

## SEXUAL DYSFUNCTION IN WOMEN WITH DIABETES MELLITUS

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*Key words: female sexual dysfunction, spinal cord reflex, vasoactive intestinal peptide, nitric oxide synthase, phosphodiesterase 5, estrogen, androgens, progesterone, prolactin, drugs, preclinical trial, clinical trial, metabolic syndrome, sildenafil*

### Summary

*Sexual dysfunction may be one of the chronic complications in women with diabetes, thus deserving further research. This review provides a definition of sexual dysfunction, its pathophysiology, preclinical and clinical trials on the issue, diabetes as a metabolic syndrome and its impact on sexual dysfunction. The possible therapeutic interventions are described.*

### INTRODUCTION

Sexual dysfunction (SD) in women with diabetes is one of the chronic complications which have not yet been extensively studied. According to the American

Foundation of Urological Diseases (AFUD), female sexual dysfunction (FSD) includes four elements:

- hypoactive sexual desire disorder (HSDD; reduced frequency of sexual intercourse, aversion to intercourse),
- female arousal disorder (FAD; inability to achieve arousal),
- female orgasmic disorder (FOD; inability to achieve orgasm), and
- sexual pain disorder (SPD; dyspareunia)

Sexual functioning consists of several phases: desire, arousal, plateau, orgasm, and resolution (1). Sexual arousal results from a spinal cord reflex. Spinal segments are under excitatory and inhibitory control from supramechanisms, i.e. hypothalamus with its excitatory and androgen receptors. The afferent end is the pudendal nerve, and the efferent one is a coordinated somatic (bulbocavernous, including S2, S3 and S4 sacral segments, which result in muscle contraction) and autonomic nervous system (vaginal and clitoral cavernous autonomic nerves, resulting in clitoral, vaginal and labial enlargement).

Nervous fibers contain neuropeptide Y, vasoactive intestinal peptide (VIP), nitric oxide synthase (NOS), calcitonin gene-dependent peptide, and substance P. VIP induces vaginal muscle relaxation, while nitric oxide (NO) plays a major role in the relaxation *via*

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phosphodiesterase 5 (PDE 5) and cyclic guanosine monophosphate (cGMP) (2). Nevertheless, the main organ and the site of central activity are the brain and progesterone receptors that play the major role. Testosterone is a precursor of estrogen, but its concentration in the brain is 7 to 10 times higher than that of estrogen. Testosterone increases blood flow, either directly or *via* estrogen. It is primarily responsible for libido and the sexual desire itself, as the first stage of sexual functioning.

Estrogen increases both brain and peripheral blood flow in the presence of sexual stimulation. It acts through NO secreted by endothelial cells and causes vasodilatation, thus being one of the main factors in the second stage of sexual functioning.

Some other hormones such as oxytocin and endorphin have a positive effect on sexual functioning. In contrast to these, PRL and progesterone have a negative impact (1). The first two stages of the above sexual functioning can be explained mainly by the neuroendocrine mechanisms described.

Regarding sexual functioning in diabetic women, it should be pointed out that “healthy women” also suffer from SD. Among healthy married couples, SD is present in 40% of men and 63% of women (3). The prevalence of SD in women is approximately 25%-63% in the USA. A survey of 1749 women aged 18-59, carried out in February 1999, showed that SD was present in 43% of the study women, of which 58% reported the lack of interest, 22% decreased sexual desire, 14% arousal problems, and 7% dyspareunia (4). A study carried out in 2005 was aimed at establishing the prevalence of SD in 703 healthy women from Austria. Among these, 22% reported sexual desire disorder, 35% arousal problems and 39% orgasmic ones. Pain disorders were reported by 12.8% of women, most frequently by those aged 20-39. In women aged 60-69, 50% reported having a commonly reduced sexual desire and 30% had more than two sexual intercourses *per* month. Fifty percent stated that a healthy sexual life was important (5).

## CAUSES OF SEXUAL DYSFUNCTION

The causes of SD in women can be roughly divided into psychological, i.e. sociocultural, and organic ones. Among organic non-gynecological causes, hormonal abnormalities, autonomic neuropathy (parasympathetic nervous system releases endothelial nitric oxide synthase (eNOS)) as a complication of diabetes mellitus, and atherosclerosis and vascular insufficiency should be stressed (3).

Hormonal abnormalities are primarily related to testosterone, the main hormone maintaining eNOS concentration, and conditions causing its deficiency: ovariectomy, chemotherapy, gonadotropin-releasing hormone (GnRH) agonist, spironolactone or corticosteroid therapies – suppress adrenocorticotrophic hormone (ACTH) secretion (adrenal insufficiency) (1).

Androgens play an important role in the pathophysiological mechanism, their deficiency being manifested as a poor general condition, lethargy, loss of interest, fatigue, reduced pubic hair, loss of bone mass, vasomotor symptoms, depression and headache. A question is raised about their normal values, and how menstruation and menopause affect their concentration. Androgen insufficiency may be presumed only if androgen values are at or below the lowest quartile of the normal values (6).

Although some reports provide evidence that androgen was beneficial in improving sexual desire, results from a study in 1000 women carried out in 2005 (JAMA) confuted that androgens were predictive of SD. The study included randomly selected women between 18 and 75 years of age. Women with polycystic ovary syndrome, thyroid diseases and those using oral contraceptives were excluded from the study. No correlation was found between testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS) and SD. DHEAS has been observed to be somewhat more sensitive in women aged 18-45 (7). More recent studies have focused on androgen glucuronide (androgen degradation metabolite) as an objective parameter of androgen activity in women (8).

In addition to androgen, thyroid diseases affect vaginal lubrication and orgasm and are associated with increased coital pain. Increased prolactin values also affect SD by inhibiting pulsatile GnRH secretion. A study in 48 women with hypothalamic/pituitary diseases revealed a decreased sexual desire in 79.2%, reduced vaginal lubrication in 64.6% and orgasmic disorder in 68.7% of study women (6).

Drugs affecting SD most are antipsychotics and neuroleptics as well as antidepressants (selective serotonin reuptake inhibitors (SSRIs), as they increase prolactin levels, consequently reducing sexual desire (1,3,6). Medications that cause disorders of desire include psychoactive medications (antipsychotics, barbiturates, benzodiazepines, SSRIs, lithium, tricyclic antidepressants), cardiovascular and antihypertensive medications (antilipid medications, beta blockers, clonidine, digoxin, spironolactone), hormone preparations (danazol, GnRh agonists, oral contraceptives), and others (histamine H<sub>2</sub>-receptor blockers and promotility agents, indomethacin, ketoconazole, phenytoin sodium). Medications that cause disorders of arousal include anticholinergics, antihistamines, antihypertensives and psychoactive medications (benzodiazepines, SSRIs, monoamine oxidase inhibitors and tricyclic antidepressants). Medications that cause orgasmic dysfunction are methyl dopa, amphetamines and related anorexic drugs, antipsychotics, benzodiazepines, SSRIs, narcotics, trazadone and tricyclic antidepressants (9).

## SEXUAL DYSFUNCTION AND DIABETES – CLINICAL TRIALS

In 1971, Kolodny compared 125 women with diabetes and 100 women without diabetes. In the group of women with diabetes aged 18-42, 35% reported anorgasmia as compared with 6% in the control group. There was no correlation with age, diabetes duration or neuropathy, while an association was recorded between anorgasmia and diabetes (see ref. 10).

In his study from 1977, Ellenberg observed reduced libido and orgasm in 18% of 100 diabetic women ( see ref. 4). In 1981, Jensen found no difference in sexual

functioning between diabetic women on insulin therapy aged 26-45 and healthy population. He compared 80 diabetic women and men with 40 healthy women and men. The prevalence of SD was 27.5% in diabetic women and 25% in the control group ( see ref. 4 and 10).

In 1985, Schreiner-Engel found no difference in the sexual functioning of women with type 1 diabetes as compared to the control group, unlike type 2 diabetes where such a difference was observed (see ref. 4).

In 1986, Newman and Bertelson established a 47% prevalence of SD in women with diabetes. Among these, 32% reported problems with lubrication, 21% decreased sexual desire, 21% dyspareunia, and 15% problems with orgasm. Eighty-nine percent of these women reported that their problems occurred after they had been diagnosed with diabetes. This study found no association between SD and complications of diabetes. In 1989, Campbell *et al.* suggested that SD in women with type 2 diabetes was influenced by obesity. In the 1990s, although studies by Slob *et al.* and Wincze *et al.* were based on objective measurements, i.e. assessing labium minus temperature as a measure of arousal in combination with visual erotic stimulation, there was no difference between women with diabetes and control subjects. Wincze *et al.* used vaginal plethysmography and found a significant difference between women with and without diabetes (see ref. 10). Enzlin *et al.* compared 120 women with type 1 diabetes with 180 healthy women in 2002. The prevalence of SD was 27% in women with diabetes and 15% in healthy women, with a significant difference found only for decreased lubrication. It was concluded that patients with more diabetes complications also had more elements of SD (11). Erol *et al.* compared 72 women with type 2 diabetes (mean age 38.8) and 60 healthy women. Seventy-seven percent had decreased libido, 62.5% reported arousal problems, 37.5% vaginal dryness, 41.6% vaginal discomfort and 49% had problems with orgasm (12). In his study in 240 men and women with type 1 diabetes carried out in 2003, Enzlin *et al.* aimed to establish the prevalence of SD, describe how physiological variables, diabetic complications and SD correlated with diabetes; and identify the

predictors of SD. Twenty-seven percent of women with type 1 diabetes showed elements of SD. In women, but not in men, SD was related to depression and quality of partner relationship (13). A study including 127 married women (21 with type 1 diabetes, 50 with type 2 diabetes, and 56 healthy women as a control group) from 2005 revealed a prevalence of SD of 71% in type 1 diabetes, 42% in type 2 diabetes, and 37% in the control group. No predicting factors were observed (14).

Diabetes most frequently affects sexual arousal, which is manifested by decreased genital sensitivity and lubrication. Vaginal dryness results in dyspareunia. The age, diabetes duration and control, as well as its complications have not been associated with female SD. The answer most probably lies in androgens, estrogens and medication (15).

The endocrinological basis of SD in diabetes was most comprehensively investigated in the study conducted by Salonia *et al.* (16). Sexual function and endocrine profile in women with type 1 diabetes were investigated during follicular and luteal phases of menstrual cycle and compared to control group. The study included 50 female patients with type 1 diabetes and a control group of 47 healthy women. The patients aged >18 were on intensified insulin therapy, with good hypertension control, treated hyper- and hypothyroidism, free of chronic diabetes complications, and involved in a stable heterosexual relationship for 6 months, without use of oral contraceptives. A set of validated instruments including the Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), and Beck's Inventory for Depression (BDI) were used as basic methods. The basic parameters analyzed were glycated hemoglobin (HbA<sub>1c</sub>), free triiodothyronine (fT3), free thyroxine (fT4), prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, free testosterone (FT), sex hormone-binding globulin (SHBG), DHEAS,  $\Delta$ 4-androstenedione, 17 $\beta$  estradiol and progesterone. During the follicular phase, patients and control subjects had similar FSFI scores. During the luteal phase, patients had significantly lower FSFI scores and significantly higher FSDS scores, while BDI was

equal. During the follicular phase, patients had lower estrogenic profile, as well as  $\Delta$ 4-androstenedione, DHEAS, and fT4 and fT3 than control subjects. During the luteal phase, total testosterone levels were higher in patients than in control subjects, while 17 $\beta$  estradiol and progesterone levels were lower in patients than in control subjects (16).

SD can also be an early sign of diabetes. An example is a case of a 29-year-old woman with a sexual arousal disorder of sudden onset, in the absence of any gynecological or psychological cause. One month later she was diagnosed with severe type 1 diabetes (17).

In addition to arterial hypertension, obesity and dislipidemia, hyperglycemia is part of the metabolic syndrome. Research was therefore conducted in an attempt to establish the association between the metabolic syndrome and female SD. Careful comparison was made between 100 control women without metabolic syndrome and women with metabolic syndrome, mean age 40 years. Patients with diabetes and cardiovascular disease were excluded from the study. The methodology was based on the FSFI questionnaire, consisting of 19 questions, with a maximum score 36 (FSFI score: <23 poor, 23-29 satisfactory, >30 excellent). C-reactive protein (CRP) and its association with the metabolic syndrome were also assessed. The FSFI score of >30 was achieved by 56% of women with the metabolic syndrome and 79% of women from the control group. FSFI score of 23-29 was obtained in 37% of women with the metabolic syndrome and 19% of those from the control group. Nine percent of women with the metabolic syndrome had FSFI score <23, while only 2% of women from the control group achieved this result. Women with the metabolic syndrome were observed to have a higher CRP level: 2.2 vs. 0.8 mg/L (18). Only FSFI was proven to be significantly predictive, i.e. giving a realistic picture of subjective improvement in sexual function in women receiving placebo, ginkgo, or some other specific therapy (19).

The American Society of Hypertension has published a correlation between arterial hypertension and SD, also based on the results of FSFI questionnaire. About 400 women aged 31-60 were included, 216 of them hypertensive and 201 normotensive. Women with

essential hypertension had a twofold prevalence of SD recorded in those with normal blood pressure levels; also, the rate of SD increased with age and duration of hypertension. The rate of SD was 41.2% in women with hypertension (47.8% in those treated with antihypertensive agents and 32.5% in untreated patients; 51.8% in poorly controlled and 27.2% in those with good regulation) as compared to 19.4% in normotensive women. With respect to age, 21.2% of SD cases were found to develop at 31-40, 37.7% at 40-50 and 56.8% at 51-60 years of age. In hypertension lasting for less than 3 years, SD occurred in 32.9% and in that lasting for more than 6 years SD was present in 78.6% of cases (20).

Another study was conducted by Esposito *et al.*, in an attempt to establish association between obesity and female SD using FSFI questionnaire. Fifty-two women with FSFI score  $\leq 23$  were compared with 66 controls with a relatively satisfactory FSFI score  $>23$ . A significant correlation was established between FSFI and body mass index (BMI), but not with waist-to-hip ratio. Out of 6 parameters evaluated, only sexual desire and pain at intercourse did not correlate with BMI, in contrast to arousal, lubrication, orgasm and sexual pleasure (21).

## SEXUAL DYSFUNCTION AND DIABETES – PRECLINICAL TRIALS

A preclinical trial in mice with streptozotocin-induced diabetes compared to control group was carried out with the aim to determine the impact of diabetes on vaginal blood flow, tissue morphology and enzymes such as arginase I, eNOS and cGMP-dependent protein kinase expression (PKG), i.e. key enzymes in the regulation of smooth muscle relaxation. The expression of estrogen and androgen receptors was also investigated. The results were as follows: eight weeks after the administration of streptozotocin, vaginal blood flow was significantly reduced on stimulation; histologic analysis of vaginal tissue revealed a reduction in the epithelial thickness and muscle tissue atrophy; diabetic rats also had reduced eNOS (by 40%) and arginase I (by 57%). With the reduction of arginase eNOS is also reduced. Both arginase and eNOS increase with estrogenic

stimulation, but, in contrast to these, PKG is increased (2x). Diabetic rats had lower estradiol levels and higher testosterone levels in comparison with controls. Estradiol concentration and endometrial thickness in diabetes were decreased in comparison with control group. However, testosterone level was higher due to insulin dependence of the aromatase enzyme which converts testosterone to estradiol (22).

Another preclinical study examined whether central (intracerebroventricular) immunoblockade of galanin-like peptide (GALP) would reduce sexual behaviors and luteinizing hormone. GALP is expressed in the hypothalamic arcuate nucleus and is regulated by leptin and insulin. It stimulates gonadotropin secretion. Type 1 diabetes is associated with reduced expression of GALP. The authors report that GALP antibodies reversibly reduced serum levels of LH and carried out further analyses to determine whether GALP administration could restore normal plasma LH levels. GALP increased serum levels of LH in the group of diabetic rats that received intracerebroventricular GALP. The third aim of the study was to investigate whether the administration of GALP antibody could block the effect of insulin and leptin. The treatment with insulin and leptin was found to normalize LH (23).

A preclinical research investigated vaginal structure using histochemistry and transforming growth factor beta 1 (TGF- $\beta$ 1) expression using immunohistochemistry. Twenty rats were divided into control and experimental groups. The experimental group received i.v. streptozotocin. Blood glucose values and vaginal structure were analyzed after 4 weeks. The mean blood glucose concentrations were 50-85 and 429-590 mg/dL in the control and experimental group, respectively. Diabetic animals showed reduced epithelial thickness and decreased vaginal submucosal vasculature. Collagen tissue was more dense and irregular. TGF- $\beta$ 1 showed immunoreactivity in the collagen connective tissue, fibroblasts and smooth muscle fibers (24).

A very interesting preclinical investigation in mice established increase in sexual function with olmesartan, angiotensin II type 1 (AT(1)) receptor antagonist. Olmesartan most probably crosses the

blood-brain barrier, and AT1 receptors are located at various sites in the brain. However, the exact mechanism needs to be determined (25).

## BASIC THERAPEUTIC MEASURES

- non-pharmacologic treatment: communication, lifestyle modification such as reduction in body weight and regular exercise (metabolic syndrome)
- pharmacological treatment: estrogen, progesterone, androgen. Short-term estrogen administration is acceptable, but in the long run it reduces bioavailability of androgen and estrogen. Progesterone-like medroxyprogesterone acetate (MPA) does not affect SHBG. Androgens (dehydroepiandrosterone (DHEA), DHEA-S, T, dihydrotestosterone (DHT) have a lot of side effects (↓high-density lipoproteins (HDL), hirsutism, acne, hepatotoxicity)
- herbal therapy: ginkgo biloba, L-arginine (releases NO)
- tibolone: available in Europe and Australia at present, and is expected to be approved by the Food and Drug Administration soon. Its metabolites have an estrogenic, androgenic and progestogenic effect (*via* NO). It has been observed to improve vaginal lubrication, arousal and sexual desire, but not the frequency of intercourse as compared to placebo
- apomorphine SL: possible effect on sexual desire
- sildenafil (PDE-5 inhibitor) (26)

Many studies have investigated the effect of sildenafil on SD. We present two of them: a double-blind, crossover, placebo-controlled study was undertaken to verify whether sildenafil was effective in 36 type 1 diabetic women. The study consisted of two 8-week periods of sildenafil 100 mg, washout, and placebo.

Methods: HbA<sub>1c</sub>, testosterone, FT, prolactin, color doppler ultrasonography (resistance index (RI), pulsatility index (PI), peak systolic velocity (PSV) and end-diastolic velocity (EDV) of clitoral arteries). Thirty-two women completed the study. The mean HbA<sub>1c</sub> value was 8.0%±1.8%, and testosterone, FT, and prolactin concentrations were normal. Sildenafil was found to improve arousal, orgasm and sexual enjoyment, and dyspareunia in women with type 1 diabetes. RI was significantly lower and both PI and PSV were significantly higher compared with the placebo and control group (27).

The effectiveness of sildenafil in modifying clitoral blood flow was also studied. Thirty women with type 1 diabetes treated with insulin therapy and 39 healthy women participated in the study. Each woman received 100 mg of sildenafil. Translabial color doppler ultrasonography was used to measure RI, PI, PSV and EDV of clitoral arteries at 1 and 4 h of sildenafil intake. One hour after the administration of sildenafil, all of the above parameters were significantly better ( $p < 0.05$ ) compared with the 4-h values (28).

## CONCLUSION

SD in both men and women with diabetes deserves further research. Causes are many, and the neuroendocrinological background is complex. However, given that diabetes is the cause of this diabetes complication, the focus should be on the metabolic syndrome as such, as well as on its individual constituent parts. Numerous drugs, even antihypertensives, affect this diabetic complication. As regards therapy, substances affecting PDE 5 give great hope, and VIP agonists have also been investigated recently.

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