Efficacy of sildenafil citrate in the treatment of female sexual dysfunction

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Abstract:

Sexuality is one of the most important components of quality of life in both sexes. Female Sexual Dysfunction are a complex, poorly understood and underestimated health problem although it is a highly prevalent include disorders of desire, arousal, orgasm and sexual pain associated with self-distress. Pathophysiology of FSD has been related to several factors. In response to an overwhelming demand for therapy for FSD several drugs are undergoing development and testing, such as hormonal replacement therapy, PDE5, prostaglandin E1 and flibanserin beside psychotherapy.

Aim of the work: Evaluate the effect of sildenafil citrate in treatment of female sexual dysfunction.

Patient, Materials and Methods: An observational study had been done on 43 females complaining of FSD who were fulfilling the inclusion criteria. They were taken oral sildenafil citrate 25mg daily for 6 weeks and were evaluated by 19–items Female Sexual Function Index (FSFI) questionnaire before and after treatment.

Results: Our results showed that 34.4% became normal with score >26.5; while 65.6% showed some improvement but still have FSD (FSFI<26.5). There was significant improvement in all female sexual domains in FSFI ranged from 21% to 69%. There was significant improvement of total score in both 1st degree circumcision more than 2nd degree circumcisions with 41%- 35% respectively .

Conclusion: We concluded that the treatment of patients with FSD by sildenafil citrate 25mg daily for 6 weeks had significant improvement effect on all subtypes of FSD according to FSFI questionnaire.

Introduction

Female sexual dysfunction (FSD) is an wide term comprising a range of common disorders, including hypoactive sexual desire, reduced subjective and/or physical genital arousal (poor sensation, vaso-congestion, lubrication), sexual pain and inability to achieve orgasm/satisfaction, which are multidimensional by nature and often coexisting [1]. According to recent estimates, sexual dysfunction has occurred in 40%–45% of women and 20%–30% of men at least once in their lifetime. For many years, studies have focused mainly on male erectile dysfunction while female sexual disorders (FSDs), although more frequent than male sexual disturbances, have been hardly considered [2].

FSD is a serious general health problem which is usually neglected in the general population while affecting the women's quality of life to a great extent [3]. Lack of sexual health and security will result in anger, depression, drug abuse, lack of physical and psychological capability for parenting and child care, lack of sufficient skills for having a healthy emotional relationship, inability to flourish in the society, infanticide and even death [4].

There is growing recognition of FSD as an important women's health concern. Despite an increased awareness of the pathophysiologic components to FSD currently, there are no drugs approved for FSD. In response to an overwhelming demand for therapy for FSD, several drugs are undergoing development and testing [5]. Most studies regarding the pharmacological treatments for sexual dysfunction have been conducted on males but female sexual dysfunction has been less taken into account [6]. Pharmacological treatments have been considered for female sexual dysfunction mainly focusing on improvement of androgen deficiency, increase of blood flow to the genital area and stimulation of the central nervous system[7].

Estrogen, progesterone and testosterone are the main effective hormones in females' sexual response, so these compounds have been used for hormone therapy in some studies. Nonetheless, testosterone has been less welcomed due to its side-effects which include hirsutism and acne [8, 9]. According to some researches, sildenafil citrate is effective in treatment of orgasm as well as arousal disorders in female sexual dysfunctions. Sildenafil citrate is among the phosphodiesterase type 5 (PDE5) inhibitors which improve female sexual dysfunction through increasing blood flow

to corpus cavernosum of clitoris, vagina and labia minor [10].

PDE5 inhibitors (sildenafil, tadalafil, vardenafil) physiologically enhance the production of guanosine monophosphate (GMP) from cyclic guanosine monophosphate (cGMP) this molecule promotes the relaxation of the smooth muscle cells, causes vasodilatation and increases blood flow in genital organs. The engorgement of penile corpora cavernosa in men and clitoris and labia minora in women are the main modifications of genital organs during sexual arousal Furthermore, the ultrafiltration of plasma through capillary vaginal vessels contributes to vaginal lubrication. According to emerging data, PDE5 is expressed in vaginal, clitoral, and labial smooth muscles [2]. However, in rare cases, its consumption might be accompanied by complications, such as mild headache, urinary tract infection and nausea [10].

Aim of the study

This study aims to evaluate the effect of sildenafil citrate in treatment of female sexual dysfunction.

Patient and methods

our study was performed at the out-patient clinic of dermatology, venerology and andrology department, South Valley University on 43 women complaining of sexual dysfunction were recruited at period from November 2015 till June 2017 to evaluate efficacy of sildenafil citrate in the treatment of female sexual dysfunction. The experimental design was approved by the Institutional Ethics and Research Committee of Faculty of Medicine, South Valley University, Egypt. Informed written consent was obtained from each woman before enrollment in the study.

Inclusion criteria included:

Sexually active women at least once weekly who were 18-60 years old clinically diagnosed having female sexual dysfunction and with normal hormonal profile. Patients were in a stable, heterosexual relationship that is secure and communicative and they must be reliable, honest, compliant, and agree to co-operate with all trial evaluations as well as to be able to perform them. Finally there was Normal sexual function of male partner by using the International Index of Erectile Function (IIEF-5) [11].

Exclusion criteria included:

Women with a history of hypertension and on anti-hypertensive treatment and Coronary heart disease or on treatment with vasodilator (nitrates and alpha blocker) and those with impaired hepatic function or those who Taking any medication with a known influence on

sexual function (e.g Anti-Depressant and Anti-Psychotic drugs). No pregnancy or breast feeding for last 6 months.

Each patient was subjected to full medical history (including the personal, medical, menstrual, obstetric, contraceptive and sexual history) and clinical examination including general and local examination.

Each patient completed the 19-items (FSFI) questionnaire at the begining of the study and at the end of study after 6 weeks from taking sildenafile citrate 25mg daily on empty stomach. Which its individual items were assigned to six separate domains of female sexual function score for most of each ranges (0-6): desire(1.2-6), arousal, lubrication, orgasm, satisfaction and pain and the total score ranges (1.2 -36). With A score $\leq$ 26.5 is classified as FSD [12].

Each male partner was completed the 5 items international index of erectile function (IIEF-5) questionnaire for assessment of erectile function and ED severity. The questions were about erection confidence, erection firmness, maintenance ability, maintenance frequency and satisfaction. The score ranges between "5-25" as follow: 5-7 (severe ED), 8-11 (moderate ED), 12-16 (mild to moderate), 17-21 (mild ED), 22 -25 (no ED) before his wife taking the treatment to make sure normal male sexual factor.

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 20) as follows: Description of quantitative variables as mean, SD and range, Description of qualitative variables as number and percentage, Paired T-test was used to compare the difference in means between the two groups, Correlation coefficient test (r) was used to rank variables against each other either positively or inversely. Correlation is significant at the 0.05 level (-tailed) based on normal approximation and Multivariate Linear Regression Analysis was used to investigate factor affecting FSFI score.

Results

Our study was a quasi-experimental pre-post-test single group design. It was performed on 43 women complaining of sexual dysfunction with a mean of age (30.5 ± 6.4) years old. 37.2% of women in our study were had 1st degree Circumcision and 62.8% were had 2nd degree circumcision.

At the start of this study, 100% of participants had been complaining of FSD with score less than 26.5 of FSFI questionnaire, while after completing 6 weeks of treatment 34.4% of women

became normal had score more than 26.5 on FSFI questionnaire but 65.6% women still having FSD as they had score less than 26.5 on FSFI. At the end of study 11 woman not able to complete the study and missed follow up (Table. 1 and figure. 1).

Table 1: FSD Diagnosis according to FSFI among the studied sample

	Category	
At Baseline (n = 43)	• FSD	43 (100%)
	• Normal	0 (0%)
After Treatment (n = 32)	• FSD	21 (65.6%)
	• Normal	11 (34.4%)

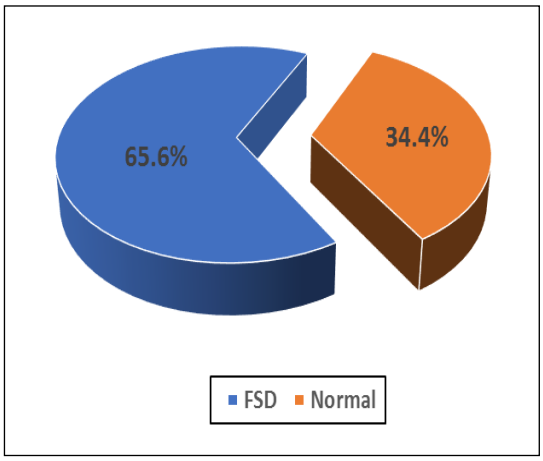

Fig.1: FSD Diagnosis according to FSFI among the studied sample after Treatment**.**

The six female sexual domains and the total FSFI score were compared before and after treatment with sildenafil 25mg daily for 6 weeks. There was a statistically significant improvement in all female sexual domains in FSFI and in total FSFI score (P-value < 0.001). Improvement in domain ranged as follow: orgasm 69% is the best followed by desire 68%, lubrication 64%, Arousal 48%, Satisfaction 42% and pain 21% while total score improvement by 41%. (Table. 2 and figure. 2-3)

Table 2: Comparative Analysis of the studied groups (Before vs. After Treatment).

FSFI Item	Baseline	After Treatment	P-value*	Percent Change	Absolute Change
Desire	2.49 ± 1.3	4.18 ± 1.1	**< 0.001**	1.69	68%
Arousal	2.80 ± 0.9	4.13 ± 1.3	**< 0.001**	1.33	48%
Lubrication	2.81 ± 0.9	4.61 ± 1.4	**< 0.001**	1.80	64%
Orgasm	1.80 ± 0.7	3.04 ± 1.4	**< 0.001**	1.24	69%
Satisfaction	3.29 ± 0.7	4.67 ± 1.4	**< 0.001**	1.38	42%
Pain	3.81 ± 0.7	3.15 ± 0.9	**< 0.001**	0.66	21%
Total	16.98 ± 3.0	23.80 ± 5.6	**< 0.001**	6.82	41%

*Paired T-test was used to compare the difference in means between the two groups

--Significance level is considered when $p \leq 0.05$

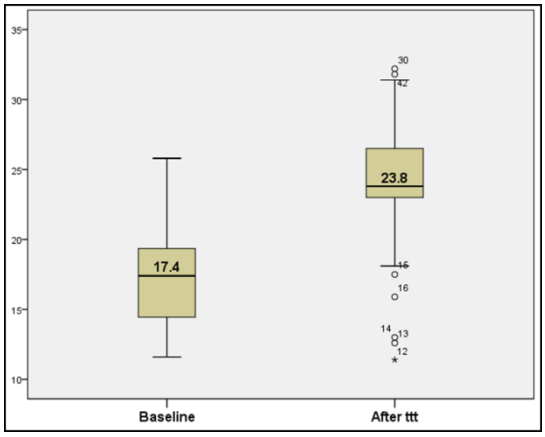

Fig. 2: Effect of Treatment on the Total Score among the Studied Cohort.

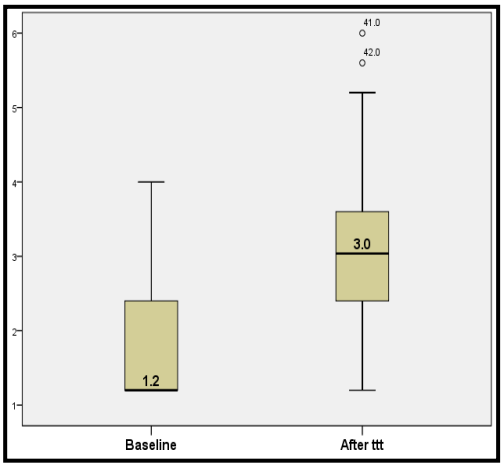

Fig. 3: Effect of Treatment on the Orgasm Score among the Studied Cohort.

We were also found that there was statistically significant (p-value<0.001) improvement of percentage after treatment of 1st vs. 2nd degree Circumcision in desire,

lubrication, orgasm domains and total score. (Table.3 and figure. 4-5).

Table 3: Improvement percentage after treatment(1st vs. 2nd Degree Circumcision).

FSFI Item		**Baseline**	**After Treatment**	**P-value***	**Percent Change**	**Absolute Change**
Desire	**1st degree**	2.40 ± 1.1	4.38 ± 0.7	**< 0.001**	1.98	83%
	2nd degree	2.78 ± 1.4	4.06 ± 1.1	**< 0.001**	1.28	46%
Arousal	**1st degree**	3.00 ± 1.1	4.58 ± 1.1	**< 0.001**	1.58	53%
	2nd degree	2.48 ± 0.9	3.86 ± 1.1	**< 0.001**	1.38	56%
Lubrication	**1st degree**	3.26 ± 1.4	5.03 ± 1.2	**< 0.001**	1.77	54%
	2nd degree	2.90 ± 0.9	4.36 ± 1.2	**< 0.001**	1.46	50%
Orgasm	**1st degree**	2.10 ± 0.9	3.46 ± 1.1	**< 0.001**	1.36	65%
	2nd degree	1.76 ± 1.1	2.79 ± 1.3	**< 0.001**	1.03	59%
Satisfaction	**1st degree**	3.80 ± 0.9	5.08 ± 1.1	**< 0.001**	1.28	34%
	2nd degree	3.17 ± 0.9	4.43 ± 1.2	**< 0.001**	1.26	40%
Pain	**1st degree**	3.85 ± 0.6	3.70 ± 0.8	**< 0.001**	0.15	4%
	2nd degree	3.31 ± 0.9	3.05 ± 0.7	**< 0.001**	0.26	9%
Total	**1st degree**	18.41 ± 3.9	25.88 ± 4.4	**< 0.001**	7.47	41%
	2nd degree	16.76 ± 3.3	22.57 ± 4.7	**< 0.001**	5.81	35%

*****Paired T-test was used to compare the difference in means between the two groups

--Significance level is considered when $p \leq 0.05$

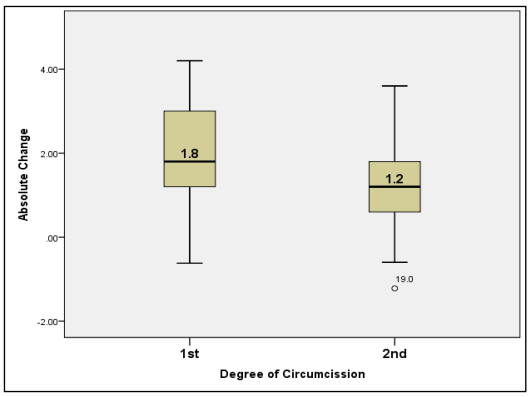

Fig. 4: Effect Circumcision Degree on the Sexual Desire Score.

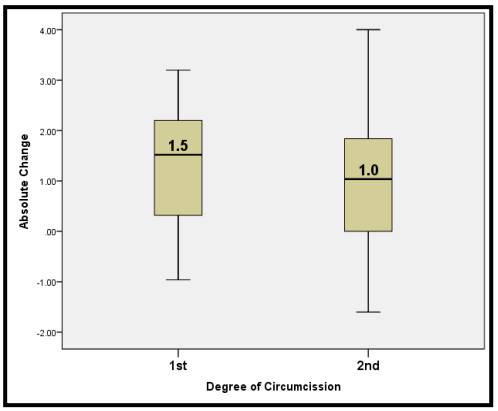

Fig. 5: Effect Circumcision Degree on the Orgasm Score.

After treatment, we found that there was a significant positive correlation between type of delivery and FSD according to FSFI, while there was significant negative correlation between marriage duration, No. of children, older child age, degree of circumcision and FSD according to FSFI after treatment (Table.4 and figure.6).

Table 4: FSD Correlates among the studied Cohort (After Treatment).

	FSFI	
	r*	**P-value**
Age	-0.122	> 0.05
Marriage Duration	**-0.270**	**= 0.040**
No. of Children	**-0.342**	**= 0.012**
Older Child Age	**-0.191**	**= 0.032**
Younger Child Age	0.073	> 0.05
Type of Delivery	**0.465**	**= 0.001**
Degree of Circumcision	**-0.403**	**= 0.004**
Contraceptive Use	**-0.039**	> 0.05

*Pearson's correlation coefficient

**Correlation is significant at the 0.05 level (-tailed), based on normal approximation

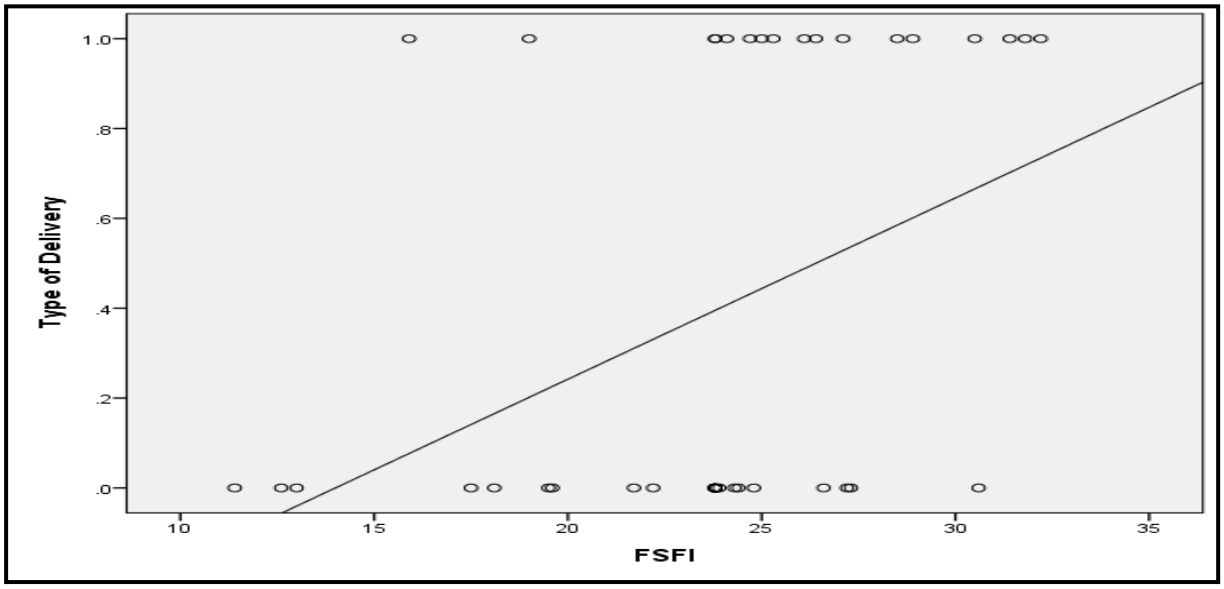

Figure 6: Correlation between FSFI and Type of Delivery**.**

The last table showed that the multivariate linear regression analysis of the significant factors affecting FSD. After adjusting for age, the final linear regression model contained six predictors; marriage duration, number of children, age of the older and younger offspring, mode of delivery and the degree of circumcision.

The effect of FGM (Female Genital Mutilation) was confirmed by the current study; where women with 2nd degree FGM had decreased FSFI score by 1.67-point (0.7 – 6 points) compared with those with 1st degree FGM and this was statistically significant (p = 0.032).(Table. 5)

Table 5: Multiple Linear Regression Analyses of the associations of FSFI with Correlates of FSD**.**

	Estimate	**SE**	**t-stat**	**P-value**
Intercept	**28.19 (24.41: 31.98)**	**1.84**	**3.58**	**< 0.001**
• **Age**	-0.09 (-0.73: 0.56)	-0.31	0.28	= 0.787
• **Marriage Duration**	**-2.03 (-5.51: -1.46)**	**1.68**	**2.34**	**= 0.044**
• **No. of Children**	**-1.48 (-3.93: -0.97)**	**1.18**	**-1.25**	**= 0.047**
• **Older Child Age**	**-0.73 (-1.13: -0.33)**	**0.19**	**-3.79**	**= 0.001**
• **Younger Child Age**	**0.98 (0.26: -1.67)**	**0.35**	**2.82**	**= 0.009**

• **Type of Delivery**	**-0.18 (-2.51: -0.74)**	**0.25**	**-2.37**	**= 0.043**
• **Degree of Circumcision**	**-1.67 (-5.98: -0.65)**	**0.21**	**2.94**	**= 0.032**

*CI= Confidence Interval **LRT=Likelihood Ratio Test

Discussion

Female sexual dysfunction (FSD) is a common distressing multifactorial problem necessitating a multidisciplinary evaluation and treatment approach and has a negative impact on quality of life and medication compliance [13]. Sexual dysfunction presents itself as a lack of sexual desire, arousal, sexual stimulation disorder, orgasmic disorders and pain. Its development involves psychological, physiological and medical factors and often a combination of all three [14]. According to the sexual response cycle there are four subtypes of FSD can occur individually or in combination with each other [15].

There are different methods of treatment due multiple subtypes of FSD. Among these methods psychotherapy, lubricants, tibolone, hormonal replacement therapy (estrogen or testosterone) and PDE5i have been used in the treatment of all subtypes of FSD across a lot of studies [16, 17]. Sildenafil, a selective type-5 PDEi, was approved for the treatment of male erectile dysfunction. Although sildenafil was not approved for use in women, it has been studied for the treatment of FSD since 1996 [18]. It enhance the NO pathway in smooth muscle relaxation by preventing cGMP catabolism with PDE5 as NO stimulates the formation of cGMP by guanylate cyclase and cGMP is broken down by phosphodiesterase [19, 20]. It allows the concentration of cGMP in the erectile tissues to remain elevated. Elevation of cGMP enhances smooth muscle relaxation, vasodilation and cavernosal engorgement. As cGMP is present in vaginal and clitoral, it improves vaginal and clitoral blood flow which is a necessary state for arousal and orgasm in women. PDE5 inhibitors may have a role in improving the vaso-congestion and lubrication in the arousal and orgasmic phases of the female sexual response [21].

Our study results showed that 34.4% of participants became normal and their score was >26.5; while 65.6% showed some improvement but still have FSD (FSFI<26.5). There was significant improvement in all female sexual domains in FSFI. Improvement in domain of orgasm 69% was the best. There was significant improvement of total score in both 1st degree circumcision more than 2nd degree circumcisions with absolute change 41%- 35% respectively. But improvement

of pain disorder was better after treatment in 2nd degree circumcision 9% than in 1st degree circumcision 4%.

Multiple previous studies were done on effect of sildenafil on FSD. ***Nurnberg et al., 1999*** showed an improvement in orgasmic functioning and sexual arousal with sildenafil in female patients on selective serotonin re-uptake inhibitors. The patient's sexual function was assessed in investigator-conducted interviews. Sildenafil appears to be an effective intervention for antidepressant-induced sexual dysfunction**.** This was with agreement with our results which showed that there were significant improvements in orgasm (69%), lubrication (64%) and arousal (48%) [22].

Also there was another study with agreement to our study results were done by ***Nurnberg et al., 2008*** which compared effect of sildenafil versus placebo in 98 premenopausal women previously sexually functioning, who were in remission from depression on serotonin re-uptake inhibitors. They were assessed by the Clinical Global Impression sexual function scale and FSFI. The women receiving sildenafil were had significant greater improvements in sexual function than those who had taken placebo [23].

As well as, There were two studies agreed to great extent with our study results, but they were used a higher dose of sildenafil. First one was an open-label study on 48 women with sexual arousal disorder done by ***Berman et al., 2001*****a** had demonstrated significant physiological increases in genital blood flow and genital sensation with sildenafil 100 mg compared with baseline, also significantly increased subjective desire, arousal, lubrication and satisfaction after 6 weeks of sildenafil use as assessed by questionnaire [24]. The Second one was non-placebo controlled study done by ***Berman et al., 2001b*** on 35 postmenopausal women with FSD demonstrated improved sexual response: vaginal lubrication, sensation, satisfaction and ability to reach orgasm with 100 mg sildenafil [25].

In addition there were another different three studies were done by Caruso and his colleagues, they were with agreement with our results in that, there were significant ($p = 0.001$) improvement in all as aspects of FSD including desire, arousal, lubrication, satisfaction, orgasm and dyspareunia when use sildenafil 25mg.One of them was on the use sildenafil 25mg and 50mg in 53 young premenopausal women with sexual arousal disorder was done by ***Caruso et al., 2001***. They found that there were significant improvement in female arousal

disorder and other sexual qualitative functions such as enjoyment and orgasm and increased clitoral sensibility and it may possibly have an indirect therapeutic role in quantitative aspects of sexual functioning such as the frequency of sexual fantasies and thoughts, and the frequency of sexual intercourse. 70.5% of women wanted to continue treatment with sildenafil [26].

The other one by ***Caruso et al., 2003*** was worked on the effect of sildenafil in 68 women with sexual dysfunction that were free of any disease and measured by questionnaire which, reported significantly improved subjective arousal(P, 0.001), orgasm (P, 0.05) and sexual satisfaction (P, 0.001) compared to the placebo group [27]. But in the third one used a higher dose of sildenafil in diabetic women***, Caruso et al., 2006*** had done on 36 premenopausal women with type 1 diabetes mellitus and FSAD using 100mg sildenafil versus placebo. Assessment of the participant was in the form of a self-fill questionnaire and Doppler ultrasound measurement of clitoral artery blood flow. Sildenafil significantly increased clitoral blood flow compared with placebo (P, 0.001) and improved subjective arousal, orgasm and dyspareunia (P, 0.05) [28].

On other hand, there were multiple previous studies in disagreement with our study results and had pointed out that sildenafil has very little effect or ineffective in the treatment of female sexual dysfunction. ***Kaplan et al., 1999*** were examine the effects of sildenafil on sexual functioning in a group of postmenopausal women with FSD, about half of whom were using hormone replacements, with self-assessed sexual dysfunction. They performed an open-label trial of 50 mg sildenafil were taken once daily for at least 6 months on 33 postmenopausal women with sexual arousal disorder, hypoactive sexual desire disorder or anorgasmia. They have been assessed by sexual questionnaires. They found that sildenafil was safe but with limited efficacy, overall sexual function did not improve significantly although there were changes in vaginal lubrication and clitoral sensitivity. Only 20% of the women reported significant improvements [29].

A study was performed using multiple doses of sildenafil by ***Basson et al., 2002*** as a large randomized, placebo controlled, double-blind study in 781 oestrogenised and estrogen-deficient postmenopausal women with FSAD who had received 10mg, 50mg or 100 mg of sildenafil or placebo. Response to treatment was

measured by questionnaire. The drugs were well-tolerated at all doses but, there was no subjective improved sexual response with sildenafil. As they reported that any genital physiological effect of sildenafil was not perceived as improving the sexual response in oestrogenised or estrogen-deficient women with a wide range of sexual dysfunction that include FSAD. They were suggested that future studies should focus on women without decreased desire syndromes [30].

Likewise, ***Basson and Brotto, 2003*** had randomized, double-blind and placebo-controlled study on 34 oestrogenised postmenopausal women with acquired genital FSAD and impaired orgasm. But the participants had received Sildenafil 50 mg or placebo administered and they had been discriminated between woman with low and high vaginal pulse amplitude. Across all participants, sildenafil had not improve neither arousal, nor orgasm, as well as subsequent analyses comparing high versus low vaginal pulse amplitude responders revealed significantly reduced latency to orgasm and increased subjective sexual arousal and perception of genital arousal in the low vaginal pulse amplitude group of women [31].

On other hand, ***Alexander et al., 2011*** had done a comparison between the effects of sildenafil and placebo to evaluate the efficacy, safety and tolerability of oral sildenafil in women with female sexual arousal disorder as a result of spinal cord injuries in Double-blind, placebo-controlled, flexible-dose study on 129 women were treated with sildenafil or placebo. The dose could be increased from 50 to 100 mg or decreased to 25 mg once during the treatment period depending on efficacy and tolerability. They found non-significant difference between sildenafil versus placebo in the percentage of successful sexual activities at end of treatment versus baseline. So they concluded that the drug had no clinically-significant effect [32].

Conclusion

We concluded that the treatment of patients with FSD by oral sildenafil citrate 25mg daily on empty stomach for six weeks had significant improvement effect on all subtypes of FSD such as desire, arousal, lubrication, orgasm, satisfaction and pain according to FSFI questionnaire and also had significant improvement in total score of FSFI. The FGM had significant effect on female sexual response.

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