EFFECT OF SILDENAFIL CITRATE (VIAGRA) ON PENILE VASCULATURE AND CARDIODYNAMICS IN DIABETIC MALES WITH AND WITHOUT NEUROPATHY

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Background: Erectile and cardiovascular dysfunctions in diabetes are important signs resulting probably due to pelvic autonomic neuropathy with damage to the parasympathetic nervierignetes. Direct evidence for a neuropathic etiology comes from studies that show structural changes in autonomic nerve fibers supplying the corpora cavernosa. The present study deals with the diabetic neuopathies prevailing in men and the possible role of sildenafil citrate (Viagra) treatment for these neurogenic cardio-sexual disturbances. **Methods:** Penile mid shaft circumference and length, penile pulse amplitude, both systolic and diastolic blood pressures, and heart rate were measured in response to erotic stimulation by film and fantasy and the effect of the treatment of sildenafil citrate (50 mg oral dose) was noted in 50 insulin dependent diabetes mellitus (IDDM) and in 50 non insulin dependent diabetes mellitus (NIDDM) patients with and without an objective evidence of neuropathy, having an age span in between 20 and 65 years and a duration of diabetes distributed over 1-25 years with their age matched non diabetic controls. **Results:** Sildenafil treatment showed a significant increase ($P<0.0005$) in penile mid shaft circumference and length, and penile pulse amplitude, where as both systolic and diastolic blood pressures and heart rate exhibited a significant decrease ($P<0.025$ and $P<0.005$ respectively) in both IDDM and NIDDM diabetic neuropathic patients. However this difference was found to be non-significant in both types of diabetic patients without neuropathy and when compared with their respective control subjects. **Conclusion:** Oral administration of sildenafil citrate is an effective first line therapy for erectile dysfunctions in diabetic impotent men with neuropathic etiology (irrespective of their type of diabetes) with out much altering the cardiodynamic profile. These results further explain how to manage sexual disorders as part of diabetic care, and suggest rules for sildenafil prescription in diabetic neuropathic patients.

Key Words: Diabetes; Neuropathy; Erectile/cardiovascular response; Sildenafil citrate.

INTRODUCTION

Erectile dysfunction (ED) has been linked increasingly to cardiovascular risk factors and comorbidities. Considering the potential risk associated with sexual activity, guidelines were developed (Princeton I) for assessment and management of patients with varying degrees of cardiac risk. These guidelines are most recently updated (Princeton II) based on new data concerning the link between ED and cardiovascular disease and the availability of additional phosphodiesterase type 5 inhibitors vardenafil, tadalafil[1]. Despite the need for careful risk assessment in all cases, sexual activity remains safe for the large majority of patients. However, all patients presenting with complaints of ED should be carefully assessed for the presence of cardiovascular risk factors like obesity, hypertension, hyperlipidemia, diabetes and its associated complications particularly neuropathy[2].

Direct evidence for a neuropathic etiology of diabetic erectile dysfunction comes from studies that show structural changes in autonomic nerve fibers supplying the corpora cavernosa[3]. Emission disturbances that occur in diabetes are associated with involvement of the sympathetic fibers that sub serve the seminal vesicles, vas deferens, and bladder trigone[4].

Testicular anesthesia, presence of a neurogenic bladder, and delayed bulbocavernous reflex response latency are indirect evidence for a neuropathic etiology of the patient's complaints[5]. Failure of ejaculation secondary to emission disturbances due to sympathetic denervation of the vas deferens is another manifestation of autonomic neuropathy, usually seen in more advanced stages[6-7]. It is now established that sexual dysfunction is a common complication of diabetic autonomic neuropathy both in men and in women[8-9-10-11]. Despite the general agreement of previous investigators that the prevalence of impotence in diabetic men approximates 50 per cent, there is controversy surrounding the etiology of this problem.

Postural hypotension is the most common neurological dysfunction of diabetic autonomic neuropathy[12-13].

Diabetic autonomic neuropathy changes blood pressure homeostasis in a number of ways. The efferent limb of the baroreceptor reflex is composed

of sympathetic vasoconstrictor fibers to the splanchnic, skin, and striated muscle vessels and sympathetic cardiac fibers. Interruption of these fibers interferes with three compensatory mechanisms: vasoconstriction, i.e., a drop in systolic blood pressure of 30 mmHg or greater. The lack or inadequacy of the expected increase in heart rate differentiates the orthostatic hypertension of autonomic neuropathy from those seen under hypovolaemic conditions such as dehydration or acute blood loss[14-15.]

Marked decreases in both systolic and diastolic supine blood pressure have been described in diabetic impotent patients with idiopathic autonomic dysfunction following food ingestion[16-17]. However, the pathologic basis |of diabetic autonomic neuropathy is still incompletely understood.

One interesting new breakthrough in the treatment of erectile and cardiovascular dysfunctions using oral drugs lies in the substance sildenafil citrate (Viagra[TM]) seems to be a most promising discovery[18]. Sildenafil is a potent and selective inhibitor of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), which is responsible for the degradation of cGMP in the corpus cavernosum[19-20.]

Sildenafil has a peripheral site of action on erections. It potently enhances the relaxant effect of nitric oxide (NO) on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Increased levels of cGMP are involved in smooth muscle relaxation, which in turn leads to penile erection. cGMP is converted back to guanosine monophosphate (GMP), a cGMP precursor, by the action of phosphodiesterase type 5 (PDE5). Sildenafil prevents the breakdown of cGMP thereby preventing premature detumescence. Furthermore, treatment with sildenafil is well tolerated and is associated with minimal adverse events that rarely cause discontinuation of the treatment. It relaxes vascular smooth muscle, resulting in modest reductions in blood pressure that are insufficient to stimulate a reflex increase in heart rate. Sildenafil does not affect the force of cardiac contraction, and cardiac performance is unaffected. Sildenafil is mildly vasodilating in the coronary circulation and does not increase the risk of ventricular arrhythmia. Among men with erectile dysfunction treated with sildenafil, the adverse event profile is similar overall to that in men with comorbid cardiovascular disease (CVD), it is similar between those with and without CAD, and it is similar between those who take and those who do not take antihypertensive drugs (regardless of the number or class).

MATERIALS AND METHODS

For experimental purposes and for the studies of diabetic neuropathy, after getting the permission from the local ethical committee, 50 insulin dependent (IDDM) and 50 non insulin dependent (NIDDM) diabetic male patients with and without evidence of neuropathy and 50 age matched non diabetic male controls were selected. Every male aged between 20 to 65 years with duration of the onset of the disease to 1 to 25 years was included.

The presence of diabetic complications were assessed by a review of the medical record. Neuropathy was present if the records indicated absence of ankle jerk, decreased vibration sense or pin prick sensation in the feet or hands, or there was history of neuropathic pain, foot ulcer, or symptoms compatible with autonomic neuropathy (differential diagnosis) including postural hypotension, intermittent diarrhea especially nocturnally, epigastria fullness, bladder dysfunction, diminished sweating in the legs, gustatory sweating and hypoglycemic unawareness. The criteria for the presence of symptomatic autonomic neuropathy were two or more severe or three or more mild/moderate features.

Impotence was determined according to the method described previously[21]. Men were considered candidates for this study when they had complained of erectile dysfunction with diabetic neuropathy for 6 or more months. All candidates had normal results on magnetic resonance image studies of the hypothalamic pituitary axis as obtained by their medical records.

Diabetic treatment was recorded as diet alone, oral hypoglycemic agent or insulin. Inquiry was made of other drug therapy, angina pectoris, previous myocardial infarction or cardiac failure, intermittent claudication, thyroid dysfunction, previous sympathectomy or other abnormality that might predispose to organic impotence such as neurological disease or previous injury.

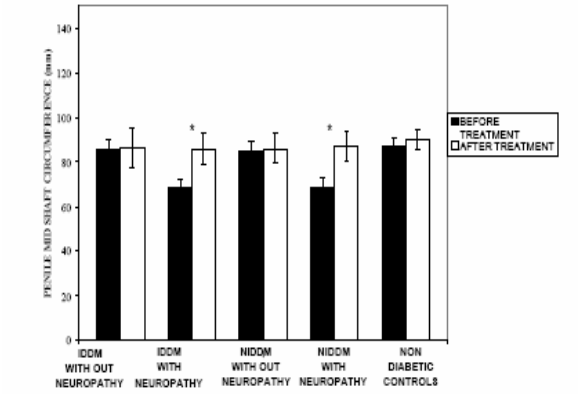
To assess the efficacy and safety of oral sildenafil citrate (Viagra[TM]-Pfizer) in the treatment of erectile dysfunctions in both IDDM and NIDDM diabetic men with and without neuropathy and in age matched non diabetic controls, subjects home and clinical practice centers in the local vicinities, were randomized to receive sildenafil citrate (50 mg), but not more than once daily, for 12 months. Self-reported ability to achieve and maintain an erection for sexual intercourse according to the International Index of Erectile Function and adverse events were recorded according to the method described previously[22].

Erectile and cardiovascular responses were assessed using simultaneous monitoring of penile mid shaft circumference & length, penile pulse amplitude, systemic arterial systolic & diastolic blood pressures & heart rate during laboratory based erotic stimulation with film and fantasy before and after the sildenafil treatment in all the subjects according to the method described previously[21-17].

The degree of erection to erotic film & fantasy distinguished between neuropathic & non-neuropathic etiologies. The initial approach was tentative so that it was easy for the individuals to decline without embarrassment. If there was apparent willingness, a more definite request was made. All the parameters were statistically analyzed using Student t-test. In all the instances probability ($p<0.05$) was regarded as statistically significant.

RESULTS

The data for the measurement of penile mid shaft circumference in response to film and fantasy before and after the administration of 50 mg of oral dose of sildenafil citrate in 50 IDDM and 50 NIDDM diabetics (with and without neuropathy) and in 50 age matched non diabetic control subjects is shown in Figure- 1.

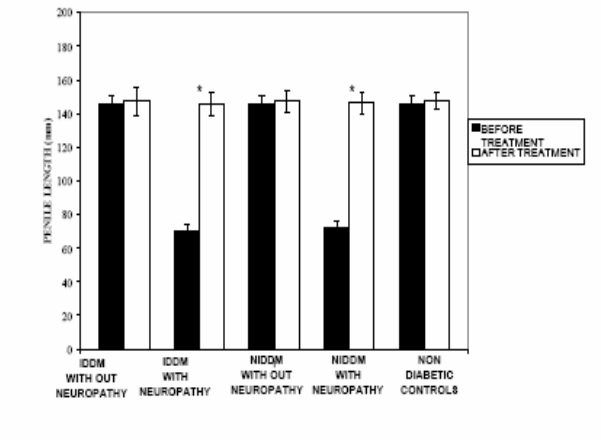


*IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of sildenafil citrate for t-test. * = p<0.0005*

Figure-1: Changes in penile mid shaft circumference (mm) before and after oral administration of sildenafil citrate (50 mg dose) in response to erotic film and fantasy in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.

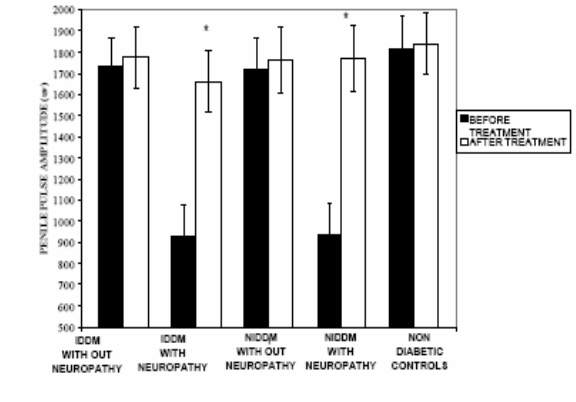
A consistent increase in the values of penile circumference in both IDDM and NIDDM diabetic patients with neuropathy was observed with a significant statistical difference ($P<0.0005$) after the sildenafil treatment, the increase being about 26% averagely.

Exactly in a similar manner, values of penile length and penile pulse amplitude showed a significant increase ($p<0.0005$) in both types of sildenafil treated diabetic neuropathic patients when compared with the values obtained from untreated patients (Figures 2 & 3). However this difference was found to be non-significant in both types of diabetic patients without neuropathy before and after oral administration of sildenafil and when compared with their respective control subjects.



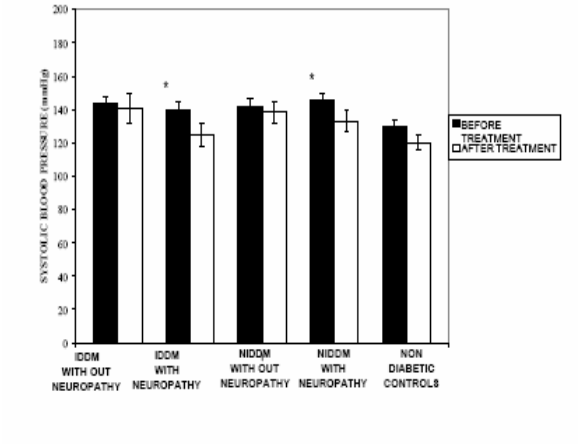
*IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of Sildenafil citrate for t-test. * = p<0.0005*

Figure-2: Changes in penile length (mm) before and after oral administration of sildenafil citrate (50 mg dose) in response to erotic film and fantasy in insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.



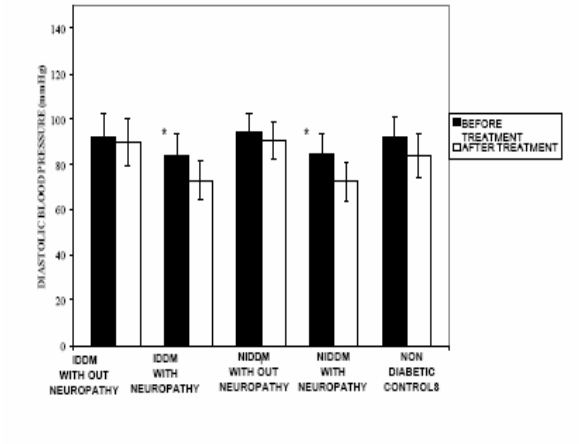
*IDDM and NIDDM (with and without neuropathy) values are compared before and after ora administration of Sildenafil citrate for t-test. * = p<0.0005*

Figure-3: Changes in penile pulse amplitude (μv) before and after oral administration of sildenafil citrate (50 mg dose) in response to erotic film and fantasy in insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.



*IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of Sildenafil citrate for t-test. * = p<0.025*

Figure-4: Changes in systolic blood pressure (mmHg) before and after oral administration of sildenafil citrate (50 mg dose) in response to erotic film and fantasy in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.

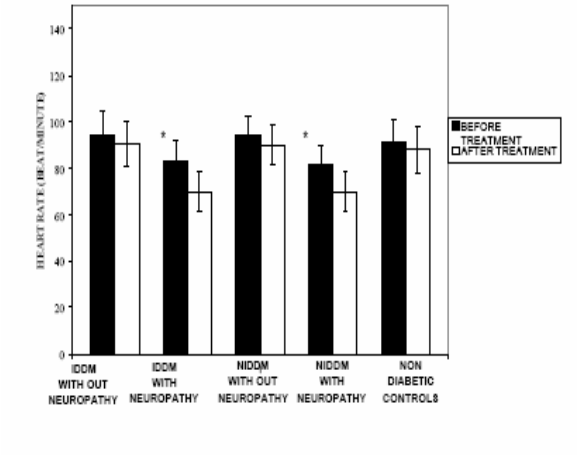


*IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of Sildenafil citrate for t-test. * = p<0.025*

Figure-5: Changes in diastolic blood pressure (mmHg) before and after oral administration of sildenafil citrate (50 mg dose) in response to erotic film and fantasy in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.

In contrast, an inverse relationship was found when systolic and diastolic blood pressures and heart rate values were measured in the same group of patients. Both IDDM and NIDDM diabetic neuropathic treated patients showed a significant decrease ($p<0.025$) in the values of systolic and diastolic blood pressure (Figures-4 and 5) and comparatively a more significant decrease ($P< 0.005$) in values of heart rate (Figure-6). However, both types of treated diabetic patients without neuropathy showed a non-significant difference in levels systolic and diastolic blood pressures and heart rate when compared with the untreated patients and their age matched control subjects.

An interesting feature in these experiments was about 7% decrease in the values of systolic and diastolic blood pressure and about 6% decrease in the values of heart rate after the oral administration of 50 mg of sildenafil in non-diabetic controls. In addition, no difference was observed when the IDDM and NIDDM values were compared with each other either before or after the oral administration of sildenafil in all groups (data not shown).



*IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of Sildenafil citrate for t-test. * = p<0.005*

Figure-6: Changes in heart rate (beat/minute) before and after oral administration of sildenafil citrate (50 mg dose) in response to erotic film and fantasy in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.

DISCUSSION

Laboratory assessment of erectile response to erotic stimuli has been used for many years to assess sexual preferences as the out come of modification of deviant sexual behavior[21], but only one published study[23] has used this procedure in the investigation of erectile dysfunction. In the recent years, there has been increasing recognition that many cases of erectile dysfunctions are due, at least in part, to physical factors. This has led to a renewed interest in the physiological mechanism of normal erection and search for methods of investigating erectile function that may have diagnostic value. Evidence indicates that erection may involve the activation of several separate mechanisms[24]. In addition to parasympathatically mediated arterial vasodilatation, there may also be active reduction of venous

drainage[25] and the active closure of intra cavernosal arterio-venous shunts[26]. None of the established methods of investigating penile dysfunction is wholly satisfactory. The most widely used techniques for laboratory studies are either concerned with physiological state of non-erect penis e.g. measurement of penile blood pressure[27-28] or involve invasive procedures such as xenon washout[25], arteriography and artificial erection[29-30] and the usual non-invasive method of investigating the erect penis is to measure erections during sleep. However, this does necessitate over night observation of the patient[21].

In a study laboratory based procedure for monitoring penile diameter and dorsal penile arterial pulse during presentation of erotic stimuli has been described in the normal subjects[10]. The results indicate the aspects of the erectile response, which may be vulnerable to different pathological processes[31]. The etiology of erectile impotence associated with diabetes mellitus has been reported to be neuropathic abnormality in the male genital organ and/or vascular change in the corpora cavernosa. However, the diagnostic assessment and the treatment of the neuropathic factor has been impended by the lack of an objective laboratory test.

Sildenafil citrate relaxes vascular smooth muscle, resulting in modest reductions in blood pressure that are insufficient to stimulate a reflex increase in heart rate. These blood pressure reductions are similar for healthy men and men with coronary artery disease (CAD) or who use antihypertensive drugs. Sildenafil does not affect the force of cardiac contraction, and cardiac performance is unaffected. Sildenafil is mildly vasodilating in the coronary circulation and does not increase the risk of ventricular arrhythmia. During exercise and recovery, sildenafil does not cause clinically significant alterations in hemodynamic parameters in men with CAD, and it has no negative effects on coronary oxygen consumption, ischemia, or exercise capacity[32].

The present study has therefore been designed to compare the efficacy of sildenafil citrate on erectile and cardiovascular responses to erotic stimulations in IDDM and NIDDM diabetics (with and without neuropathy) and in age matched non-diabetic controls. The stimuli utilized were fantasy and film. Both of these stimuli produced striking differences between those in whom neuropathic and induced erectile factors were likely to under lie their sexual dysfunctions.

Our results indicated that during the period of erotic stimulation to film and fantasy penile mid shaft circumference, penile length, and penile pulse amplitude exhibited a significant increase ($P<0.0005$) after the oral administration of 50 mg of sildenafil (Viagra) in both IDDM and NIDDM diabetic neuropathic patients. However this difference was found to be non-significant in both types of diabetic patients without neuropathy before and after oral administration of sildenafil and when compared with their respective control subjects.

Penile rigidity is the most important determinant of the quality of an erection. Based on published evidence it is suggested that a penile rigidity of >70% is adequate for sexual intercourse[33]. Because sildenafil is believed to exert its beneficial effects by inhibiting the phosphodiesterase type-V enzyme and, therefore, increasing the intracellular levels of cGMP in the corporal smooth muscle, it would not be expected to produce an erectile response when used in the absence of a drive on the nitric oxide-cGMP pathway. This drive can be provided by physiological mechanisms that can be initiated by visual or other forms of sexual stimulations. As such, sildenafil may be expected to enhance relaxation of the corpus cavernosal smooth muscle, which in turn increases blood flow into the cavernosal spaces, thus leading to increased intracavernosal pressure, a key factor in producing an erect penis [34-35].

Our results suggest that oral administration of sildenafil improves the quality of erection in both IDDM and NIDDM neuropathic group of patients. We thus conclude that sildenafil citrate is an effective first-line therapy for erectile dysfunction in diabetic men with impotence of neuropathic etiology. These results further explains, how to manage sexual disorders as part of diabetic care, and suggests rules for sildenafil's prescription in diabetic neuropathic patients.

In contrast to above mentioned findings we found a decrease in the values of systolic and diastolic blood pressures ($P<0.025$) and heart rate ($P<0.005$) in both types of diabetic neuropathic patients after the sildenafil treatment, where as this difference was found to be non significant in both types of non neuropathic diabetics when compared with their respective control subjects. A decrease in pressure responses and heart rate after the sildenafil treatment in IDDM and NIDDM diabetic neuropathic patients is probably due to a decrease in peripheral resistance due to overall greater severity of neuropathy in these individuals with sympathetic and parasympathetic damage rather than from the effect of parasympathetic damage in particular. In this context, Jackson[36] observed in one couple tested, that administration of beta-adrenergic receptor antagonist prior to intercourse reduced the pressure response in both sexes. This can be taken as an alternative interpretation of our results. Our data indicate that

change in penile pulse amplitude is not produced passively by change in systemic blood pressure, or by the gross alteration in physical properties of penis consequent upon erection. The increase in penile pulse amplitude during arousal is therefore likely to reflect local vascular events, markedly affected by sildenafil treatment. These results are in conformity with the previous findings[37]. However, a strict relationship between penile blood flow and penile pulse amplitude cannot yet be assumed until we have further evidence.

Our results in general suggest that parallel development of circumference, length and penile pulse amplitude increase is associated with more rapid erection, whilst if penile amplitude increase does not occur at all, erections tends to be smaller in degree.

In conclusion, these results suggest that sildenafil citrate is an effective and well-tolerated treatment for erectile dysfunction in patients with diabetic neuropathy. It does not cause major decreases in blood pressure. It is associated with small additive decreases rather than large synergistic decreases. However, experimental studies to date do not suggest that sildenafil citrate causes a coronary artery steal phenomenon[38]. Because there is a small but finite risk of having a cardiac event with sexual activity with the oral administration of sildenafil, it is recommended to ask the diabetic neuropathic patients about their cardiac status before the administration of sildenafil, since it may produce systemic vasodilatory properties and can potentially lowers the blood pressure.

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