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ERECTILE DYSFUNCTION IN DIABETES AND ROLE OF DELPHINIUM DENUDATUM WALL

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ABSTRACT
Erectile dysfunction is the persistent inability to achieve or sustain a penile erection of adequate rigidity to make intercourse possible or satisfactory. Diabetes mellitus is the most common organic cause for erectile dysfunction, the onset of which starts about 15 years earlier in the diabetic than in the non-diabetic population. Erectile dysfunction increases with age and presence of vascular co morbidities. Approximately present in 7% in the 2nd, 18% in the 5th, 25% in the 6th and 80% in the 8th decades. Nitric oxide (NO) is the major chemical mediator resulting in relaxation of smooth muscle cells in the erectile tissue, thus allowing the erection to occur. Nitric oxide release results in the release of cyclic GMP (cGMP), which is broken down by PDE-5. The PDE-5 inhibitors prevent breakdown of cGMP thereby enhancing erection under situations of normal sexual stimulation. The importance of a thorough history and clinical examination along with an understanding approach, and a serious attempt to stabilize blood sugar levels cannot be overemphasized, Clinical history should include time course (sudden onset may correlate with reversible cause such as medication, psychosocial stress, psychiatric complaint), cause (psychogenic vs. organic), and change in libido. Delphinium denudatum has been established to be safe and effective in the management of erectile dysfunction, reduces the oxidative stress in the nerves by the regulation of redox signalling and inhibiting the excess reactive oxygen species (ROS).

KEYWORDS: Erectile Dysfunction, Diabetes Mellitus, Delphinium Denudatum Wall.

1. INTRODUCTION
The world is facing an unprecedented epidemic of diabetes. According to international diabetes federation 415 million adults have diabetes worldwide.[1] Erectile dysfunction (ED) is a chronic complication of diabetes mellitus and is defined as "the persistent inability to attain or maintain an erection sufficient for sexual intercourse". It is the commonest sexual dysfunction in men, is increasingly common with aging, may affect up to 10% of the non diabetic male adult population, and is even more common among patients with diabetes. It may be defined as primary, in which cases there has never been normal sexual function, or secondary, which occurs after a period of normal sexual function: Erectile dysfunction in diabetes is invariably secondary.[2] Avicenna, (980-1037AD) an Arab philosopher and physicist, gave more definite evidence of possible familiarity with diabetic disorders in his 'Canon of medicine' in which he mentioned two specific complications of diabetes namely gangrene and collapse of sexual function.[3]

2. MATERIAL AND METHODS
Exploration of published articles associated to erectile dysfunction in diabetics was conducted and abstracts and full articles were incorporated for the groundwork of this review from online basis. I have measured for the review in the progression obtained from scientific publications with validation based methods and information Scrutiny. The databases utilized for obtaining information are scientific research publications from indexed journals available through Pub Med, Scopus, Google Scholar and Science Direct. The inclusion criteria were primarily literature of well-designed and controlled studies with obvious results precise for erectile dysfunction in diabetics.

3. RESULTS
3. 1Definition
Erectile dysfunction (ED), defined as the consistent or recurrent inability of a man to achieve and/or sustain a penile erection sufficient for sexual activity, is one of the most common sexual dysfunctions in men. Erectile dysfunction is more common with advancing age, and since the aged population will increase, its prevalence will continue to rise.[4,5]

3.2 Epidemiology
Diabetes is an iceberg disease, although increase in both prevalence and incidence of diabetes have accused

globally. Diabetes mellitus is the most common organic cause for erectile dysfunction, the onset of which starts about 15 years earlier in the diabetic than in the nondiabetic population. In the Massachusetts Male Aging Study (MMAS), the age-adjusted prevalence of minimal, moderate, or complete erectile dysfunctionwas 17, 25 and 10% among 1238 men without diabetes and 8, 30 and 25% among 52 treated men with diabetes, respectively.[6] Thus, although the number of diabetic subjects in the MMAS was low, this population based study showed an increased prevalence particularly of complete erectile dysfunction among men with diabetes. In the Cologne Male Survey.[7] the prevalence of erectile dysfunctionwas threefold increased, reaching 60% among men with diabetes compared with only 19% in the general population. The presence of diabetes was related with an increased odds ratio for erectile dysfunction by 3.95 (2.98–5.23). The prevalence of erectile dysfunction in the younger age groups (40–60 years) with diabetes was as high as in the older groups without diabetes (60–80 years). Thus, in presence of diabetes the progress of erectile dysfunction starts about 20 years earlier than in the nondiabetic population. The rough incidence rate of erectile dysfunction in the MMAS was 26 cases/1000 man-years in 847 men aged 40–69 without erectile dysfunction at baseline who were followed for an average of 8.8 years.[8] Population projections for men in this age group suggest an estimate of 617.715 new cases of erectile dysfunction per year for the United States. The age adjusted risk of erectile dysfunction was higher for men with lower education, diabetes, heart disease, and hypertension. The incidence rate of erectile dysfunction in men with diabetes was twofold increased, with 50 cases/1000 man-years. In a population based study from southern Wisconsin the prevalence of erectile dysfunction among 365 patients with type 1 diabetes increased with increasing age from 1.1% in those aged 21–30 years to 47.1% in those 43 years of age or older and with increasing duration of diabetes.[9] In a study from Italy including 9868 men with diabetes, 45.5% of those aged more than 59 years reported erectile dysfunction. Risk factors and clinical correlates included the following (OR [95% CI]): autonomic neuropathy (5.0 [3.9–6.4]), diabetic foot (4 [2.9–5.5]), peripheral neuropathy (3.3 [2.9–3.8]), peripheral arterial disease (2.8 [2.4–3.3]), nephropathy (2.3 [1.9–2.8]), poor glycemic control (2.3 [2–2.6]), retinopathy (2.2 [2.0–2.4]), hypertension (2.1 [1.6–2.9]), and diabetes duration (2 [1.8–2.2]).[10] In another survey from Italy the combination of diabetes and hypertension was the major risk factor for erectile dysfunction, giving an OR (95% CI) of 8.1 (1.2–55) as compared with diabetes without hypertension at 4.6 (1.6–13.7), hypertension without diabetes at 1.4 (0.7–3.2), current smoking at 1.7 (1.2–2.4), and exsmoking at 1.6 (1.1–2.3).[11] However, even when neuropathic complications are present, psychiatric illness such as generalized anxiety disorder or depression may be important contributors to erectile dysfunction in men with diabetes.[12] Therefore, a psychogenic factor must not be ignored in many patients.

3.3 Physiology and Pathophysiology

Penile erection is a neurovascular process modulated by psychological factors and hormonal status depending on suitable trabecular smooth muscle and arterial relaxation in the corpus cavernosum. On sexual stimulation, nerve impulses cause the release of cholinergic and NANC neurotransmitters that mediate erectile function by relaxing the smooth muscle of the corpus cavernosum. The main neural mediator of erection is nitric oxide (NO), which activates guanil cyclase to form intracellular cyclic guanosine monophosphate (GMP), a potent second messenger for smooth muscle relaxation. Cyclic GMP in turn results in the activation of a specific protein kinase, which phosphorylates certain proteins and ion channels, resulting in a drop of cytosolic calcium concentrations and relaxation of the smooth muscle. when returning to the flaccid state, cyclic GMP is hydrolyzed GMP by phosphodiesterase (PDE) type5.[13,14] In the corpus cavernosum four PDE isoforms have been identified (types 2–5), but PDE 5 is the main isoform, whereas the others do not appear to have an important role in erection.[15] The pathogenesis of erectile dysfunction in diabetes is believed to be multifactorial as it may be related to neuropathy, accelerated atherosclerosis, and alterations in the corporal erectile tissue. Such alterations may include smooth muscle degeneration, abnormal collagen deposition, and endothelial cell dysfunction.[16] If permanent, these corporal degenerative changes can limit the achievement of any pharmacotherapy. Advanced glycation end products have been revealed to quench nitric oxide and to be elevated in human diabetic penile tissue. It has been hypothesized that advanced glycation end products may mediate erectile dysfunction through upregulation of inducible nitric oxide synthase and downregulation of endothelial NOS (eNOS).[17] In addition, protein kinase C activation by diabetes may decrease NOS activity[18] as shown in the figure 1.

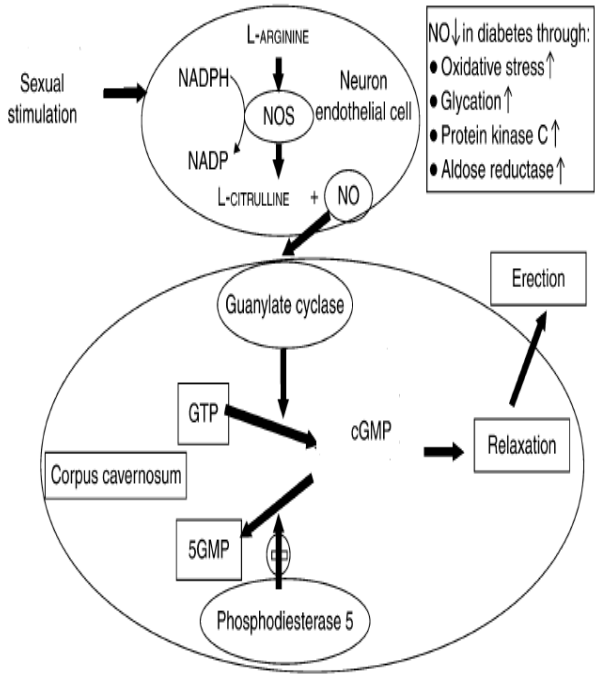

Figure. 1: Mechanism of erectile function.

3.4 Diagnosis

A good clinical history and a complete physical examination are the basis of assessment. It is important to establish the nature of the erectile problem and to differentiate it from other forms of sexual difficulty, such as penile curvature or premature ejaculation. A discussion with the partner is advisable and will verify the problem, but might also disclose other causes of the difficulties, for example, vaginal dryness. The significance of psychological and organic factors may be determined from the clinical history. Drugs which may be related with erectile dysfunction include tranquillizers (phenothiazines, benzodiazepines), antidepressants (tricyclics, selective serotonin reuptake inhibitors), and antihypertensives (β-blockers, vasodilators, central sympathomimetics, ganglion blockers, diuretics, ACE inhibitors).[19]

Three-Step Diagnostic approach of Erectile Dysfunction
Step. 1: General sexual history Clinical examination; relevant laboratory parameters Information about treatment options.
Step. 2: Therapeutic trial with PDE5 inhibitor.
Step. 3: Intracavernous pharmacotesting: color Doppler or duplex ultrasound of penile arteries.[20]

Most clinicians believe that at a minimum serum testosterone and prolactin levelsshould be assessed in all men with erectile dysfunction in diabetes[21]: Veves et al established that only 1 patient out of 110 was found to have a low testosterone, FSH, and LH levels.[22] The history and clinical examination will help to determine if a hormonal etiology of the erectile dysfunction in a particular patient is likely.

3.5 Delphinium denudatum in the Management of erectile dysfunction

Delphinium denudatum wall
introduction

Root of Delphinium denudatum Wall (Jadwar) is an active drug of central nervous system inUnani system of medicine**.** The generic name of *Jadwar* is derived from a Greek word, which means Dolphin, as the nectary resembles the figure of a dolphin. The word Jadwar is Arabic form of Persian *Zadwar*, which means the huge purifier or antidote. The Persian name *Mahe-Parveen* (moon and pleaides) is possibly given to this plant as it blossoms in the commencement of summer when the pleaides rise. In India, *Jadwar* was named as *Narbasi / Nirbisi*because of its antidotal properties. *Nir* means to oppose or to remove and *Bisi* means *Bis* or *Vish* (poison). *Bis* of *Nirbisi* are also used for *Bish* or aconite, as *Jadwar* is the antidote for aconite poisoning. Delphinium species *(Larkspurs*), an annual or perennial, erect and hardy ornamental herb are grown for their beautiful flowers. Delphinium ajacis, D. consolida, D.elatum, D. grandiflorum, D. laxiflorum, D. montanum, D. palmatifidum, D.peregrinum, D. bescens, D. Staphisagria, and D. triste are used medicinally in Europe, of which 15 species occur in India, out of which Delphinium denudatum Wall (Ranunculaceae) is being used medicinally.

Botonical name: Delphinium denudatum wall.[23,24]
Family: Ranunculacae
Vernacular names
Unani: *Jadwar khatai, Maatiriyak, Saataryoos*[25,26]
Urdu: *Jadwa, Nirbisi, Mahe-parveen*[23,27,28]
Hindi : *Nirbisi*[23,24]
Persian: *Jadwar, Maheparveen,*[23,25]
Arabic: *Jadwar, Antalae sauda, Balatularz, Zhadwar*[25]
English: Carcuma zedoaria, Larkspur.[26,28]
Tamil: *Nirbasi.*[24]
Telgu: *Nirvisi*[24]

Habitat

Delphinium denudatum (jadwar) commonly occurs on the grassy slopes in western temperate Himalayas, from Kumaon to Kashmir at an altitude of 2,400- 3,600 m. It also occurs in Punjab, Sirmoor and Lahore.[23,24,26]

Morphology

A Glabrous branching herb 60-90 cm in height, leaves radical 5-15 cm, across, orbicular, long stalked, divided nearly to the base segments, 5-9, narrow, pinnately lobed, often toothed; stem leaves few, shortly stalked, upper sessile, more or less deeply 3 lobed, lobesnarrow, mostly entire, flowersfew, scattered, 2.5-3.8 cm, long, spur cylindrical, nearly straight. Sepals spreading, varying from deep blue to faded grey, petals blue, follicles 3, inflated, glabrous or sparsely hairy. The rhizome is blackish brown, externally marked by longitudinal wrinkles and bears numerous small circular scars that are the remains of lateral roots.[23,24]

Parts used: Tubers (Roots) and seeds.[24]

Temperament: Hot^3 dry[3,28]

Ethno botanical actions

Aphrodisiac,[24,28,29] Neurotonic[28,29] Anodyne,[24] Appetizer,[23] Caminative,[24] Digestive,[24] Anti-inflammatory,[24] Cardiotonic,[24] General body tonic.[28]

Dosage: 500mg-BD.[28,29]

Contraindications: Persons with hot and dry temperament.[28]

Correctives: Milk.[28]

Compound formulations

Habb-e-Jadwar,[28,29] *Khameera gauzaban jadwar ood saleb wala*,[28,29] *Zimad warme loazataen.*[27,28] *Marham jadwar*.[28,29]

Chemical Constituents

The roots contain campesterol, stigmasterol, sitosterol, cholesterol, delta- avenasterol and alkaloids including denudatine, denudatidine, condelphine,talatizidine and iso-talatizidine.[26]

The roots also contain an oil, the fatty acid composition of the oil is: capric 2.3; lauric 1.6; myristic 3.8; palmitic 16.0; palmitoleic 2.5; stearic 1.3; oleic 23.0; linoleic 30.2; and linolenic 19.30%.[24] Some species contain the alkaloids Delphinine and Staphisagrine, both soluble in alcohol, as alkaloid Delpho –curarine has been extracted from the root.[30]

Scientific report

Delphinium denudatum Wall possesses neuroprotective properties that help to preserve the nerve functions and slows the progression of disease. Ethanolic extract of delphinium denudatum, possesses the antioxidative properties and reduces the oxidative stress in the nerves by the regulation of redox signalling and inhibiting the excess reactive oxygen species (ROS).[31]

4. CONCLUSION

Erectile Dysfunction is very common amongst middle aged and elderly men with type2 diabetes mellitus and may develop in younger men with type1 diabetes mellitus and is a troublesome chronic complication of diabetes mellitus The significance of a detailed history and clinical examination together with an understanding approach, and a serious effort to stabilize glycaemic control cannot be overemphasized, Clinical history should include time course (sudden onset may correlate with reversible cause such as medication, psychosocial stress, psychiatric complaint), cause (psychogenic vs. organic) and change in libido. Information of spontaneous nocturnal or morning erections indicate intact neurologic reflexes and penile blood flow. Decreased libido may indicate endocrinologic or psychogenic cause. Medical and social history (including partner report) should address cardiac disease symptoms and risk factors (HTN, DM, dyslipidaemia and smoking).Support and counselling should be available for all men with erectile dysfunction. Delphinium denudatum has been proven to be safe and effective in the management of erectile dysfunction, reduces the oxidative stress in the nerves by the regulation of redox signalling and inhibiting the excess reactive oxygen species (ROS). Main problems in this area remain the dearth of large multicenter trials, and lack of randomised controlled trials using comparator therapies rather than a placebo.

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