JCD

REVIEW ARTICLE

Erectile Dysfunction

Dr Deepak K. Jumani

Sexual Health Physician and Counselor, Mumbai Police

***Abstract:** It is been estimated that about 35%-75% of men with diabetes will experience at least some degree of erectile dysfunction -- also called ED or impotence -- during their lifetime. Men with diabetes tend to develop erectile dysfunction 10 to 15 years earlier than men without diabetes. As men with diabetes age, erectile dysfunction becomes even more common. Above the age of 50, the likelihood of having difficulties with an erection occurs in approximately 50%-60% of men with diabetes. Above age 70, there is about a 95% likelihood of having some difficulty with erectile function. Until recently, erectile dysfunction (ED) was one of the most neglected complications of diabetes. In the past, physicians and patients were led to believe that declining sexual function was an inevitable consequence of advancing age or was brought on by emotional problems. This misconception, combined with men's natural reluctance to discuss their sexual problems and physicians' inexperience and unease with sexual issues, resulted in failure to directly address this problem with the majority of patients experiencing it.*

Luckily, awareness of ED as a significant and common complication of diabetes has increased in recent years, mainly because of increasing knowledge of male sexual function and the rapidly expanding armamentarium of novel treatments being developed for impotence. This review focuses on in depth coverage of the condition.

Introduction

The golfing icon Tiger Woods might have ditched his pregnant wife and possess a harem of 11 mistresses at last count, yet women still wish to woo him for reasons varying from his great physique to the big moolah he possesses. Tiger Woods is neither in WWF ring nor the superhero with eight pack abs. The mistresses who have been ditched and dumped could not stop talking about Tiger's physique. All the mistresses have been quite ga-ga over his sexual prowess. He is balanced. Often men with great looks fail to satisfy their partners due to erectile dysfunction (ED) and other related problems. Many of them shy away from even talking about it. This is such a symptom which patients do not talk about and doctors do not ask about.

Erectile dysfunction is trouble attaining and sustaining an erection sufficient for sexual intercourse. At least 25% of the time, the penis does not get firm enough, or it gets firm but softens too soon. Often, the problem develops gradually. One night it may take longer or require more stimulation to get an erection. Another time, an erection may not be as firm as usual, or it may end before orgasm. Failing to have an erection one night after you have had several drinks – or even for a week or more during a time of intense emotional stress – is not ED. Nor is the inability to have another erection soon after an orgasm. Nearly every man occasionally has trouble getting an erection.

Even though ED is often associated with older men, it is being found in an increasing number of younger men as the prevalence of diabetes increases around the world. Diabetes is the biggest health tsunami of our century. There are 382 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. In fact India and China, let us

call it Chindia, are the diabetes capital of the worlds. The commonest complication of diabetes is ED. So Chindia are the ED capital of the world.

Diabetic impotence (or diabetic ED) is common for many reasons. Causes of impotence in men with diabetes can vary. Many medications for blood pressure, ulcers, depression, and heartburn can have side effects such as ED. Diabetes itself causes some men to have ED simply because impairments in the nerves, muscles, and blood vessels do not allow for the penis to receive the proper amount of blood needed to achieve and maintain an erection.

What Causes Erectile Dysfunction in Men?

The primary cause is that the primary arteries and other blood vessels of the penis become narrow so that they are unable to carry enough blood to promote engorgement. This is thought to be caused by microvascular degenerative changes in the smooth muscle. In addition, there is disturbance of both somatic and autonomic nerve systems in men with diabetes whose pudendal nerves and bulbocavernous and urethroanal reflexes have longer latencies of somatosensory-evoked potentials. In addition, there are abnormalities in local levels of vasoactive intestinal peptide, prostaglandins, endothelins, and other mediators.

Since so much of the sexual arousal process is in the mind, it is always important to assess whether psychogenic factors are playing a part in ED. Any stressful relationship or life event has the potential to cause ED, but nocturnal erections and erections during masturbation may remain unaffected. By contrast, organic ED is due to the causes mentioned above. When damage to the nerves is a factor, there will be clues such as lack of ability to masturbate, absent cremasteric reflex, and bladder dysfunction. Analysis of the blood flow may reveal a vasculogenic origin, which may be confirmed by the man's smoking, low blood pressure in the penis or poor blood flow, no nocturnal or morning erections, and a gradual onset of erectile failure. Hormonal factors include loss of libido, gynecomastia, lack of masculinization, and decreased facial hair growth.

There are of course other factors, such as obesity, drug use – both prescription and non-prescription – including, ironically, drugs used to treat diabetes, prolaspe of the intervertebral discs, and vascular occlusion due to high cholesterol levels. Even the plaques of Peyronie's disease can cause ED.

Test for all these physical factors can be carried out when treatment is being considered for diabetic men with ED. In addition, a hormonal profile including measurement of at least free and total testosterone and thyroid-stimulating hormone levels is considered a good practice. The measurement of testosterone needs to be taken carefully since there is considerable diurnal variation in the level of this hormone. Other tests which are available to the physician include nocturnal penile tumescence studies, intracavernosal injection, arteriography, and duplex penile ultrasonography, though this battery of test tends to be reserved for the more seriously affected men.

Evaluation

History and Examination in Patients with ED

The causes of failure to achieve or maintain a satisfactory erection can include psychogenic or organic (i.e., vascular, neurogenic, or endocrine) "abnormalities." Apart from diabetes, other potential causes need to be considered. The history aims to define the dysfunction and to identify any possible contributory factors. If there is a partner, his or her presence is helpful. Relevant areas to question are discussed further.

Is the problem a lack of tumescence or early collapse of erection or both? How long have it been going on. And did it start suddenly or gradually? Do spontaneous or early morning erections ever occur? Is libido normal or sexual stimulation present? Is there a problem with orgasm or ejaculation, and what is considered normal? Details of the current relationship, the partner's attitude, and the couples' expectations should be enquired. What remedies have been tried already?

Current medical history

It is useful to look for endocrine abnormalities (hair loss, gynecomastia, weight gain, and change in heat tolerance), vascular disease (exercise-related chest or leg pain), and neurological disorder (problems with sensation, coordination, and motor dysfunction).

Past medical history

Enquire about pelvic surgery, radiotherapy or trauma, psychiatric or psychological problems. Many drugs can cause ED – thiazide diuretics, β-blockers, antidepressants, tranquilisers, anxiolytics, and H2 antagonists.

Lifestyle

As well as smoking and alcohol, ask about recent major life changes and the use of recreational or body building drugs.

Information from the above should provide strong clues as to the origin of the dysfunction. Sudden onset, the presence of some erection, ejaculatory problems, and major life events and/or psychological cause whereas gradual onset, no tumescence, the presence of risk factors, a past history of pelvic disease or treatment, certain medication or illicit drug use, smoking and heavy alcohol consumption suggest an organic cause.

Examination

Often examination can be limited to the genitalia, looking for anatomical abnormalities (e.g., retractably of the foreskin

if present, hypospadias or fibrosis in the penile shaft), the presence of pubic hair, and any evidence of pelvic atrophy. Either the history or the initial examination may indicate further examination such as looking for the presence of secondary sexual characters (breasts, beard growth).

Investigations

A stamp test is the simplest test to rule out organic psychogenic ED. A strip of four to six postage stamps (any kind) is used for each test. The test needs to be done for three nights. The man needs to wear brief-type undershorts that have a fly. Place the penis through the fly, leaving most of the pubic hair against the body. Wrap the strip of stamps snugly around the shaft of the penis. The stamps need to overlap so the overlapped stamp can be moistened to seal the ring. When the stamp has dried, carefully place the penis back inside the shorts and wear them while sleeping.

They help protect the stamps from falling off. In the morning, check to see if the stamp ring has been broken along the perforations. If the tearing of the stamps awakens the man during the night, check for an erection and how rigid the erection is. All men with normal physiological erectile function will have an erection during normal sleep. The test may help determine if the cause of ED is psychological or physical.

Some sophisticated gadgets are NTPR tests (Nocturnal Penile tumescence test, also called as Rigiscan) are also used for evaluating ED. But this test need admission and is expensive.

Every patient is asked to fill up IIEF (International Index of Erectile Function) questionnaire which enables us to evaluate ED.

Further investigations are indicated by the clinical findings. A free serum testosterone is the preferred screening investigation for suspected hypogonadism. Other investigations may be appropriate such as thyroid function, prostrate-specific antigen and prolactin. Extensive endocrine investigations are usually unnecessary.

Interventions

Some patients may not be enthusiastic about medical intervention for ED. As a first step, optimizing glycemic control encouraging smoking cessation and treating underlying causes, such as altering problem medication, may be helpful. If the difficulty is thought to be psychogenic then an exploration of surrounding issue may identify the cause. Often performance anxiety and lack of self-confidence may be contributory. Sometimes offering an explanation, reassurance, and clear unbiased information about treatment options, respecting patient's wishes, may be sufficient. However, referral for psychosexual therapy may be indicated if simple measures do not work.

Pharmacological Options

The availability of phosphodiasterase type 5 inhibitors (PDE5) have revolutionized the treatment of ED. In the absence of contraindications, these agents are the current first-line pharmacological intervention.

Phosphodiasterase type-5 inhibitors

This class of drugs selectively inhibits phosphodiasterase 5, an enzyme that breaks down cyclic guanosine monophosphate, an intracellular second messenger that maintains smooth muscle relaxation and maintains penile blood flow. These drugs have no effect on the libido and do not produce an erection in the absence of sexual stimulation. Although effective and well-tolerated in many, 30–35% fail to respond. There are currently three agents available: sildenafil, tadalafil, and vardenafil. All are taken orally prior to sexual activity and can be quite effective. The dose in one in 24 hours.

It is important to know their contraindications like severe liver dysfunction, hypotension, recent stroke or heart attacks, unstable angina, hereditary degenerative retinal disorders, and concurrent treatment with nitric oxide or nitrates. Cautions should be taken in anatomical penile deformity (e.g., angulation, cavernosal fibrosis, Peyronie's disease), conditions predisposing to priapism (e.g., sickle cell disease, multiple myeloma, leukemia), and concurrent treatment with cemetidine. Side effects included headache, flushing, dyspepsia, vomiting, transient visual disturbances (which consists of a bluish tinge to white colors and last less than 20 minutes), raised intra-ocular pressure, and nasal congestion.

Sildenafil was the first available oral drug for ED; it should be taken 1 hour before sexual activity and has duration of action of 4 hours. The usual starting dose is 50 mg with a subsequent dose range of 25–100 mg. It has to be taken on a light meal as food affects the absorption.

Tadalafil should be taken at least 60 minutes before sexual activity and has duration of action of 36 hours. The usual staring dose is 10 mg, with the maximum dose of 20 mg. It should be used with caution in hepatic or renal impairment. In addition to the above, it is contraindicated in mild heart failure, uncontrolled arrhythmias, and uncontrolled hypertension. Back pain and myalgia have been reported as side effects in addition to those listed above. However a low dose of 5 mg per day for a long time is also useful. There is no relation to food and hence can be taken before or after meals.

Vardenafil, which is not available in our country, should be taken approximately 25–60 minutes before sexual activity, although the onset of effect will be delayed if taken with a fatty meal. Its cautions are similar to sildenafil. It has a duration of action of 4 hours. Side effects include less commonly drowsiness, hypertension, tachycardia,

palpitation, back pain, myalgia, and facial edema. This is not available in our country.

When the PDE5 fails and before moving on to another treatment, the following should be considered for *incorrect use of drug or noncompliance*.

One study reported that 81% of the men took sildenafil incorrectly and education solved the problem in 40%. Other points are that they should be aroused and that is the way these medications work, If you take these pill and read Hanuman Chaleesa or Bhagwat Geeta or watch Lead India it may never work, and to avoid food or excessive alcohol that may delay or reduce drug absorption. Patients' need to be warned that some may require up to six to eight doses before optimal response occurs.

L-Arginine is thought to enhance the action of nitric oxide, which relaxes muscles surrounding blood vessels supplying the penis. As a result, blood vessels in the penis dilate, increasing blood flow, which helps maintain an erection. The difference in how they work is that sildenafil blocks an enzyme called PDE5, which destroys nitric oxide and L-arginine is used to make nitric oxide.

We have several preparation of L-arginine singly or with combination of several herbal preparations available which can be tried. These are safe and have no side effects. Some of the commonly used herbal preparations are Enlarge, Nano Leo, Erogenm, etc. The herbs are *Ginseng*, *Ginkobiloba*, *Pausinystalia yohimbe*, *Tribulus terrestris*, *Mucuna pruriens* French pine bark, etc.

Alprostadil

This agent is also known as prostaglandin E1. It is administered by intracavernosal injection (Caverject or Viridial) or intraurethral application (MUSE), both as a diagnostic test or treatment for ED. The dose depends upon the preparation and response. The aim is to produce an erection lasting for 1 hour. Patients can self-administer after proper training. The contradictions are predisposition to prolong erection, concurrent use of other agents for ED, and penile implants. The urethral application is contraindicated in urethral stricture, severe hypospadias, urethritis, balanitis local reactions at injection site, testicular pain and swelling. However the dose has to be properly judged and a dreadful complication of priapism has to be kept in mind.

Apomorphine

This drug is a dopamine agonist that activates specific neural events in the paraventricular nucleus of the hypothalamus. Oxytocinergic pathways then relax smooth muscle in the corpus cavernosum, which leads to erection within 20 minutes of use. The dose is one sublingual tablet 2 or 3 mg not to be repeated within 8 hours. Apomorphine is contraindicated in recent myocardial infarction, severe unstable angina, and severe heart failure. It is not recommended in combination with other treatments for the ED and should be used with caution in renal or hepatic impairment, in the elderly uncontrolled hypertension, and anatomical deformities of the penis. Apomorphine's side effects include nausea, dyspepsia, dizziness drowsiness, rhinitis, cough, flushing, taste disturbance, sweating, and yawning.

Other treatments

These include vacuum devices and penile prosthesis. The cost of this prosthesis ranges from Rs. 10,000 to over 4 lakhs. Referral to a suitable specialist is usually advisable for these treatments.

A novel therapy called *extracorporeal shockwave* therapy has also been tried and has claimed to be working on the principles same as of lithotripsy and produces angiogenesis in the cavernous tissue.

Although most patients with ED can be managed safely and effectively in primary care, specialist referral should be considered to an André Cryosurgeon if the patient has never had an erection and/or if there is severe vascular problem and/or if the patient opts for an intervention beyond the practitioner's competence. The treatment surgeon's offer is penile implants.

The newer therapies in the pipeline are *guanosine cyclase stimulators* and *agonists*, *Rho-kinase inhibitors*, *sonic hedgehog with nano particles*, *gene therapy*, and *stem cell therapy*.

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. Stress, mental tension, and even alcoholism increase the chances of ED, so you need to keep a check on alcohol and drug intake. A little precaution would keep you away from tensions that can lead to ED. Do not be scared if you are suffering from ED; just speak your heart before your partner. There is nothing surreal than pure emotions in times of distress. 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.

A proper counseling is a must for every patient before initiating any treatment for ED. So now you know which direction to take if you wish to be the Tiger in your relationship!

References

1. Feldman HA, Goldstein I, Hatzichristou DG, *et al*. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. *J Urol.* 1994;151(1):54–61.
2. Aytaç IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *Br J Urol Int*. 1999;84(1):50–5.
3. De Boer BJ, Bots ML, Lycklama AAB, *et al*. Erectile dysfunction in primary care: Prevalence and patient characteristics. The ENIGMA study. *Int J Imp Res.* 2004;16(4):358–64.
4. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: Prevalence and predictors. *J Am Med Assoc.* 1999;281(6):537–44.
5. Hellstrom WJG, Bivalacqua TJ. Peyronie's disease: Etiology, medical, and surgical therapy. *J Androl.* 2000;21(3):347–54.
6. Burchardt M, Burchardt T, Baer L, *et al*. Hypertension is associated with severe erectile dysfunction. *J Urol.* 2000;164(4):1188–91.
7. Bivalacqua TJ, Champion HC, Hellstrom WJG, *et al.* Pharmacotherapy for erectile dysfunction. *Trend Pharmacol Sci.* 2000;21(12):484–9.
8. Lue TF. Erectile dysfunction. *New Engl J Med.* 2000;342(24):1802–13.
9. Steers WD. Neural pathways and central sites involved in penile erection: Neuroanatomy and clinical implications. *Neurosci Biobehav Rev.* 2000;24(5):507–16.
10. Shabsigh R, Rajfer J, Aversa A, *et al*. The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Prac.* 2006;60(9)1087–92.
11. Gratzke C, Angulo J, Chitaley K, *et al.* Anatomy, physiology, and pathophysiology of erectile dysfunction. *J Sex Med.* 2010;7(1):445–75.
12. Jackson G, Rosen RC, Kloner RA, *et al.* The second Princeton consensus on sexual dysfunction and cardiac risk: New guidelines for sexual medicine. *J Sex Med*. 2006;3(1):28–36 .
13. Rajfer J, Rosciszewski A, Mehringer A. Prevalence of corporeal venous leakage in impotent men. *J Urol.* 1988;140(1):69–71.
14. Burnett AL. The role of nitric oxide in erectile dysfunction: Implications for medical therapy. *J Clin Hypertens* 2006;8(12):53–62 .
15. Maggi M, Filippi S, Ledda F, *et al.* Erectile dysfunction: From biochemical pharmacology to advances in medical therapy. *Eur J Endocrinol.* 2000;143(2):143–54.
16. Burnett AL, Ricker DD, Chamness SL, *et al*. Localization of nitric oxide synthase in the reproductive organs of the male rat. *Biol Reprod.* 1995;52(1):1–7.
17. Gonzalez CM, Brannigan RE, Bervig T, *et al*. Protein and gene expression of nitric oxide synthase isoforms I and III in the rat penile shaft. *J Androl.* 2001;22(1):54–61.
18. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol Clin North Am*. 2005;32(4):379–95 .
19. von Keitz A, Rajfer J, Segal S, *et al*. A multicenter, randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. *Eur Urol.* 2004;45(4):499–507.
20. Porst H, Padma-Nathan H, Giuliano F, *et al.* Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: A randomized controlled trial. *Urol*. 2003;62(1):121–5.
21. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. *J Sex Med.* 2009;6(5):1232–47.
22. Vardi Y. Microvascular complications in diabetic erectile dysfunction: Do we need other alternatives? *Diab Care*. 2009;32(Suppl 2):S420–2.
23. Jackson G, Betteridge J, Dean J, *et al*. A systematic approach to erectile dysfunction in the cardiovascular patient: A consensus treatment – update 2002. *Int J Clin Prac.* 2002;56(9):663–71.
24. Andersson K-E, Nehra A, Lue T, *et al.* Erectile physiological and pathophysiological pathways involved in erectile dysfunction. *J Urol*. 2003;170(2):S6–14.
25. Gongora Castillo C, Alvarez Gomez de Segura I, Bonet Furgeri H, *et al.* Impotence of arterial origin: Experimental models and assessment of sexual behavior in rats. *J d'Urologie.* 1993;99(3):122–6.
26. Goldstein I, Krane RJ. Drug-induced sexual dysfunction. *World J Urol.* 1983;1(4):239–43.
27. Morales A, Gingell C, Collins M, *et al.* Clinical safety of oral sildenafil citrate (VIAGRA) in the treatment of erectile dysfunction. *Int J Imp Res*. 1998;10(2):69–74.
28. Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: From angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Dis.* 2006;5(8):689–702.
29. Murad F, Mittal CK, Arnold WP, *et al.* Guanylate cyclase: Activation by azide, nitro compounds, nitric oxide, and hydroxyl radical and inhibition by hemoglobin and myoglobin. *Adv Cyclic Nucl Res*. 1978;9:145–58.
30. Ignarro LJ, Wood KS, Wolin MS. Activation of purified soluble guanylate cyclase by protoporphyrin IX. *Proc Nat Acad Sci USA*. 1982;79(9):2870–3.
31. Humbert P, Niroomand F, Fischer G, *et al*. Purification of soluble guanylyl cyclase from bovine lung by a new immunoaffinity chromatographic method. *Eur J Biochem.* 1990;190(2):273–8.
32. Ko F-N, Wu C-C, Kuo S-C, *et al.* YC-1, a novel activator of platelet guanylate cyclase. *Blood.* 1994;84(12):4226–33.
33. Mülsch A, Bauersachs J, Schäfer A, *et al.* Effect of YC-1, an NO-independent, superoxide-sensitive stimulator of soluble guanylyl cyclase, on smooth muscle responsiveness to nitrovasodilators. *Br J Pharmacol.* 1997;120(4):681–9.
34. Mizusawa H, Hedlund P, Brioni JD, *et al.* Nitric oxide independent activation of guanylate cyclase by YC-1 causes erectile responses in the rat. *J Urol.* 2002;167(5):2276–81.
35. Selwood DL, Brummell DG, Budworth J, *et al*. Synthesis and biological evaluation of novel pyrazoles and indazoles as activators of the nitric oxide receptor, soluble guanylate cyclase. *J Med Chem.* 2001;44(1):78–93.
36. Stasch J-P, Becker EM, Alonso-Alija C, *et al*. NO-independent regulatory site on soluble guanylate cyclase. *Nature.* 2001;410(6825):212–5.
37. Stasch J-P, Alonso-Alija C, Apeler H, *et al*. Pharmacological actions of a novel NO-independent guanylyl cyclase stimulator, BAY 41-8543: In vitro studies. *Br J Pharma.* 2002;135(2):333–43.
38. Evgenov OV, Pacher P, Schmidt PM, *et al.* NO-independent stimulators and activators of soluble guanylate cyclase: Discovery and therapeutic potential. *Nat Rev Drug Discov.* 2006;5(9):755–68.
39. Stasch JP, Hobbs AJ. NO-independent, haem-dependent soluble guanylate cyclase stimulators. *Handbook of Experimental Pharmacology.* Berlin: Springer; 2009: 277–308.
40. Friebe A, Koesling D. Mechanism of YC-1-induced activation of soluble guanylyl cyclase. *Mol Pharmacol*. 1998;53(1):123–7.
41. Margulis A, Sitaramayya A. Rate of deactivation of nitric oxide-stimulated soluble guanylate cyclase: Influence of nitric oxide scavengers and calcium. *Biochem*. 2000;39(5):1034–9.
42. Russwurm M, Mergia E, Mullershausen F, *et al.* Inhibition of deactivation of NO-sensitive guanylyl cyclase accounts for the sensitizing effect of YC-1. *J Biol Chem.* 2002;277(28):24883–8.
43. Straub A, Benet-Buckholz J, Fröde R, *et al*. Metabolites of orally active NO-independent pyrazolopyridine stimulators of soluble guanylate cyclase. *Bioorg Med Chem.* 2002;10(6):1711–7.
44. Miller LN, Nakane M, Hsieh GC, *et al*. A-350619: A novel activator of soluble guanylyl cyclase. *Life Sci*. 2003;72(9):1015–25.
45. Bischoff E, Schneider K. A conscious-rabbit model to study vardenafil hydrochloride and other agents that influence penile erection. *Int J Imp Res*. 2001;13(4):230–5.

46. Bischoff E, Schramm M, Straub A, *et al.* BAY 41-2272: A stimulator of soluble guanylyl cyclase induces nitric oxide-dependent penile erection in vivo. *Urology.* 2003;61(2):464–7.
47. Kalsi JS, Ralph DJ, Madge DJ, *et al.* A comparative study of sildenafil, NCX-911 and BAY41-2272 on the anococcygeus muscle of diabetic rats. *Int J Imp Res*, 2004;16(6):479–85.
48. Stasch J-P, Schmidt P, Alonso-Alija C, *et al*. No- and haem-independent activation of soluble guanylyl cyclase: Molecular basis and cardiovascular implications of a new pharmacological principle. *Br J Pharmacol.* 2002;136(5):773–83.
49. Schmidt PM, Schramm M, Schröder H, *et al*. Identification of residues crucially involved in the binding of the heme moiety of soluble guanylate cyclase. *J Biol Chem.* 2004;279(4):3025–32.
50. Stasch J-P, Schmidt PM, Nedvetsky PI, *et al*. Targeting the heme-oxidized nitric oxide receptor for selective vasodilatation of diseased blood vessels. *J Clin Invest*. 2006;116(9):2552–61.
51. Schmidt P, Schramm M, Schröder H, *et al.* Mechanisms of nitric oxide independent activation of soluble guanylyl cyclase. *Eur J Pharmacol.* 2003;468(3):167–74.
52. Schindler U, Strobel H, Schönafinger K, *et al*. Biochemistry and pharmacology of novel anthranilic acid derivatives activating heme-oxidized soluble guanylyl cyclase. *Mol Pharmacol.* 2006;69(4):1260–8.
53. Nakane M, Hsieh G, Miller LN, *et al*. Activation of soluble guanylate cyclase causes relaxation of corpus cavernosum tissue: Synergism of nitric oxide and YC-1. *Int J Imp Res.* 2002;14(2):121–7.
54. Baracat JS, Teixeira CE, Okuyama CE , *et al*. Relaxing effects induced by the soluble guanylyl cyclase stimulator BAY 41-2272 in human and rabbit corpus cavernosum. *Eur J Pharmacol.* 2003;477(2):163–9.
55. Gur S, Kadowitz PJ, Hellstrom WJ. Exploring the potential of no-independent stimulators and activators of soluble guanylate cyclase for the medical treatment of erectile dysfunction. *Curr Pharm Design*. 2010;16(14):1619–33.
56. Andersson K-E, Wagner G. Physiology of penile erection. *Physiology Rev.* 1995;75(1):191–236.
57. Walsh MP. The Ayerst Award Lecture 1990. Calcium-dependent mechanisms of regulation of smooth muscle contraction. *Biochem Cell Biol.* 1991;69(12):771–800.
58. Bivalacqua TJ, Champion HC, Usta MF, *et al*. RhoA/Rho-kinase suppresses endothelial nitric oxide synthase in the penis: A mechanism for diabetes-associated erectile dysfunction. *Proc Natl Acad Sci USA.* 2004;101(24):9121–6.
59. Park K, Kim SW, Rhu KS, *et al.* Chronic administration of an oral Rho Kinase inhibitor prevents the development of vasculogenic erectile dysfunction in a rat model. *J Sex Med*. 2006;3(6):996–1003.
60. Li WJ, Park K, Paick JS, *et al.* Chronic treatment with an oral Rho-kinase inhibitor restores erectile function by suppressing corporal apoptosis in diabetic rats. *J Sex Med*. 2011;8(2):400–10.