Sildenafil improves sexual functioning in premenopausal women with type 1 diabetes who are affected by sexual arousal disorder: a double-blind, crossover, placebo-controlled pilot study

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Objective: To verify whether sildenafil is effective in type 1 premenopausal women affected by sexual arousal disorder (SAD).
Design: Double-blind, crossover, placebo-controlled study.
Setting: Gynecological diabetic outpatient clinic and sexual clinic.
Patient(s): Thirty-six type 1 premenopausal diabetic women affected by SAD.
Intervention(s): Two 8-week periods of sildenafil 100 mg, washout, and placebo, by two possible sequences.
Main Outcomes Measure(s): Each woman submitted blood samples to measure HbA_{1c}, and T, free T (FT), and PRL. Efficacy was assessed [1] subjectively by the Personal Experiences Questionnaire based on the 5-point Likert scale, quantifying arousal, desire, orgasm, enjoyment of sexual activities, and frequency of sexual relationships; and [2] objectively by translabial color Doppler ultrasound to measure the resistance index (RI), pulsatility index (PI), peak systolic velocity (PSV), and end diastolic velocity of clitoral arteries.
Result(s): Thirty-two women completed the study. The mean HbA_{1c} value was 8.0% ± 1.8%, and plasma concentrations of T, FT, and PRL were normal. Sildenafil seems to improve arousal, orgasm and sexual enjoyment, and dyspareunia in women affected by type 1 diabetes. However, by flowmetric measurements, the mean RI was significantly lower and both the mean PI and PSV of the clitoral arteries were significantly higher compared with baseline and placebo.
Conclusion(s): Sildenafil seems to improve subjective sexual aspects and can be used to treat objectively genital arousal disorder of premenopausal women with type 1 diabetes. (Fertil Steril® 2006;85:1496–501. ©2006 by American Society for Reproductive Medicine.)

Key Words: Clitoral color Doppler sonography, female sexual dysfunction, type 1 diabetes, sexual arousal disorder, sildenafil

There is evidence that women with sexual dysfunction will commonly have physiologic abnormalities such as vasculogenic dysfunction (1) or diabetes (2) that contribute to their overall sexual health problems. The sexual function of diabetic women has received little attention in clinical research, even though diabetes recently has been shown to increase the risk of female sexual dysfunction (3, 4). In diabetic rats, diabetes induces vaginal tissue fibrosis and adverse effects on the hemodynamic mechanism of clitoral engorgement (5). Diabetic women could have decreased sexual desire depending on the indirect effect of diabetes resulting from the increased prevalence of depression (6). On the other hand, changes in sexual genital pathways such as diminished clitoral sensation, vaginal dryness, vaginal discomfort, orgasmic dysfunction, and dyspareunia might be the mechanisms that involve damage to the vascular and autonomic nervous system (4, 7) and cause alterations in the nitric oxide (NO) production and its efficacy (8).

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The most commonly reported sexual problem in women with diabetes is sexual arousal disorder (SAD) (4, 9). Physiologically, in the sexual arousal phase, sexual excitement is accompanied by pelvic vasocongestion and swelling of the external genitalia, including clitoral and vaginal engorgement; clitoral engorgement appears to be mainly a hemodynamic phenomenon characterized by smooth muscle relaxation (10–12). Diabetes is usually associated with atherosclerosis and microangiopathy (13), and diabetic subjects may have chronic cavernous arterial insufficiency. This could also be the case of male erectile dysfunction (ED). Men with diabetes have an approximately threefold higher risk for ED than men without diabetes (14). The pathophysiology of ED in diabetic men is known to be related to vascular and neuronal origin (15). In male rabbits, diabetes produces penile cavernous trabecular smooth muscle fibrosis based on the degree of hyperglycemia (16).

Several pharmacological agents, some with central-acting mechanisms and some with locally acting vascular effects, are therapeutically useful in the treatment of ED (17). Selective phosphodiesterase type 5 (PDE5) inhibitors, taken

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orally, are effective for men with ED and concomitant type 1 diabetes (18–21). Previous studies suggested that sildenafil, which acts by inhibiting cyclic GMP-specific PDE5, may improve the sexual health of women affected by sexual difficulties such as arousal disorders and may indirectly improve other aspects of sexual life (22, 23).

Because subjects affected by chronic illness such as diabetes may suffer from a sexual dysfunction due to neurovascular alterations, research needs to be carried out to find drugs that are effective in treating the pathological effects to improve the quality of sexual life.

This double-blind crossover placebo-controlled study was designed to determine whether sildenafil, taken orally, was able to improve sexual genital arousal in type 1 diabetic women with SAD using subjective and objective instruments to measure the efficacy of the drug.

MATERIAL AND METHODS

Setting and Sample

This was an independent study performed at the Research Group for Sexology of the Department of Microbiological and Gynaecological Science, School of Medicine, University of Catania, Catania, Italy. The Institutional Review Board of the department approved the study. Based on the differences between placebo and sildenafil 50 mg, that is, a difference of 2 in the female sexual arousal disorder score (22), with α (two-sided) = 0.05 and $1 - \beta = 0.95$, to obtain a SD of 1.6, the sample size for independent two sample *t*-tests was calculated as 15 subjects for each arm. Thus 36 consecutive premenopausal women aged 27–43 years, with a mean age (±SD) of 34 (±3.6) and a body mass index of 25.3 ± 3.8, affected by type 1 diabetes that was being treated with insulin therapy, and visiting the outpatient Sexology Service for SAD were invited to participate.

All the subjects gave their written informed consent before entering the study, which was conducted in accordance with the Helsinki Declaration. However, the subjects could terminate participation at any time. The study was not advertised, and no remuneration was offered.

The sample consisted of volunteers who had had a stable, satisfying heterosexual relationship for at least 6 month and subjectively normal sexual desire toward their partners (see Instruments section). Women were excluded from the study if they had a history of hypertension, coronary artery disease, or thromboembolic disorder; impaired hepatic and renal function and neoplasia; were taking hormone therapy or oral contraceptives; had a history of smoking and alcohol abuse; did not have a sexual partner; were affected by situational sexual dysfunction with their partner; or had a partner with sexual dysfunction.

All patients admitted to the screening phase had regular menstrual cycles (mean cycle length 26.7 ± 4.2 days), with ovulation. To confirm the ovulatory cycle, ultrasound was performed on days 10, 12, and 15 of the cycle and serum P concentrations were measured at days 21 and 25 of the cycle. Menstrual cycle was defined as ovulatory when the serum P was >18 IU/mL. The P level was measured using commercially available enzyme-linked immunoassorbent assay (ELISA) kits (Elecsys System 2010; Roche, Monza, Italy). Moreover, during the screening period subjects underwent a physical examination, including assessment of vital signs and an ECG.

Data on use of medications, body mass index (BMI), and neuropathic, nephropathic, and retinopathic events due to microvascular pathology were recorded. A venous blood sample was collected on the day of enrollment to determine hemoglobin glycosylated (HbA_{1c}). HbA_{1c} was determined using the Cobas Integra assay (Roche, Basel, Switzerland), where the normal rage is 4.0%–6.0%. Subjects with HbA_{1c} ≥10% were excluded from the study because they were considered to be affected by diabetes that was not well-controlled. Blood samples were obtained from all study participants to measure hormonal levels of T, FT, and PRL. Hormones were sampled during the morning on cycle days 12–17. Plasma T and PRL were measured using commercially available ELISA kits (Elecsys Systems 2010). Plasma levels of FT were also measured using ELISA kits (DSX System; DRG Instruments GmbH, Marburg/Lahn, Germany).

Instruments

Each woman underwent a Sexual History Interview (SHI) (24) that was conducted in a private room alone with the female sexual disorder therapist: 60–90 minutes were needed for the interview, and 15–30 minutes to write the justification. Information was sought about any changes in number of sexual fantasies and arousal and about other sexual experiences such as orgasmic and coital frequency and enjoyment of sexual activities. Women with dysphoric arousal, a sensation of unpleasant genital engorgement (25), were excluded from the study. The American Foundation for Urologic Disease definition of Female Sexual Function Disorders (26) was used to define SAD, that is, the persistent or recurring inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement or genital (lubrication/swelling) or other somatic responses.

The women with acquired sexual dysfunction and SAD were the focus of our study. Finally, one of our hypotheses was that if arousal were enhanced, orgasm could possibly be facilitated. To measure sexuality we used the Personal Experiences Questionnaire (PEQ) (27), a self-reporting questionnaire based on the McCoy Female Sexuality Questionnaire (28). Using the PEQ, it was possible to assess the efficacy of each treatment with respect to baseline values. Qualitative items were answered on a 5-point Likert scale, ranging from 1, not at all, to 5, a great deal. Quantitative items were answered as 0, never; 1, less than once a week; 2, once or twice a week; 3, several times a week; 4, once a day/sometimes

twice; and 5, several times a day. The PEQ was completed by each woman and handed back to the fieldworker.

Finally, each woman underwent color Doppler ultrasound to measure clitoral blood flow. Ultrasound was performed using a SonoAce 8800 (Medison Co., Seoul, Korea) with a 7.5-MHz linear transducer by the same investigator. Each woman was scanned in the gynecological position. The Doppler translabial probe was placed sagittally on the clitoris at an angle of <20 degrees, without exerting any significant pressure on the tissues. After identifying the clitoral artery using color flow mapping, the Doppler probe was positioned over the vessel and at least three sequential Doppler waveforms were obtained. The peak systolic velocity (PSV), the end diastolic velocity (EDV), the resistance index (RI = PSV − EDV/PSV), and the pulsatility index (PI = PSV − EDV/mean flow velocity of clitoral artery) were calculated.

Study Design

A double-blind, crossover, placebo-controlled study design was performed. The efficacy of treatment was the primary end point based on the proportion of successful attempts, defined as sexual arousal levels, occurring after dosing. Safety was considered a further end point of this study, data being collected throughout the study period, and included recording adverse events, vital signs, and changes in laboratory test values for standard hematology and biochemistry variables. Patients provided information recorded on diary cards and were reviewed at each study visit concerning sexual activity.

After defining inclusion criteria at the screening, according to a computer-generated list of random number groups, each woman was randomly allocated to one of the two possible sequences, each of which constituted two medication series: sildenafil 100 mg/placebo (A sequence) and placebo/sildenafil 100 mg (B sequence). Women were assessed before being treated and during each treatment by one investigator. Both the woman and the attending doctor carrying out the procedure were blinded to the two drugs. The investigator was not involved in the recruitment of the women and did not know the computer-generated randomization list and the assignment of the treatment group according to the sequence of recruitment. The codes were broken after the study was completed.

The crossover study design was used to define whether the treatment with sildenafil was effective with respect to placebo. Each woman took sildenafil or placebo 1 hour before each sexual intercourse. The usage of the drug was not more than once daily. Each woman received each treatment for 8-week periods. There was a 7-day washout period between treatments. We chose a 1-week washout period on the basis of our previous studies using a similar intervention by which we did not observe any carryover effect (22, 34). During treatments, HbA_{1c} was measured weekly. The PEQ was used at baseline, at the washout, and after treatments. Arterial clitoral color Doppler ultrasound was performed at baseline and during the usage of drugs.

All adverse events reported by the woman were recorded, irrespective of any random relationship with the study drug.

Statistical Analysis

Intention-to-treat analyses were performed for all efficacy variables and included all patients who had a baseline evaluation and had at least one efficacy assessment after the baseline visit. We included in the analysis the subjects that had missing information on one or more questionnaire items. The last observation carried forward was used to select data such that missing data were replaced by values from the last available assessment during treatment before the respective assessment. Furthermore, women who stopped treatment for adverse events were included in the analysis.

For comparisons among baseline, sildenafil 100 mg, and placebo sexual PEQ scores, the nonparametric Wilcoxon's rank-sum test was used. Separate analyses were performed for the arousal score (primary end point) and desire, orgasm, enjoyment of sexual activities, satisfaction with frequency, and frequency of intercourse. Paired Student's *t*-test was performed to compare changes between baseline sildenafil and placebo values of clitoral arterial blood flow. Considering the order in which the treatments were allocated, data was analyzed by Student's *t*-test, using the Bonferroni method of correction for multiple comparisons if a significant *F* ratio was found. Scores are presented as means ± SD. $P<.05$ was considered statistically significant. Statistical analysis was carried out using the *Primer of Biostatistics* statistical computer package (29).

RESULTS

Of the 36 women enrolled in the study, 32 women aged 27–41 with a mean age (±SD) of 33 (±3.1) and a BMI 25.0 ± 3.5 provided information at each treatment to be included in the analyses. Four women were excluded after assessment at baseline: [1] two for anovulatory cycles and [2] two for refused treatment. The mean duration of diabetes was 12.1 ± 8.5 years, and the mean HbA_{1c} value was 8.0% ± 1.8%. Plasma concentrations of T (0.4 ± 0.6 ng/mL; normal range, 0.3–1.2 ng/mL), FT (1.3 ± 0.7 pg/mL; normal range, 0.3–3.2 pg/mL)19, and PRL (10.5 ± 3.5 ng/mL; normal range, 5–25 ng/mL) were normal.

Moreover, 4 (12.5%) of 32 women in the B sequence did not complete the study for adverse events, all during sildenafil usage. They stopped taking the drug for [1] headache, vision problems, and nausea (n = 1), [2] vision problem and headache (n = 1), and [3] headache and nausea (n = 2). Therefore, the incidences of the most commonly recorded adverse events reported by subjects during the use of sildenafil were headache (12.5%), nausea (6.2%), and vision problem (6.2%). Each adverse event was predominantly transient and mild in nature.

TABLE 1

Qualitative and quantitative aspects of sexuality during the treatment with sildenafil 100 mg and placebo.

Sexual activity	Baseline	Sildenafil	Placebo	P^a	P^b	P^c
Desire	4 ± 1.3	3.9 ± 0.5	4.1 ± 0.6	NS	NS	NS
Arousal	2.9 ± 1.2	3.7 ± 0.5	3.2 ± 0.3	<.01	NS	<.001
Orgasm	2.8 ± 1.4	3.8 ± 0.8	3.1 ± 0.6	<.05	NS	<.001
Enjoyment	3.5 ± 1.1	4 ± 0.5	3.7 ± 0.6	NS	NS	<.001
Satisfied by frequency	3 ± 1.1	3.2 ± 0.7	3.1 ± 0.4	NS	NS	NS
Frequency of intercourse	1.8 ± 1	2.3 ± 0.5	2.4 ± 0.6	NS	<.05	<.05
Frequency of fantasies	2.1 ± 0.8	2.3 ± 0.4	2.2 ± 0.6	NS	NS	NS
Dyspareunia	2.3 ± 1.1	1.4 ± 0.8	2 ± 0.7	<.05	NS	<.05

Note: Values are means ± SD. NS = nonsignificant. *P* values are determinated by nonparametric Wilcoxon's rank-sum test.

[a] Sildenafil vs. placebo.

[b] Placebo vs. baseline.

[c] Sildenafil vs. baseline.

Caruso. Sildenafil treatment of diabetic women. Fertil Steril 2006.

During the study, each women had well-controlled diabetes. The mean HbA_{1c} value obtained during each treatment was similar to that observed at baseline (P=NS). The BMI did not show any significant variation with respect to baseline values (P=NS).

The sexual interview showed that the mean duration of sexual dysfunction was 3.5 years (range, 2.2–4.5 years). Subjects mainly reported arousal and orgasm difficulties and dyspareunia. Moreover, they reported a decrease in sexual satisfaction and in sexual activity.

The mean (±SD) usage of sildenafil and placebo was, respectively, 2.1 (±0.4) and 2.9 (±0.4) times weekly. It is interesting to note that all women recorded using each drug for all sexual activities.

Changes in sexuality produced by drug administrations were noticed though the analysis of PEQ items. Table 1 shows the changes from baseline of qualitative and quantitative sexual behaviors according to the treatment and the efficacy of sildenafil and placebo. Data indicate that sildenafil improved [1] the experience of arousal (P<.001), orgasm (P<.001), and enjoyment (P<.001) with respect to baseline; and [2] the experience of arousal (P<.01) and orgasm (P<.05) with respect to placebo. Excluding the frequency of intercourse (P<.05), each aspect of sexuality during placebo intake was similar to that observed at baseline (P=NS). During sildenafil intake, dyspareunia decreased with respect to baseline and placebo (P<.05). Finally, desire and frequency of fantasies did not change during both treatments with respect to baseline (P=NS).

All women enrolled in the study underwent baseline color Doppler ultrasound; at the end of the A sequence, 32 women (response rate, 88.9%) underwent color Doppler ultrasound, while at the end of the B sequence 28 women (response rate, 77.7%) underwent color Doppler ultrasound.

Table 2 shows the results of the color Doppler ultrasound measurements and statistical analysis. In both the A and B sequences of drug administration, sildenafil improved clitoral blood flow with respect to placebo (P<.05). During sildenafil administration, the mean PSV (16.78 ± 1.65) markedly increased and the mean EDV (−5.1 ± 1.2) significantly decreased from baseline. On the contrary, placebo was not able to produce any change with respect to baseline (P=NS). Moreover, the mean RI (0.71 ± 0.32) was significantly lower and the mean PI (1.81 ± 0.77) was significantly higher compared with both baseline and placebo values (P<.05).

Conclusions

Our study was the first to take into consideration type 1 diabetic women treated with sildenafil. In our pilot study, the treatment with 100 mg sildenafil was effective in modifying both sexuality and clitoral blood flow in premenopausal women with type 1 diabetes.

Techniques measuring hemodynamic changes in the vagina and clitoris using clitoral tissue concentrations of hemoglobin, vaginal luminar pressure, and clitoral intracavernosal pressure could involve noninvasive instruments (8). However, we should use more direct diagnostic procedures to evaluate hemodynamic events of vaginal and clitoral pathways. The color Doppler ultrasound has become a first-level diagnostic procedure to measure the penile blood flow of men with ED (30) and might be a useful method to study the female sexual response by measuring clitoral blood flow (31). By color Doppler ultrasound, we observed a decreased mean RI and an increased mean PSV and PI of the clitoral

TABLE 2

Sildenafil-mediated changes on clitoral arterial blood flow in premenopausal women with type I diabetes.

	Baseline	Sildenafil	Placebo	P^a	P^b	P^c
Resistance index	0.88 ± 0.12	0.71 ± 0.32	0.87 ± 0.11	<.05	NS	<.05
Pulsatility index	1.24 ± 0.35	1.81 ± 0.77	1.27 ± 0.38	<.001	NS	<.001
Peak systolic velocity (cm/sec)	7.38 ± 1.7	16.78 ± 1.65	7.58 ± 1.81	<.001	NS	<.001
End diastolic velocity (cm/sec)	0.88 ± 1.7	−5.1 ± 1.2	1.1 ± 0.17	<.001	NS	<.001

Note: Values are means ± SD. NS = nonsignificant.
[a] Sildenafil vs. baseline.
[b] Placebo vs. baseline.
[c] Sildenafil vs. placebo.

Caruso. Sildenafil treatment of diabetic women. Fertil Steril 2006.

artery. These changes may be due to the vasodilator effect of sildenafil on female genital tissues. Sildenafil was shown to be able to inhibit cGMP hydrolysis by high-affinity selective PDE5 inhibition in intact cells and in soluble extracts of human clitoral corpus cavernosum smooth muscle cells. Moreover, the finding of NO in human clitoral tissue (32) and vaginal tissue (33) could sustain the activity of sildenafil on female peripheral genital targets.

Some interesting clinical data showed sildenafil to be effective on both premenopausal (22) and postmenopausal (23) women affected by SAD, and data on asymptomatic premenopausal women using sildenafil to study the effects of the PDE5 inhibitor on the genital pathway showed increased sexual activity, mainly in genital arousal (34). Ours was the first study on the effects of sildenafil on clitoral blood flow in diabetic women using color Doppler ultrasound. An interesting study was conducted with healthy postmenopausal women to examine the effects of sildenafil on both clitoral and uterine blood flow by color Doppler ultrasound (35). After sildenafil administration each mean index showed improvement in blood flow, even if the Doppler measurements of the clitoris and uterus were not equal, probably due to the dense concentration of PDE5, which is highly expressed in clitoris erectile tissue in comparison to other female genital tissues (36, 37).

Besides studying the effect of diabetes on arousal, orgasm, and desire and its role in provoking sexual pain, we took into consideration the change of sexual enjoyment and both satisfaction with and frequency of sexual activity. In contrast to previously reported data, in our study women with type 1 diabetes did not suffer from sexual desire dysfunction (6, 38, 39), which was investigated by both the SHI and the PEQ. Because diabetes produces vascular pathologies and microangiopathy, vasoactive drugs could be used to treat genital arousal dysfunction in diabetic women. In the human corpus cavernosum, the release of NO from the nonadrenergic noncholinergic nerves and/or the endothelium activates guanylyl cyclase and increases intracellular cGMP levels; cGMP modulates intracellular calcium and, in turn, regulates smooth muscle contractility and erectile function.

Davis et al. recently affirmed that no single androgen level is predictive of low female sexual function and the majority of women with low DHEAS levels did not have low sexual function; however, they said that their results were not in conflict with T being used pharmacologically to treat hypoactive sexual desire disorder (HSDD): sex steroids influence female sexual function, but there is no serum androgen level that defines female androgen insufficiency (40).

Even if Davis et al. found no evidence of association between sexual disorders and low serum total and FT levels, in our study we included only women with normal plasma concentrations of both steroids because androgens may play an important role in modulating the physiology of vaginal tissue and contribute to female genital sexual arousal by enhancing NO synthase activity (41). Moreover, there are several studies that showed the efficacy of androgen treatment of women affected by sexual dysfunction such as HSDD (9, 10, 40, 42).

Assessment of quality of life in subjects affected by diabetes is increasingly believed to be a crucial parameter to take into account before concluding on the efficacy of new therapies. The quality of life of diabetic subjects depends on several daily aspects, among which is sexuality. The integration of clinical and psychosocial care could be helpful in both identifying subjects that need a treatment reexamination and improving the quality of life of the subject. Based on the results of our study, we believe that diabetic women affected by sexual dysfunction such as sexual arousal disorder could use PDE5 inhibitors.

Sex therapists are discovering that integrating adjunctive use of the new sexual pharmaceuticals with sex therapy can accelerate the therapeutic process and improve outcome. As new drugs will be developed and approved for female sexual dysfunctions, opportunities for medical and nonmedical sex therapies will increase. In fact, sex therapists, like ourselves, have already begun research into the efficacy and safety of new sexual drugs.

Nevertheless, our pilot study had two limitations: the first was the small number of diabetic women undergoing both subjective and objective sexual evaluation; the second was that we took into consideration only diabetic subjects affected by genital sexual arousal disorder who were attending the Sexology Service for sexual dysfunction. Therefore, we need to study the effect of diabetes on the sexuality of women from the Diabetes Service and to measure both the subjective and objective sexual aspects.

Consequently, in this study we were not able to have a control group of diabetic women without sexual disorders, even if the women were studied prospectively and thus their pretreatment status could serve as a reference for the outcome. Finally, based on the same limitations of our study, we think that further prospective studies are needed to determine the efficacy of sildenafil in improving the quality of sexual life in a large group of subjects with diabetes.

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