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Review

Sexual Dysfunction in Diabetic Women: An Update on Current Knowledge

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Abstract: Diabetes mellitus (DM) is one of the most common chronic diseases worldwide and its prevalence is expected to increase in the coming years. Therefore, updated knowledge of all diabetic complications and their management is essential for the proper treatment of these patients. Sexual dysfunctions are one of the long-term complications of DM in both genders. However, female sexuality is still a taboo and sexual concerns are often overlooked, underdiagnosed, and untreated. The aim of this review is to summarize the current knowledge on the relationship between sexual function and DM in women. In particular, we evaluated the prevalence, etiology, diagnostic approaches, and current treatment options of female sexual dysfunction (FSD) in diabetic patients.

Keywords: female sexual dysfunction; sexual health; sexual distress; diabetes; hyperglycemia

1. Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide. The global diabetes prevalence in 2019 has been estimated to be 9.3% (463 million people) and this number is expected to increase by 25% in 2030 and by 51% in 2045 [1]. DM is associated with many long-term systemic complications among which sexual dysfunction is one of them in both genders. In recent years, this aspect has been more extensively studied in men than in women. Sexual dysfunctions in diabetic women are often overlooked due to social taboos on female sexuality [2]. Nevertheless, the analysis of the National Health and Social Life Survey showed that sexual dysfunctions are more frequent in women (43%) than in men (31%) in the US population [3]. In recent years, the attention on female sexual dysfunction (FSD) has been growing. The World Health Organization (WHO) declared female sexuality to be not only part of health quality but also a basic human right [4]. Therefore, the aim of this review is to summarize the current knowledge on the relationship between sexual health and DM in women. In detail, we evaluated the prevalence, etiology, diagnostic approaches, and treatment options of FSD in diabetic women.

2. Physiology of the Female Sexual Response

Masters and Johnson first described the physiological responses to sexual stimulation in their book *Human Sexual Response*, published in 1966 [5]. According to their model, the female sexual response can be divided into four phases: excitement, plateau, orgasm, and resolution. At the same time, later, Kaplan introduced the aspect of "desire" and proposed a three-phase model consisting of desire, arousal, and orgasm [6]. However, women often describe an overlapping of sexual response phases in a variable order. Therefore, more recently, Basson suggested that the female sexual response is not a linear progression of phases but it can be considered a circular sex response cycle with

overlapping phases. This model also introduced the importance of multiple psychosocial factors such as emotional intimacy, satisfaction with the relationship, self-image, and earlier negative sexual experience, which can significantly impair female sexuality [7].

Sexual desire is regulated by the effects of various neurotransmitters. Upon activation of the central nervous system and related limbic-hippocampal structures responsible for sexual arousal, electrical signals are transmitted through the parasympathetic and sympathetic nervous system. During sexual arousal, genital vasocongestion occurs as a result of increased blood flow. Increased blood flow to the clitoral cavernosal and labial arteries results in increased clitoral intracavernous tumescence, and engorgement and eversion of the labia minora. The vaginal canal is lubricated and it dilates as a result of relaxation of the vaginal wall smooth muscle [8]. Thus, as in men, sexual response is a neurovascular-dependent event. Previous studies have shown that the nitric oxide-cyclic guanosine monophosphate–phosphodiesterase type 5 pathway plays a pivotal role in modulating blood flow and smooth muscle relaxation in both clitoris and vagina [9]. The vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) are nonadrenergic/noncholinergic neurotransmitters (NANC) which are involved in modulating vaginal relaxation and secretory processes. Moreover, sexual hormones play a significant role in regulating female sexual function [8].

3. Female Sexual Dysfunction

Many studies report a high prevalence of sexual dysfunctions in women. In contrast, FSD is often undiagnosed and almost always undertreated [10]. Thus, data on the real prevalence of FSD are difficult to obtain and they are generally underestimated. According to the data of "The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study", involving 31,581 US women, sexual problems (desire, arousal, and orgasm) affect 43.1% of women. Hypoactive sexual desire is the most common dysfunction reported by 39% of women, low arousal by 26%, and orgasm problems by 21% [11]. In Europe, the "Women's International Sexuality and Health Survey" (WISHeS), conducted in 1356 women from Germany, United Kingdom, France, and Italy, reported a prevalence of FSD in 29% of women [12].

FSD is a heterogeneous group of disorders that can be related to desire, arousal, orgasm, or sexual pain [13]. During the last decades, several definitions and classifications of FSD have been proposed. Figure 1 reports the history of the main classifications of FSD and the main classifications of FSD are described in Table 1.

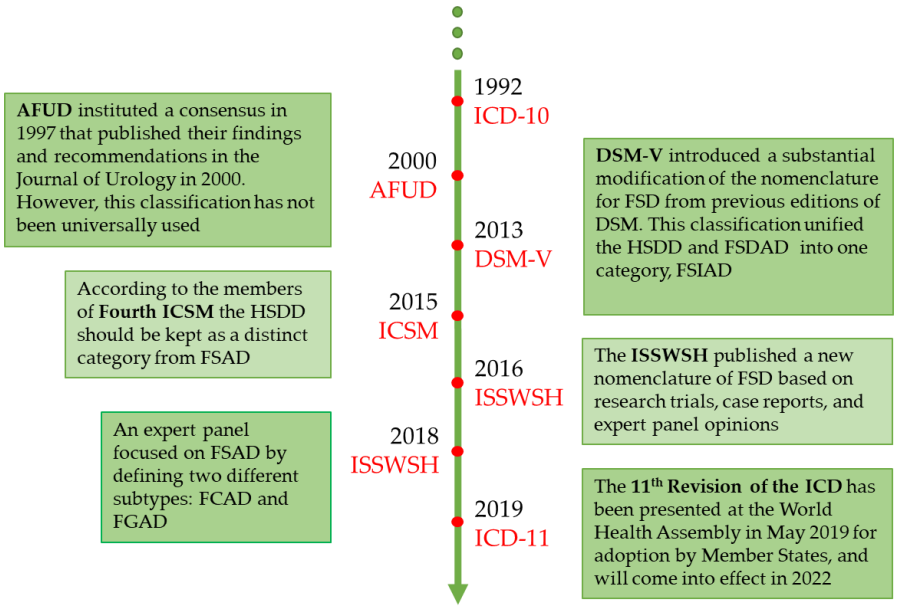

Figure 1. History of the main classifications of female sexual dysfunctions.

Table 1. The main classifications of female sexual dysfunctions proposed during the past decades.

ICD		DSM	ICSM	ISSWSH	
ICD-10	**ICD-11 (Proposed)**	**DSM-V**	**Fourth ICSM**	**ISSWSH-2016**	**ISSWSH-2018**
1. Lack or loss of sexual desire	Hypoactive sexual desire dysfunction	1. Female sexual interest/arousal disorder	1. Hypoactive sexual desire dysfunction	1.Hypoactive sexual desire disorder	1.Hypoactive sexual desire disorder
2. Sexual aversion	*Recommended for deletion*	2. Female orgasmic disorder	2. Female sexual arousal dysfunction	2. Female genital arousal disorder	2. Female sexual arousal disorder: *-Female cognitive arousal disorder -Female genital arousal disorder*
3. Lack of sexual enjoyment	Female sexual arousal dysfunction	3. Genito-pelvic/ penetration disorder	3. Female orgasmic dysfunction	3. Persistent genital arousal disorder	3. Persistent genital arousal disorder
4.Failure of sexual response			4. Female genital-pelvic pain dysfunction	4. Female orgasm disorders	4. Female orgasm disorders
5. Orgasmic dysfunction	Orgasmic dysfunction		5. Persistent genital arousal disorder	5. Female orgasmic illness syndrome	5. Female orgasmic illness syndrome
6. Non organic vaginismus	Sexual pain penetration disorder		6. Postcoital syndrome (Postorgasmic illness syndrome)		

ICD: International Classification of Diseases and Related Health Problems. DSM: Diagnostic and Statistical Manual of Mental Disorders. ICSM: International Consultation on Sexual Medicine. ISSWSH: International Society for the Study of Women's Sexual Health.

According to the current epidemiology, the more recent classifications International Consultation on Sexual Medicine (ICSM), ISSWH, and ICD-11 suggest that the hypoactive sexual desire should be kept as a distinct category from the dysfunction of female sexual arousal [14]. Moreover, in recent years, sexual distress has become a key element for the definition and the diagnosis of FSD. It can be manifest as thoughts of concern, frustration, hopelessness, or distressing behaviors such as avoidance of sexual situations [14].The International Classification of Diseases and Related Health Problems, 10th Edition (ICD-10), published in 1992, and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by the American Psychiatric Association, published in 2013, have been widely used internationally. The 11th Revision of the ICD contains a new chapter on disorders related to sexual health in which modifiable psychological factors do not exclude the diagnosis of sexual dysfunction [15]. ICD-11 has been presented at the World Health Assembly in May 2019 for adoption by Member States, and will come into effect in 2022. In 2015, expert members of the Fourth International Consultation on Sexual Medicine (ICSM) reviewed previous classifications and proposed a new version. In 2016 the International Society for the Study of Women's Sexual Health (ISSWSH) published a new nomenclature of FSD based on research trials, case reports, and expert panel opinions [16]. An expert panel focused on sexual arousal disorders in women (FSAD) convened in February 2018. This panel revised the ISSWSH nomenclature published in 2016 to include female cognitive arousal disorder (FCAD) and modify the definition of female genital arousal disorder (FGAD), two subtypes of FSAD [13].

4. Sexual Dysfunctions in Women with Diabetes Mellitus

4.1. Epidemiology

Data on the prevalence of FSD in diabetic women are few and often discordant because of the lack of standardization in methods and the ongoing changes in FSD definitions and classifications [17]. However, previous studies have shown a higher prevalence of FSD in diabetic compared to nondiabetic women [18]. A meta-analysis showed a higher frequency of FSD in diabetic women than in healthy controls with an odds ratio of 2.27 in type 1 diabetes (DM1), 2.49 in type 2 diabetes (DM2), and 2.02 when considering any form of diabetes [19]. Another Italian study has shown a significantly higher prevalence of FSD in women with DM1 than in the control group (36.4% vs. 5.2%, respectively) [17]. According to a recent meta-analysis, involving 25 studies and 3892 women with an age range of 18–72 years, the overall prevalence of FSD in women DM2 was 68.6% (95% CI 61.6–75.3%) [2]. Results of meta-regression analysis have also shown a statistically significant increase in FSD prevalence in diabetic women over the years [2]. All the phases of sexual cycle response, including desire, arousal, lubrication, orgasm, and satisfaction, are impaired in diabetic women. Meeking and colleagues described a reduction in sexual desire (64%), loss of vaginal lubrication (70%), difficulty of achieving orgasm (50%), decrease satisfaction (47%), loss of genital sensation (36%), and dyspareunia (43%) in 270 women with diabetes aged 21–65 [20].

4.2. Pathogenesis

The pathogenesis of FSD in diabetic women is complex and multifactorial including both psychological and organic causes.

4.2.1. Psychological Factors

In contrast to diabetic men, several epidemiological studies have shown that psychosocial factors are more important than organic factors in the pathogenesis of FSD in both DM1 [21] and DM2 [22]. Diabetic patients have an increased risk to develop depressive symptoms compared to the healthy population [23]. Depression may significantly impair the quality of life of these patients, including sexual function [24]. Therefore, depression is recognized as the most significant risk factor for FSD in diabetic women and it may impair sexual health at different levels.

Sexual dysfunctions can also be side effects of psychopharmacological therapies, such as antidepressants, antipsychotics drugs, mood stabilizers, and anxiolytic drugs [25–27]. Additionally, other psychological problems such as altered self-image, feelings of loneliness, or isolation, loss of attractiveness are common in diabetic women [20]. Several studies have shown a higher risk of FSD in women with higher body mass index (BMI). Although organic factors may have a role in this increased prevalence, an increased BMI can also strongly alter the self-image of women, impairing the quality of sexual life [17].

4.2.2. Organic Factors

Although psychosocial factors seem to have a key role in the pathogenesis of sexual dysfunction in diabetic women, organic factors, including hyperglycemia, neurovascular alterations, hormonal changes, and recurrent genital infections can also contribute to the onset of FSD.

Hyperglycemia decreases the hydration of vaginal mucous membranes, causing a lubrication decrease and, in turn, dyspareunia [20]. Besides, hyperglycemia may increase the risk of vaginal infections [20]. Urinary tract infections (UTI) and mucosal candidiasis are common and often more severe in the diabetic population compared to healthy people [10]. In diabetic women, *Candida albicans* is the most frequent cause of vulvovaginal candidiasis [28]. Hyperglycemia increases the risk not only for incident infection but also for recurrence [28]. Numerous pieces of evidence support the link between lower urinary tract dysfunction and FSD [10]. In particular, the presence of urinary incontinence doubles the risk for decreased libido, vaginal dryness, and dyspareunia [29].

As previously reported, the sexual response is a neurovascular event also in women. It is well known that the chronic insult of hyperglycemia on the endothelium results in endothelial dysfunction. The potential mechanisms involved in endothelial dysfunction include the accumulation of advanced glycation end products, an increase in oxygen-free radicals, and a decreased bioavailability of nitric oxide (NO) [30]. In diabetic men, endothelial dysfunction and the decreased bioavailability of NO result in an insufficient relaxation of the vascular smooth muscle of the corpora cavernosa and in erectile dysfunction [30]. Similar to diabetic men, sexual dysfunctions may be associated with vascular alterations in women with DM. Studies in experimental animals have shown that DM1 alters the contractile and relaxant capacity of vaginal musculature, reduces clitoral and vaginal blood flow, and causes fibrosis of clitoris and vaginal tissue [31–33]. In diabetic women, vascular damage results in decreased vaginal blood, leading to a significantly impaired arousal response [34]. The lack of lubrication is one of the most common sexual problems in diabetic women [19] and it may explain the increased prevalence of dyspareunia, difficulty to achieve orgasm, and hypoactive sexual desire observed in diabetic women compared to healthy controls [19]. A positive relationship between the clitoral pulsatility index with metabolic syndrome and some of its components, especially insulin resistance, has been reported [35]. The pulsatility index is assessed by clitoral eco-color Doppler ultrasound and reflects clitoral vascular resistance to blood flow, which is associated with microvascular lesions [35]. Higher clitoral resistance was also associated with a reduction of sexual arousal, increased anxiety symptoms, and body image concerns [35]. In men, it has been clearly demonstrated that erectile dysfunction is a marker of increased cardiovascular risk [36]. In women, this association is less clear and sexual dysfunctions are not considered an independent marker of increased cardiovascular risk [37]. However, inadequate methodologic tools to explore cardiovascular risks in patients with FSD could have an important role in this gender difference [37].

Moreover, diabetic neuropathy may alter the normal transduction of sexual stimuli, contributing to the pathogenesis of sexual dysfunctions [38]. It has also been hypothesized that unexplained vulvodynia could be a sign of sensory diabetic neuropathy [39].

Steroid hormonal changes can also play a role in the pathogenesis of FSD in diabetic women. Steroid hormones are important to preserve the anatomy and function of female structures involved in sexuality [40]. It has been shown that DM interferes with steroid hormones at different levels. Insulin and insulin-like growth factors can regulate the activities of important enzymes of steroidogenesis, such as aromatase and 3ß-hydroxysteroid dehydrogenase [41,42]. Additionally, insulin and other growth factors stimulate the proliferation of vaginal epithelium in mice and, in the vagina, estrogens up-regulate the expression of insulin-like growth factor 1 [43,44]. Moreover, diabetes is often associated with other endocrine disorders, such as polycystic ovarian syndrome or thyroid diseases, which may contribute to the impairment of sexual function in diabetic women [45].

Regarding the relationship between the type of the therapeutic strategy for DM and sexuality, previous studies have shown a higher prevalence of FSD in women with multiple-dose injection compared to continuous subcutaneous insulin infusion [17,30]. This difference could be related to lower glycemic variability in patients undergoing the latter compared to the former [46]. Recently, Corona and colleagues have investigated the effects of novel antihyperglycemic drugs on the sexuality of both women and men. On one side, the increased risk of genital fungal infections may impair sexual function in both women and men. In contrast, the promising metabolic effects and positive (glucagon-like peptide-1 receptor agonists (GLP1RA) and sodium-glucose type 2 cotransporter inhibitors-SGLT2i) or neutral (dipeptidyl peptidase IV inhibitors-DDP4i) effect on weight could improve the gonadal and sexual function in diabetic patients [10].

4.3. Diagnosis

Recently, the International Society for the Study of Women's Sexual Health has developed a process of care (POC) that provides practical recommendations to diagnose sexual dysfunction in women [14]. This POC is addressed to clinicians with any level of competence in sexual medicine and

not only to specialists in sexual medicine. Most women find it difficult to talk about their sexual life and would like clinicians to bring up the topic to give them the opportunity to speak about sexual health. For this reason, as first step, the POC recommends a patient-centered communication in which the clinician asks about sexual satisfaction or problems. If sexual dysfunction is identified, a four-step model is proposed. This includes eliciting the story, naming/reframing attention to the problem, empathic witnessing of the patient's distress and the problem's impact, and referral or assessment and treatment. The aim of this communication is to discover the negative effect that the problem is having on the woman's life. In fact, distress is a key element for the diagnosis of FSD, as emphasized by the more recent classifications [14].

Self-administered questionnaires can be very useful. The Female Sexual Function Index (FSFI-19) is one of the most used psychometric diagnostic tests to identify FSD [47]. A reliable short version of this questionnaire, FSFI-6, is well validated for the screening of sexual dysfunction in women. It includes six domains: desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia. The score for each question ranges from 0 or 1 to 5. A total score of ≤19 allows identifying those women who need further investigation, including the full version FSFI-19 and a patient-centered interviewing [48]. In addition, another version of the FSFI-6, the Female Sexual Dysfunction Index-6 (FSDI-6), has been recently developed [49]. A question on the interest in having a satisfying sex life was added in FSDI-6 to better investigate the level of distress that may arise from the identified sexual problems.

Since women with sexual dysfunctions have a decreased perception of the orgasmic intensity compared to healthy women, recently, a new quick and easy psychometric tool, the Orgasmometer-F, has been validated for measuring the orgasmic intensity in women [50].

A physical examination should be performed to identify potential contributing factors including infections, inflammatory, atrophy, and neoplasms [14].

However, if objective investigation methods such as dynamic penile echo color Doppler can be used in men with erectile dysfunction, objective diagnostic approaches are rarely performed in clinical practice for women [37]. This inadequate evaluation of FSD is one of the main factors responsible for the lack of association between sexual dysfunction and cardiovascular health in women [37]. The main marker of sexual arousal is the increase in blood flow in the genital region. Therefore, during the years, different diagnostic systems have been validated to study the blood flow in female genitalia, including indirect measures of heat dissipation (vaginal thermistors, labial thermistor, heated oxygen electrode), vaginal photoplethysmography (VPP), and Doppler ultrasonography [37]. VPP is one of the most used tools to evaluate genital arousal in women. It consists of a clear acrylic, tampon-shaped device that contains a light source that illuminates the capillary bed of the vaginal wall and the blood circulating within it. A phototransistor detects light and the amount of back-scattered light depends on the transparency of engorged and nonengorged tissue thus, in turn, this is an indirect measure of vasocongestion. The Doppler ultrasonography is a quick and noninvasive technique that provides a real-time assessment of anatomy and blood flow of female genitalia [37]. Women with DM1 showed lower clitoral peak systolic velocity, end-diastolic velocity, and higher resistance index compared with healthy controls. After the administration of 100 mg sildenafil, the mean resistance index significantly decreases, indicating an improvement of the clitoral blood flow [51]. The clitoral pulsatility index (PI) has been correlated with metabolic syndrome and with a subjective decrease of the sexual arousal [49]. During the years, several other methods have been developed to evaluate genital blood-flow-including clitoral VPP, laser-Doppler perfusion imaging (LDPI), dynamic contrast and noncontrast MRI, pudendal arteriogram, or to the assess muscular and neural system-including clitoral electromyography. However, none of these methods is well validated and each method has advantages and disadvantages [52].

4.4. Treatment

No specific guideline is available for the treatment of sexual dysfunction in diabetic women. The change of lifestyle, including weight loss and physical activity, is the first step for the treatment of

FSD in diabetic patients. In fact, overweight/obesity is an established and independent risk factor for sexual dysfunction. Bond and colleagues reported that 60% of obese women seeking bariatric surgery had FSD. They also found that after six months from bariatric surgery the FSFI scores significantly increased (from 24.0 to 29.4) and 68% of women with FSD at baseline resolved their problem [53]. Diabetic women with higher adherence to a Mediterranean diet showed a lower prevalence of FSD compared to women with lower adherence to diet [54]. In an ancillary study of the Look AHEAD, a randomized trial evaluating the long-term effects of an intensive lifestyle intervention (ILI) on cardiovascular morbidity and mortality, overweight/obese women with DM2 were also evaluated for sexual function. Specifically, they evaluated changes in sexual function of 229 women in the ILI group compared with the controls who only received support and education. After one year, women with FSD at baseline had an improvement of their FSFI compared to the control group [55].

Psychotherapy, treatment of depression if present, and an adequate glycemic control also play a pivotal role in the improvement of sexual health [30].

Various pharmacological options may also be used. Hormonal replacement therapy is approved for postmenopausal women [30], whereas the use of androgens to treat FSD is still debated. A meta-analysis including 43 studies and 8480 postmenopausal women showed that testosterone administration is associated with a significant increase in the number of satisfying sexual events (mean difference 0.85, 95% CI 0.52.1.18) and sexual desire (standardized mean difference 0.36, 95% CI 0.22–0.50) [56]. However, oral testosterone was associated with an increase in low-density lipoprotein (LDL), whereas nonoral testosterone did not significantly affect lipid profile [56]. In the same year, a Position Statement on testosterone therapy for women recommend that in postmenopausal women with hypoactive sexual desire disorder (HSDD) with or without estrogen therapy, testosterone exerts a beneficial effect on sexual function at doses within the physiological premenopausal range (Level I, Grade A) [57]. However, although testosterone has been studied for the treatment of FSD for several years, at present, no androgen therapy has been approved for FSD by the Food and Drug Administration (FDA). A recent review of testosterone trials for the treatment of FSD has shown that there are several limitations in these studies, including heterogeneity of the sample enrolled, different instruments to evaluate outcomes, and loss of control for confounders factors. These limitations have a key role in the lack of approval for any testosterone treatment for women in several countries [58]. Phosphodiesterase type 5 inhibitors (PDE5), mediating vascular smooth muscle relaxation and increasing vasodilatation, are a very effective treatment for erectile dysfunction in men. In contrast, few successes have been reported for these drugs in the treatment of FSD [59]. Other pharmacological strategies include ospemifene, a selective estrogen receptor modulator, that has been shown effective for the treatment of vulvovaginal atrophy in postmenopausal women with vaginal dryness [60] or flibanserin, 5-HT1A agonist/5-HT2A antagonist, for women with HSDD [61]. Additionally, several nonpharmacological options can be proposed, including vaginal lasers, lubricants, moisturizers, and pelvic floor physical therapy [14]. The management of sexual dysfunction in diabetic women should be performed by a multidisciplinary team, including a diabetologist, a specialist in sexual health, and psychotherapeutics. Further studies are needed to provide effective therapeutic options for sexual dysfunction in diabetic women.

5. Conclusions

DM is one of the most common chronic diseases worldwide and its prevalence is expected to increase in the coming years. Therefore, updated knowledge of all complications present in diabetes and their management is essential for proper treatment of these patients. Despite sexual dysfunctions being one of the long-term complications in both genders, sexuality in female diabetic patients is still taboo and sexual dysfunctions are underestimated. Data on FSD in diabetic women are few also due to the lack of standardization in methods and the ongoing changes in FSD definitions and classifications. Moreover, in contrast to men, objective diagnostic approaches are rarely performed in the clinical practice for FSD.

Sexuality has a fundamental role in health quality. Thus, information and education of both patients and clinicians on sexual dysfunction are the basis for the appropriate management of FSD. Additionally, clinicians not specialists in sexual health should investigate the sexual dysfunction of their diabetic patients and if a problem is suspected or found, women should be referred to other specialists for further assessment and treatment. In fact, the management of sexual dysfunction in diabetic women should be performed by a multidisciplinary team that includes diabetologists, specialists of sexual health, and a psycotherapeutist.

In conclusion, more attention should be dedicated to this frequent complication of diabetes, adequate methodological tools should be developed for a proper diagnosis and further studies are needed to provide effective therapeutic options for sexual dysfunction in diabetic women.

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