International Journal of Innovative Studies in Medical Sciences (IJISMS)

ISSN 2457-063X (Online) **www.ijisms.com** *Volume: 3 Issue: 1 | 2019*

Erectile Dysfunction in Diabetes: An Overview

Amin M Ibrahim MBBS Msc

Department of General Medicine Ayodele Medical Center, Lagos, Nigeria

ABSTRACT: *Erectile dysfunction is the persistent inability to achieve erection hard enough for sexual intercourse. Penile erection is initiated by various stimuli which leads to the release of NO from the nerve endings causing vasodilation and increased blood flow into the erectile tissues. This is accompanied by significant reduction in venous return creating the penile rigidity that is required for penetration. Erectile dysfunction may be vascular, psychogenic, neurological or drug related. The prevalence increases with increasing age. It could be as high as 90% in some selected populations of patients with diabetes which has prompted the call for screening of DM patients for the presence of ED. Different questionnaires are available for this purpose. The pathophysiology of ED in DM is related to multiple mechanisms including endothelial dysfunction, accumulation of advanced glycation end products, oxidative stress and neuropathy. The relationship between ED and cardiovascular disease has been studied and results suggests thatED could be a warning sign for future cardiovascular events. The first line treatment of ED is with phosphodiesterase 5 inhibitors which is effective in more than half of cases. Other treatment modalities are intracarvenosal injections, penile implants and vacuum devices which are equally effective in patients with diabetes.*

Keywords; *Diabetes mellitus, Erection, erectile dysfunction, Complications.*

1. INTRODUCTION

Erectile dysfunction (ED) is a common yet an underestimated problem in diabetes.This is due to the unwillingness of patients to discuss sexual problems and inadequate questioning of healthcare providers about the sex life of individuals with diabetes. Sexual enjoyment is among the determinants of the overall quality of life. Hence, sexual problems like ED negatively impact the quality of life in individuals with diabetes mellitus (DM). Patients with DM often have multiple organic co-morbidities which can greatly affect sexual functioning. Also, psychogenic conditions e.g. depression are common in the diabetic population which can also cause or aggravate ED. The recognition of ED as an important diabetic complication has recently gained attention largely due to the numerous studies indicating a high prevalence of the problem in individuals with diabetes. This has lead to the call for screening of individuals with DM for ED and those with ED for DM.

2. PHYSIOLOGY OF PENILE ERECTION

Penile erection occurs as a result of complex interplay between neurological, psychogenic and vascular factors. The initiating event is usually visual, auditory, olfactory, tactile or imaginary stimuli[1] or direct mechanical stimulation. The erectile tissuesof the penis consist of paired corpora carvenosa and corpus spongiosum which contains the urethra. The tissues are supplied by the branches of the internal pudendal artery[2] which arises from the internal iliac artery[3]. Penile enervation is derived from the pudendal and carvenosal nerves and receives both sympathetic and parasympathetic supply[4]. In the flaccid state the sympathetic component dominates while the parasympathetic stimulation is responsible for erection[5]. Impulses generated by various stimuli travel in the parasympathetic neurons in the carvenous nerve[5] stimulating the release of acetylcholine in the nerve terminals and triggers a cascade of cellular events that end up in vasodilatation and smooth muscle relaxation.

Nitrous oxide (NO) is the major neurotransmitter mediating vasodilatation and carvenous smooth muscle relaxation[6]. It is released from both the nonadrenergic and noncholinergic neurons (NaNc) and the endothelium[6]. Initially known as the endothelium derived relaxing factor, it stimulates smooth muscle guanylate cyclase production thereby amplifying the synthesis of cyclic guanine monophosphate (cGMP)[5,6]. cGMP activates specific protein kinases causing phosphorylation of ion channels leading to inhibition of ca^{2+} and K^{+} influx and smooth muscle relaxation. Flaccidity results when cGMP is hydrolyzed to guanosine monophosphate by phosphodiesterase type 5 (PDE5) which is a key regulator of cGMP activity[5].

During penile erection the dilatation of the carvenous and helicine arteries[7] (and arterioles) permits increased blood flow into the coporacarvenosa which is the most important erectile tissue. Blood flow to other penile tissues is increased as well. This leads to the expansion of the sinusoids accompanied by venous compression thus reducing venous outflow. The emissary veins are occluded by the stretching of the tunica albuginea providing further inhibition of the venous outflow[8,9]. These events collectively results in increased intracarvenosal pressure and full penile erection is achieved. Further increased pressure is obtained with the compression of the base of the penis

by reflex contraction of the ischiocarvenous muscle yielding a rigid erection[6,8].

3. AIETIOLOGY OF ERECTILE DYSFUNCTION

(a) Vascular; hypertension, atherosclerosis, diabetes mellitus, hyperlipidemia, obesity, peyronnie's disease

(b) Psychogenic; Depression, psychological stress, performance anxiety, relationships problems

(c) Hormonal; Androgen deficiency, hyperprolactinemia

(d) Neurological; multiple sclerosis, surgical procedures on the lumbar spine, stroke, spinal cord injury, Alzheimer's disease

(e) systemic illness; chronic renal failure

(f) Drugs; antihypertensives, antiandrogens, antidepressants, alcohol use, cigarette smoke, antiepileptics, finastride.

4. PREVALENCE OF ERECTILE DYSFUNCTION IN DIABETES

The prevalence of ED among people with DM varies remarkably. This variation often reflects the regional or population characteristics, acceptable definition, study design and diagnostic criteria[10]. Despite these differences in reported prevalence the vast majority of authors agree that ED is a problem of significant magnitude in individuals with diabetes. Available data from epidemiological studies have indicated that it affects more than half of adults with diabetes and the prevalence is higher with increasing age[11]. It is three times more likely to occur in those with diabetes than in the general population[12]. Results from a systematic review and meta-analysis of 145 studies comprising 88,577 patients revealed an ED prevalence of 52% in people with diabetes[13]. A cross sectional study from Tanzania reported a prevalence of 55.1%[14]. In this study the average duration of diabetes was 9 years. ED occurs at a younger age in men with diabetes and it is usually more severe[15]. It is also associated with a less favourable response to therapy. Routine screening of individuals with DM for ED has been advocated[13] although the level of adherence to such practice is likely low at the moment. A hospital based survey in Ethiopia reported ED prevalence of approximately 70% with a mean age of 43 years and a duration of diabetes of 6 years[16]. 5.2% of the study population suffered from severe ED while 32.9% and 31.7% had mild and moderate disease respectively. Of note is the somewhat higher proportion reported in studies from Japan. Sasaki et. al. reported 90% in the age range of 40-79 years[17]while Yamasaki et. al. documented 60% compared to 20% in control[18]. The Dogo study which suggested an inverse relationship between physical activity and ED recorded moderate to severe ED in 64.4% and severe ED in 51.1%[19].

Results of some studies evaluating the prevalence of erectile dysfunction

Authors	Prevalence	Study type	Sample size	Country
Kouidrat et. al	52.5%	Meta-analysis	N= 88,577	-
Saed et. al.	69.9%	Cross sectional	N= 249	Ethiopia
Sasaki et. al.	90%	Cross sectional	N= 1118	Japan
Tuan Vo et. al.	84%	Cross sectional	N= 151	Vietnam
Mutagaywa et. al.	55.1%	Cross sectional	N= 312	Tanzania
Kemp and Rheeder	95%	Cross sectional	N= 150 (> 50 years old)	South Africa
Grover et. al.	49.4%	Cross sectional	N= 3921	Canada
Goyol et. al.	77.2%	Cross sectional	N= 348	India
Yang et. al.	75.2%	Cross sectional	N= 5477	China

5. PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION IN DIABETES

The implicated events in the pathophysiology of ED in DM are essentially vascular and neurogenic. Hormonal consideration is of lesser significance[20]although it is necessary for sexual desire. The pathogeneticmechanisms are closely related to those of other microvascular complications. The role of advanced glycation end products (AGEs) have been well studied and documented. AGEs are products formed due to the non enzymatic reaction between reducing sugars and proteins[21]. The products formed from these complex reactions are often irreversible and initiate a cascade of cellular interactions that enhance several pathologic molecular processes which are capable of mediating vascular dysfunction. Of significance among these events is the increased deposition of extracellular matrix in connective tissues leading to increased collagen cross linking which is associated with vascular wall thickening and arterial stiffness[22]. Other effects of AGEs include stimulating the production of adhesion molecules and growth factors, increased expression of pro-inflammatory cytokines and oxidation LDL[23] among others. Some of these alterations have been clearly demonstrated in the carvenosa tissues of diabetic patients. Experiment withstreptozotocin induced diabetic animals illustrated a higher concentration of AGEs in diabetic rats when compared to controls[24]. In human studies, pentosidine which is an advanced glycation productwas found to be elevated in the coporacarvenosa but not in the serum of diabetic patients[25]. Pentosidine is the prototypical glucose mediated cross-linked molecule formed between lysine and Arginine which is one of the very few AGEs that can be accurately quantified[26]. This accumulation of AGEs in the erectile tissues distorts the microstructural architecture and interferes with the extensibility and relaxation that is required for sustained penile erection[21].

Reduced NO is the hallmark of endothelial dysfunction[27] and a typical characteristic of diabetic vasculopathy. NO is the most important vasoactive mediator in the physiological cascade of erection[28]. The vasodilation and smooth muscle relaxation that is induced by NO via the formation of cGMP are mandatory for erection to occur. Penile tissues from diabetic men demonstrated an increased expression of arginase[29]which is a competitor with nitric oxide synthase in the synthesis of NO from L-arginine. Intracellular accumulation of AGEs initiates a series of molecular events that culminate in the reduction of NO levels in carvenosa tissues[30]. AGEs also stimulate the production of reactive oxygen species[31] which further impairs the vascular integrity necessary for penile erection.

Diabetic neuropathy is another possible mechanism of DM induced ED. Nerve damage involving both the somatic and autonomic nerves could impair impulse transmission that results in erection[32]. Abnormalities in the pudendal nerve evoked potentials as well as abnormal bulbourethral and urethroanal reflexes have been documented in diabetes[32]. Decreased autonomic nerve mediated relaxation of the penile smooth muscle has equally been demonstrated in diabetic patients[33].

Although, diabetic patients are known to have reduced testosterone levels, evidence linking reduced testosterone to ED is unconvincing. Consequently, research findings have ascribed a peripheral role for the hormone in the cascade of penile erection[34]. However, response to PDE5 inhibitors has been obtained in conjunction with testosterone supplementation when PDE5 inhibitors alone failedto produce adequate erection[35].

Other postulated mechanisms include increased endothelins and endothelin B binding sites, upregulation of the Rho/Rho-kinase pathway and impaired cGMP-dependent protein kinase-1 (PKG-1)[36]. Endothelins are peptides secreted by the endothelium which are capable of mediating vasoconstriction in the penile tissues and these peptides are elevated in the plasma of diabetic patients[36]. PKG-1 is required for cGMP induced intracellular calcium levels changes withsubsequent opening of calcium dependent potassium channels which leads to cellular hyperpolarization and carvenosal smooth muscle relaxation[37].

ED and Cardiovascular disease

It has recently been suggested that ED is an independent risk factor for coronary artery disease (CAD)[38]. The shared pathophysiological origin i.e. endothelial dysfunction makes a case for the aggressive evaluation and management of ED to militate against future cardiovascular events. The arterial size hypothesis has been postulated to explain the macrovascular link between ED and CAD[39]. It is considered that the systemic nature of atherosclerosis precludes the extensive involvement of the vascular system. However, the development of symptoms occurs earlier in organs supplied by smaller arteries before those supplied by larger ones. Hence, ED occurs earlier than CAD due to the size difference in the vascular diameter of the penile and coronary arteries[39]. CAD follows when the atherosclerotic process has progressed sufficiently enough to reduce coronary blood flow which is usually a couple of years after the onset of ED. This view is not only logical but is supported by substantial clinical evidences. Studies have illustrated that ED precedes CAD in 66% of cases and may precede a major cardiovascular event by up to 5 years[40,41]. Also, a meta-analysis of 12 prospective trials revealed that ED significantly increased the risk of CVD and all course mortality[42].

ED and Diabetic Neuropahty

In the Dogo study, Severe ED was independently associated with neuropathy in Japanese T2DM patients who were less than 65 years old[43]. In a cohort of patients with ED, neurophysiological testing identified peripheral neuropathy in 61.1% while pudendal neuropathy was diagnosed in 14.4%[44]. Autonomic neuropathy is present in about 43% of diabetic patients with ED[45]. When cardiovascular tests for the evaluation of autonomic function are employed; around 53% of patients had abnormal test results[46].

6. RISK FACTORS

These include increasing age, duration of diabetes, poor glycemic control, hypertension, hyperlipidemia, sedentary lifestyle, smoking and associated diabetic complications. Depression worsens ED and some drugs used to treat depression can cause ED.

7. SCREENING FOR ED

Screening for ED in DM has been advocated by several researchers. This is necessary considering the results from numerous epidemiological studies indicating a high prevalence of ED in DM and its predictive role in CVDs. Patients should be screened upon diagnosis[13,47] and subsequently as necessary. The evaluation for associated risk factors e.g. hypertension, obesity and hyperlipidemia should equally be carried out and these conditions should be managed accordingly as they are associated risk factors. In non diabetic patients who present with ED it is essential that they are screened for diabetes because it could be the underlying aetiology[48]. Analysis of data from the National Health and Nutrition Examination Survey revealed that 11.5% of men with ED had undiagnosed DM compared to 2.8% men without ED. The prevalence was highest (19.1%) in men aged 40-59 years[49]. Of significance is that the survey did not observe any significant association between undiagnosed hypertension or hypercholesterolemia with ED.

Questionnaires for ED screening

Several questionnaires are available for the screening of erectile dysfunction e.g. international index of erectile function (IIEF), sexual health inventory for men (SHIM), erectile function domain of IIEF (IIEF-EF) e.t.c[50]. The SHIM is a five item version of the international index for erectile function. It is both sensitive and specific and used for the assessment of ED severity. It has a total score of 25. A score of 1-7 is severe ED, 8-11 is moderate ED and 12-16 is mild-moderate ED. A score of 22-25 rules out ED while 17-21 signifies mild ED[51].

International index for erectile function (IIEF)
Sexual Health Inventory for Men (SHIM)
Erectile Function Domain of the IIEF (IIEF-EF)
Erection Hardness Grading Scale (EHGS)
Self-Esteem and Relationship Questionnaire (SEAR)
Erection Dysfunction Inventory of Treatment Satisfaction (EDITS)
Quality of Erection Questionnaire (QEQ)
Sexual Experience Questionnaire (SEX-Q)

8. TREATMENT OPTIONS

PHOSPHODIESTRASE 5 (PDE5) INHIBITORS; the advent of these drugs has ushered in a new era of therapeutic effectiveness in the management of ED. The introduction of sildanefil in 1998 and the subsequent licensing of tadalafil, valdenafil and avanafil has made many individuals with ED report improved and satisfactory intercourse with the use of these pharmacological agents[52]. They are also well tolerated with only minor adverse effects. Severe adverse events are generally rare. PDE5 enzymes hydrolyze cGMP to 5′-GMP in the coporacarvenosa smooth muscle leading to detumense after erection. The inhibition of this enzyme allows for the persistence of erection for the duration of the drug action. After oral administration, maximum serum concentration can be achieved in 30 mins to one hour except for tadalafil which is about 2 hours and can be effective for more than 36 hours[52].

The most common adverse reactions are headache, flushing, nasal congestion, nasopharyngitis and dyspepsia[52]. Rare cases of priapism have been reported[53]. Sudden hearing loss and non-atretic anterior ischemic optic neuropathy[54] (NAION) were also reported in post marketing studies. Visual abnormalities (bluish discolouration)also occurs for which the FDA has recommended the discontinuation of therapy[52]. PDE5 inhibitorsare contraindicated in patients taking nitrates and should be used with caution in those currently on alpha blockers[52]. The vasodilatory effect could lead to hypotension. They are effective for the treatment of ED in DM but the but the response is usually lower when compared to those without DM. In a multicenter double blind randomized placebo controlled trial conducted by the Sildanefil Diabetes Study Group, 56% of those on sildanefil had improved erection compared to 10% in the placebo group[55]. In similar trials, both tadalafil[56] and verdernafil[57] had statistically significant improved erection and were well tolerated by diabetic patients.

INTRACARVENOSAL INJECTIONS (ICI)

The major component of ICI is prostalgladin E1 but could contain a combination of other vasoactive substances e.g. piperverine, phentolamine or atropine sulfate[58]. They can be used in patients who do not respond to PDE5 inhibitors or in those for whom they are contraindicated. ICI is safe and effective in diabetic patients. Although the most common complaint is pain, the compliance rate among diabetic patients is still high compared to the general population[59].

PENILE IMPLANTS

This mechanical device has a high success rate in the treatment of ED. Due to the invasive nature it is reserved from men in whom other measures have failed[20]. It is a 2 or 3-piece inflatable penile prosthesis implanted surgically. 86% of DM patients who had penile implants reported that it was still function after five years[60].

OTHERS

Vacuum erection devices and intraurethral suppositories are also used in the treatment of ED with different degrees of success. Data on their use and effectiveness in diabetic patients is limited[20].

Newer therapies; Apormorphine which is a doperminergic agent has been studied for use in ED. Its major side effect is hypotension[61]. Melanocortin receptor agonists (melanotan II and Bremelanotide), soluble guanylate cyclase activators and Rho-kinase inhibitors are also undergoing trials[61]. Extracoporal shock wave therapy is another promising modality that is hypothesized to improve blood flow and endothelial function which results in erection[61].

CONCLUSION

The challenge of preventing and managing ED in DM is enormous. Hence, it requires significant attention. The importance of screening for ED in DM cannot be over emphasized. Early detection accompanied by holistic intervention decreases the chances of severe disease and delays or averts future cardiovascular events. Healthcare professionalsshould question patients on their sexual performance during routine visits and avoid waiting for the patients to make the complaint first. Lifestyle modifications that reduce complications should be recommended for all patients with diabetes along with the treatment of co-morbidities. Although, more severe in patients with DM; reliable evidences have illustrated the effectiveness of conventional ED therapies in DM. Failure of one treatment modality does not exclude the effectiveness of another.

REFERENCES

[1] Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. Pharmacol Rev. 2011 Dec;63(4):811-59

[2] Okolokulak E, Volchkevich D. Vascularization of the male penis. RoczAkad Med Bialymst. 2004;49:285-91.

[3] İlkerSelçuk, MuratYassa, İlkan Tatar, and EmreHuri. Anatomic structure of the internal iliac artery and its educative dissection for peripartum and pelvic hemorrhage. Turkish Journal of Obstetrics and Gynecology 2018 Jun; 15(2): 126–129.

[4] Bella A.J., Brant W.O., Lue T.F. (2008) Physiology of Penile Erection and Pathophysiology of Erectile Dysfunction. In: Bertolotto M. (eds) Color Doppler US of the Penis. Medical Radiology (Diagnostic Imaging). Springer, Berlin, Heidelberg

[5] Ahmed I. El-Sakka and Tom F. Lue. Physiology of Penile Erection. TheScientificWorld Journal (2004) 4 (S1), 128–134.

[6] Jon Cartledge,SuksMinhas &Ian Eardley. The role of nitric oxide in penile erection. Expert Opinion on Pharmacotherapy Volume 2, 2001 - Issue 1. Pg. 95-107.

[7] Creed KE, Carati CJ, Keogh EJ. The physiology of penile erection. Oxford Review of Reproductive Biology. 1991;13:73-95.

[8] EugenMolodysky Shi-PingLiu Sheng-JeanHuangGeng-LongHsu. Penile vascular surgery for treating erectile dysfunction: Current role and future direction. Arab Journal of Urology Volume 11, Issue 3, September 2013, Pages 254-266

[9] Cheng-HsingHsieh, Ju-TonHsieh, Shang-JenChang, I-NiChiang, Stephen Shei-DeiYang. Penile venous surgery for treating erectile dysfunction: Past, present, and future perspectives with regard to new insights in venous anatomy. Urological ScienceVolume 27, Issue 2, June 2016, Pages 60-65

[10] Elizabeth SelvinArthur L. Burnett, Elizabeth A. Platz Prevalence and Risk Factors for Erectile Dysfunction in the US. February 2007Volume 120, Issue 2, Pages 151–157.

[11] Maria Ida Maiorino, Giuseppe Bellastella, and Katherine Esposito. Diabetes and sexual dysfunction: current perspectives. Diabetes MetabSyndrObes. 2014; 7: 95–105

[12] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. Journal of Urology 1994 Jan; 151(1):54-61

[13] Y. Kouidrat, D. Pizzol, T. Cosco, T. Thompson, M. Carnaghi, A. Bertoldo, M. Solmi, B. Stubbs, and N. Veronese. High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies. Diabetic Medicine Vol. 34 Issue 9 Sep. 2017. Pg. 1185-1192

[14] Reuben Kato Mutagaywa, JanethLutale, MuhsinAboud, and Benjamin Anathory Kamala. Prevalence of erectile dysfunction and associated factors among diabetic men attending diabetic clinic at Muhimbili National Hospital in Dar-es-Salaam, Tanzania. The Pan African Medical Journal. 2014;17:227.

[15] Penson DF, Latini DM, Lubeck DP, Wallace KL, Henning JM, Lue TF, Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database.Diabetes Care. 2003 Apr; 26(4):1093-9.

[16] AwoleSeid, HadguGerensea, ShambelTarko, Yosef Zenebe, and RahelMezemir. Prevalence and determinants of erectile dysfunction among diabetic patients attending in hospitals of central and northwestern zone of Tigray, northern Ethiopia: a cross-sectional study.BMC Endocrine Disorders. 2017; 17: 16.

[17] Hideyuki Sasaki, Hiroshi Yamasaki, Kenichi Ogawa, KishioNanjo, Ryuzo Kawamori, YasuhikoIwamoto, Shigehiro Katayama, Masafumi Shirai. Prevalence and risk factors for Japanese Diabetics. Diabetes Research and Clinical Practices Vol. 70 Issue 1 October 2005 Pg. 81-89.

[18] Yamasaki H, Ogawa K, Sasaki H, Nakao T, Wakasaki H, Matsumoto E, Furuta H, Nishi M, Ueda K, Iwo K, Nanjo K. Prevalence and risk factors of erectile dysfunction in Japanese men with type 2 diabetes.Diabetes Research and Clinical Practice 2004 Dec;66 Suppl 1:S173-7.

[19] Hisaka Minami, Shinya Furukawa, Takenori Sakai, TetsujiNiiya, Hiroaki Miyaoka, Teruki Miyake, Shin Yamamoto, SayakaKanzaki, Koutatsu Maruyama, Keiko Tanaka, Teruhisa Ueda, HidenoriSenba, MasamotoTorisu, Takeshi Tanigawa, Bunzo Matsuura, Yoichi Hiasa, and Yoshihiro Miyake. Physical activity and prevalence of erectile dysfunction in Japanese patients with type 2 diabetes mellitus: The Dogo Study. Journal of Diabetes Investigation 2018 Jan; 9(1): 193–198.

[20] David F. Penson and Hunter Wessells. Erectile dysfunction in Diabetic patients. Diabetes Spectrum 2004 Oct; 17(4): 225-230.

[21] D. Neves (2013) Advanced glycation end-products: a common pathway in diabetes and age-related

erectile dysfunction, Free Radical Research, 47:sup1, 49-69.

[22] Baumann M. Role of advanced glycation end products in hypertension and cardiovascular risk: human studies. Journal of AmericanSociety of Hypertension 2012;6:427–435.

[23] Richard Bucala, Zenji Makita, Gloria Vega, Scott Grundy, Theodor Koschinsky, Anthony Cerami and Helen Vlassara. Modification of Low density Lipoprotein by Advanced Glycation End-products Contribute to the Dyslipidemia of Diabetes and Renal Insufficiency. Protocol for the National Academy of Sciences USA. Vol. 91 pp. 9441-9445. Sep. 1994. Medical sciences.

[24] J.J. Cartledge I. Eardley J.F.B. Morrison. Advanced glycation end-products are responsible for the impairment of corpus cavernosal smooth muscle relaxation seen in diabetes. BJU International 2001 87: 394-401

[25] Seftel AD, Vaziri ND, Ni Z, Razmjouei K, Fogarty J, Hampel N, Polak J, Wang RZ, Ferguson K, Block C, Haas C. Advanced glycation end products in human penis: elevation in diabetic tissue, site of deposition, and possible effect through iNOS or eNOS. Urology. 1997 Dec;50(6):1016-26.

[26] Masahiro Yamamoto, Toru Yamaguchi, Mika Yamauchi, Shozo Yano, and Toshitsugu Sugimoto. Serum Pentosidine Levels Are Positively Associated with the Presence of Vertebral Fractures in Postmenopausal Women with Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, Volume 93, Issue 3, 1 March 2008, Pages 1013–1019.

[27] Mashudu Mudau, Amanda Genis Amanda Lochner Hans Strijdom Endothelial dysfunction: the early predictor of atherosclerosis. Cardiovascular Journal of Africa 2012 May; 23(4): 222–231.

[28] Burnett, A. L. (2006), the Role of Nitric Oxide in Erectile Dysfunction: Implications for Medical Therapy. The Journal of Clinical Hypertension, 8: 53-62.

[29] Bivalacqua TJ, Hellstrom WJ, Kadowitz PJ, Champion HC: Increased expression of arginase II in human diabetic corpus cavernosum: in diabetic-associated erectile dysfunction. Biochemical and Biophysical Research Communications 2001 283:923 –927

[30] Su J, Lucchesi PA, Gonzalez-Villalobos RA, Palen DI, Rezk BM, Suzuki Y, et al. Role of advanced glycation end products with oxidative stress in resistance artery dysfunction in type 2 diabetic mice. Arteriosclerosis Thrombosis and Vascular Biology 2008;28:1432–1438.

[31] Lal MA, Brismar H, Eklöf AC, Aperia A. Role of oxidative stress in advanced glycation end product-induced mesangial cell activation. Kidney Int 2002;61:2006–2014

[32] Vernet, D., Cai, L., Garban, H., Babbit, M. L., Murray, F. T., Rajfer, J., & Gonzalez-Cadavid, N. F. (1995). Reduction of penile nitric oxide synthase in diabetic BB/WORdp (type I) and BBZ/ WORdp (Type II) rats with erectile dysfunction. Endocrinology, 136, 5709–5717.

[33] Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ, Cohen RA: Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. *N Engl J Med* **320**:1025 –1030, 1989

[34] Mills TM, Wiedmeier VT, Stopper VS. Androgen maintenance of erectile function in the rat penis. Biology of Reproduction. 1992 Mar; 46(3):342-8.

[35] Rosenthal BD, May NR, Metro MJ, Harkaway RC, Ginsberg PC. Adjunctive use of AndroGel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. Urology. 2006 Mar; 67(3):571-4.

[36] Vrushali S. Thorvea , Ajay D. Kshirsagara, Neeraj S. Vyawaharea , Vipin S. Joshib , Kundan G. Ingalea , Reshma J. Mohitea. Diabetes-induced erectile dysfunction: epidemiology, pathophysiology and management. Journal of Diabetes and Its Complications 25 (2011) 129–136.

[37] Chang, S., Hypolite, J. A., Velez, M., Changolkar, A., Wein, A. J., Chacko, S., &DiSanto, M. E. (2004). Downregulation of cGMP-dependent protein kinase-1 activity in the corpus cavernosum smooth muscle of diabetic rabbits. American Journal of Physiology Regulatory Integrative and Comparative Physiology, 287, R950–R960.

[38] Graham Jackson. Erectile dysfunction and cardiovascular disease. Arab Journal Urology 2013 Sep; 11(3): 212–216.

[39] Montorsi P, Ravagnani PM, Galli S, Rotatori F, Briganti A, Salonia A, Rigatti P, Montorsi F. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. American Journal of Cardiology. 2005 Dec 26;96(12B):19M-23M. Epub 2005 Nov 4.

[40] Hodges L.D., Kirby M., Solanki J., O'Donnell J., Brodie D.A. The temporal relationship between erectile dysfunction and cardiovascular disease. Int J ClinPract. 2007;61:2019–2025

[41] Inman B.A., Sauver J.L., Jacobson D.J., McGree M.E., Nehra A., Lieber M.M. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc. 2009;84:108–113.

[42] Dong J.Y., Zhang Y.H., Qin L.Q. Erectile dysfunction and risk of cardiovascular disease: meta-analysis

of prospective cohort studies. J Am CollCardiol. 2011;58:1378–1385

[43] Furukawa S, Sakai T, Niiya T, Miyaoka H, Miyake T, Yamamoto S, Maruyama K, Ueda T, Senba H, Todo Y, Torisu M, Minami H, Onji M, Tanigawa T, Matsuura B, Hiasa Y, Miyake Y. Diabetic peripheral neuropathy and prevalence of erectile dysfunction in Japanese patients aged <65 years with type 2 diabetes mellitus: The Dogo Study. International Journalof Impotence Research 2017 Jan;29(1):30-34

[44] Consuelo Valles-Antuña, Jesus Fernandez-Gomez, Fernando Fernandez-Gonzalez. Peripheral neuropathy: an underdiagnosed cause of erectile dysfunction.BJU International 2011, 108: 1855-1859.

[45] Ghafoor A, Zaidi SM, Moazzam A. FREQUENCY OF AUTONOMIC NEUROPATHY IN PATIENTS WITH ERECTILE DYSFUNCTION IN DIABETES MELLITUS. Journal of Ayub Medical College Abbottabad. 2015 Jul-Sep;27(3):653-5.

[46] Quadri R, Veglio M, Flecchia D, Tonda L, De Lorenzo F, Chiandussi L, Fonzo D. Autonomic neuropathy and sexual impotence in diabetic patients: analysis of cardiovascular reflexes. Andrologia. 1989 Jul-Aug;21(4):346-52.

[47] M. H. Colson, G. Roussey. Screening and managing erectile dysfunction in diabetic patients (Review). Sexologies, Volume 22, Issue 1, January–March 2013, Pages 3-9.

[48] Carrillo-Larco RM, Luza-Dueñas AC, Urdániga-Hung M, Bernabé-Ortiz A. Diagnosis of erectile dysfunction can be used to improve screening for Type 2 diabetes mellitus. Diabetic Medicine. 2018 Jul 20.

[49] Sean C. Skeldon, Allan S. Detsky, S. Larry Goldenberg, and Michael R. Law. Erectile Dysfunction and Undiagnosed Diabetes, Hypertension, and Hypercholesterolemia. Annals of Family Medicine July/August 2015 vol. 13 no. 4 331-335.

[50] Yuan YM, Zhou S, Zhang K. Questionnaires on the diagnosis and treatment of erectile dysfunction. Zhonghua Nan KeXue. 2008 Dec;14(12):1121-5.

[51] Sexual Health Inventory for Men (SHIM). Urology SA. http://www.urologysa.com.au/pdf/sexual-health-inventory-for-men-shim.pdf

[52] Sharon A. Huang and Janette D. Lie. Phosphodiesterase-5 (PDE_5) Inhibitors in the Management of Erectile Dysfunction. Pharmacy and Therapeutics. 2013 Jul; 38(7): 407, 414-419.

[53] Staxyn (vardenafil ODT), prescribing information. Wayne, N.J.: Bayer Healthcare/GlaxoSmithKline; revised April 2011

[54] Egan R, Pomeranz H. Sildenafil (Viagra) associated anterior ischemic optic neuropathy. Arch Ophthalmol. 2000 Feb; 118(2):291-2.

[55] Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA. 1999 Feb 3;281(5):421-6.

[56] Sáenz de Tejada I[1], Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care. 2002 Dec; 25(12):2159-64.

[57] Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T; Vardenafil Diabetes Study Group. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care. 2003 Mar;26(3):777-83.

[58] Israilov S, Niv E, Livne PM, Shmueli J, Engelstein D, Segenreich E, Baniel J. Intracavernous injections for erectile dysfunction in patients with cardiovascular diseases and failure or contraindications for sildenafil citrate. International Journal of Impotence Research. 2002 Feb; 14 (1):38-43.

[59] Perimenis P, Gyftopoulos K, Athanasopoulos A, Barbalias G. Diabetic impotence treated by intracavernosal injections: high treatment compliance and increasing dosage of vaso-active drugs. Eur Urol. 2001 Oct;40(4):398-402; discussion 403

[60] Carson CC, Mulcahy JJ, Govier FE: Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study.

[61] Chintan K. Patel and Nelson Bennett. Advances in the treatment of erectile dysfunction: what's new and upcoming. Version 1. F1000 Res. 2016; 5: F1000 Faculty Rev-369.