin score, gastro-intestinal and pulmonary symptoms, and pain were investigated. Sexual dysfunction was established in 102/165 (61.8%). This dysfunction was higher in patients of advanced age with a high Rodnan skin score and marked pulmonary symptoms.

A recent study included 30 sexually active female patients with SSc and 30 healthy control subjects. Sexual dysfunction was found in 26/30 (86.6%) of the SSc patients and in 6/30 (20%) of the control group ($P = 0.0001$). Significant differences were determined between the groups with respect to sexual desire, arousal, lubrication, orgasm, sexual satisfaction, and pain. There was no significant relationship between the subgroups of SSc patients, duration of disease, lung involvement, and FSFI scores. The SF-36 scores in the patient group were significantly lower than those in the control group [34].

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. Major problems that cause sexual dysfunction for male and female patients with SSc are pain, limited physical ability, negative body image, fatigue and depression.

The exercise capacity of those patients is significantly reduced. Symptoms such as dyspnea, fatigue, and cough in these patients can also affect sexual activity in both sexes [41].

Raynaud's phenomenon can affect the tongue and nipples, sclero-

sis of the fingers and digital ulcers may interfere with touch and foreplay.

Finally, fatigue, which is a common symptom of SSc, can decrease quality of life by diminishing the ability to engage in meaningful personal and social activities and has important implications for employment, compliance with medical treatments and the use of healthcare services [42].

4.1. Sexual functioning in women with systemic sclerosis

Bhaduria et al. [43] showed that more than half of systemic sclerosis patients reported a decrease in the number and intensity of orgasms, compared to <20% of control subjects. Skin tightness, reflux-heartburn, and muscle weakness adversely affected sexual relations more in systemic sclerosis than in control subjects.

In female patients, the most common physical problems associated with female sexual dysfunction include vaginal dryness, vaginal stenosis, dyspareunia, Raynaud's phenomenon, fatigue, joint pain, joint contractures, muscle weakness and changes in breast skin. All these factors lead to diminished libido, decreased vaginal lubrication, and satisfaction. In addition, changes in the skin in these patients, especially in the face, can affect self-confidence in women, which can also lead to sexual dysfunction [41,43].

When the skin becomes stiffer around the vaginal introitus, penetration becomes painful, and changes in the vaginal mucosae causing lubrication disorder contribute to this painful penetration [3,41].

Raynaud's phenomenon, which affects fingers, toes, tongue and nipples, is another reason, why the cuddling, foreplay, and oral sex could become uncomfortable and unpleasant.

In our study, the major reasons for decreased sexual activity in married women with SSc were fatigue, altered body image, and pain [44].

Physical problems, emotional problems and partnership difficulties arising from disease relatedness contribute to a less active and often less enjoyable sex life. The pleasure of intercourse can become diminished by pain of joint movement, or difficulty in finding positions that do not cause discomfort.

The management of impaired sexuality in women with SSc was less studied but there are some general recommendations for women that may help to continue enjoying an active, fulfilling sexual life: a medical provider, physical therapist, occupational therapist, psychotherapist, and sex therapist [45].

4.2. Sexual functioning in male with systemic sclerosis

The prevalence of erectile dysfunction in men with SSc has been reported to be approximately 12%–81% in different studies [3,46]. The exact pathogenesis of this erectile dysfunction in SSc is not clearly defined.

Underlying vasculopathic, microangiopathic and fibrotic changes, and neuropathic/disautonomic factors are currently thought to be

responsible [3,47]. 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 [48]. Other 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 erectile dysfunction in SSc. Some studies have reported that total testosterone and prolactin levels in blood are correlated with erectile dysfunction in men with SSc [47].

Some treatment options have been used to cause the relaxation of smooth muscle cells and temporarily increase arterial blood flow in the penis. Phosphodiesterase-5 (PDE-5) inhibitors are recommended as a first-line option for pharmacotherapy. The most commonly used are sildenafil, tadalafil, and vardenafil. Proietti et al. [48], found that once-daily tadalafil improves both vascular measures of cavernous arteries and so erectile function.

It is also recommended to eliminate general cardiovascular risk factors including lifestyle, psychological, or drug-related factors.

In summary, sexual dysfunction is a common problem in both men and women with systemic sclerosis. Sexual dysfunction in the female patient is considerably more complex and it has been less studied. Erectile dysfunction is the dominant issue in males, and seems to be tightly related to vascular dysfunction and fibrotic changes. Further research regarding sexual dysfunction in patients with systemic sclerosis is strongly needed.

5. Sjogren's Syndrome

Sjogren syndrome (SS) is a chronic systemic autoimmune disease of unknown origin characterized by sicca symptoms of the mouth and eyes (xerostomia and xerophthalmia), together with a variety of extraglandular symptoms (disabling fatigue, interstitial lung disease, neurologic involvement, and arthritis). Primary SS (pSS) is the second most common systemic autoimmune disease that usually affects women more than men.

While dryness of mucosal surfaces is the main characteristic feature of this disease, other mucosal surfaces can also be involved such as nasal and vaginal mucosa. Women with pSS often experience vaginal dryness and dyspareunia which can play a major role in sexual dysfunction and had the greatest impact on quality of life [49]. Kissing can be difficult and unpleasant due to the dry mouth [3]. Many studies showed also that patients with pSS have more depressive symptoms than healthy controls and that depression and fatigue is associated with higher ESSPRI scores [50] and so an altered quality of life. Van Nimwegen et al. reported depression as being the most important predictor of sexual dysfunction in patients with SS [51].

Previous studies have largely focused on vaginal symptoms and

dyspareunia, but only a few studies highlighted sexual dysfunction and distress in women with SS. Maddali Bongi et al. [52] found that 68% of the patients reported alterations in their sexual ability because of the symptoms of pSS, especially vulvar or vaginal dryness, dyspareunia and reduced sexual drive.

In a recent study, Van Nimwegen et al [51] demonstrated that women with pSS have significantly more sexual dysfunction in the domains of desire, arousal, orgasm, lubrication and pain compared with healthy controls.

Sexual function has been measured by self administered questionnaire, namely the Female Sexual Function Index (FSFI), in three included studies [51,53,54], and was compared between pSS patients (102 patients) and healthy controls (99 participants). A random-effects model was used in all domains, and the pooled results displayed significant difference between pSS patients and healthy controls. The SMD of the FSFI scores of pSS patients were lower than that of controls on each domain of sexual function: desire, arousal, lubrication, orgasm, satisfaction, pain and total FSFI.

Recently, Isik H et al [55] found that patients with SS had lower sexual function scores compared to age-matched controls and 80.4% of them were sexually dissatisfied according to previously determined cut-off values (FSFI score of <26). All domains of sexual function, including desire, arousal, orgasm, lubrication, pain, and satisfaction were affected in these women. The authors demonstrated that women who used lubricants experienced that sexual satisfaction was improved with lubricant use, so it can be advised to SS patients by their physician even if they are premenopausal [55]. The same study found that physical function scores in life quality tests positively correlated with sexual function scores. If a patient has a better physical function and less physical restriction, she tends to have more satisfaction.

Two studies [51,53] found that sexual dysfunction does not correlate with the measurement assessed by physicians using the validated EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI), however it is more associated with the self-reported symptoms of the syndrome as rated by the EULAR Sjogren's Syndrome Patients' Reported

Index (ESSPRI).

For sicca symptoms of pSS, patients can be offered local symptomatic treatment of vaginal dryness with lubricants, topical oestrogens and moisturizers. Jozkowski et al [56] concluded that lubricant use recommendations from health professionals and sex educators could be helpful. If necessary, patients can be referred to a gynaecologist or sexologist.

Treatment with biologic drugs (rituximab and abatacept) have a beneficial effect on disease activity, fatigue and quality of life and thus may also improve sexual function.

In summary, women with pSS experience significantly more sexual dysfunction and depression than healthy controls. Sexual function in pSS could be influenced by age, increased vaginal dryness pain and fatigue, as well as psychological consequences of the disease that can strongly alter the quality of patients life.

6. Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disorder characterized by the occurrence of venous or arterial thrombosis and/or recurrent fetal loss, in addition to serum antiphospholipid antibodies (aPL), mainly lupus anticoagulant and anticardiolipin antibodies (aCL). To date, few studies have evaluated erectile function in subjects with primary APS [57].

Gallinaro et al [57] compared 11 APS male patients with 22 healthy. Erectile dysfunction was frequently observed in APS versus controls (45.5 vs. 4.5%, $p=0.0096$), especially moderate/severe erectile dysfunction ($p=0.0081$). The total International Index of Erectile Functions (IIEF) score (49.6 vs. 67.1, $p=0.019$), erectile function (19.6 vs. 28.1, $p=0.005$) and intercourse satisfaction (7.8 vs. 11.9, $p=0.009$) were lower in patients than in controls. This alteration was linked to arterial events and longer disease duration. Sadetski et al [58] demonstrated that almost all primary antiphospholipid syndrome patients have psychological alterations. In this study, sexual limitations was observed in 20 % of patients.

Erectile dysfunction in APS patients can be multifactorial. It is reasonable to speculate that a thrombotic mechanism and the impairment of the penile vascular system may be implicated in the pathophysiology of this erection dysfunction. Other factors can be associated with erectile dysfunction such as age, disease activity and drug use [16]. Some case reports showed thrombosis of penile vessels leading to erectile dysfunction [59].

Rabelo-Júnior CN et al [60] observed normal testicular function in a small group of primary antiphospholipid syndrome (PAPS) patients, in spite of morphofunctional penile abnormalities. They concluded that this alteration may lead to an issue about fertility or fear of impaired sexual function (impotence) in male patients with APS.

Another cross-sectional study was conducted by Rabelo-Júnior CN et al [61] in ten SLE-APS male patients and 20 healthy controls. The authors identified that intravenous cyclophosphamid was the major factor for severe and potentially permanent damage to the tests in SLE-APS patients. They observed for the first time an association of reduced penile size with erectile dysfunction and previous arterial thrombosis in these patients.

In summary, male patients with APS may have erectile dysfunction and low intercourse Satisfaction. This sexual dysfunction is probably associated with arterial events and duration of the disease and may cause psychological problems with a consequent reduction of health-related quality of life.

7. Behçet Disease

Behçet's disease (BD) is an inflammatory disorder of unknown etiology which is characterized by recurrent aphthous stomatitis, genital ulceration and can be accompanied by dermatological, ocular, neurological, intestinal, urogenital and cardiopulmonary symptoms

Sexual dysfunction in male and female patients with BD has been reported in many studies [62-68] and it was associated with depression, arthritis and neurological and vascular involvement.

In fact, patients suffering from chronic recurrent and painful disease such as BD may have negative feelings, distress and dissatisfaction in all aspects of their life.

In male patients with BD, the prevalence of erectile dysfunction varied from 43.9 to 90% among patients [66,69]. It has been reported that erectile dysfunction according to the International Index of Erectile Functions (IIEF) was significantly higher in patients with BD than control group. IIEF scores were negatively correlated with BD Index in the patient group [63].

Koçak et al. Concluded that depressive mood correlates with the sexual status of BD patients, and this may be because of the depressive effect of BD as a chronic disease [62].

Yıldız et al. reported that the five parameters of IIEF score were significantly lower in patients with BD ($p < 0.001$). The authors found that the Hospital Anxiety and Depression Scale in patients with BD were significantly higher than healthy control subjects ($p < 0.001$). Sexual dysfunction was found to be associated with age, duration of disease, psychological status and quality of life in this study [66].

Female sexual dysfunction is also common in the previous studies and significantly associated with depression rather than to active organic manifestations, such as genital ulcers [67].

Yetkin et al. [64] investigated sexual dysfunction and depression in a group of premenopausal women with mucocutaneous BD; The study included two groups based on the presence or absence of genital ulcerations and compared with a group of age-matched healthy volunteers. The authors found that both depression and sexual dysfunction were more common among BD patients than in controls. In particular, depression and sexual dysfunction were found in the 32% and 56% of the patient group, respectively (vs 14.8% and 41% of the control group, respectively). The pain domain of FSFI (Female Sexual Function Index) was significantly higher in BD group than in control group.

The origin of sexual dysfunction in this vasculitis is multifactorial, being related to different factors such as mucocutaneous involvement, the high frequency of psychiatric involvement [67,71,72] and to the side effects of various treatments used for treating the disease.

In their study, Hiz et al. [63] suggested that sexual dysfunction is an association with psychological status and history of arthritis whereas Erdogru et al. [73] suggested that it was associated with neurological involvement in patients with BD.

Vascular pathologies of BD can lead to sexual dysfunction [64] in BD; moreover, mixed neurological and vasculogenic pathologies can lead to sexual dysfunction in Neuro-Behçet' disease.

In a recent study, Hayriye et al [68] have included prospectively a total of 25 patients with neurological involvement, 22 patients with Behçet's disease (BD) without neurologic involvement and 19 persons in control group. A semi-structured interview guided by a Arizona sexual experience scale (ASEX) questionnaire, Beck Depression Inventory and Beck Anxiety Inventory was applied to all of the patients. The sexual dysfunction was significantly higher in patients with neurological involvement (47.9%) compared to BD patients without neurological involvement (35.4%) and control group (16.7%) ($p = 0.001$). The authors showed that neurological involvement in BD had a negative effect on sexuality in all but especially on arousal and vaginal lubrication/penile erection function based on ASEX questionnaire. This higher prevalence of sexual dysfunction in neuro-Behçet'diseases may be a result of derangement of parasympathetic pathways, limbic or other brain areas, yet, the exact locations of the derangement are not known. Moreover, male sexuality was more affected by BD than female sexuality.

In another hand, it seems relatively frequent that patients with BD develop a neurobehavioural syndrome, characterized by euphoria, bipolar disorders and paranoid attitudes, loss of insight/disinhibition, and indifference to their disease, defined as 'neuropsych-BD' [67,70] and this may have a great impact on the quality of life of these patients.

Aksu et al reported that the cause of erectile dysfunction in their two patients with BD without neurological involvement was severe venous leak shown by penile Doppler ultrasound and cavernosography [65].

Considering also the hormonal aspects of BD, Yetkin et al. showed that BD patients have lower levels of total testosterone and DHEASO₄; which may allow to speculate on the presence of low androgen levels that may also contribute to sexual dysfunction in these patients [64].

Finally, treatment with glucocorticoids may also have side effects with great impact on sexual

function, due to change in body image, as well as leading to depression and psychosis. Furthermore, several drugs used to treat a frequent comorbid condition may also have an impact on sexual function. Tricyclic antidepressants and serotonin reuptake inhibitors may lead to a significant decrease of libido [67].

In summary, such a systemic and complex disease like BD is at

high risk of developing sexual dysfunction for many different organic and psychological reasons. Therefore, management strategies including psychotherapeutic interventions and behavioral based sexual therapies might help improve the quality of life in patients with BD.

8. Conclusion

Sexuality is an often neglected area of quality of life in patients with chronic systemic and auto-immune diseases. Manifestations and symptoms of disease can impair sexual functioning, but this can be much improved by adequate intervention and counseling. Sexual dysfunction is multifactorial and it is influenced by physical as well as psychological consequences of the diseases, such as pain, fatigue, stiffness, functional impairment, depression, anxiety, negative body image, reduced libido, hormonal imbalance and side effects from treatments.

In order to improve the sexual health and quality of life of patients with systemic and auto-immune diseases, the management of patients of both genders should include regular family planning and sexual counselling. It is mandatory to implement for active interventions that aimed to treat or prevent sexual dysfunction among those patients. In addition, the presence of a psychologist or trained health professionals could be helpful in association with specific lifestyle clinical practice guidelines for patients. A multidisciplinary approach is essential in order to offer preventive measures for these patients.

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