Int J Diabetes & Metabolism (2009) 17:45- 52

The effect of Sildenafil citrate (Viagra^{TM}) on the frequency, duration, and degree of nocturnal penile tumescence in diabetic neuropathic men

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Abstract
The present study deals with the effects of sildenafil citrate (Viagra) on the nocturnal sleep related erectile dysfunctions in diabetic neuropathic men. In this investigation 50 type 1 and 50 type 2 diabetic patients with and without an objective evidence of neuropathy, aged between 15 to 60 years with a duration of diabetes distributed over 1-20 years were included along with their age matched non diabetic controls. Subjects were evaluated for nocturnal penile tumescence (NPT) and rigidity testing and the effect of oral administration of 100 mg. of sildenafil citrate (Viagra) was noted on the above-mentioned parameters. Both types of diabetic neuropathic patients exhibited a highly significant decrease in all nocturnal tumescence parameters including frequency, duration, and degree. However, both type 1 and type 2 patients without neuropathy showed a non-significant difference in the above-mentioned parameters than their respective control subjects, thus suggesting that impotence and altered nocturnal erectile responses are likely to be associated with an increased frequency to autonomic neuropathy in these patients irrespective of their type of diabetes. Treatment with oral administration of 100 mg. of sildenafil in both type 1 and type 2 diabetic neuropathic patients indicated significant increase ($P<0.0001$) in all the parameters of NTP and rigidity testing, however this difference was not significant in both types of diabetic patients without neuropathy before and after oral administration of sildenafil and when compared with their respective control subjects thus suggesting that oral administration of sildenafil citrate improves the quality of nocturnal erection in both type 1 and type 2 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 will improve our insight into the management of sexual disorders as part of diabetic care, and suggest guidelines for the prescription of Viagra in diabetic neuropathic patients.

Key words: Sildenafil, nocturnal penile tumescence, diabetes, neuropathy

Introduction

Erectile dysfunction (ED) etiology in diabetes is multifactorial, including neuropathy, vascular disease, endocrine disorders, psychogenic factors, and anti-diabetes drugs[1]

Diabetic autonomic neuropathy (DAN) is one of the most severe and common complications of diabetes. Major clinical manifestations of DAN include resting tachycardia, orthostatic hypotension, constipation, loss of penile erection and/or retrograde ejaculation and ED. In men, DAN may cause ED with an incidence estimated to be between 35 and 75%.[2,3,4,5] A complete workup for erectile dysfunction in diabetic neuropathic men may include measurement of nocturnal penile tumescence tests to assess penile, pelvic, and spinal nerve function and measurement of penile and brachial blood pressure.

Received on: 09/01/2009
Accepted on: 06/06/2009

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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.[6] The patient may complain of the insidious onset and gradual progression (over 6 months to 2 years) of inability to attain and/or maintain an adequate erection as well as loss of morning erections although libido remains normal. 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. Absence of nocturnal tumescence as measured by penile strain gauge monitoring is helpful in establishing the organic nature of the impotence.[7,8,9,10] It is now established that sexual dysfunction is a common complication of diabetic autonomic neuropathy in both men and in women.[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.[12, 13]

Many clinicians have used the nocturnal penile tumescence (NPT) study to assist in the differential diagnosis of psychogenic from organogenic sexual dysfunction. The foundation of the test rests on the observations of regularly occurring erection cycles during sleep in healthy, sexually

functional men,[14] and abnormally diminished or absent sleep-related erection cycles in organically sexually dysfunctional men[15]

Measurements of NPT thus provide an objective and quantitative method for evaluating changes in erectile pattern. Furthermore, assessment of NPT is useful for the differentiation of organic/neuropathic from psychogenic erectile dysfunction.[16, 17]

One interesting new breakthrough in the treatment of erectile dysfunction using oral drugs lies in the substance sildenafil (Viagra). Sildenafil is an oral selective inhibitor of type 5 cGMP-specific phosphodiesterase enzyme (PDE-5) that is the predominant isozyme in the corpus cavernosum that degradates cGMP. The sildenafil-dependent PDE-5 inhibition results in an increase of cGMP together with a consequent decrease of intracellular ca^{2+}, finally resulting in penile smooth muscle relaxation and vasodilatation.[18, 19,20,21,22] Until now, the efficacy of sildenafil on erectile function has been assessed by self-filled questionnaires concerning sexual activity or visual erotic stimulation[23] or by visual erotic stimulation and simultaneous penile rigidity monitoring.[24] These types of studies provide results concerning psychogenic and/or reflexive erections, which are dependent at least in part on the psychological pattern of the subjects.

Sleep-related erections represents a valid clinical model useful to investigate the effects of sildenafil on penile physiology for the continuous monitoring of sleep-related erections by means of a device, providing quantitative and qualitative parameters of penile erections.[25,26] Moreover, nocturnal erections are poorly or not affected by external factors for example embarrassment, state anxiety, which can interfere with penile erections when studied on awake subjects.[27,28,29] Therefore, monitoring sleep-related nocturnal penile erections constitutes a useful tool to evaluate the pure effects of sildenafil on erectile function.

While many studies have demonstrated abnormal findings from NPT studies in sexually dysfunctional diabetic men, measurement of NPT with special reference to diabetic neuropathy is limited. The current study has been undertaken to determine relationship between sildenafil citrate therapy and changes in sleep-related erections in diabetic neuropathic men.

Materials and Methods

For experimental purposes and for the studies of diabetic neuropathy, after approval from the local ethical committee, 50 type 1 and 50 type 2 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 1 to 25 years of the disease was included.

The presence of diabetic complications was 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 of Bancroft and Bell[30] as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance and was further assessed using the International Index of Erectile Function (IIEF)-5: a multidimensional scale for assessment of erectile dysfunction as described previously.[31] The IIEF is a multidimensional, self-administered questionnaire (15-questions) addresses the relevant domains of male sexual function (that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). The IIEF demonstrates the sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction. Men were considered candidates for this study when they had complained of erectile dysfunction with diabetic neuropathy for 6 or more months.

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™-Pfizer, USA) in the treatment of erectile dysfunctions in both type 1 and type 2 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 (100 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.[31]

Nocturnal penile tumescence and rigidity testing were done in a sleep laboratory setting simultaneously using polysomnography and portable Rigi-Scan monitor according to the methods described previously.[32] In brief, RigiScan was applied to the patients in a standard fashion at the beginning of the test session. Loops were placed around the base and subcoronal regions of the penis near but not overlapping the mercury strain gauges to measure penile dimensions at a similar location. Loop positions were checked after each nocturnal penile tumescence event and locations were kept constant. Sleep staging and nocturnal penile tumescence were graphed every thirty seconds. Degree of nocturnal penile tumescence was defined as increase in penile circumference over the flaccid state,

measured in millimeters at the base. Maximum episodes were defined as deviations from the baseline recording of 80 -100% of greatest circumference estimated to be full by direct observation. Frequency was defined as the mean number of total or maximum tumescence episodes per night. Duration was defined as the mean time per night spent in tumescence. Although no clear consensus exists on which measured parameters are best to monitor, we chose what appeared to be the best, overall measures of tumescence and rigidity: average maximum rigidity of the tip lead, average maximum tumescence of the base lead, change in tumescence at the base, total area under the curve of the tip lead rigidity, and total area under the curve of bases lead tumescence.

Four men with normal nocturnal tracings were rejected for study because they were proven to have psychological impotence. Of the remaining men who qualified, 2 declined the study, 1 withdrew during the study and 1 was deleted from the study by for not following the protocol.

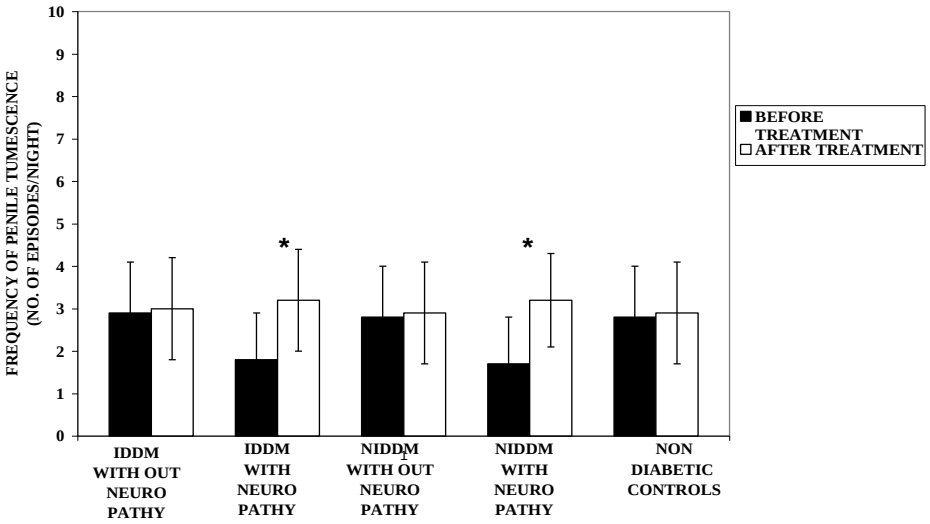

Figure 1: Frequency of penile tumescence (No. of episodes/night) before and after oral administration of sildenafil citrate (100 mg dose) in type 1 (IDDM) and type 2 (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls. Values are means ± S.D

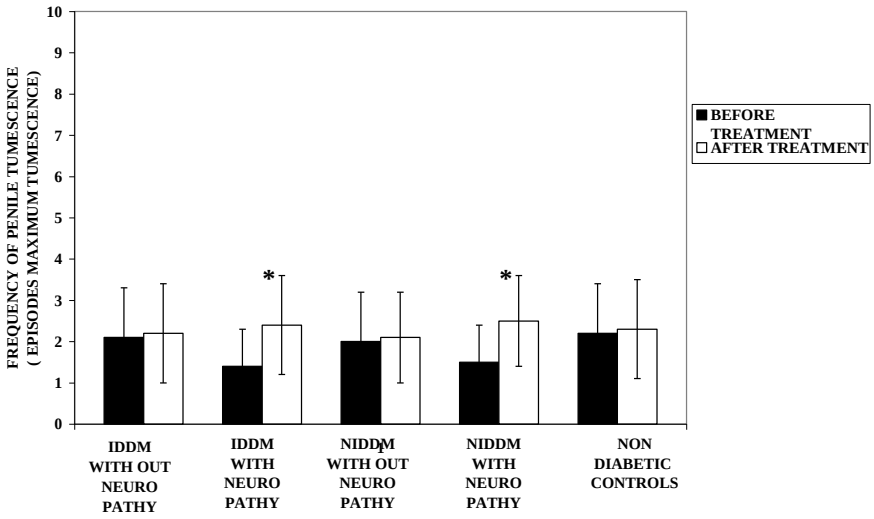

Figure 2: Frequency of penile tumescence (Episodes maximum tumescence) before and after oral administration of sildenafil citrate (100 mg dose) in type 1 (IDDM) and type 2 (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls. Values are means ± S.D

Results

The sleep and penile tumescence variables were compared by the Student's t-test for the significant differences between the means of treated/untreated neuropathic and non-neuropathic men. In all instances probability ($p<0.05$) was regarded as statically significant.

The data for the measured values of frequency of nocturnal erectile episodes including number of episodes per night and episodes maximum tumescence before and after the oral administration of 100 mg of oral dose of sildenafil citrate in 50 type 1 and 50 type 2 diabetic men (with and without neuropathy) and in 50 age-matched non-diabetic controls are shown in Figures 1 and 2. In both the parameters, sildenafil-treated diabetic neuropathic patients showed a highly significant increase of about 72% and 71%, respectively compared with the values obtained from untreated patients ($p<0.0001$).

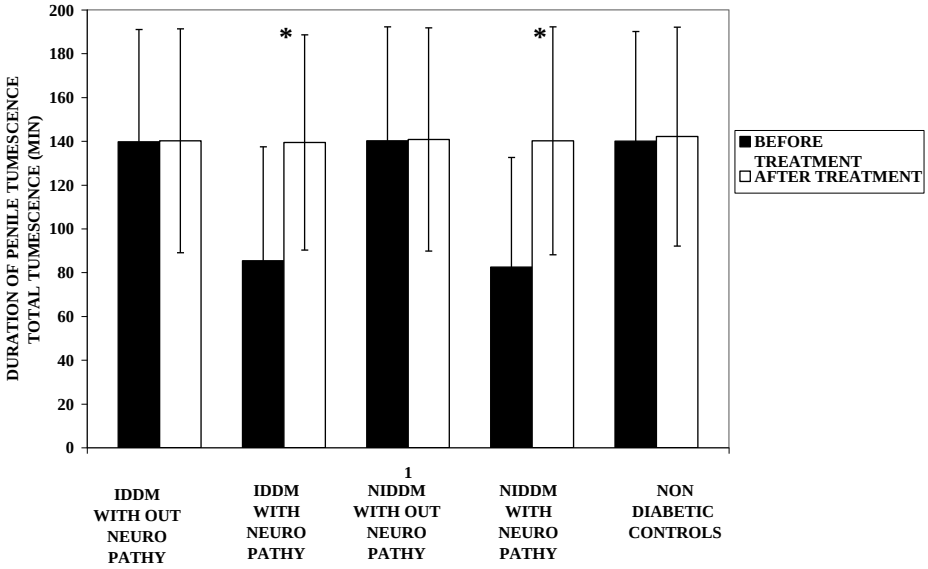

Figure 3: Duration of penile tumescence (Total tumescence-min) before and after oral administration of sildenafil citrate (100 mg dose) in type 1 (IDDM) and type 2 (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls. Values are means ± S.D.

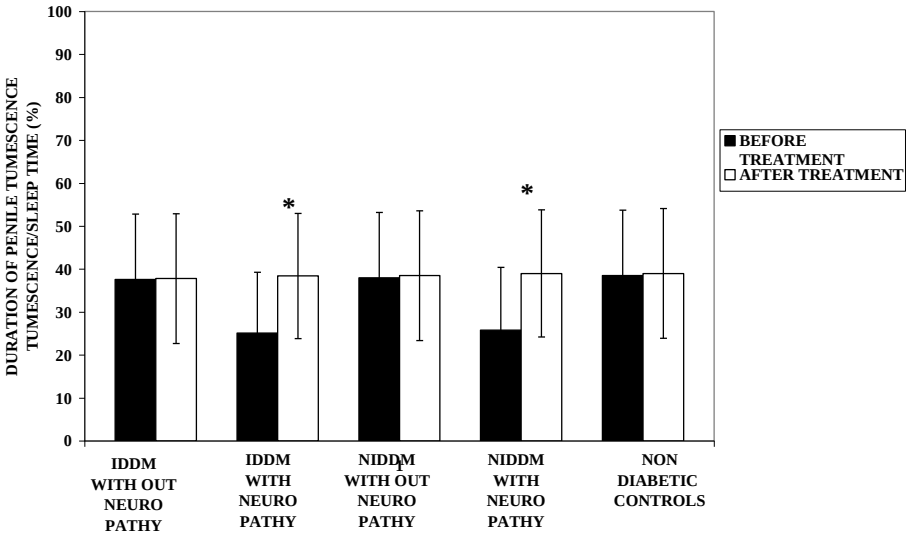

Figure 4: Duration of penile tumescence (Tumescence /sleep time-%) before and after oral administration of sildenafil citrate (100 mg dose) in type 1 (IDDM) and type 2 (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls. Values are means ± S.D.

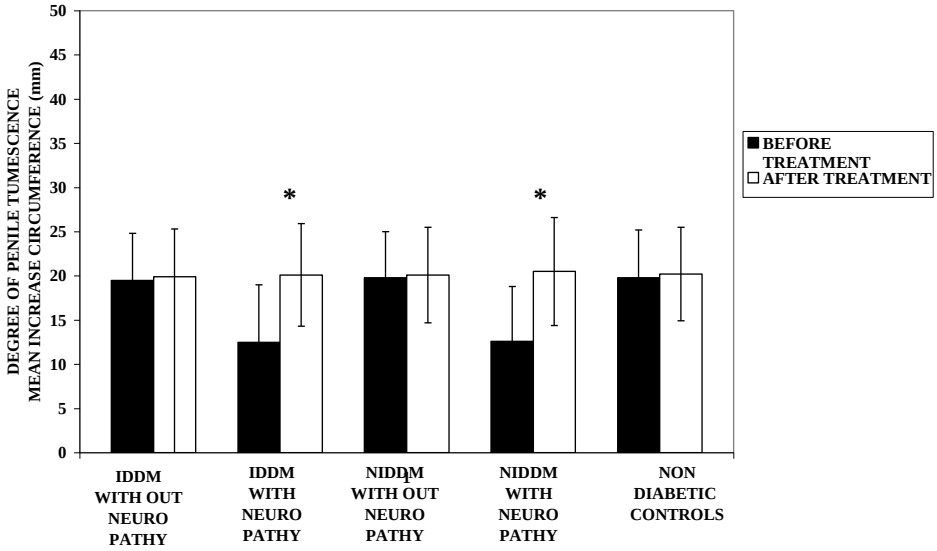

Figure 5: Degree of penile tumescence (Mean increase circumference-mm) before and after oral administration of sildenafil citrate (100 mg dose) in type 1 (IDDM) and type 2 (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls. Values are means ± S.D.

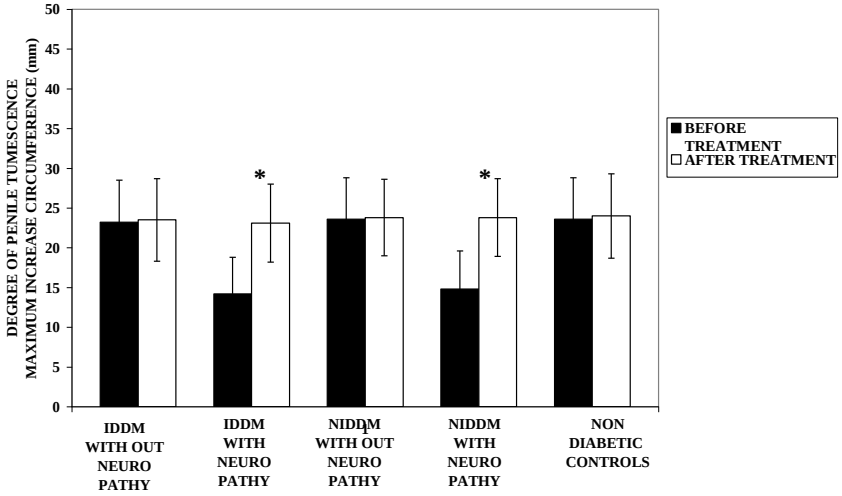

Figure 6: Degree of penile tumescence (Maximum increase circumference-mm) before and after oral administration of sildenafil citrate (100 mg dose) in type 1 (IDDM) and type 2 (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls. Values are means ± S.D.

Similarly as shown in Figures 3 and 4, both types of sildenafil-treated diabetic neuropathy patients showed a significant increase ($p< 0.0001$) in the values of the duration of penile tumescence including total tumescence (min), and tumescence/sleep time (%) when compared with their respective untreated patients.

A comparison of the measured values of the degree of penile tumescence including mean increase in circumference (mm) and maximum increase in circumference (mm) in controls and in both type 1 and type diabetic 2 subjects (with and without neuropathy) is presented in Figures 5 and 6. The values of the mean/maximum increase in the penile circumference measured from type 1 and type 2 neuropathic sildenafil-treated patients compared with the values obtained from untreated patients showed a consistent and highly significant increase of about 60% and 63%, respectively

($p<0.0001$). In all the cases however, values of the frequency, duration and degree of nocturnal erectile episodes were not significant in both type 1 and type 2 patients without neuropathy before and after oral administration of sildenafil, and when compared with their respective controls of the same age groups.

Discussion

The association between diabetes mellitus and erectile impotence is well known but information about prevalence and the nature of this relationship remains unclear.

In recent years, nocturnal penile tumescence (NPT) monitoring has been increasingly employed as a physiological test of organic impotence. Diabetic patients with erectile disorders have shown significantly less NPT during rapid eye movement (REM) sleep than psychogenically impotent and control individuals.[33]

There are no controlled studies that have included psychosexual, sleep and NPT measures in a clinically well-defined diabetic group of men who are otherwise healthy and are not selected because of sexual problems. It is thus evident that there is an extensive clinical literature available on the erectile disorders of diabetic men but still there is a lack of controlled investigation on nocturnal studies on diabetic neuropathy that have taken into account the effect of concurrent illnesses and medication on sexual function.

The aim of the present study therefore includes the comparison of sleep recordings and NPT parameters between both type 1 and type 2 diabetics (with and without neuropathy) according to well-defined criteria of erectile impotence.[31] The differential diagnosis and clinical management of these complications by the use of oral administration of sildenafil citrate (Viagra) was determined. Viagra is used as quality drug for the management of men with erectile dysfunction. This is a breakthrough compared to previously available treatments, such as intracavernosal and intraurethral prostaglandin therapies, vacuum devices or penile implants.[34,35]

The present study demonstrated that both type 1 and type 2 diabetic men with established autonomic neuropathy showed decreased penile sensitivity compared to non-neuropathic type 1 and type 2 diabetics and age-matched non-diabetic healthy control subjects. The abnormally diminished frequency, duration and degree of tumescence episodes during sleep paralleled the erectile difficulties reported by both type of diabetic neuropathic patients.

It seems reasonable to speculate that widespread NPT decrement in these patients reflect the sub-clinical impairment that placed the poorly controlled diabetic patients at risk for eventual erectile difficulties.

The association of diabetic complications and sexual problems is in agreement with previous reports.[30,36,37,38] The markedly impaired NPT activity in diabetic patients with symptomatic neuropathy or retinopathy supports the notion that peripheral neurovascular pathology is involved in pathogenesis of erectile impotence. Diabetic patients who met the criteria for neuropathy in this study did have significantly diminished penile blood pressure (unpublished observation). The assessment of sleep architecture suggests, in addition, that abnormal autonomic nervous processes may also contribute to diabetic erectile dysfunctions.

There is growing evidence that a central autonomic dysregulation not involving peripheral autonomic pathology may be associated with severe erectile impotence, sexual disturbances and diminished NPT.[39] In our results, a significant decrease in NPT parameters in diabetic neuropathic men is in conformity with previous findings.[27,40]

NPT recording may provide a sensitive indicator of physiologic changes in erectile capacity during the course of diabetes, which had been previously ignored due to the exclusive focus on impotent patients.

The observation that the moderately dysfunctional diabetic patients (non-neuropathic) had less NPT decrement than the neuropathic group suggests, however, that the relationship between erectile failure rates and NPT measures is not a close one. Psychological and interpersonal factors, in addition to physiological capacity are likely to play an important role in success or failure of erectile experiences.[41]

Conclusions from this study on a carefully selected group of patients should be used with caution. The results, unconfounded by the effect unrelated medical disorders, clearly demonstrate that diabetic neuropathy has a broad effect on male sexuality and that, physiologically, is associated with altered NPT deficits.

This finding has diagnostic relevance as NPT monitoring is being increasingly employed for the objective assessment of impotence of neuropathic origin. The diagnostic utility of NPT method is based on the notion that in psychogenic impotence sleep erections are normal while in neuropathic impotence nocturnal erections are impaired in correspondence to the patient's deficient waking erectile function. The present results suggest that impaired NPT may reflect subtle erectile deficiencies that are nevertheless, compatible with regular coital activity. However, care should be exercised in the interpretation of abnormal NPT finding for the differential diagnosis of diabetic erectile disorders.

To judge objective sexual capability, we used nocturnal penile tumescence and rigidity monitoring and, instead of using exogenous testosterone, which can suppress the hypothalamic pituitary axis, we used sildenafil citrate (Viagra™, 100 mg. oral dose) in a population of both type 1 and type 2 diabetics (with and without neuropathy). Sildenafil citrate is an orally active and selective inhibitor of PDE5. When sexual stimulation causes local release of nitric oxide, sildenafil enhances the effect of nitric oxide on corpus cavernosus by increasing the levels of cGMP in this

tissue. Sildenafil is rapidly absorbed following oral administration, has an onset of action within 25 to 60 minutes after dosing[24] and a plasma half-life of approximately 4 to 10 hours.

Sildenafil has been shown to be a well tolerated treatment in the patients with erectile dysfunction of various etiologies.[20,42]

Sildenafil citrate as reported previously[43] in this type of population elevates circulating androgen levels by stimulating Leydig cells indirectly by means of stimulating GnRH production from the hypothalamus.

Apart from the significant rise in androgen levels over a moderate period of time of about 2 months (data not shown), we found a clear statistically significant improvement that occurred in the subject's nocturnal penile tumescence and rigidity measurements in both type 1 and type 2 diabetic neuropathic patients.

Our findings thus conclude that sildenafil citrate is a well-tolerated and highly effective oral therapy for diabetic male erectile dysfunction with established neuropathic cause and may represent a new class of drugs for the treatment of this condition. Although the efficacy varies depending on baseline sexual function and etiology, there was no group of diabetic neuropathic patients in whom this medication completely lacked efficacy. In other words, it is worth trying sildenafil citrate for erectile dysfunctions in these patients if there are no contraindications.

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