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***Sexual Dysfunction in Diabetes Mellitus***

## ***Sexual Dysfunction in Diabetes Mellitus***

It is universally appreciated that long-standing diabetes is associated with sexual dysfunction in men, the state of inquiry into sexual dysfunction in diabetic women is rudimentary. Perhaps it is because women do not complain of sexual dysfunction to physicians, and therefore it is not perceived as a problem; or perhaps it is because sexual dysfunction in women masqueraded as other symptoms such as mood swings, depression, vaginitis, cystitis, and loss of libido<sup>1</sup>.

Male sexual dysfunction may be classified as follows: ***diminished libido; dysfunction of emission, ejaculation, or orgasm; erectile dysfunction; and priapism***<sup>2,3</sup>. The most common of the various sexual dysfunctions is erectile dysfunction or impotence<sup>3</sup>.

Erectile dysfunction (ED) is defined as the persistent inability to attain or maintain penile erection sufficient for sexual intercourse. The 1992 National Institutes of Health Consensus Development Conference<sup>4</sup> recommends use of the term "*erectile dysfunction*" rather than "*impotence*" because it more accurately defines the problem and has fewer disparaging connotations.

Regardless of the primary cause, erectile dysfunction can have a negative impact on self-esteem, quality of life and interpersonal relationships<sup>5</sup>.

Most normal men have occasional episodes of erectile failure, especially at times of stress, fatigue, or distraction. Only when the rate of failure approaches 25 percent is it proper to invoke the clinical diagnosis of impotence<sup>6</sup>.

***Diabetes results in ED in 50-75% of men.*** In men with diabetes, the incidence of ED is 9% from age 20 to 29 years; and increases to 95% by age 70! It may be the presenting symptom of diabetes. ***More than 50% of men develop ED within 10 years of the diagnosis,*** and it may precede the other complications of diabetes. Neuropathy, vascular disease, glycation of cavernosal elastin, nutrition, endocrine disorders, and psychogenic factors, as well as drugs used in the treatment of diabetes and its complications, are among the multiple causes of ED in diabetes. Gradual onset and progression are the hallmarks of organic ED. Decreased rigidity and incomplete tumescence occur before total failure; morning or dream-related erections are lost along with spontaneous, tactile, visual, or fantasy induced erections. Organic ED is present with all partners and with masturbation, but there is no loss of libido. Sudden loss of erections with a particular partner while maintaining morning erections and nocturnal penile tumescence suggests a psychogenic cause<sup>7</sup>.

Likelihood of erectile dysfunction increases with age but is not an inevitable consequence of aging. The onset of erectile dysfunction occurs earlier in the

diabetic population; in fact, impotence affects diabetic patients an average 10 to 15 years earlier than in the general population<sup>7</sup>. Embarrassment of patients and reluctance of both patients and health care providers to discuss sexual matters candidly contribute to underdiagnosis of erectile dysfunction.

Erectile dysfunction can be effectively treated with a variety of methods. Many patients and health care providers are unaware of these treatments, and the dysfunction thus often remains untreated. Increased availability of new diagnostic procedures help in the selection of an effective, cause-specific treatment.

### **Physiology of Erection**

Erection is predominantly a hemodynamic process, mediated by neurogenic, endothelial, endocrine, and cortical (psychogenic) influences. It begins with blood flow increases into the large vascular corpora cavernosa which comprise much of the penile shaft. Flow varies according to the contractile state of smooth muscle lining the corporal arterioles and sinusoids. In the flaccid state, corporal smooth muscle tone is high and there is only basal arterial flow into the penis. In addition, venous outflow is facilitated by copious arteriovenous (A-V) shunts. On sexual stimulation, the smooth muscle relaxes, arterioles dilate, and blood flows in, engorging the corporal sinusoidal spaces. This engorgement and its restriction by the band-like tunica albuginea compress the venous plexuses and A-V shunts, impairing venous outflow. The net effect is a strong erection that may approach systemic arterial pressure. Detumescence occurs when smooth muscle tone returns, blocking arterial inflow and opening venous channels.

### **Mediators**

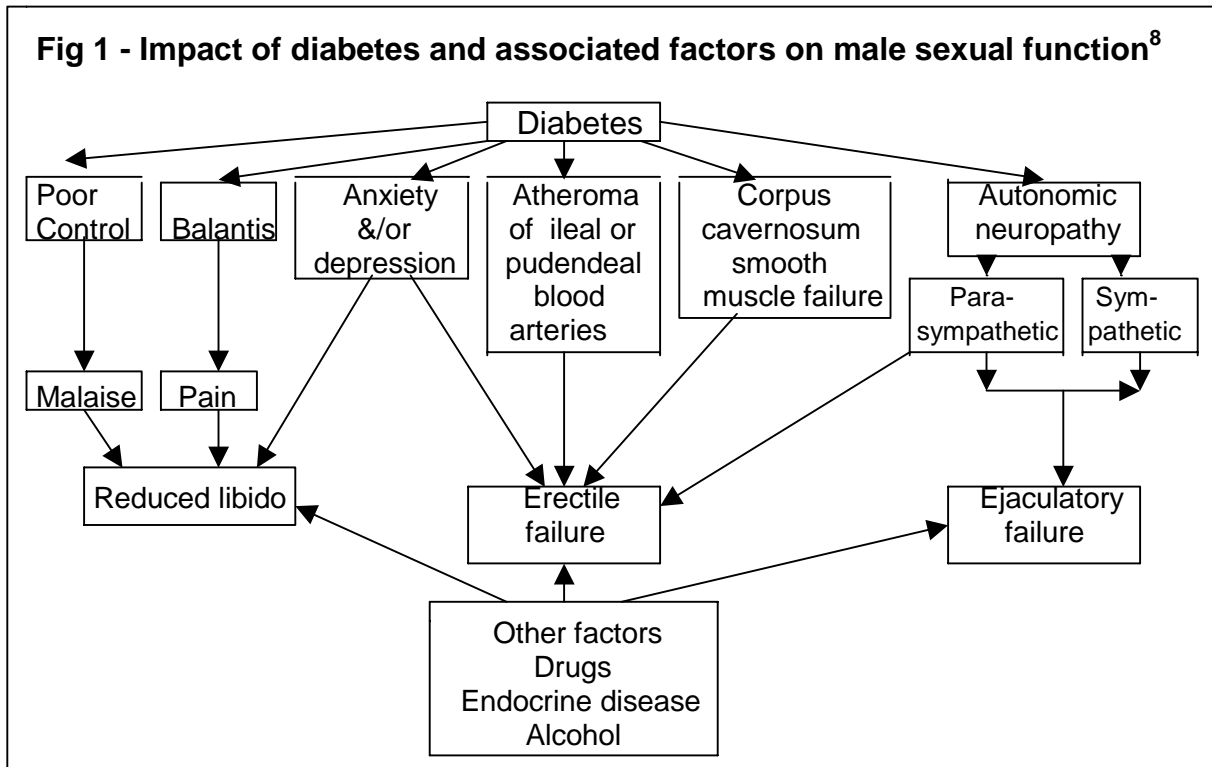
In the flaccid state, penile vascular smooth muscle contraction is maintained by sympathetic alpha-adrenergic tone, which results in norepinephrine release. The vasodilation of erection can be triggered by parasympathetic stimulation releasing acetylcholine and by nonautonomic neurotransmission believed to involve vasoactive intestinal peptide. Vascular endothelial cells contribute to relaxation by releasing endothelium-derived relaxing factor (EDRF), a locally active vasodilator. Prostaglandins produced by corporal tissue are also capable of both smooth-muscle contraction and relaxation and may play a regulatory role. Although androgens have a clear effect on sexual development, behavior, and libido, their influence on erectile capacity is less well defined. Erection can occur with visual stimuli, even if circulating testosterone levels fall to castration levels. However, nocturnal erections are lost.

## Control Centers

Erections may be triggered by psychic (cortical) stimulation or reflexly by tactile stimulation of the genitals. In most instances, both are operable and synergistic. A host of erotic stimuli can elicit cortical and subcortical responses, which are transmitted to the medial anterior hypothalamus, integrated, and projected down into the spinal reflex centers. There they modulate sympathetic and parasympathetic outflow to corporal smooth muscle.

There are two spinal reflex centers. The sympathetic one is in the thoracolumbar region. It controls adrenergic tone and sustains the vasoconstriction of the flaccid state. The parasympathetic reflex center occupies the midsacral region and effects vasodilatation. Tactile stimulation of the genitals produces afferent impulses carried by the internal pudendal nerve, which synapses in the reflex erectile center (sacral cord segments, 2-4). From there, efferent impulses pass over the pelvic nerves (nervi erigentes) to the parasympathetic plexuses innervating the corpora cavernosa.

Fig.1 depicts the interplay of diabetes and other factors leading to erectile dysfunctions.



## **Diagnostic and Therapeutic Evaluation of Diabetes-Related Erectile Dysfunction**

The initial evaluation for erectile dysfunction in the diabetic man begins with a sexual, psychosocial, and medical history, a physical examination, and routine laboratory tests.

### **I Patient history**

- Medical, sexual and psychosocial history
- Determine level of libido
- Rule out ejaculatory or orgasmic dysfunction

### **II Physical examination**

- Abnormal penile curvature
- Palpable corporal fibrosis

### **III Endocrinologic and laboratory evaluation**

- Routine hematology and chemistry profile, fasting blood glucose, HgA1c
- Lipid-cholesterol profile
- Hormonal profile (testosterone, LH, FSH)
- Rule out hyperprolactinemia (serum prolactin level)
- Rule out thyroid disease, other pituitary disorders, adrenal disease

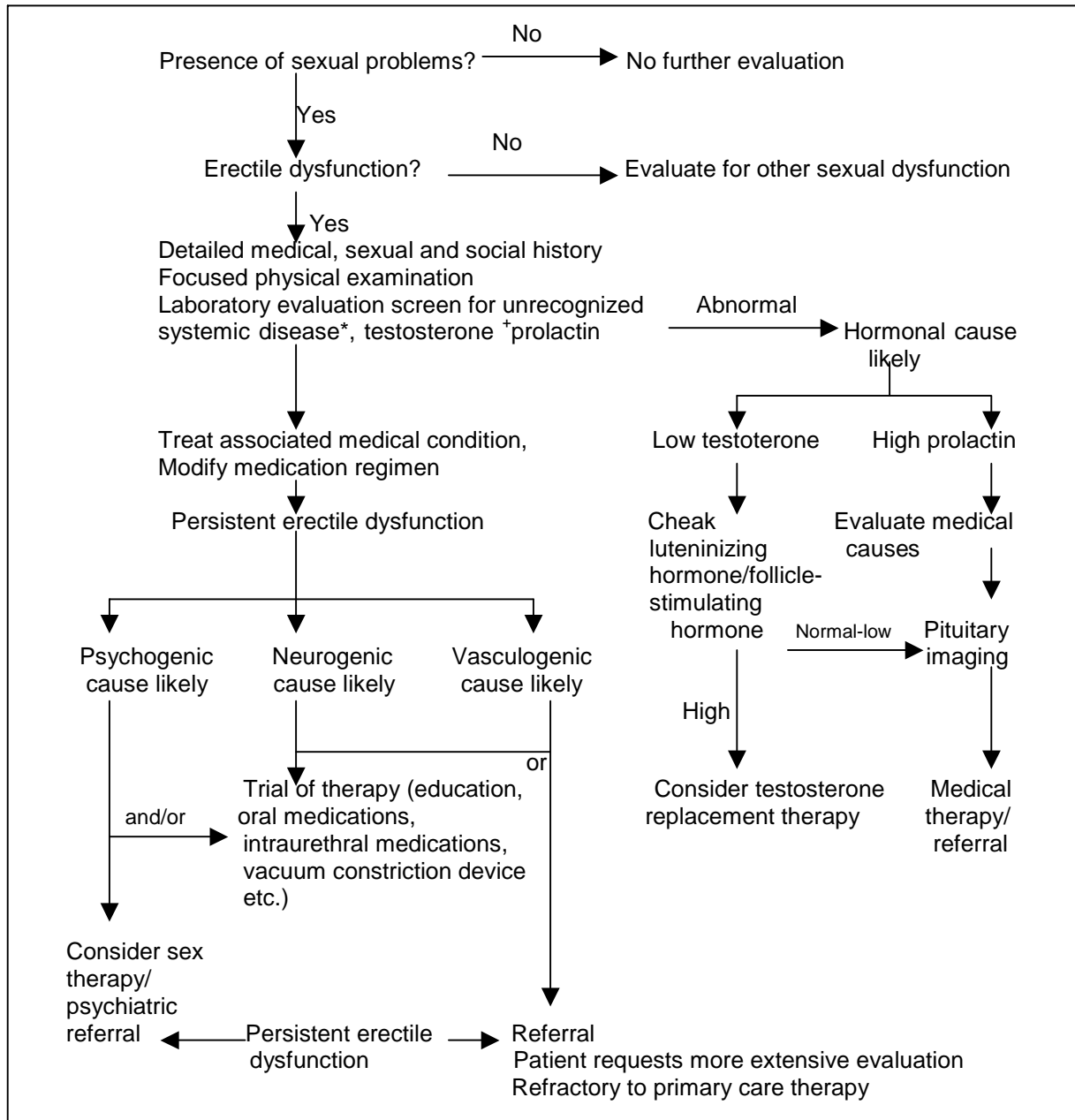
### **IV Vascular evaluation (in selected cases)**

- Office intracavernosal injection test
- Visual sexual stimulation
- Penile duplex Doppler ultrasonography
- Dynamic infusion pharmacocavernosometry and cavernosography
- Cavernosal tissue biopsy

### **V Neurologic evaluation (performed in selected patients)**

- Biothesiometry (vibration perception sensitivity testing)
- Nocturnal penile tumescence testing
- Single breath beat-to-beat variation (autonomic parasympathetic neuropathy)
- Single potential analysis: cavernous electrical activity (peripheral neuropathy)
- Dorsal nerve somatosensory evoked potentials
- Sacral latency testing

**Fig. 2: Alogarithm for Evaluation of Patient with Erectile Dysfunction**



\*-- Screening panel: complete blood count, urinalysis, renal function, lipid profile, fasting blood sugar, and thyroid function.

\*-- First-morning, free testosterone level.

Many noninvasive erectile function tests are utilized, including nocturnal penile tumescence testing, penile duplex Doppler ultrasonography, visual sexual stimulation, penile biothesiometry, and others. More invasive diagnostic tests, such as dynamic infusion pharmacocavernosometry and cavernosography, internal pudental angiography, cavernous electrical activity monitoring, and

cavernosal tissue biopsy can also be utilized. Once the initial diagnosis of erectile dysfunction is made, the remainder of the evaluation process should be individualized for each patient, as there is no universally agreed upon diagnostic algorithm for the evaluation of all impotent patients. Table 1 enlists likely causes of erectile dysfunction based on clinical presentation.

**Table 1: Likely Causes of Erectile Dysfunction Based on Clinical Presentation<sup>9</sup>.**

### **Psychogenic causes**

- Young age with abrupt onset
- Onset associated with specific emotional event
- Dysfunction in certain settings while normal function in others
- Persistence of nocturnal erections
- Excessive life stressors—work, relationships
- Mental status findings suggestive of depression, psychosis or anxiety disorder

### **Organic Causes**

#### ***I*** Vasculogenic—arterial

- Persistent interest in sex
- Older age with gradual onset
- Impaired function in all settings
- Presence of chronic disease (particularly diabetes, hypertension)
- Use of prescription/ over-the-counter medications associated with erectile dysfunction
- Smoking
- Elevated blood pressure, evidence of peripheral vascular disease (bruits, decreased pulses, skin and hair changes consistent with arterial insufficiency)

#### ***II*** Vasculogenic—venous

- Inability to maintain erection once established
- Prior history of priapism
- Local anomalies of the penis

#### ***III*** Neurogenic

- History of spinal cord/pelvic trauma or surgery
- Presence of chronic disease (diabetes, alcoholism)
- Presence of neurologic condition (multiple sclerosis, stroke)
- Abnormal neurologic examination of genitals / perineum

#### ***IV*** Hormonal

- Loss of interest in sexual activity
- Small atrophic testis
- Low testosterone, elevated prolactin

Table 2, lists drugs that are commonly associated with sexual dysfunction.

**Table 2: Drug Most Commonly Associated with Sexual Dysfunction**

Medication (Type of sexual dysfunction)
<b>Antihypertensive medications</b>
a. Diuretics
b. Thiazides (Erectile dysfunction, decreased libido)
c. Spironolactone (Erectile dysfunction, decreased libido)
d. Sympatholytics
i Central agents (methyldopa, clonidine) (Erectile dysfunction, decreased libido)
ii Peripheral agents (reserpine) (Erectile dysfunction, ejaculatory dysfunction)
iii Alpha blockers (Erectile dysfunction, ejaculatory dysfunction)
iv Beta blockers (particularly nonselective agents) (Erectile dysfunction, decreased libido)
e. Psychiatric medications
i Antipsychotic agents (Multiple phases of sexual function)
ii Antidepressants, Tricyclic antidepressants (Decreased libido, erectile dysfunction)
iii Monoamine oxidase inhibitors (Multiple phases of sexual function)
iv Selective serotonin reuptake inhibitors (Ejaculatory dysfunction, erectile dysfunction)
v Anxiolytic agents, Benzodiazepines (Decreased libido)
f. Antiandrogenic
i Digoxin (Decreased libido, erectile dysfunction)
ii Histamine H <sub>2</sub> -receptor blockers – cimetidine (Decreased libido, erectile dysfunction)

g. Others

- i Alcohol (long-term heavy use)  
(Decreased libido, erectile dysfunction)
- ii Ketoconazole  
(Decreased libido, erectile dysfunction)
- iii Niacin  
(Decreased libido)
- iv Phenobarbital  
(Decreased libido, erectile dysfunction)
- v Phenytoin  
(Decreased libido, erectile dysfunction)

With more sophisticated diagnostic evaluations, primary organic factors influencing erectile performance in patients with diabetes mellitus are being found with increasing frequency. The secondary psychologic reaction to these organic factors should be addressed simultaneously. Successful management of the diabetic patient with primary organic erectile dysfunction and secondary psychologic impotence demands attention to both dysfunctions.

**Table 3: Treatment options for diabetic erectile dysfunction include the following:**

**General Measures**

- Improving diabetic control
- Reduce alcohol intake
- Withdraw causative drugs

**Nonhormonal therapy**

- Alpha-2 adrenergic blocking agents (yohimbine hydrochloride)
- Type-specific phosphodiesterase inhibitors (sildenafil citrate)

**Hormonal therapy**

- Hypogonadotropic hypogonadism: parenteral testosterone
- Hyperprolactinemia/pituitary tumor: cessation of causative medications(e.g., estrogen, alpha-methyl dopa); bromocryptine; extirpative surgery)

**Noninvasive therapy**

- Vacuum erection devices
- Intravavernosal injection of vasoactive agents (mixture of papaverine, phentolamine, prostaglandin E1)

### **Invasive therapy**

- Penile prosthesis (malleable versus inflatable device)
- Microvascular arterial bypass surgery

### **Nonhormonal Therapy**

The most widely used oral nonhormonal medication for the treatment of erectile dysfunction is yohimbine hydrochloride, an alpha-2 adrenergic blocking agent. Yohimbine has long been considered an aphrodisiac; its effect on erectile dysfunction was first published 25 years ago. Other oral medications, including more potent alpha-2-adrenergic blocking agents, as well as type-specific phosphodiesterase inhibitors (sildenafil citrate), are currently under use and/or investigation for use in the treatment of erectile dysfunction.

### **Hormonal Therapy**

Hormonal therapy should only be used in the treatment of diabetic erectile dysfunction in the presence of concomitant hypogonadal disorders (hypogonadotropic hypogonadism or hypergonadotropic hypogonadism) or hyperprolactinemia. Furthermore, testosterone replacement therapy in diabetic patients should only be considered if the diagnosis of hypogonadism is based on several repeat values of low serum testosterone levels from early morning specimens.

Hyperprolactinemia in patients with diabetes is treated by cessation of medication causing hyperprolactinemia (e.g., estrogens, alpramethyldopa), administration of bromocriptine, or surgical ablation or extirpation of a pituitary prolactin-secreting tumor.

### **Vacuum Erection Devices**

Majority of these have three common components a vacuum cylinder, a vacuum pump that creates negative pressure within the chamber, and a constrictor or tension band that is applied to the base of the penis after the erection is achieved. The erection resulting from the vacuum device differs from the physiologically induced erection. The latter type is achieved by the initial relaxation of the corporal smooth musculature, thus, allowing for engorgement of blood into the lacunar spaces. In a vacuum-induced erection, corporal smooth muscle relaxation does not occur initially, and blood is simply trapped in both the intracorporeal and extracorporeal compartments of the penis.

Complications associated with use of a vacuum erection device may include difficulty with ejaculation, penile pain, ecchymoses hematomas, and petechiae (especially if the device used for >30 minutes).

## **Intracavernosal Injection of Vasoactive Agents**

Papaverina hydrochloride, phenoxybenzamine, phentolamine mesylate, and the prostanoid prostaglandin E<sub>1</sub> are commonly used drugs. The mechanism of action of papaverine hydrochloride and prostaglandin E<sub>1</sub> is via direct smooth muscle relaxation. Therefore when injected intracavenosally, they maximize arterial inflow as well as corporal veno-occlusion via relaxation of both arterial and trabecular smooth musculature, respectively. Phentolamine, on the other hand, blocks adrenergically induced muscle tone and therefore, does not alone initiate erections but is effective in prolonging the erectile response. A variety of solution containing the previously mentioned agents are being used in clinical practice papaverina alone, papeverine and phentolamine, prostaglandin E<sub>1</sub> alone, phentolamine and prostaglandin E<sub>1</sub> or a mixture of all three. The two most important complications of intracavenosa pharmacotherapy are prolonged erections and localized fibrotic changes of the corpora cavernosum.

## **Penile Prosthesis**

Throughout the 1970s and early 1980s, the development of penile prostheses proceeded along two distinct lines: the malleable or rigid prosthesis and the multicomponent inflatable prosthesis. More recently, self-contained inflatable devices have been introduced.

Diabetic patients thought to have psychogenic impotence, who have failed appropriate psychological or behavioral sex therapy and who have no psychological contraindications for therapy, may be treated in the same manner.

## **Vascular Surgery**

The ultimate goal of microvascular arterial reconstructive surgery for the treatment of vasculogenic erectile dysfunction is to increase blood flow to the penis during erections by bypassing the site of arterial obstruction.

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### **Comments of Opinion Leaders:**

*"Sexual dysfunction in diabetes is an important problem, which should be investigated thoroughly and managed effectively by the physician. With the availability of state of the art investigation facilities and modern drugs, management of sexual dysfunction is no longer empirical. Testosterone replacement or sildenafil should not to be indiscriminately prescribed. Good glycaemia control plays an important role in progression of neuropathy and total well being of the patients".*

**- Dr. K M Prasanna Kumar,  
Bangalore**

*"Sexual dysfunction in males is a common, distressing manifestation of autonomic neuropathy, whose progression is associated with poor glycemia control. Various landmark trials have proven beyond doubt the role of tight glycemia control in symptomatic relief & slowing of the relentless progression of neuropathy".*

**- Dr. G. B. Sattur,  
Hubli**

*"Erectile dysfunction is a common sexual problem in diabetes resulting from autonomic neuropathy. A good glycemia control has now been proved to prevent or delay the development like in other chronic micro vascular complications".*

**- Dr. R. G. Naik  
Mumbai**

*"Diabetic men have all possible types of sexual dysfunction. In the early poorly controlled stages, they have loss of libido, later neuropathy and vasculopathy are responsible for the erectile failures. Retrograde ejaculation is a specific dysfunction due to diabetic autonomic neuropathy.*

*Good diabetic control, manages to postpone neuropathic and vascular complications and hormone replacement are a few useful treatment measures".*

**- Dr. K. Kannam  
Madurai**