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POSSIBLE NEUROGENIC ROLE OF SILDENAFIL CITRATE (VIAGRA) ON THE REGULATORY PATTERN OF PITUITARY-TESTIS AXIS IN DIABETIC MALES WITH AND WITHOUT NEUROPATHY

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ABSTRACT

Sexual dysfunctions due to neurogenic impotence decrease the testosterone levels through a central effect on the hypothalamic-pituitary axis. The present study deals with the effect of sildenafil citrate (Viagra) treatment for these neurogenic sexual disturbances on the reversibility of this neuro-endocrine pattern of the serum levels of pituitary-gonadal hormones.

In this investigation 50 insulin dependent (IDDM) and 50 non insulin dependent (NIDDM) diabetic male patients with and without an objective evidence of neuropathy and 50 age matched non diabetic male controls were selected. Every male had age between 20 to 65 years with duration of diabetes distributed over 1 to 20 years.

During treatment with sildenafil citrate (50 mg. oral dose) serum total testosterone, free testosterone, serum PRL, FSH and LH were measured.

Treatment with 50 mg. of oral sildenafil citrate reversed this neuro-endocrine release pattern in both IDDM/ NIDDM neuropathic men by exhibiting a significant increase in serum total and serum free (urinary) testosterone levels ($p<0.001$) and a significant decrease in the levels of serum prolactin (PRL) and follicle stimulating hormone (FSH). Decrease in luteinizing hormone (LH) was found to be less significant ($p<0.01$). However both types of non neuropathic diabetics treated with sildenafil citrate showed a non significant difference in the in the serum levels of the above mentioned pituitary-gonadal hormones when compared with the untreated groups and their respective control subjects.

These findings conclude that sildenafil citrate has a direct effect on the pituitary-testicular axis and is a well tolerated and highly effective oral therapy for restoring the potency with established neuropathic cause (irrespective of the type of diabetes) and may represent a new class of autonomically acting drug for the treatment of this condition. In other words it is worth trying sildenafil citrate for erectile dysfunctions of neuropathic etiology.

Keywords: Diabetes; Neuropathy, Pituitary-gonadal hormones; Sildenafil citrate therapy.

INTRODUCTION

The occurrence of a characteristic type of peripheral nerve disorder in-patients with diabetes mellitus has long been recognized. The first writing on diabetic impotence has been reported by Naunyn and Van Noorden (1927) and the first detailed review of diabetic autonomic neuropathy was the classic article of Rundles (1945) after which autonomic neuropathy was recognized as an entity.

Neuritic symptoms of diabetics including pains, coetaneous hyperesthesia, and the nocturnal intensification have been noted (Ellenberg and Webster 1966). The neurologic complications of diabetes mellitus were thus clearly recognized more than 50 years ago. In

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spite of the advancing knowledge in recent years regarding the nature and treatment of diabetes, including its complications, subject of diabetic neuropathy has become more confused (Ando *et al.,* 1984) and is still probably the most common complication in diabetics, and yet it remains poorly understood and inadequately explored (Ando et al., 1984).

In reviewing the pertinent literature, now it has become evident that diabetes can cause dysfunction of every part of autonomic nervous system, however the pathologic basis of diabetic autonomic neuropathy is still incompletely understood (Rastogi *et al.,* 1974; Ellenberg 1980; Lugnier *et al.,* 1993).

Endocrine causes of the impotence associated with diabetes have been suggested by different workers (Schoffling *et al.,* 1963; Rubin and Babbott, 1985). Vascular complications of diabetes may produce impotence on the basis of large vessel disease. The neurologic factor, long felt to be important in the pathogenesis of erectile difficulties in |diabetic males, has been re-emphasized by the demonstration of a high association of neurogenic vesicle abnormalities in a group of impotent diabetics (Ellenberg, 1971). In addition to impotence other types of sexual dysfunction may complicate diabetes including retrograde and premature ejaculation (Ellenberg and Webster, 1966). Schoffling *et al.,* (1963) reported that two-third of their patients with impotence and diabetes had decreased urinary excretion of pituitary gonadotropin with an increase in the urinary excretion of 17-Ketoseroides. In addition sexual disturbances with low plasma testosterone levels were also reported (Schoffling *et al.,* 1963). Further documentation of the low plasma testosterone levels of impotent diabetic men has been reported (Rivarola *et al.,* 1970); however in a previous study gonadotropic secretion values were found to be normal in the patients with well-controlled diabetes (Kent, 1966). Klinefelter's syndrome has been implicated as a possible significant factor because of the suggested associated higher prevalence of diabetes or family history of diabetes (Webster and Hammer, 1983). In addition, thickening of testicular tissues and diminution in the number of Leydig cells has also been reported (Schoffling, 1965). It seems, therefore that there is no consistent or acceptable support for an endocrine basis of impotence. However, there is considerable clinical evidence with a neuropathic basis for diabetic impotence. In a routine survey of 200 diabetic male patients, 118 (59%) were found to be impotent (Ellenberg, 1971). Of these 118 impotent diabetics, 104 (88%) had clinical evidence of neuropathy. Other supporting factors include the simultaneous occurrence of impotence and diabetic visceral neuropathy (Murray *et al.,* 1987).

There are conflicting reports of pituitary-gonadal functions in diabetic neuropathic patients. Normal luteinizing hormone (LH) (Rastogi *et al.,* 1974) and blunted follicular stimulating hormone (FSH) (Distiller *et al.,* 1999) have been reported, while blunted LH but normal FSH responses have also been reported (Ali *et al.,* 1993). Other aspects of pituitary functions have been studied with the demonstration of raised plasma thyrotropin (TSH) and growth hormone (GH) levels (Hansson *et al.,* 1973). Increased prolactin (PRL) responses have been reported with a significantly decreased level of plasma testosterone in insulin-dependent diabetes (Ando *et al.,* 1984; Ali *et al.,* 1993).

Nocturnal increase of plasma testosterone has been well established (Yaggi *et al.,* 2006). Luteinizing hormone does not show a similar increase throughout the night, where as PRL does, suggesting the possibility of other hormone influences on testosterone. Ando (1984) measured FSH and PRL in their sleeping subjects but found no relation between these hormones and testosterone. Moreover, PRL shows a consistent rise during the hours of sleep, similar to testosterone, where as LH shows little or no increase in the integrated levels as the night progresses. Furthermore, FSH has been implicated in augmenting testosterone release in both

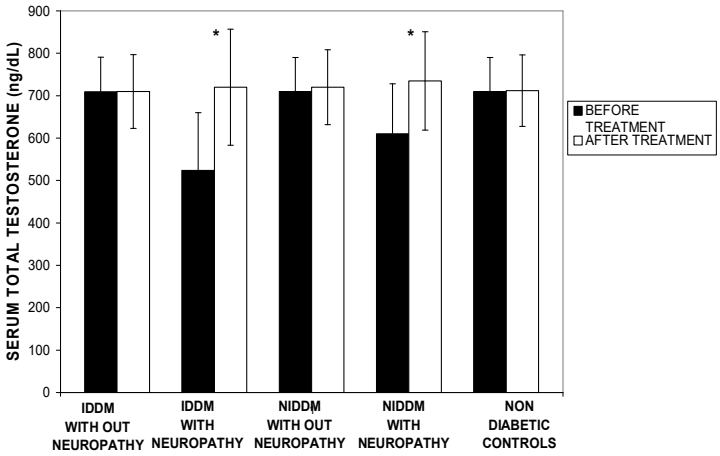

Fig. 1: Change in serum total testosterone levels before and after oral administration of sildenafil citrate (50 mg. dose) in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.
IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of viagra for *t*-test. * = $p < 0.001$

animals and humans, and PRL has been implicated in testosterone release in animals. However, the mechanism responsible for this nocturnal alteration in the secretary pattern of pituitary-gonadal hormonal release is not completely understood.

Different workers have sought to implicate endocrine factors in it pathogenesis, but without consistency. Normal serum testosterone levels have been frequently reported (Ellenberg, 1971) in impotent diabetic patients. Schoffling *et al.* (1963) claimed successful restoration of potency with testosterone therapy, but most reports describe it as ineffective.

One interesting new breakthrough in the treatment of erectile dysfunction using oral drugs lies in the substance sildenafil (*Viagra*^{TM}) seems to be a most promising discovery. Viagra is a potent and selective inhibitor of the cyclic guanosine mono-phosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), which is responsible for the degradation of cGMP in the corpus cavernosum (Goldstein *et al.,* 2002; Fujiswa and Sawada, 2004). Viagra 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 viagra 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). Viagra prevents the breakdown of cGMP thereby preventing premature detumescence. Furthermore, treatment with viagra is well tolerated and is associated with minimal adverse events (e.g., headache, flushing, and dyspepsia) that rarely cause discontinuation of treatment (Park 2005).

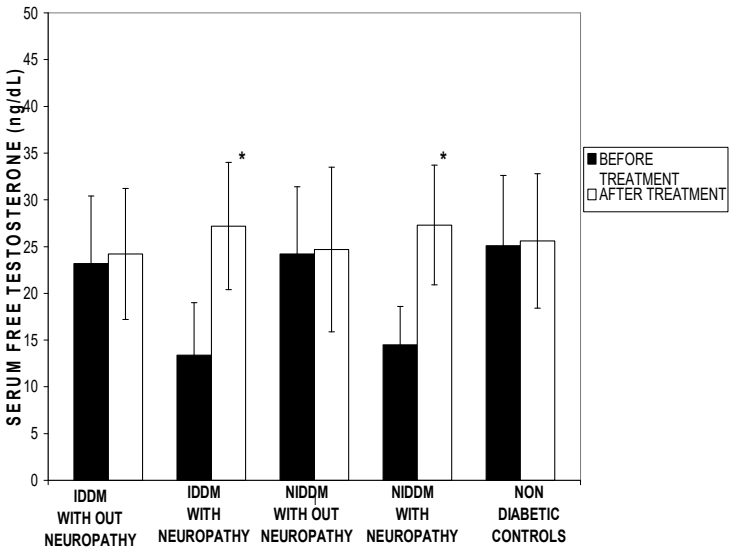

Fig. 2: Change in serum free (urinary) testosterone levels before and after oral administration of sildenafil citrate (50 mg. dose) in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.
IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of viagra for t-test. * = $p < 0.001$

Previously reported investigations indicate that in a group of diabetic neuropathic men examined for impotence, who along with mildly low testosterone levels did not have elevated gonadotropin levels and in whom endogenous testosterone levels could be restored to the normal range by the use of sildenafil citrate (Fabbri *et al.,* 1988; Jinnini *et al.,* 1999). More over since psychological behavioral therapies, pharmacological therapies using prostaglandin E1, and mechanical therapies like vacuum devices and penile prostheses restore the testosterone levels and LH bioactivity (Carosa *et al.,* 2002) our current work is designed to study the effect of sildenafil citrate on raising levels of circulating testosterone secretion in relation to the hypothalamic-pituitary axis in diabetic neuropathic men to restore erectile functions.

The results of these studies may serve as a diagnostic tool for the clinical management and diagnosis of gonadal dysfunctions in the patients with established diabetic/penile neuropathy.

MATERIALS AND METHODS

For experimental purposes and for the studies of diabetic neuropathy, 50 insulin dependent (IDDM) and 50 non insulin dependent (NIDDM) diabetic male patients with and without an objective 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 20 years was included.

The presences 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

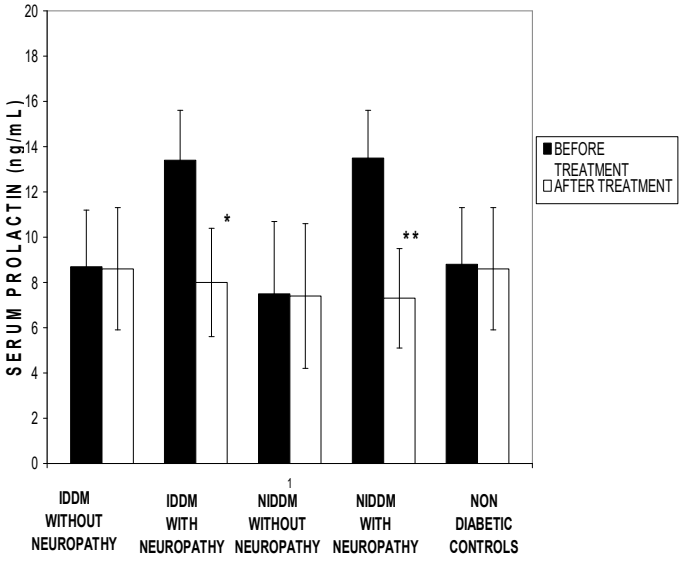

Fig. 3: Chang in serum prolactin levels before and after oral administration of sildenafil citrate (50 mg. dose) in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.
IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of viagra for t-test. * = $p< 0.01$; ** = $p< 0.005$

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 un-awareness. 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 methods described previously (Bancroft and Bell 1985; Rosen *et al.,* 1997). Men were considered candidates for this study when they had complain of erectile dysfunction with diabetic neuropathy for 6 or more months and low serum free testosterone levels and normal (un stimulated)) serum gonadotropin levels in an early (0800-1000h) sample. 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 diabetic men with and without neuropathy, subjects home and clinical practice centers in the local vicinities, were randomized to receive sildenafil citrate (50 mg orally), but not more than once daily, for 12 months. Self-reported ability to achieve and maintain an erection for sexual intercourse according to the Inter-national Index of Erectile Function and adverse events were recorded according to the

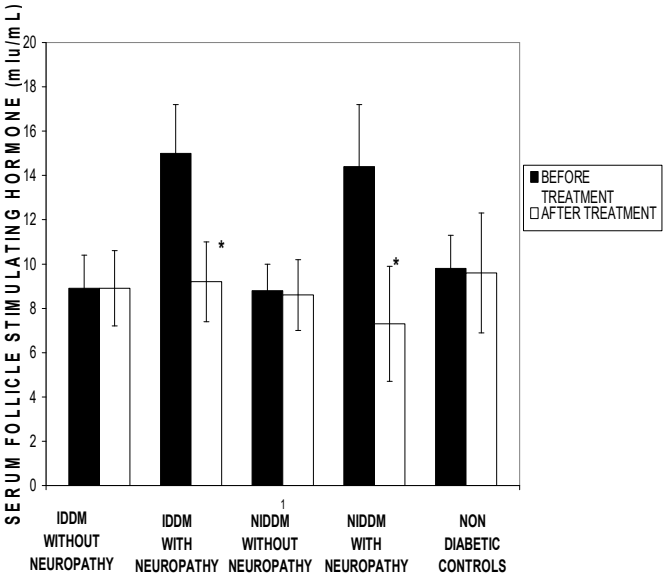

Fig. 4: Chang in serum follicle stimulating hormone levels before and after oral administration of sildenafil citrate (50 mg. dose) in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.
IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of viagra for *t*-test. * = $p< 0.005$

method described previously (Rosen *et al.,* 1997).

During treatment with drug, serum total testosterone, free testosterone, serum PRL, FSH and LH were measured within 2 hours of taking the last tablet of sildenafil citrate (3 hours after the meal approximately) by established methods (Christiansen *et al.,* 1996) using double antibody coat-A-count kit system (Diagnostic Product Corporation, Los Angeles, CA, USA). Blood was sampled in heparinized tubes. Serum was separated from the cells by centrifugation. Urine samples were mixed with boric acid (one gram/100mL). Both the serum and urine samples were aliquoted to avoid repeated thawing and freezing and were stored frozen at -20^0C, untill used. Prior to assay the samples were allowed to come to room temperature and were mixed by gentle swirling or inversion.

The hormonal levels were statistically analyzed using student *t*-test. In all instances probability ($p<0.05$) was regarded as statistically significant.

RESULTS

The data for the estimated serum level of total testosterone before and after the administration of the 50 mg. of oral dose of viagra in 50 IDDM and 50 NIDDM diabetic men (with and without neuropathy) and in 50 age matched non-diabetic controls is shown in Figure-1.The values of serum total testosterone estimated from sildenafil treated diabetic neuropathic patients compared with the values obtained from untreated patients showed a highly significant difference ($p<0.001$). In both types of diabetic neuropathics increase in the values of serum total testosterone after the oral administration of viagra was found to be almost all equal to the values of the control subjects.

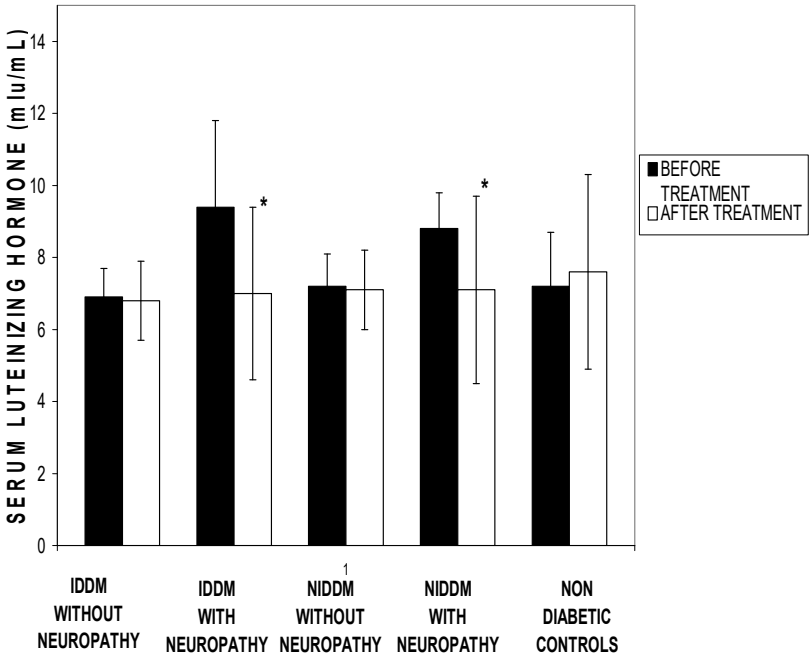

Fig. 5: Change in serum Luteinizing hormone levels before and after oral administration of sildenafil citrate (50 mg. dose) in insulin dependent (IDDM) and non insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non diabetic control subjects. Values are means ± S.D.
IDDM and NIDDM (with and without neuropathy) values are compared before and after oral administration of viagra for t-test. * = $p < 0.01$

However this difference was found to be non-significant in both IDDM and NIDDM patients with out neuropathy before and after the oral administration of viagra, and when compared with their respective controls of same age group. Since the analysis of the total serum testosterone levels revealed a highly statistical significant difference in both types of diabetic neuropathic patients, it was decided to investigate the serum free (urinary) excretion of testosterone as well. In these experiments controls and the patients were the same subjects who were investigated in the first instance. These results are presented in Figure-2. A significant increase ($P<0.001$) in the excretion of serum free testosterone was again noted in both types of diabetic neuropathic patients after the administration of viagra and the release pattern of serum free testosterone was found to be directly proportional as serum total testosterone. In contrast an inverse relationship was found when PRL, FSH and LH levels were studied in the same specimens. Both types of diabetic neuropathics showed a significant decrease ($p<0.005$) in serum PRL and FSH levels (Figures 3 and 4) and comparatively less significant difference ($P<0.01$) in serum LH level (Figure 5). However both types of treated diabetic patients with out neuropathy showed a non significant difference in serum levels of PRL, FSH and LH when compared with the untreated patients and their age matched control subjects. 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 viagra in all the groups (data not shown).

DISCUSSION

The increased frequency of impotence in the diabetic male has long been recognized (Ellenberg 1980). Despite improvement in the treatment of diabetes since the early insulin era there has been not any significant decrease in the frequency of diabetic impotence (Ellenberg 1980; Faerman *et al.,* 1972; Kolodny *et al.,* 1974). Thus the prevalence of impotence with increasing age in diabetic men aged between 20-60 years is still approximately 18-71% (Schoffling *et al.,* 1977) which is considerably a greater corresponding value as compared to normal male population (Kolodny *et al.,* 1974).

Using linear logistic regression model for analysis the three most significant associations with impotence were found to be the age, treatment with either insulin or oral hypoglycemic agent, or symptomatic autonomic neuropathy. The largest co-relation was found in the patients with symptomatic autonomic neuropathy. It is generally assumed that the diabetic impotence is due solely to autonomic neuropathy affecting these nerves (Ellenberg 1971). Impotence in particular is therefore a common complain which in normal subjects is frequently Psychogenic (Faerman 1972, Kolodny *et al.,* 1974) but in diabetics mostly due to autonomic neuropathy (Ellenberg 1971), or angiopathy (Cooper 1972). Different workers have sought to implicate endocrine factors in its pathogenesis but without consistency. Rubin and Babbott (1985) demonstrate that gonadal disturbances in the male diabetics are common. Schoffling *et al.* (1963) have shown that there seem to be an endocrine basis for the sexual dysfunction of diabetics and that the testicular hypo function in these patients can not be regarded as an indefinable complication of diabetic neuropathy.

Normal serum testosterone levels have been frequently reported (Kent 1966; Ellenberg 1971) in impotent diabetic patients. Although Schoffling *et al.* (1963) claimed successful restoration of potency with testosterone therapy however most reports describe it as ineffective (Kolodny 1974; Allen *et al.,* 1993; Rhoden *et al.,* 2002). More recently there have been conflicting reports of pituitary gonadal functions in diabetic patients. Increased prolactin responses have been reported with a significantly decreased level of testosterone in insulin dependant diabetes (Ahn *et al.,* 2002).

In another investigation it has been found that erectile dysfunction in men with diabetes is often associated with diabetic neuropathy and peripheral vascular disease (Goldstein *et al.,* 1982; Braunstein 1987). It occurs at an earlier age in men with diabetes than in men in general population. Several studies have demonstrated a high prevalence (35%-75%) of erectile dysfunctions with diabetes**.** In men with treated diabetes in the MMAS, the age-adjusted prevalence of complete erectile dysfunction (no erection) was 28%, which was approximately 3 times higher than the prevalence of complete erectile dysfunction in the entire sample of men (10%) (Feldman *et al.,* 1994). However, the pituitary-gonadotropin functional change, which occurs in a large number of male diabetics with established autonomic neuropathy, is still not very clearly understood.

Sildenafil citrate is an orally active and selective inhibitor of PDE5, and has been shown to be a well tolerated treatment in the patients with erectile dysfunction of various etiologies (Goldstein *et al.,* 2002). Sildenafil citrate as reported more recently (Chen *et al.,* 2003; Zhang *et al.,* 2006) elevates circulating androgen levels by stimulating the leydig cells indirectly by means of stimulating GnRH production from the hypothalamus.

In the present study we have tried to determine the effect of oral administration of sildenafil citrate on general release pattern of different pituitary-gonadal hormonal levels, (Testosterone, PRL, FSH, LH) in both IDDM

and NIDDM diabetic males (with and without neuropathy) and their age matched non diabetic control subjects. Our results indicated low serum total testosterone and serum free testosterone levels in both types of diabetic neuropathic patients in general, where as these levels were found to be non-significant in our non neuropathic diabetics when compared with their age matched non diabetic controls. Previous investigators have found low serum total & free testosterone levels in some impotent diabetic neuropathic men or diabetic men in general (Murray *et al.,* 1987; Saenz 1988; English *et al.,* 2000; Sieminska *et al.,* 2003). These differences between free and total testosterone levels could reflect an increase in sex hormone-binding globulin capacity or affinity, although sex hormone binding globulin was not determined directly (Ando *et al.,* 1984, Carosa *et al.,* 2002) Alternatively changes in free testosterone my be more sensitive indicator of testicular deficiency.

Our results of serum testosterone levels are therefore in conformity with the previous findings (Ali *et al.,* 1993; Backer *et al.,* 2000; Aversa *et al.,* 2003).

Our results further indicated a general increase in serum PRL, FSH, and LH levels in both IDDM/NIDDM diabetic neuropathic patients when compared with non-neuropathic diabetics and their age matched non-diabetic controls. These results are in conformity to earlier findings (Rastogi 1974; Daubresser *et al.,* 1978; Jackson 2004). It is to be believed that these men have some kind of organic disease (hypogonadism/neurogenic impotence). It is therefore suggested the possibility of some testicular dysfunction as a result of vascular disease (autonomic neuropathy) in our diabetics.

Recent morphological findings in the testis of neuropathic diabetic men of increased interstitial collagen, thinking of seminiferous tubule wall, peritubular and intertubular fibrosis and tubular sclerosis also suggest a primary gonadal disorder (Guval 2004). The low serum testosterone, and increased serum PRL, FSH and LH levels in our diabetic men with neuropathy therefore further suggest some kind of gonadal disorder (Hypogonadotropic hypogonadism) which may be due to testicular necrosis, and thickening of seminiferous tubules as a result of autonomic lesion. However further studies using randomized placebo and androgen treatment are needed to confirm these findings.

Sildenafil has been shown to be a well tolerated treatment in the patients with erectile dysfunction of various etiologies (Price 2001; Goldstein 2002). In this study, treatment with 50 mgs of oral sildenafil citrate significantly improved the erectile function in both types of diabetic neuropathic men by increasing the serum total and serum free testosterone levels by about 20%, and 100% respectively and by decreasing serum PRL, FSH and LH by about 60% when compared with the untreated specimens.

These results support the findings of a placebo controlled pilot study of 21 diabetic men with erectile dysfunction, who were evaluated for the efficacy of sildenafil citrate (25 or 50 mgs) using penile plethysmography during sex stimulation, a global efficacy question and a patient event log (Price 2001; Israilov *et al.,* 2005). Our findings thus conclude that sildenafil citrate is a well tolerated and highly effective oral therapy for diabetic male erectile/gonadal dysfunction with established neuropathic cause and may represent a new class of autonomically acting drug for the treatment of this condition. It may have a direct effect on pituitary-testis axis probably due to the higher frequency of full sexual activity. Although efficacy varies depending on baseline sexual function and etiology, there was no group of diabetic neuropathic patients in whom this medication completely lacked efficacy. A slow but steady decline in the level of circulating androgens is known to occur in diabetic neuropathic men (Jackson 2004). Declining levels of total testosterone, free testosterone, and bioabailable testosterone, have suggested decreasing

testicular function (Nakanishi *et al.,* 2004). Altered gonadotropic ratios and rhythm impulses, and lowered bioabailable/ immunoassay ratios of gonadotropins have supported the impact of neuropathy on the hypothalamic-pituitary axis, thus suggesting that neuropathy in these diabetic men affects the entire hypothalamic gonadotropin-leyding cell axis.

Our work reported in this research thus provide strong evidence of using sildenafil citrate in a diabetic neuropathic population for the purpose of restoring sexual functions regulated by pituitary-gonadal axis.

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