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FEMALE SEXUAL DYSFUNCTION AND DISORDERS (T LORENZ & R NAPPI, SECTION EDITORS)

Female Sexual Dysfunction as a Warning Sign of Chronic Disease Development

Vincenza Di Stasi[1,2] · Nunzia Verde[3] · Elisa Maseroli[1,2] · Irene Scavello[1,2] · Sarah Cipriani[1,2] · Tommaso Todisco[1,2] · Mario Maggi[1,4,5] · Linda Vignozzi[1,2,5]

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Abstract

Purpose of Review Female sexual dysfunctions (FSD) in chronic diseases are often multi-factorial, integrating several bio-psychological and socio-environmental components. The aim of this review is to summarize existing evidence on the association between the most common chronic conditions and FSD and also to frame systematically experimental findings into a comprehensive overview on candidate mechanisms through which chronic diseases drive FSD pathogenesis.

Recent Findings In men, it is now clear that several chronic diseases favour the development of sexual dysfunction (SD), especially erectile dysfunction (ED), by an integration of multiple pathogenic factors. More importantly, in men, ED has been recognized as a *harbinger* of several serious underlying medical conditions, including the cardiovascular ones. Conversely, the nature of the relationship between SD and chronic diseases in women remains controversial and, in contrast to the well-established associations with ED in men, FSD is not yet acknowledged as a warning sign of other systemic diseases. In this review of literature, we try to demonstrate that this is changing because there are some clinical and research evidences about the importance to recognize FSD in chronic disease. Specifically, we summarize the recent findings about the relation between cardio-metabolic, respiratory, renal, neurologic and rheumatic diseases and FSD.

Summary Management of FSD is an important task to improve the overall quality of life of patients suffering from chronic, longstanding and often progressive diseases. It is also possible that sexual symptoms might be a warning sign for unrecognized conditions, although this is far to be completely understood. Further studies are needed to fully understand and treat this emerging topic in specific clinical settings.

Keywords Female sexuality · Chronic diseases · Gender medicine

Vincenza Di Stasi and Nunzia Verde contributed equally to this work.

This article is part of the Topical Collection on *Female Sexual Dysfunction and Disorders*

✉ Linda Vignozzi
linda.vignozzi@unifi.it; l.vignozzi@dfc.unifi.it

[1] Department of Experimental, Clinical, and Biomedical Sciences "Mario Serio", University of Florence, Viale Pieraccini 6, 50139 Florence, Italy

[2] Andrology, Women's Endocrinology and Gender Inconguence Unit, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

[3] Medicine and Surgery, Section of Endocrinology, Federico II, University of Naples, Naples, Italy

[4] Endocrinology Unit, Medical-Geriatric Department, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

[5] Istituto Nazionale Biostrutture e Biosistemi, Rome, Italy

Introduction

Female sexuality is influenced by several factors, ranging from organic to relational and socio-psychological conditions. To date, there is an increasing interest on the role of female sexual dysfunction (FSD) in the *consideration* of the *diagnostic* and *therapeutic* management of chronic diseases. Women with chronic illness and physical disability may need professional healthcare to deal with sexual problems in order to improve their quality of life. It has long been established that erectile dysfunction (ED) is a warning sign for cardiovascular risk in men, even for men without known classical risk factors [1]. In contrast to the male counterpart, there is little evidence focusing on the association between chronic diseases and female sexual wellness. Chronic diseases can cause sexual dysfunction through different mechanisms. The aim of this

review is to summarize existing evidence on the association between the most common, chronic, non-oncological conditions and FSD. The objective of our review is also to frame systematically experimental findings into a comprehensive overview on candidate mechanisms through which chronic diseases drive FSD pathogenesis. In particular, we focused on cardio-metabolic, respiratory, renal, neurologic and rheumatologic diseases that have not been deeply analysed so far (Fig. 1). We decided to omit data on the characteristics of female sexual dysfunction in women affected by cancer, since it has been extensively discussed elsewhere [2].

FSD and Cardio-Metabolic Diseases

Even though the prevalence of FSD in patients with cardiovascular diseases (CVD) appears higher than that in the general population, paucity of data hinders in deciphering causality from this association. Indeed, the associations between female sexual health and several cardiovascular risk factors (hypertension, hyperlipidaemia, metabolic syndrome/obesity, diabetes and coronary heart disease) have been poorly explored. However, given the similarities to male ED (that is, female genital arousal disorders might occur when genital blood flow is impaired), it can be derived that CVD risk factors associated with ED might cause similarly FSD in women. More importantly, it remains unclear whether the presence of vascular-mediated FSD could be a warning sign of cardio-metabolic disease, such as diabetes mellitus (DM), metabolic syndrome (MetS), hypertension and dyslipidaemia, and/or a harbinger for an overall cardiovascular risk.

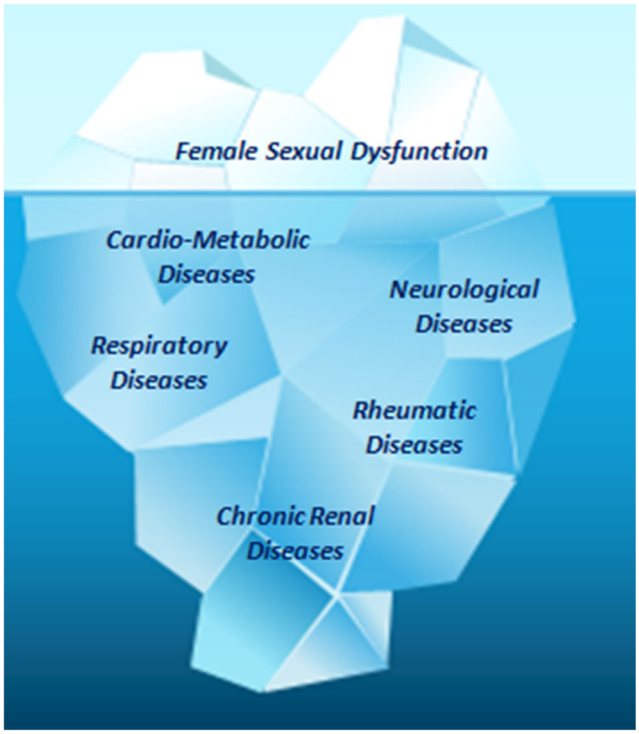

Fig. 1 FSD as a warning sign? Graphical representation of female sexual dysfunction (FSD) as the tip of the iceberg of many common chronic diseases

Diabetes Mellitus

DM is a metabolic condition often investigated as a possible determinant for FSD in women. In particular, in research on DM, women with type 1 diabetes mellitus (T1DM) have frequently demonstrated a Female Sexual Function Index (FSFI) score below the clinical cutoff points [3–6]. In fact, in a multivariate model, the presence of T1DM predicted lower FSFI scores independently from the age, duration of diabetes, body weight and presence of angiopathy [6]. Maiorino and colleagues found that some psychopathological conditions, such as depression, were independent predictors of FSFI score in the overall group of diabetic women [5]. Accordingly, an impaired sexual function was demonstrated only in T1DM women on multiple daily injections of insulin (MDI), but not in those wearing an insulin pump [5]. These data lend support to the concept that, although DM is a chronic disease with important neurovascular complications, its related psychological comorbidities might play a major role in the pathogenesis of DM-related FSD.

Comparative data about the impact and prevalence of FSD in women with T1DM and type 2 diabetes mellitus (T2DM) indicated that T1DM women suffer from a more severe sexual impairments compared to T2DM [3, 4]. This is caused, most probably, by the longstanding natural history of T1DM, which has a longer time to orchestrate pathological consequences and complications. Moreover, T1DM, as several other chronic diseases, is more often characterized by a negative attitude toward sexuality [7], which is more frequently worsened by anxiety [8]. While anxiety is more common in T1DM [8], depression has been reported to be more frequent in T2DM [9]. Several studies found that decreased sexual desire is the FSD more often reported by women with DM [10], especially in T2DM. In these patients, a depressive state plays a major role in explaining this association [9, 11]. Additionally, insulin resistance is a predisposing condition for the development of T2DM and is correlated to FSD [12]. Preclinical studies using a streptozotocin (STZ)-induced T1DM in rodents have consistently reported decreased sexual behaviour (decreased lordosis quotient and lordosis intensity) [13, 14] and increased aggressiveness in hyperglycaemic female animals, which were partially counteracted by insulin treatment [15].

Moreover, arousal and lubrication are also impaired in women with DM [16•], most probably through neurovascular alterations, which compromised both clitoral tumescence and vulvar sensitivity [17]. A few studies reported a clear correlation between impaired arousal and reduced vascular genital flow in DM women [18]. In a recent review, our group

reported that approximately 60% of the analysed studies showed an impairment of orgasmic function and an increase in pain, whereas sexual satisfaction was the least affected domain [16•]. In a previous study on 71 FSD patients, we also demonstrated that clitoral pulsatility index (PI) correlated with MetS (in particular with insulin resistance), number of MetS components and obesity, independently of age, smoking habit and years of menopause. Women with a higher clitoral PI, which reflects higher vascular resistance, reported a decreased subjective sexual arousal [17]. Accordingly, in a recent small study enrolling 38 T1DM women who underwent microbiopsy of the clitoral body during surgical procedure for a benign gynaecological pathology, Caruso and colleagues described the presence of ultrastructural abnormalities (increased glycogen and lipoic deposits, cytoplasmic vacuoles) in clitoris smooth muscle cells (SMCs) [19].

In conclusion, although clinical and preclinical studies demonstrate that FSD frequently coexists with DM in the females, a cause-effect relationship between these two clinical conditions is not fully demonstrated. Further longitudinal studies are needed to clarify this topic.

Dyslipidaemia

Esposito et al. [20] first reported an increased prevalence of FSD in premenopausal patients with dyslipidaemia. In particular, these authors found that high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were independent predictors of a lower FSFI score. Later, Baldassare and colleagues demonstrated that an increased Framingham risk score, an index of cardiovascular disease prognosis, was associated to an almost doubled odds of developing FSD [21]. Interestingly, a recent study suggested a potential pathogenic mechanism underlying this association. In fact, in women seeking medical care for FSD, decreased HDL-C levels and increased triglycerides and total cholesterol levels were correlated to an increased vascular resistance in the clitoris, with a parallel worsening of the FSFI arousal score; this association was independent of menopausal status and age [13].

Hypertension

In a retrospective study, fertile female patients with a history of mild hypertension presented decreased vaginal lubrication, less frequent orgasm and more frequent pain, as compared with healthy controls [22]. More recently, a similar study reports that hypertensive women were 1.67 times more likely to have FSD as compared to normotensive ones; in particular, all the FSFI domains, except desire, were more often compromised in the first group as compared to the other one [23]. Noteworthy, two independent meta-analysis confirmed a significantly higher risk of sexual dysfunction in women with hypertension as compared with the normotensive group [24, 25]. This increased risk was not modified by any of the analysed anti-hypertensive treatments (alpha-/beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and diuretics). In fact, there was no statistical difference of sexual dysfunction in women with hypertension who were treated vs. untreated [25]. In contrast to findings in other chronic illnesses reviewed above, another study revealed that FSD in hypertensive women is unrelated to psychological symptoms, such as depression and anxiety [26]. Therefore, the contribution of organic components seems to play a major role in the pathogenesis of hypertension-associated FSD. However, further studies are needed to deeply investigate pathogenic mechanism(s) underlying FSD in hypertensive women and the relative impact of anti-hypertensive drugs and psychological comorbidities.

FSD and Respiratory Diseases

Respiratory diseases are also conditions that can worsen the quality of life and, for different aspects, sexual wellbeing.

Asthma

Asthma is characterized by airway inflammation, hyperresponsiveness, reversible bronchial obstruction and airway symptoms [27]. A recent Spanish study reported that female patients with asthma scored lower in all the FSFI domains, with the exception of pain, compared with controls [28]. In this study, patients with asthma showed a more severe impairment in the arousal domain than in the other sexual domains. To further support this association, the severity of FSD was found to decrease as a function of asthma control level [28]. However, also in patients with asthma, psychological and emotional conditions, including being afraid of initiating sexual intercourse (similar to initiating other physical activities), seemed to play a relevant role in mediating FSD. In line with this hypothesis, FSFI satisfaction score was the less compromised domain [29]. Accordingly, in a group of patients occurring in emergency room for disease reactivation, sexual wellbeing was found to be one of the most frequent quality of life aspects which were reported as impaired by asthma [30].

Obstructive Sleep Apnoea Syndrome

Obstructive sleep apnoea syndrome (OSAS) is another important chronic lung disease, which is characterized by repetitive episodes of apnoea and upper airway collapse during sleep. In a recent review, the prevalence of FSD in patients with OSAS varied from 32.2 to 71 % [31]. Interestingly, even though in a case-control study, desire, arousal and orgasm scores were reported to be all significantly reduced in the OSAS group

compared to controls, FSFI domains did not correlate either with specific OSAS severity scale or with other scales related to frequent OSAS consequences [32]. Two of these consequences can be daytime sleepiness and depression symptoms [32]. One of the most common female sexual dysfunctions was diminished desire in two groups of women with OSAS (mild and moderate-severe) as compared to controls, but once again without any significant correlation with OSAS severity [33].

In a more recent Italian study enrolling premenopausal obese women with OSAS, sexual symptoms and distress were mainly related to nocturnal hypoxia (which is tightly dependent on OSAS severity) but not with the use of antidepressant medications [34]. This is an important finding to be discussed since depression and the use of antidepressant are often recognized as the major determinants in the observed association between FSD and chronic diseases. In line with this view, depression frequently affects OSAS groups with a higher prevalence than in general population. However, at least in men, other pathogenic mechanisms should be recognized as potential link between OSAS and sexual dysfunction. Indeed, it is well known that male OSAS patients frequently demonstrated a hypogonadotropic hypogonadism, and this reduction of testosterone levels significantly correlated with a reduction of sexual desire [33]. This data suggests that some non-psychological determinants might play a role in the pathogenesis of hypoactive desire disorder, at least in male patients with OSAS.

Although testosterone is known to play a relevant role not only in male but also in female sexuality, the potential contribution of alterations in androgens has not been studied in female subjects with OSAS. Moreover, a marked decrease in lubrication was described in moderate OSAS patients [33]. It can be speculated that this alteration is secondary to low sexual desire and/or a result of associated hormonal unbalance. In support of the view that hormonal influences play a significant role, there is a higher prevalence of OSAS in patients with polycystic ovary syndrome (PCOS) phenotype, and in particular in those overweight/obese and with insulin resistance [35]. This might be due to the fact that obesity increases risk for OSAS by altering normal upper airway mechanics during sleep [35]. However, it has also been proposed that OSAS increases gonadotropin-releasing hormone as well as luteinizing hormone and follicle stimulating hormone pulsatility leading to a hormonal unbalance in the PCOS phenotype. Interestingly, it has also been described that the prevalence of OSAS increases after menopause in women receiving no hormonal replacement therapy [36]. Finally, another potential mechanism linking OSAS to FSD based on nitric oxide (NO) has been suggested: in fact, it was previously demonstrated that circulating NO is decreased in OSAS and increases using therapy as C-PAP [37]. NO is the most important neurotransmitter mediating vascular relaxation in both vaginal and clitoral tissue [33]. Therefore, reduction of NO might contribute to the impaired lubrication. In conclusion, it may be suggested that OSAS induce FSD by endothelial NO alterations, hormonal dysregulation and metabolic and psychological disturbances, although more research is needed [38].

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disorder caused by mutations of a gene that encodes a chloride-conducting transmembrane channel (CFTR). This disease affects several body systems, including the pancreas, liver, sweat glands and reproductive apparatus, although morbidity and mortality are mostly caused by a respiratory impairment [39]. In female patients, CF could be associated to both reproductive and sexual complications. In a case-control study, 16% of 188 young patients with CF had sexual dysfunction; in addition, only 55% of women with CF had vaginal sex with a male partner, as compared to 66% of control group [40]. This fact could be related to the concerns and/or difficulties of these girls to initiate sexual relations due to specific symptoms associated with the disease. For example, in this study, one third of women with CF reported coughing during or after sexual activity for at least half of time. In another study, using a gender-specific version of Sexual Satisfaction Questionnaire (SSQ), there was a correlation between sexual satisfaction and quality of life in both male and female CF subjects. In all patients (male and female), SSQ scores correlate with the majority of domains of Cystic Fibrosis Questionnaire [41]. Moreover, women with CF have also other specific sexual and reproductive complications, including disorder of pubertal timing and irregular menses, increased odds for vulvo-vaginal infections (mainly candidiasis), urinary incontinence and decreased fertility [42–45]. Finally, we should consider that CF patients face important physical, psychological and social challenges that can deeply affect their self-sexual esteem.

FSD and Renal Diseases

Chronic Renal Disease

SD is common in terminal chronic renal disease (TCRD) women, with a significant impact on the quality of life [46, 47]. Specifically, SD affects 80% of women in haemodialysis (HD) and 25–30% of female patients with renal transplantation (RT) in reproductive age [48, 49]. The reasons for SD in dialysis patients include physiologic alterations, comorbidities, treatments and psychological aspects.

Basok and colleagues showed that FSD worsens as a function of chronic renal disease progression and that pre-dialytic patients scored worst on the FSFI [50]. Interestingly, RT was the best treatment option to improve sexual function. In contrast, Raggi et al., investigating sexual life before and after RT,

found an important decrease in desire and frequency of sexual intercourse after RT, even if the quality of life and quality of relationship were preserved [51]. Filocamo et al. reported that, before RT, 41% of women under dialysis were sexually active and 62.5% of them reported FSD. After RT, 88% of these women were sexually active and 32.3% reported FSD [52]. These results suggest that RT induced an important improvement of sexual function as demonstrated by increased FSFI scores, as well as a concomitant decrease of prolactin levels. Another study, which aimed to compare sexual function between women receiving RT and HD, concluded that RT was associated with better sexual outcomes, in particular with an improvement in sexual satisfaction and a decrease in sexual fear [47]. Another study reported a worsening in almost all parameters of sexual function during HD treatment, followed by a significant improvement after RT, almost reaching the level observed in controls [53]. Moreover, one study analysed the arterial stiffness and cardiovascular (CV) outcome in patients (both men and women) on HD with or without sexual dysfunction [54]. Interestingly, arterial stiffness, an early marker of CV mortality, was higher in end-stage renal disease patients with SD than in patients without SD [54]. Similar results were previously reported in men with ED, for which SD is now considered an early manifestation of a possible CV disease [55, 56]. Further studies are needed to demonstrate that a sexual symptom could be an early predictor of CV events in these women.

FSD and Neurologic Diseases

The impact of neurologic disease on female sexual dysfunction is complex, since several shared pathogenic mechanisms might underpin these conditions. For example, sexual dysfunction could be not only a direct complication of the neurological disease per se but also a side effect of the medication used to treat the condition or of a (negative) psychological reaction of patients to the symptoms of the neurological disorder.

Migraine

Migraine is a chronic disorder affecting 17% of women [57]. It is associated with several FSD conditions such as higher sexual pain, satisfaction disorder and difficulties in lubrication and orgasm [58, 59]. Few studies have investigated the effects of primary headaches (migraine and tensio-type headache) on sexual function [59, 60]. They essentially show a significant reduction of all domains of FSFI [59, 60]. In particular, a significant association was found between FSD and primary headaches [60, 61]. Interestingly, different contributing factors were evaluated, but neither BMI nor hormonal alterations significantly mediated the association between migraine and FSD [60]. In contrast, anxiety and depression seems to play a major role in the pathogenesis of migraine-associated SD [62]. In particular, Dogan was the first to study if, in women with migraine, FSD was due to depression and/or anxiety or to any endocrinologic alteration. Indeed, one of the most important triggers of migraine is hormonal fluctuations, especially those occurring during the perimenopause [63]. This implies that the large drop in estradiol levels, which can occur during reproductive life transitions and/or during hormonal contraception, might affect the course of migraine. Indeed, FSD, and in particular reduced arousal and lubrication, is often present in women with migraine [63]; however, these symptoms seem to be more related to depression and anxiety and not to frequency or severity of migraine [63]. Interestingly, a positive correlation was also found between prolactin level and reduced desire and lubrication, suggesting that this hormone might have an effect on FSD. However, conclusive evidence should not be drawn, since this correlation was not adjusted for obvious confounding factors, such as migraine medication use [63].

Parkinson's Disease

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, affecting 1% of patients over 60 years. It is characterized by motor and non-motor symptoms, related to nigrostriatal dopaminergic denervation and extra-nigral neurodegeneration [64]. Autonomic dysfunction is a relevant, multifaceted, feature of PD [65], ranging from orthostatic intolerance to vasomotor dysfunction, gastroparesis, diarrhoea, constipation, bladder disturbances, visual abnormalities and sexual dysfunction [65]. In the *Tracking Parkinson's* study, a large prospective, observational, multicentre project in the United Kingdom (UK), the most frequent sexual symptoms were reduction of vaginal lubrication and anorgasmia [66]. Another potential pathogenic mechanism of FSD associated to PD was cortical thinning in several key brain areas including the right frontal orbit, rectus and cingulum. These alterations are closely correlated with some clinical manifestations including the sexual desire disorder in the mid-stage PD patients [67].

In PD, the quality of sexual life and sexual self-esteem are impaired [68, 69]. The most frequent alterations reported are orgasm dysfunctions, fear of not fulfilling sexual expectations of their partners and consequent avoidance of sexual activity [70]. Another important contributing factor to FSD in PD is patient's depression that can lead to an avoidance of sexual activity for the fear of a possible partner's rejection; at the same time, partners of PD patients develop low sexual motivation for the fear to be ignored [68, 71, 72]. In PD patients, SD is also emphasized by drug therapy, especially tricyclic antidepressants and atypical neuroleptics [73, 74]. In conclusion, PD influences patients' sexuality negatively,

independently of age, disease duration or disease severity [70]; however, women show lower sexual dysfunction and impairment of their sexual relationship than men [70].

Epilepsy

SD is common in epileptic women; however, quantification of SD is limited by the paucity of validated scales [75, 76]. SD in epileptic women is associated to sexual desire reduction, pain during sex, vaginal dryness, anorgasmia, fear of being rejected, fear of seizure during sexual intercourse, fear of unwanted pregnancy and physical disability due to use of antiepileptic drugs [77]. Depression and anxiety have a potential impact on sexual function also in these patients [78]. Since epileptic women often take several medications, it is difficult to distinguish the illness-specific and/or pharmacologic impact on sexual function [79]. Animal studies support the hypothesis that hypo-sexuality occurs as a result of epileptiform neural activity in the temporal lobe, but not in the motor cortex [79]. Several studies report an orgasmic dysfunction in epileptic women [80–83], as demonstrated by the significant decrease of the genital blood flow during erotic visual stimulation, which suggests a possible relation with altered neural activity in the limbic and frontal areas by epileptic activity. Moreover, the decreased genital blood flow could also contribute to orgasmic dysfunction [84]. With regard to medication-induced hormone alterations, several studies report a decrease of free testosterone levels, due to an increased sex hormone binding globulin production by the liver, which caused sexual arousal insufficiency and SD [85, 86]. In summary, SD is common in epileptic patients and impacts on quality of life and relationships.

Stroke

Stroke is associated to negative changes in sexual functioning, including decreased libido and alterations in arousal, orgasm and vaginal lubrication [87]. One complication of this literature is a narrow age range in the mean age of patients enrolled in most studies, which is generally between 60 and 65 years [88]. In the literature, there are only descriptive studies, reporting a prevalence of SD ranging from 29 to 94.8% (in both genders), but it was not clear if SD was more often reported in men or in women [88–90]. Further studies are needed to understand sexual concerns, activity and dysfunction in women following stroke [91], especially in the younger age bands. The anatomic location of the stroke seems to be related to the extent of sexual function impairment. For example, SD occurs more frequently in women with a right hemispheric stroke [92], which is also more frequently associated to emotional lability [93]. Although hypo-sexuality is the most common post-stroke event, some patients exhibit hypersexuality [94]. Available studies report a reduction in coital frequency, changing from weekly to monthly or even less often, which was mainly the result of sexual dissatisfaction, occurring in the post-stroke period [95]. Associated parallel reduction of libido, orgasm and vaginal lubrication was also described in women following stroke [96]. Women affected by stroke seem to suffer also from a lower sense of emotional closeness including loss of intimacy [97]. Recently, a panel of experts reached a high level of consensus that sexual rehabilitation should start during the sub-acute phases of stroke recovery, once patient is medically stabilized, and continue across the chronic stages of stroke recovery [98]. These results will be used to design an intervention to address sexuality after stroke. In the literature, there are no available data on sexual function prior to stroke in male and female patients. This is a limitation to identify comorbidities and risk factors associated with stroke that can contribute to SD (i.e., hypertension, dyslipidaemia, diabetes, metabolic syndrome and smoking) [16•].

Spinal Cord Injuries

Spinal cord injuries (SCI) lead to significantly impaired functional capacity of patients including devastating motor, sensory and autonomic deficits [87]. Sexual dysfunction is one of the most frequent disabilities reported in women with SCI [99]. However, sexually active women can obtain sexual pleasure and orgasm through psychogenic stimulation (in case of lower spinal cord lesions) or genital stimulation (in case of higher spinal cord lesions) [100]. One study found significant association between the psychogenic genital responsiveness and the degree of combined pinprick plus light touch with an important role of thoracic and lumbar sympathetic fibres to promote increased genital blood flow [101]. In Australia, the SR-iSCI-sexual database provides information regarding patient-reported sexual functioning after spinal cord disease to facilitate comparative studies [102]. In these patients, sexual rehabilitation has a central role, emphasizing both genital function and psychosocial factors [103, 104]. Self-exploration should include not only clitoral stimulation, but also vaginal, G spot and cervix stimulation [105]. Locomotor training (LT), an effective therapeutic strategy for improving motor outcomes following SCI, improves bladder, bowel and sexual function, most probably because of existing overlap of lumbosacral spinal circuitries that regulate pelvic-visceral and locomotor functions [106]. Thus, activating lumbosacral spinal circuits chronically by LT might promote adaptive changes to other systems such as those controlling urogenital and bowel functions [107, 108]. In another small study, the multi-step, non-invasive neuro-rehabilitation protocol, named the Walk Again Neuro-Rehabilitation (WA-NR), induced an improvement in nociceptive, tactile and proprioceptive function, along with a significant improvement in multiple visceral functions (bladder control, bowel function and sexual functions in some

patients) [109, 110]. These clinical benefits were most probably due to a complex reorganization in the body perception, with a major sensory recovery that occurs in the areas of the body innervated by portions of the spinal cord below the original anatomical lesion [110]. Medical treatment could include phosphodiesterase type 5 inhibitors to improve GBF [111, 112], flibanserin as an antidepressant [113] or device such as the Eros clitoral therapy device (CTD) [114].

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and neurodegenerative disease with a typical onset between 30 and 40 years [115]. SD is considered one of the most common symptoms of the disease, affecting 40–80% of female patients [116] with a significant impact on the quality of life [117]. There are three types of SD in MS patients. Primary SD is caused by direct demyelination in regions affecting sexual response with consequent inability to achieve orgasm and difficulties with arousal. Secondary SD depends on physical signs as increased fatigue, pain due to inadequate lubrication, motor deficit or muscle spasticity. Finally, tertiary SD is caused by psychological and sociological impairment, often mediated by lower self-esteem and depression [118, 119]. A recent survey detected the impact of psychiatric comorbidities on SD in female patients with relapsing-remitting MS, demonstrating the association of SD with depression and fatigue intensity, more advanced age at diagnosis and lower education level [120]. Besides a significant reduction in frequency of sexual intercourse after diagnosis, another study reported that anorgasmia was the most common FSD (58%); however, masturbation was practiced by only 23% of the patients [121], thus suggesting a possible overestimation of the problem.

FSD and Rheumatic Diseases

Several rheumatic diseases, mainly those associated to autoimmunity, occur more often in females than in males. Relationships between FSD and rheumatic chronic conditions are again unclear. Hence, there is a need to perform longitudinal studies for assessing the effect of treatments on sexual function in this unique group of patients.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease caused by immune-mediated deterioration of joints. A recent review emphasized three aspects that can cause FSD in RA: (1) physical disorders such as reduced mobility and increased pain; (2) psychological aspects such as depression, anxiety and low self-esteem; and (3) hormonal alterations [122•]. Indeed, it was previously reported that female patients with RA showed reduced androgen levels [123]. A case-control study showed that all domains of FSFI, except pain during sexual intercourse, were often compromised in RA [124]. These patients, who often have chronic pain, did not perceive this symptom as disabling [125]. Interestingly, lower satisfaction score and FSFI total score were observed in RA patients who reported prolonged morning stiffness of the joints as compared with those RA patients without this symptom [126]. Perceived depression affects sexual wellbeing in RA patients, confirming the important role of RA diagnosis on this aspect of life [127]. In fact, Khnaba et al. identified the level of pain and depression as the major determinant of SD in RA patients [128]. In another recent study in male and female patients, a correlation between physical fitness and sexual performance/satisfaction was found; specifically, the inability to rise from a chair was positively associated with a reduced sexual function, independent of disease activity and pain intensity [129]. In a cross-sectional study, the authors confirmed that women with RA had more sexual problems as compared to healthy controls, even after adjustment for confounding variables [130]. A recent study compared sexual function (as assessed by FSFI) of three female populations: those with rheumatoid arthritis (RA), those with psoriatic arthritis (PsA) and healthy women [131]. Interestingly, RA and PsA women demonstrated higher rates of sexual dysfunction across each of the FSFI domains when compared with women without inflammatory arthritis; however, there was no statistically significant differences observed between the RA and PsA groups [131]. In this study, sexual dysfunction was not found to correlate with disease activity, such as patient pain or patient global status [131]. Finally, all the reported studies highlight the need to evaluate also sexual health in the management of RA in daily clinical practice.

Sjögren's Syndrome

Sjögren's syndrome (SS) is a frequent rheumatologic autoimmune disease, characterized by a lymphocytic infiltration of the secretory glands. Numerous patients with SS manifest signs of systemic dryness, known as Sicca syndrome (SiSy) which involves the nose, the trachea, the vagina and the skin, indicating that other glands are also affected beyond the exocrine epithelia [132]. Therefore, vaginal dryness is a clinically relevant manifestation of SS in women [133]. Indeed, Maddali Bongi et al. found that the most frequently reported sexual-related symptoms in patients with SS and SiSy were vaginal/vulvar dryness, lower sexual drive and fatigue [134]. In addition, the majority of patients also reported negative changes in their sexual routine according to the onset of the disease, with a reduced frequency of sexual intercourse due to gynaecological symptoms [134]. Another notable finding of this study was that several patients reported that health

Table 1 Sexual disorders in chronic diseases basing on reported studies with related levels of evidence

Chronic diseases	Sexual disorders	Levels of evidence
Cardio-metabolic diseases		
Diabetes mellitus	• Low sexual desire often caused by psychological comorbidities is often described [8, 9]	2
	• Neurovascular alterations can impair arousal and lubrication [16•, 17]	3
	• Satisfaction seems to be the low impaired sexual component [16•]	3
Dyslipidaemia	• Reduced FSFI score [20, 21]	3
	• Increased clitoral vascular resistance with a parallel worsening of the FSFI arousal score [17]	3
Hypertension	Decreased vaginal lubrication, compromised orgasmic function and sexual pain [22]	3
Respiratory diseases		
Asthma	• Arousal disorders mainly influenced by psychiatric and emotional conditions [29]	3
	• Pain is the less impaired domain [29]	3
OSAS	• Sexual desire problems may be related to psychological component [33]	3
	• Correlation between low desire and testosterone levels [33]	3
	• Ipo-lubrication probably due to NO pathway alterations [33, 37, 38]	1, 3
Cystic fibrosis	• Disease-related symptoms (as cough) could prevent sexual intercourses and this can cause low satisfaction [40]	2
Renal diseases		
Chronic renal disease	• Renal transplantation improves sexual health in female patients [47, 51, 52]	2, 3
Neurologic diseases		
Migraine	• Strong correlation between FSD and degree of anxiety [62]	3
	• Sexual hormones impact on FSD (PRL on desire and lubrication; FSH on orgasm; LH on pain) [63]	3
Parkinson	• Decreased quality of sexual life and sexual self-esteem also due to psychological factors [68, 72]	2
	• Negative influence of specific drugs [73, 74]	2, 3
Epilepsy	• Potential impact of depression and anxiety on FSD [78]	2
	• Decreased genital blood flow [84]	2
	• Negative impact of drugs on hormonal levels [85, 86]	2
Stroke	• Influence of anatomic location on FSD [92]	2
	• Compromised quality and quantity of sexual intercourse [95, 96]	2
Spinal cord injuries	• Sexual satisfaction depends on lesion's localization [100]	2
	• Sexual rehabilitation could be useful [103, 104]	2
Multiple sclerosis	• FSD depends on anatomic alterations and physical/psychological consequences [118, 119]	2, 3
	• Anorgasmia is often reported [121]	2
Rheumatic diseases		
Rheumatoid arthritis	• SD caused by physical disorders, psychological aspects and hormonal alterations [122•, 123]	1, 2
	• Dyspareunia not always perceived as disabling [125]	3
Sjögren's syndrome	• Desire and arousal alteration as consequence of pain and lower lubrication [134, 135]	2, 3
	• Bidirectional association between mood disorders (anxiety and depression) and sexual impairment [136]	3
Systemic lupus erythematosus	• No association with disease duration [138]	3
	• Due to disease heterogeneity multidisciplinary team needed [139]	3

professional never asked them about their sexual life before the study [134]. A recent case-control study showed that FSDS score as well as all the FSFI domains, except satisfaction, were worse in SS patients; lubrication was one of the most affected domains and, in fact, SS patients reported a frequent use of lubricants [135]. Moreover, in this study, sexual problems were related to patient-reported SS symptoms, symptoms of fatigue, depressive symptoms, relationship dissatisfaction and lower mental quality of life but not with systemic disease activity [135]. In line with this, Priori and colleagues demonstrated that total FSFI score was lower not only in postmenopausal SS women but also in young fertile SS women, as compared to controls. A bidirectional association between mood disorders (anxiety and depression) and sexual impairment was also found in SS patients [136]. In contrast, no associations were found between vaginal pH

and FSFI total score or between disease activity and quality of sexual life [136].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a condition with clinical and serological heterogeneity and is more frequent in women than in men [137]. SLE is associated with strongly impaired quality of life. There are few studies investigating about the effects of this disease on sexual wellbeing. A recent study indicates that all FSFI domains were more compromised in SLE patients than in healthy controls; moreover, sexual problems seemed not to be associated with disease duration [138]. A recent meta-analysis confirmed that FSFI total score was lower in SLE patients than in controls, but no difference was found in any single FSFI domains. SLE might also affect psychological health. In this respect, Shen et al. demonstrated that body image disturbance was tightly associated with sexual problems in a group of Chinese SLE patients. This finding underlines the importance of establishing a multidisciplinary working team to assess and to also manage psychological factors and not only the organic components of SLE [139]. To date, it is still hard to understand the relation between SLE and sexual problems: organic, psychological, relational and social factors are involved but their association needs to be further investigated.

Conclusions

All chronic diseases have several consequences on patients' quality of life. In this brief review, we summarized evidence concerning sexual function and dysfunction in women affected by common chronic diseases (Table 1). Management of sexual dysfunction is an important task to improve the overall quality of life of patients suffering from chronic, longstanding and often progressive diseases. It is also possible that sexual symptoms might be a warning sign for unrecognized conditions (for example, vaginal dryness for SS, as discussed above), although this is far to be completely understood. Although in men, sexual dysfunction is recognized as a possible harbinger of chronic illness, this point is not as clear in women, probably due to many factors: FSD is more difficult to measure qualitatively or quantitatively than ED; non-genital arousal may be involved to a greater extent in women; there are differing expectations of sexual function for women, particularly in postmenopausal period; there may be greater reluctance of physicians to elicit sexual history in their female patients; and assessment questionnaires for FSD are not widely used in clinical settings.

Therefore, there is an emerging need for research in FSD to improve the tools for investigating SD in patients with chronic diseases. For example, new specific validated questionnaires could be helpful for specific groups of patients, because the available interview is not always applicable or validated in patients affected by chronic disease. However, psychopathological conditions, such as anxiety and depression, represent a crucial intertwining factor between SD and chronic diseases. Therefore, a multidisciplinary team working together to manage all the aspects and complications of the chronic disease is extremely important. Not all women are the same and healthcare professionals should have the ability to understand who wants to face this sensitive aspect of their lives.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

All reported studies with human performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards and international/national/institutional guidelines).

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