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Research Article

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THE EFFECTS OF SILDENAFIL ON SOME OF BIOCHEMICAL MARKERS IN WOMEN WITH METABOLIC SYNDROME

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ABSTRACT

Insulin resistance is usually associated with impairment in the nitric oxide (NO) production. Phosphodiesterase-5 (PDE-5) inhibitors such as NO donor may improve the metabolic syndrome in obese patients promoting a state of metabolic syndrome and damaging the vascular endothelium associated with abnormal lipid profile. The aim of this study is to determine the role of the PDE-5 inhibitor; Sildenafil in improving the sexual dysfunction, glycemic indices, lipid profile in obese diabetic women. This study included 45 women, were classified into 3 groups, 15 non-diabetic non- obese women as control, 15 non-diabetic obese women, and 15 diabetic obese women (with metabolic syndrome), they are postmenopausal women diagnosed with female sexual arousal disorder treated with 25 mg Sildenafil once daily for 3 months. The study involved measurement of fasting serum insulin (FSI), fasting serum glucose (FSG), HbA1c, B-cell function %, lipid profile, and some of inflammatory markers. Results of this study showed that daily treatment of diabetic women with Sildenafil for 3 months causing a slight improving in sexual tendency, significant improvement of glycemic indices, lipid profile and reduction of some inflammatory markers associated with metabolic syndrome. This study provided the first evidence that Sildenafil therapy improve glycemic control, lipid profile and some of inflammatory markers in diabetic women with metabolic syndrome.

Keywords: Sildenafil; diabetic women; metabolic syndrome.

INTRODUCTION

Recent studies currently estimate that 8.3% of the population has diabetes and nearly 79 million people have insulin resistance and are at risk for developing diabetes.[1] Insulin resistance and diabetes lead to a number of micro- and macro-vascular complications leading to retinopathy, nephropathy, painful neuropathy and eventually more adverse complications such as atherosclerosis, coronary artery disease and cerebrovascular disease.[2]

The increased incidence of these complications has been attributed to higher levels of inflammatory cytokines, chronic hyperglycemia leading to formation of advanced glycation end products (AGEs) and elevated levels of oxidative stress leading to endothelial dysfunction, Insulin resistance impairs nitric oxide (NO) bioavailability and obesity promotes a state of chronic inflammation and damages the vascular endothelium.[3] Phosphodiesterase-5 inhibitors restore NO signaling and may reduce circulating inflammatory markers, and improve metabolic parameters through a number of mechanisms.

Sildenafil is indicated for the treatment of erectile dysfunction in men. The nitric oxide-cyclic guanosine monophosphate pathway (NO-cGMP) involved in penile erection and enhanced by sildenafil may also play a role in some components of the female sexual arousal response.[4] The efficacy and safety of sildenafil were evaluated in estrogenized and estrogen-deficient women with sexual dysfunction that included female sexual arousal disorder.[5] Because Viagra was developed for men, not much is known about the potential side effects if women were to begin taking it. There are, however, several logical conclusions about the risks and benefits for women that we can make based on existing knowledge.[6] Researchers have theorized that Sildenafil might have the same sexual effect on women as it does for men. In a 2008 study in the *Journal of the American Medical Association*, researchers found sildenafil could possibly increase sexual function for women.[7]

Chronic administration of sildenafil in men with erectile dysfunction had improved endothelial function as indicated by marked changes in serum markers of endothelial function, increased insulin levels and a robust decrease in the inflammatory marker, high sensitivity C-reactive protein. Therefore based on this background information, this study proposes that PDE-5 inhibitors would be ideal candidates to treat insulin resistance and inflammation in obese diabetic women with metabolic syndrome.[8]

The study was designed to investigate the role of sildenafil in improving the metabolic syndrome in diabetic (type 2) obese women through follow up of body weight, BMI, lipid profile, serum uric acid. Glycemic index was determined through measurement of the serum insulin, glucose, HbA1c and anti-inflammatory activity by measuring Hs-CRP, IL-6, IL-1β, ESR.

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SUBJECTS & METHOD

Subjects

45 women (age between 50-60 years) were included in this study and classified as follow:

15 non-diabetic non- obese women as control

15 non-diabetic obese women

15 diabetic obese women (with metabolic syndrome), they are postmenopausal women diagnosed with female sexual arousal disorder treated with 25mg sildenafil once daily for 3 months. The diabetic patients were on metformin 500mg three times daily and glibenclamide 5mg once daily.

Inclusion criteria

Patient with metabolic syndrome defined as:

Fasting plasma glucose (FPG) ≥126 mg/dl

Serum concentration of TG <400 mg/dl

Serum cholesterol having 150 mg/dl

HDL <20 mg/dl

BMI >24

Exclusion criteria

Subjects with the following characters/diseases excluded from the study:

History of myocardial infarction or stroke, subjects taking nitrite, subjects taking insulin therapy, subjects with incidence of diseases (such as liver, renal or thyroid disorders).

Blood samples

Venous blood samples (10 ml) were collected after fasting for 10-12 hrs. At baseline and after 1, 2 and 3 months of sildenafil administration. The measurements were performed on frozen serum samples. The serum levels of TG, cholesterol, VLDL, LDL, HDL and fasting glucose were measured using Biotech Engineering Management Co. Ltd. UK apparatus. Glycemic control indices included FPG and hemoglobin A1C (HbA1C). HbA1c was determined using chromatography method by DS5 Drew Scientific machine (ion exchange chromatography). The statistical tests were conducted by using T-test, for comparison between group 1 and 2 to detect any change between obese and non - obese women, group 2 and 3 to detect any difference between diabetics and non- diabetics obese women and finally comparison between pre and post treatment with sildenafil. Ethical approval was obtained from the Medical Ethics Committee of College of Pharmacy, University of Baghdad; the participants signed a written informed consent to participate in the study.

RESULTS AND DISCUSSION

It was observed in the current study that the sexual function did not improve significantly. However, there were changes in vaginal lubrication and clitoral sensitivity in 80% of treated women (12 out of 15). The effects of sildenafil administration on the glycemic index in diabetic female patients with metabolic syndrome were shown in table **1**. Table shows that the value of fasting serum insulin (FSI) was significantly different in non- diabetic obese women in comparison with control and the values were elevated significantly (P<0.05) after treatment with sildenafil in comparison with the pretreatment readings, while the fasting serum glucose was not significantly different in non-diabetic obese patients in comparison with normal (non diabetic non obese women), meanwhile the diabetic women at pretreatment values showed significant elevation in the serum glucose level but this level was significantly improved (reduced) after treatment with sildenafil. On the other hand, the value of HbA1c was not significantly affected by treatment in comparison with the values of pretreatment, while there is significant differences in HbA1c in diabetics in comparison with obese and control. The B-cell function was significantly elevated (P<0.05) in obese diabetic subjects after treatment with sildenafil compared with that values of pretreatment. There is significant difference in values between pretreatment values of diabetics and those obese or non-obese non-diabetic individuals. These results may be due to amelioration of insulin sensitivity. The current study is in agreement with results of Ayala *et al* who showed that chronic inhibition of phosphodiesterase-5 improves insulin action in a mouse model of diet-induced obesity and insulin resistance. One potential mechanism by which phosphodiesterase-5 inhibition occurs may improve insulin action is prevention of endothelial dysfunction.[9]

Table 1. Effect of sildenafil on glycemic indices in women with metabolic syndrome.

Group	non-obese non-diabetic women n=15	Obese non- diabetic women n=15	Diabetic obese women/ Pre- treatment n=15	after 1 month	after 2 month	after 3 month
FSI (μ U/ml)	15.15±0.32	12.4±0.53[a]	14.31±9.03	15.30±7.22	15.31±8.03	18.11±7.20[c]
FSG (m mole/L)	5.22±0.61	6.02±0.84	9.07±2.51b	8.36±2.57	8.10±2.06[c]	7.22±1.28[c]
HbA1c	3.17±0.66	3.817±0.930	7.267±0.668[b]	7.11±0.32	7.121±0.56	7.03±0.554
B-cell function%	92.72±32	89.5±10.8	38.2 ±17.8[b]	61.78±21.8**	63.51±21.97[c]	82.6±31.4[c]

N=number of patients per group, a= significant difference (P<0.05) in comparison with control, b=significant difference (P<0.05) in comparison with obese, non-diabetics, c= significant difference (P<0.05) in comparison with pretreatment values.

The sildenafil effect on the lipid profile in diabetic female as in table **2**, showed that serum total cholesterol was significantly reduced (P<0.05) in patients taking sildenafil compared with the pretreatment values and non-significantly with value of obese diabetic subjects. At the same time, the values of serum Triglyceride and LDL were non-significantly changed by treatment in comparison with those values of pretreatment, although there were significant elevation in the values in diabetics in comparison with non-diabetics and control meanwhile the HDL was significantly elevated by treatment in comparison with those values at pretreatment.

Table 2. Effect of sildenafil on lipid profile in diabetic women with metabolic syndrome.

Group expressed as mg/dL	non-obese non-diabetic women n=15	Obese non-diabetic women n=15	Diabetic obese women/ Pre- treatment n=15	after 1month	after 2 month	after 3 month
S.T. C	198±19.2	215.4±[a]23.5	222.9±16.5	208.4±30.5[c]	183.0±29.2[c]	173.6±33.0[c]
S.T.G	211±32.3	221±41	232.4 ±64.0[b]	252.8±94.7	241.8±89.7	234.3±66.3
S.HDL	41.2±4.11	39.40±2.61	41.80±3.83	42.40 ±3.36	44.80±3.03[c]	44.00±2.68[c]
S.LDL	141±18.56	150.4±21.4	157.4 ±16.9[b]	151.20±11.26	152.60±7.80	145.50±10.88

N=number of patients per group, a= significant difference (P<0.05) in comparison with control, b=significant difference (P<0.05) in comparison with obese, non-diabetics, c= significant difference (P<0.05) in comparison with pretreatment values.

Effect of Sildenafil on some inflammatory markers in women with metabolic syndrome was seen in table **3**, indicated that the values of serum Interleukin-1β(IL-1β), ESR and serum high-sensitivity C-reactive protein were significantly reduced (P<0.05) in patients taking sildenafil in comparison with the values of pretreatment. While, the value of serum IL-6 was non-significantly reduced in 1st and 2nd month but there is significantly reduction at 3rd month (P<0.05). In addition, the values of inflammatory markers in obese subjects and pretreatments values in diabetic patients were significantly changed (P<0.05) while the value of serum interleukin-6 (IL-6) was not.

Table 3. Effect of sildenafil on some inflammatory markers in obese female diabetic patients with metabolic syndrome.

Group	non-obese non-diabetic women n=15	Obese non-diabetic women n=15	Diabetic obese women/ Pre- treatment n=15	after 1month	after 2 month	after 3month
IL-6(pg/ml)	3.628±0.869	3.735±0.374	3.75±0.73	3.555±0.425	3.250±0.532	3.854±0.398
IL-1β(pg/ml)	93.4±14.9	103.2±12.0	105±22.13	98.7±8.8	84.4±17.7[c]	85.2±14.1[c]
ESR mm/h	21.0±4.95	36.20±5.54[a]	37±6.12	35.60±5.98	32.20±5.85[c]	30.40±5.86[c]
Hs-CRP (ng/ml)	7.821±0.825	6.92±2.93	7.2±2,65	5.85±2.65[c]	5.31±2.59[c]	4.82±2.44[c]

N=number of patients per group, a= significant difference (P<0.05) in comparison with control, b=significant difference (P<0.05) in comparison with obese, non-diabetics, c= significant difference (P<0.05) in comparison with pretreatment values.

These results of current study showed that sildenafil, in a dose dependent manner, attenuated production of the pro-inflammatory cytokines, TNF-α, IL-6 and IL-1β, which are believed to play a significant role in the pathogenesis of DM.[10] In summary, biochemical findings of the present study indicate that the PDE inhibitor sildenafil ameliorates circulating inflammatory markers, improving fasting glucose levels and lipid profile.

CONCLUSION

Results of this study proved that the daily administration of sildenafil to diabetic obese women for 3 months period showed improvement in the glycemic control, lipid profile, inflammatory markers and sexual dysfunction which is associated with the metabolic syndrome. Further studies are needed to explain the molecular mechanism(s) by which sildenafil exerts its effects.

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