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New Approach to Management of Erectile Dysfunction in 2017

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Erectile dysfunction (ED), defined as the inability to achieve and or maintain an erection adequate for intercourse, it is the most common sexual complaint of men presenting to their health care providers. ED is an issue that greatly impacts a patient's quality of life and can have detrimental effects on his relationship with his partner. ED is not just his problem its their problem.

ED is most commonly classified as psychogenic, organic, or mixed etiology. Organic ED encompasses neurogenic, endocrinologic, vasculogenic, and medication, substance-induced. Risk factors for CVD such as hypertension, diabetes, smoking, obesity, and dyslipidemia are also well established risk factors for ED.

The 2012 Princeton III Consensus addresses the evaluation and management of CV risk factors in men with ED and no CVD.

In men with ED and CVD, there are various risk categories for morbid events related to sexual activity. Not surprisingly, highly active men appear to have a decreased risk of major adverse cardiac events (MACE) following episodic physical or sexual activity.

Sexual activity is equivalent to 3-5 metabolic equivalents of task (METs), as is walking one mile on flat terrain in 20 minutes or climbing two flights of stairs in 10 seconds. Exercise tolerance should be assessed prior to initiation of ED therapy in all men regardless of CV risk. As Per the Princeton III panel algorithm, if a man can exercise to 3-5 METs, he should be able to engage in sexual activity. In a patient with questionable cardiac health, the management of CV issues should always supersede and precede management of ED.

In men with hypertension, it is well established that the prevalence of ED is increased in hypertensive men compared to normotensive ones. The reported prevalence of ED in the hypertensive patient ranges from 15-46%, depending on the study population. Some antihypertensive medications are associated with some degree of ED. The agents associated with the most significant prevalence of ED include diuretics, centrally acting sympatholytics, aldosterone receptor antagonists, and beta-blockers. On the other hand, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (ATII) receptor blockers appear to have no significant negative effects on erectile function.

Diabetes is the biggest health tsunami of our century. There are 387 million diabetics across the globe and of these one-third are in India either at diabetic or pre-diabetic stage. India and China are two countries in the world where diabetes is an explosive epidemic[1]. In fact India and China, let us call it Chindia, are the diabetes capital of the worlds. Men and women with diabetes have sexual problems. The commonest complication of diabetes seen in Indian men is erectile dysfunction, low sexual desire and ejaculatory disorders. In diabetic women we observe vaginal dryness, hypoactive sexual desire disorders and depression. In diabetes certain infections which affect sexual functions & which are very common are balanoposthitis in males and vulvovaginitis, candidiasis in females.

Sexual dysfunctions in men include mainly erectile dysfunction, low sexual desire and ejaculatory disorders.

In Diabetics we see

Angiopathy

Macroangiopathy (rarely): Iliac arteries

Microangiopathy (frequently); Penile arteries and Microcirculation

Polyneuropathy Somatic nervous system: Pudendal and dorsal penile nerve

Autonomic nervous system: Parasympathetic → pelvic and cavernous nerves (Impairment of erection) Sympathetic → pelvic and cavernous nerves (Loss of emission and ejaculation)

Impairment of Neurotransmitter synthesis/release

Endothelial and smooth muscle cell dysfunction

Impairment of eNOS (NO↓)

Impairment of prostanoid synthesis (Prostacyclin: PGI_2↓, PGE_1↓)

Upregulation of arginase (NO↓)

Upregulation of protein kinase C (PKC) ß II

Impairment of KATP-channels (additionally enhanced by sulfonylurea antidiabetics)

Upregulation of insulin-like growth factor binding protein 3 (IGFBP-3) precursor

Downregulation of estrogen ß-receptor expression

Upregulation of α_1-adrenoceptors

Glycosylated hemoglobin C-induced decrease of NO-release.

Basic Pathogenesis of Erectile Dysfunction.

Penile erection is a neurovascular phenomenon that depends upon neural integrity, a functional vascular system, and healthy corpora cavernosal tissues.

Normal erectile function involves 3 synergistic and simultaneous processes:

A neurologically mediated increase in penile arterial inflow, relaxation of cavernosal smooth muscle, and restriction of venous outflow from the penis.

MOLECULAR BASIS OF ERECTILE DYSFUNCTION

Molecular basis of Neurogenic Erectile dysfunction

During radical prostetectomy even if its nerve sparing surgery there are chances of the nerves getting damaged and at a molecular level, cavernosal nerve transection profoundly decreases DNA content in the cavernosal tissue. This is accompanied by up-regulation of apoptotic genes. In caners its well known that it's the turning off the genes which triggers apoptosis. Another mechanism of cell death is when the cell percieves decreased signalling as seen in patients with spinal cord injury. All these molecular level changes not only decrease the weight of the penis but also the size and girth. All this is due to nerve disruption-induced apoptosis and hypoxia-induced damage to the corpora, leading to smooth muscle atrophy.

Molecular basis of Vasculogenic Erectile Dysfunction

Smoking, trauma, atheroscleoris lead to arterial insufficiency. This leads to many changes in the penile morphology and gene expression. The diminished blood supply to the penile nerves lead to decrease in the diameter of myelinated and demyelinated nerve fibers, which ultimately leads to depletion of the myofilaments. Additionally there are fewer endothelial cells and less nitric oxide production, ultimately leading to less corpora smooth muscle relaxation.

Another cause is venous leak which allows the blood to flow out after sexual stimulation and hence there is no rigid erection. The probable etiology is that it's the Androgen deficiency which leads to corpora smooth muscle atrophy. Testosterone also is known to stimulate the vascular endothelial growth factor, and hence Testosterone deficiency in men not only causes diminished sex drive but also induces ED at cellular level.

Molecular basis of Diabetes induced Erectile Dysfunction

Hyperglycaemia leads to generation and impaired clearance of oxygen-derived free radicals. This is oxidative stress in the microvasculature leads toproduction of Advanced Glycated end products (AGE), AGEs are products formed by non-enzymatic Maillard reactions between a protein's primary amino group and carbohydrate-derived aldehyde groups. AGEs bind with a receptor, RAGE, which mediates binding of AGEs to endothelial cells, thereby inhibiting endothelial-mediated smooth muscle relaxation via a nitric oxide pathway. The end result of this molecular cascade is impaired vasodilatation in any microvascular area, ranging from coronary vasculature to the retina to the penis.

ATP binding cassette transporters(ABC) viz A1, ABCG1 and Cholesterol 27-hydroxylase are Reverse Cholesterol transport proteins(RCT), that facilitate removal of macrophages and constitute a first line of defense against atherosclerosis, Studies revealed that ABC1 ABCG1 are identified to be suppressed by AGE. AGE also promote lipid overload through enhancing expression of proteins that facilitate lipid uptake and through suppressing reverse cholesterol transport proteins like Cholesterol 27 hydoxylase.

A new hypothesis has emerged and sounds very true is that instead of turning off the genes required for smooth muscle relaxation, there is a new pathway of calcium channeling called the Rho/Rhokinase which is turned on which leads to vasoconstriction and chronic detumescence. This is observed in diabetic rats. So if this RhoA/Rhokinase factor is inhibited the patients can get enhanced erection.

Lastly apoptosis has a critical role in diabetes induced Erectile dysfunction. Researchers have found in diabetic rats that there is a deficiency of anti-apoptosis gene βcl-2. The deficiency of this gene leads to a shift in homeostasis and cell death and organ degeneration.

Molecular basis of Testosterone on Erectile Dysfunction

Over 20 percent of men with erectile dysfunction have low testosterone. There is a clear correlation between low testosterone and severity of erectile dysfunction. In animal models it is studied that adequate androgen levels are essential for expression of NOS gene in the penis. It is also noted in these models that intra cavernosal pressure was reduced in hypo gonad models and reversed by androgen replacement therapy.

Research also suggests that there is a possible down regulation of both the production and activity of nitric oxide in the absence of testosterone in the rat, thus diminishing the response to peripheral stimulation via the nitric oxide pathway.

Several other mechanisms of hypogonadism induced ED include smooth muscle cell degeneration and increase in apoptotic activity due to diminished androgen stimulation with associated fibrosis of the corpus cavernosum. An enhanced response to mediators of vasoconstriction such as α-adrenergic stimuli is also suggested to occur in the hypogonadal environment.

A New Strategy

VEGF is a multifunctional protein, stimulating angiogenesis, inhibiting apoptosis, and increasing vascular permeability. The hypothesis is that, since endothelial cells synthesize nitric oxide, increasing the quantity of endothelial cells in the target organ will increase nitric oxide production and subsequent vasodilatation. This can prevent ischemia in the heart and, similarly, might improve erections in the penis.

Using this fact a new strategy to increase nitric oxide levels through enhancing the penile vasculature, using

recombinant vascular endothelial growth factor (VEGF) are currently being tried by transfection of VEGF into the rat penis to reverse vasculogenic ED via an increase in the levels of eNOS and inducible nitric oxide synthase (iNOS).

It was found that there was an increase intra cavernosal pressures after transfecting recombinant VEGF via an adenovirus vector They also noted an increase in regeneration of penile smooth muscle and nerves as well as endothelial cell hypertrophy and hyperplasia. In a more recent application, VEGF was demonstrated to inhibit apoptosis after intra cavernous injection, effectively restoring pressure in diabetic rat penile crura.

Christ and associates tried transfer humanhslo/maxi-K gene as this is responsible for increasing the response of smooth muscle to minimal levels of endogenous muscle relaxants such as nitric oxide in the corpora cavernosa of patients with ED.

In 2017 we shall see an amazing era of medicine and a great breakthrough in the therapeutic management of erectile dysfunction. Truly the study of human genome sequencing has made a revolutionary change in our understanding of the molecular basis of the pathology of erectile dysfunction and have paved a new road map to curative strategies.

Novel emerging molecular targets for treatment of Erectile Dysfunction:

Many men do not respond to the first line of therapy for Erectile dysfunction i.e. PDE5 inhibitors. Thus emerged the thirst for novel therapeutic drug and treatment targets.

Research suggests that endothelial microparticles, myeloperoxidase and haem oxygenase -1, are newer emerging molecular targets to treat vasculogenic ED.

Endothelial derived MPs (Endothelial Mirco-particles, EMP,) released in response to cellular damage or dysfunction as expressed by the marker CD144 were found to be elevated in diabetic patients with coronary artery disease and elevated EMP's

MANAGEMENT OF ED

Approach to a patient of ED

Making the basic sexual assessment a routine clinical practice, would have clear benefits in improving the overall health status,

The fact of erectile dysfunction, being an early sign of cardiovascular risk, supports the practice of routine assessment of sexual function, in clinical practice.

A well-elicited sexual history which includes onset, duration and severity of the ED, a detailed history of the stages of male sexual response which is desire, arousal, orgasm and resolution, morning erections and gender orientation, ensures appropriate clinical judgment and diagnosis, and also identifies possible co- existence of sexual disorders, for appropriate management.

A psychosocial history eluding to anger, depression, guilt, addictions, financial insecurities, extramarital affairs, body image issues, etc needs to be assessed.

A validated questionnaire which we use are IEF (International Index of Erectile Function) is a commonly used questionnaire for evaluation. Others include Sexual Health Inventory for Men (SHIM), Brief Male Sexual Functioning Inventory (BMSFI), etc. However these are not the alternatives to good detailed history taking.

A detailed physical examination from top to bottom is mandatory with examination of the reproductive organs for any local pathology, femoral pulses, varicocele hernia, hydrocele, phimosis, paraphimosis, herpes, peyronies disease, micropenis all signs of secondary sexual charactersticks and signs of hypogonadism, etc. Lastly a digital rectal examination has been proven to help us evaluate the status of benign enlargement of prostates in elderly males.

Ask every diabetic in your history do you have problems in making love ?

Ask history of morning erections. (If a patient is less than 40 years and gets morning erections even once a week, he has psychogenic or situational ED) This patient doesn't need any medications he only needs proper counseling.

Advice: Smoking, diet, exercise

Blood pressure: < 130/80 mm Hg

Cholesterol : TC <150, LDL<100 HDL >40

Diabetes control : HbA1c ≤ 7%

Eye examination : Annual examination

Feet examination : Everytime the patient walks in your clinic.

Guardian drugs : Aspirin, ACEI, statins

Heart risk score : UKPDS, Framingham, Hormones.

Impotence Rx : Drugs, Injectables, etc..

Other tests include

- Serum Testosterone Free and Total
- Sex Hormone Binding Globulin
- Free T3 T4 and TSH
- Serum FSH, LH Prolactin.
- USG of Scrotum and Doppler studies
- Serum PSA Free and Total
- DRE(Digital Rectal Examination)
- Questionaaires like IIEF (International Index of Erectile Dysfunction)
- One sophisticated tests which is now almost obsolete is Nocturnal Penile Tumuscence Rigidity (NPTR) Tests. 2 Electrodes are tied at the base and tip of the penis which are connected to Rigiscan and these are connected to a computer, Rigiscan detects nocturnal erections during REM sleep which are

plotted on the computer. Presence of erections indicates pyschogenic or situational ED.

- Instead of the above tests a roller of stamp can be advised to be put on the shaft of the penis and if it breaks it indicates psychogenic or situational ED.

Novel Approach to Erectile Dysfunction

In a recent study a relationship between the ratio of platelet count and absolute lymphocyte count (PLR) was studied as a marker of severity of Erectile dysfunction.

PLR value increased depending on the severity of ED. Mean PLR values were 108 in mild ED, 116 in Moderate ED and 130 in Severe ED groups.

The plateletelymphocyte ratio value is increased in moderate and severe erectile dysfunction compared with the control group (p Z 0.04 and p < 0.001).

Treatment of ED

To understand the treatment of ED one must understand that a normal vascular and neuronal endothelium produces endothelial nitric oxide synthase and neuronal nitric oxide synthase. eNOS and nNos initate the NO to enter in the corpora cavernosa spony tissue and converts Guanosine Monophosphate to Cyclic Guanosne Monophosphate with the help of an enzyme Gyanylate Cyclase. This Cyclic GMP is the main chemical which relaxes the smooth muscle cell of the Corpora and allows the blood to flow in penile vasculature. This cGMP also decreases the Calcium influx through specific protein kinases and allows the smooth muscle relaxation and erections.

But soon cGMP gets hydrolysed to 5 Guanosine monophosphate with the help of a enzyme Phosphodiastrase 5.

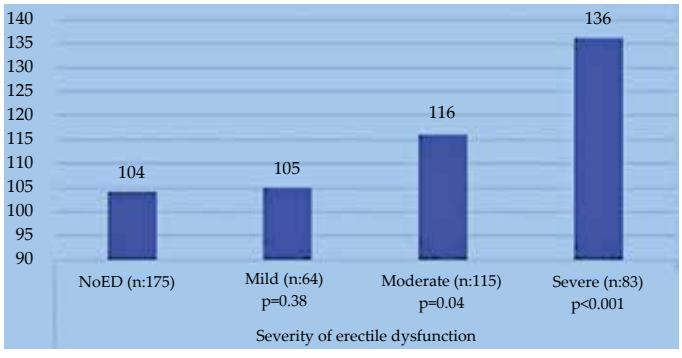

Fig. 1: Platelet / lymphocyte ratio value

So for a good enough erection one has to see that the endothelium has to be normal functional, adequate nitric oxide, guanylate cyclase activators and stimulators, cGMP to be present in more bioavailabale form to maintain tumusence and lastly something to block the PDE5 enzyme.

The first line of treatment is Oral Drugs and Counselling.

The second line of treatment is intracavernous injection of papaverine and largactil and prostaglandin, vaccum therapy and intraurethral drugs like prostaglandin, along with counselling.

The third line of therapy is Surgical treatment with Implants and counseling.

So Counselling forms the mainstay of treatment of ED

The Oral Drugs are Phosphodiesterase 5 Inhibitors (PDE5 inhibitors) (Table 1)

These drugs block the conversion of Cyclic Guanosine Monophosphate(CGMP) to 5,Guanosine Monophosphate and make CGMP more bioavailable which relaxes the smooth muscles and allows the blood to flow in the intracavernosal vasculature. (Figure 2)

The three PDE5 inhibitors available in our country are Sildenafil Citrate,Tadalafil and Udenafil.

Side Effects of PDE5 inhibitors include

- Facial flushing
- Headache
- Nasal congestion
- Dizziness

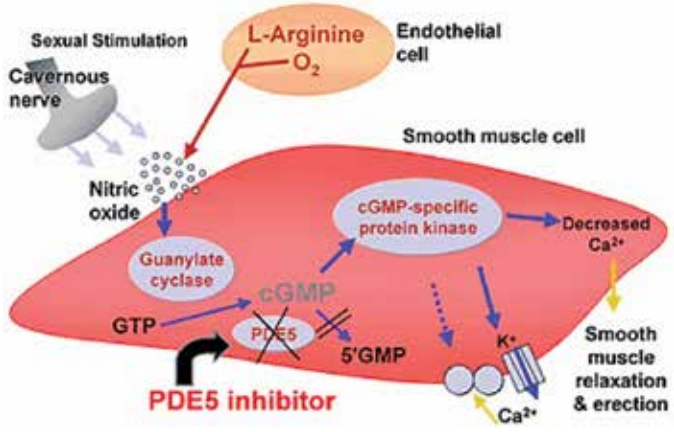

Fig. 2: Mechanism of action of PDE5I

Table 1: PDE5 inhibitors

Parameter	Sildenafil	Tadalafil	Udenafil
Doses available	25mg,50mg,100mg	5mg, 20mg	100mg
Adminstration	Taken 90-120 mins prior the act	Taken at least 120 mins prior to act	Taken at least 60 mins prior to act
Food Interaction	Avoid Fatty meals	None	None
Mean time to peak concentration (C Max)	60 min	120 min	60 mins
T1/2	3-5 hours	17.5 hours	10-12 hours

Fig. 3: Male Sexual Response

- Dyspepsia
- Visual disturbance (blue halo)
- Priapism
- Contraindications include
- Recent cardiovascular event
- Nitrates
- Hypotension
- Anatomical deformity
- Angulation, cavernosal fibrosis, Peyronie's
- Predisposition to prolonged erection

- Sickle cell disease
- Multiple myeloma
- Leukaemia

PDE 6 enzyme inhibition is less with Udenafil compared to Sildenafil - no Visual Abnormality PDE 11 enzyme inhibition with Udenafil is less than Tadalafil – No myalgia.

Now we also have mouth dissolving films of Sildenafil and Tadalafil which have faster onset of action and lesser side effects.

The newer oral drugs which shall soon be available are avanafil, mirodenafil, lodenafil carbonate and SLX2101.

The second line of treatment is Injection of papaverine and largactil with or without prostaglandin available as bimix or trimix self filled injection. Always caution the patient of priapism. The site of injections which shouldbe avoided are 12oclock position as it can damage the neurovascular bundle and 6 oclock position of the shaft of the penis as this can damage the urethra.

Vaccum devices can be advised to patients who have undergone Prostatectomy or elderly diabetics Though this devise is non invasive drug free and cost effective it is cumbersome, sometimes pts complain of pain and numbness and delayed ejaculations.

MUSE is medicated urethral insertion of drugs with the help of a device and prostaglandin pellets are introduced in the urethra.

The other non invasive treatment available is low intensity extra corporal shock wave therapy improves ED through angiogenesis.

The surgical treatment of ED is insertion of penile prosthesis or implants. The cheapest implant is made by Dr Rupin Shah which is a implant which is non inflatable and has a differential rigidity. Today we have 2 piece implants and 3 piece implants and the most widely recommended is three piece implant as these are totally concealed in body. Device is inflated to provide rigidity and deflated for concealment. Erection longevity is controllable. When deflated, the cylinders are soft and flaccid and they do expand the penis in girth.

Some observations in my practice is that many young adults have low sexual desire and have low free testosterone and high SHBG, these patients were put on testosterone replacement therapy did develop azoospermia. Many adults who had long standing co morbid conditions if put on testosterone replacement therapy did develop cardiovascular outcomes.

So the dilemma is what have to be done to improve the sexual desire of diabetics who have hypo androgenism. Its imperative to give them something which has a testosterone like effect and also does not have adverse effects of testosterone.

According to Masters and Johnsons male sexual response, one has to have a desire to get a proper arousal and if the desire is inadequate (Figure 3).

We have only focused on erection and ignored the desire which is the first to be in a male sexual response. So there exists a therapeutic gap in treatment of hypoactive sexual desire disorders in men with diabetes. But we now have a novel neutraceutical which has a tremendous effect of improving the sexual desires of our diabetic men. These neutraceuticals have L arginine which is a proven nitric oxide donor and ingredients combined with it are Saponised Fenugreek which has been studied to improve free testosterone levels to almost double and do not have any adverse side effects like synthetic testosterone. These neutraceuticals also have zinc which helps in spermatogenesis and also magnesium which has a relaxing effect and pyridoxine which helps in absorbtion of zinc and magnesium. There are many phytoneutraceuticals which have L Arginine combined with Pyknogenol, Safed Musli, Terrestris Trichuris, Asparagus adscendens,Withania somnifera, Mucuna pruriens, Ginesing and Ginkgo biloba.

These combination with L Arginine help in improving the sexual desire and not give any side effects like synthetic testosterone.. We have a ongoing study of this neutraceutical and it has been showing us a promising future.

The Newer Therapies are Regenerative therapies

Guanalyl Cyclase Activators and Stimulators as these increase the cellular cGMP concentration via the direct

activation of sGC, which results in both vasorelaxation and inhibition of platelet aggregation.

Rho- Kinase Inhibitors: Inhibition of the calcium sensitization pathway with Rho-kinase inhibitors offers a therapeutic option for the treatment of ED that does not involve the direct targeting of the NO/sGC/cGMP pathway.

Sonic Hedgehog Shh is a secreted protein important for formation of penile structures in the embryonic and early postnasal period and also for maintaining the sinusoids in aduts. Clinical evidence suggest that Shh is reduced in the penis of diabetic rats and human, and administration of exogenous Shh increased vascular endothelial growth factor and Nitric Oxide Synthase. Schwann cells in the penile nerual tracts contained abundant Shh. So Nanofiber aligned along the crushed nerve fibers during surgery observed enhanced regeneration of nerve fibres as seen on electron microscopy.

Gene Therapy: An adenoviral vector constructed to introduce a gene coding for a protein has been useful for improving ED.

Mesenchymal Stem Cell Therapy: Increasing evidences suggest the presence of penile endogenous Stem Cellss, with the regenerative potential that rely on endogenous Stem Cells/progenitor cells thus offer new insights into ED therapy.

Nano technology : Primarily this technology applies for topical delivery of drugs for on demand erectile function, Injectable gels into the penis to prevent morphology changes post prostatectomy, Hydrogels to promote CN regeneration/neuroprotection and Encapsulation of drugs to increase erectile function (primarily of PDE5i)

So a Ideal Prescription for a Diabetic having ED should be OHA/Insulin, Statin, Aspirin,Antihypertensive preferably ARBs, Nebivalol or Indepamide. Low dose Tadalafil 5mg, L-Arginine Plus, and low dose testosterone if he has low Free Testosterone.

Even though we prescribe the medicines for cure, emotional bonding makes the process faster. Talk about your fears and insecurities with your partner. Do not live under the stress for performance as for women, intercourse is all about emotional attachment. Enhance the emotional aspect and share your heart's worries with your partner. One important message which I would like to convey is that it is proven beyond doubt that ED is the earliest marker of myocardial ischemia. So if a physician just asks a simple question to every male above 30 years of age that whether he has a problem in making love…. This shall open a Pandora's box and give a physician a window of opportunity and a window of curability to work up this patient and save him from impending fatal cardiac problems. Lastly Diabetes is not an option, Not for anyone. It is how gracefully we handle the process and how lucky we are as the process handles us, and today if we are able to improve the metabolic imbalance by controlling diabetes, hypertension, dyslipidaemia we have lots of avenues to offer our patients a cure for erectile dysfunction.

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