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THE PATHOLOGICAL ASPECTS OF ERECTILE DYSFUNCTION: A TABOO OF SEXUAL HEALTH

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ABSTRACT: Normally, there are two major sexual grievances in men; Erectile dysfunction or impotence and premature ejaculation. Premature ejaculation (PE) is a condition where the orgasm or the emission of semen occurs sooner during sexual intercourse. Erectile dysfunction (ED) is a sexual dysfunction mainly characterized by the inability to either develop an erection or maintain an erection of the penis during sexual intercourse. ED is found to be more prominent in elderly and mature men. As reported in the previously conducted studies, the health-related influences for ED include hypertension, dyslipidemia, diabetes, depression, and heart ailments. As the age increases, the prevalence also increases, especially the age group of 60 to 69 years showed the highest incidences of ED. The median age was of 65 years among all the participants reporting ED. With the increasing tendency in life expectancy in the western countries, and the high prevalence of health ailments like diabetes and various Cardiovascular disorders, the impact on lifestyle and eminence of life imposed by ED in men is likely to be substantial.

INTRODUCTION: Erectile dysfunction (ED) is a sexual dysfunction mainly characterized by the inability to either develop an erection or maintain an erection of the penis during sexual intercourse. The normal sexual pathway in male humans consists of four stages: libido (sexual desire), the ability to attain and uphold an erection, ejaculation, and detumescence or penile flaccidity [1, 2, 3]. Usually there are two major sexual grievances in men; Erectile dysfunction or impotence and premature ejaculation.

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Premature ejaculation (PE) is a condition where the orgasm or the emission of semen occurs sooner during sexual intercourse [2, 3]. The erection sequence is initiated by sexual stimulation, which is a neurovascular phenomenon. The erection of the penis is the hydraulic consequence of blood inflowing and retained in the sponge-like anatomic assemblies of the penis. This entire process is often initiated due to sexual arousal, and when the signals are transmitted from the brain to the penile area.

ED has three basic mechanisms namely; failure to initiate (psychologic, endocrinologic, or neurogenic), failure to fill (arteriogenic) and the failure to store blood within the lacunar network (venous leak) [2, 4, 5]. The modern drug therapies for ED made significant advancements in 1983 when British physiologist Giles Brindley dropped his

trousers and stunned the audience of the Urodynamics Society with his papaverine-induced erection [6, 7]. The drug agent that Brindley injected into his penis was a non-specific vasodilator and an alpha-blocking agent, and the mechanism of action was corporal smooth muscle relaxation. Brindley's conclusion was the rudiments for the later development of specific, safe, and orally effective drug therapies [8, 9].

Epidemiological Facts: ED is more prominent in elderly and mature men. As reported in the previously conducted studies, the health-related influences for ED include hypertension, dyslipidemia, diabetes, depression, and heart ailments. Other influencing factors are certain lifestyle activities, alcohol consumption, cigarette smoking, *etc.* [10, 11]. In a study conducted among 2246 adult men from Denmark, it was found that the overall prevalence of ED was 52%. The prevalence of complete ED varied from 4.5% for men of 40 to 49 years age group to 43% for the older age group. As the age increases, the prevalence also increases, especially the age group of 60 to 69 years showed the highest incidences of ED. The median age was 65 years among all the participants reporting ED [12].

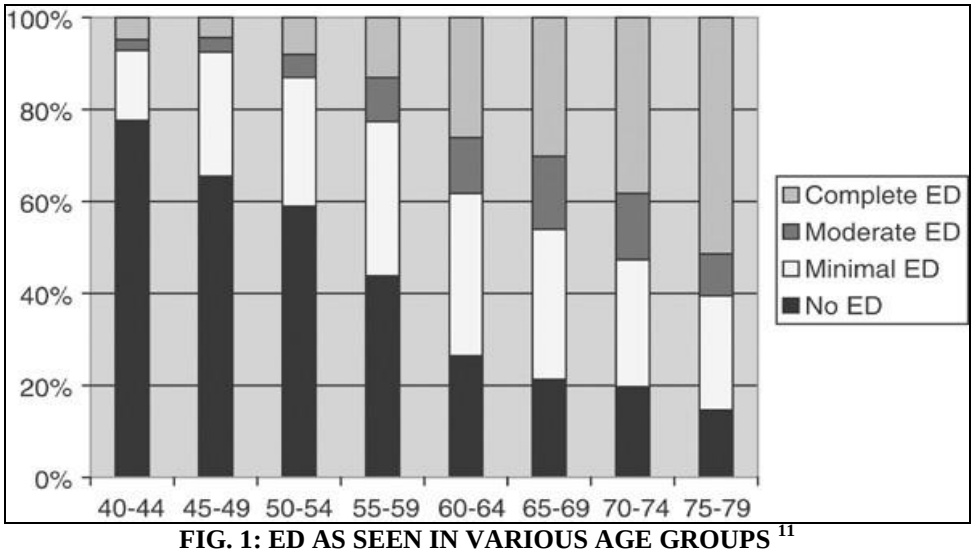

FIG. 1: ED AS SEEN IN VARIOUS AGE GROUPS [11]

As seen in the statistics, ED is a common sexual disorder that affects almost every age group and profoundly impacts the quality of life. With the increasing tendency in life expectancy in the western countries, the high prevalence of health ailments like diabetes and various Cardiovascular disorders, the impact on lifestyle and eminence of life imposed by ED in men is likely to be substantial [13, 14, 15, 16, 17, 18]. A recent study of the Massachusetts Male Aging Study (MMAS) estimates the prevalence of ED from 1995 to 2025, the worldwide prevalence of ED will probably increase from 152 million men in 1995 to around 322 million men in 2025, an upstream drift of 170 million men [19].

Physiology of Penile Erection: The penile erection is a hemodynamic incident mainly regulated by the relaxation of arteriolar and trabecular smooth muscle cells in the corpora cavernosa arbitrated *via* the NO-cGMP pathway [20]. Following sexual stimulation, the neuronal impulses cause the release of NO into the corpora cavernosa. The penile bloodflow increases, and sinusoidal spaces are expanded, preventing the venous outflow and producing an erection.

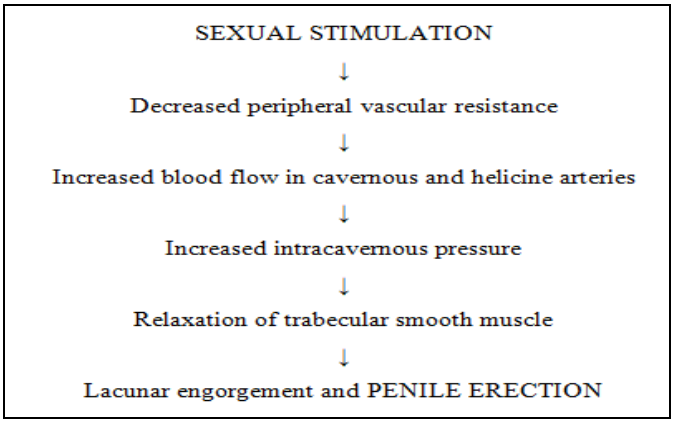

FIG. 2: THE CASCADE OF EVENTS THAT RESULTS IN THE ERECTION OF THE PENIS

Hypogonadism and ED: Hypogonadism too plays a significant role in the pathophysiology of ED. A specific threshold level of the male sex hormone testosterone is necessary for normal erectile function. Approximately 12% of patients with ED may have hypogonadism [1, 22]. Hypogonadism is a condition where gonadal function deficiency is characterized by deficient secretion of gonadal hormones or gametogenesis. Testosterone plays a major role in the central and peripheral modulation of erectile function [21, 22]. Testosterone deficiency may lead to certain conditions like increased visceral adipose tissue and insulin resistance, which leads to the development of metabolic disorders, which again contribute to a further reduction of the testosterone levels [21, 23]. Hypogonadal men develop libido, erectile or ejaculatory disorders depending on the plasma T levels. When the plasma T levels fall below the threshold level of 15nmol/L (432ng/dL) then the sexual disorders become evident [21].

Psychoneuroendocrine Causes of ED: Hypogonadal men are responsive to testosterone therapy to restore sexual desire and performance, in contrast to impotent men with normal circulating androgen concentration where the androgen therapy has no effect on erectile activity and is contraindicated [23, 24].

Hyperprolactinemia does not affect night erections or penile response to erotic stimulations suggesting that its negative effect on libido and sexual behavior is centrally mediated [25].

Recent *in-vitro* experiments showed that acute prolactin infusion caused a strong contraction of canine corpora cavernous cells, suggesting a possible peripheral action of this hormone through Intrapenile receptors. This may occur by increasing opioid tone and consequent alteration of pulsatile GnRH release [27, 28, 29]. Alteration of GnRH secretion has been hypothesized as one of the possible causes of ED in men with non-organic impotence. Men with non-organic impotence have reduced serum LH biological activity and a low immunological LH ratio [30, 31]. Subsequent experimental evidence showed that restoring adequate GnRH pulsatility in impotent men had beneficial effects on erectile capacity.

TABLE 1: TREATMENT ASPECTS FOR ED WITH PROS AND CONS

Possible treatment for erectile dysfunction	Pros	Cons
Pills (PDE-5 Inhibitors)	Easy to use, Natural Only minor side-effects Safe for most men unless they have severe heart disease or use nitrates	Expensive, Do not work well for men who have severe ED
Vacuum devices	One-time purchase Covered by insurance Few side effects	Using the pump interrupts intercourse May not be comfortable Requires practice to use correctly Erection may not be firm enough
Penile injections	Very effective for most men Can be used before starting sex	Expensive, Need to refrigerate medicine and use syringes Must learn self-injection May cause pain for some men
Penile suppositories	A small pill that melts Same medicine as injections	Expensive, Does not work for all men
Penile prostheses	Very effective for most men Becomes part of man's body Inflatable types are not visible Erection looks and feels natural Covered by insurance	Involves surgery and pain during recovery Can only be repaired surgically Erections are slightly shorter than before Destroys natural erection reflex Not a reversible treatment
Herbs and vitamins	Inexpensive , Easy to get	Does not always work May interfere with other medicines It May have unknown effects

Mechanism of Action of PDE5 Inhibitors: PDE5 inhibitors are widely considered as first-line therapy for ED [98, 99]. All the PDE5 inhibiting compounds inhibit the enzyme PDE5 competitively, thereby inhibiting the cleavage of its physiological target substance 3’5’-cGMP (acycloguanosine monophosphate). The PDE5 enzyme is found in high concentrations in the entire urogenital system, specifically in the cavernous bodies [32, 33, 34]. A certain threshold concentration of

3’5’-cGMP, the key mediator for an erection, is required for the physiological cascade of erectile initiation. The formation of 3′5′-cGMP in the cavernous tissue is activated by parasympathetic nerve stimulation resulting in nitric oxide (NO) release and guanylate cyclase activation. The enzyme PDE5 regulates the hydrolysis of 3′5′-cGMP. In men with erectile difficulties, regardless of whether their underlying etiology is psychogenic or organic, intracavernous 3′5′-cGMP concentrations are principally below the threshold level for erection. By inhibiting the enzyme PDE5 via a PDE5 inhibitor, 3′5′-cGMP cannot be further hydrolyzed, achieving the threshold concentration above which erection is triggered [33, 34, 35].

CONCLUSION: Every study conducted on this ground highlights the importance of evaluating the patients for potential ED as part of their clinical evaluation since ED can also be an indicator of additional comorbidities like cardiac disorders, high cholesterol, diabetes, *etc*. Physicians should contemplate males with even mild ED for a cardiological evaluation to detect any potential underlying cardiovascular disease.

ED is interrelated to low testosterone levels. Testosterone is vital for a typical erection to occur because of its effect on the nitric oxide pathway. Some men with a low testosterone level can develop normal erections, while some men with even normal testosterone levels have a poor erection. Consequently, it is significant to evaluate a patient for both conditions. Synchronized treatments involving testosterone replacement therapy and PDE-5 inhibitors are safe and appropriate in most cases. If a male has symptomatic hypogonadism, then testosterone replacement therapy is equally safe and effective in enlightening his physiologic, psychologic and physical well-being. Initially, all the drugs were prescribed to be administered 45 minutes before the estimated sexual activity; however, in several clinical trials of the drugs, it was testified that, on average, 32% of men responded within 16 minutes of taking the drug. In clinical practice, physicians should recommend patients take PDE-5 inhibitor agents at least one hour before a premeditated sexual encounter and remind patients that some sexual stimulation (foreplay) is needed for the treatment to take effect. This is mainly because arousal or sexual stimulation is obligatory to cause the preliminary release of nitric oxide, which is then potentiated under the PDE-5 inhibitor [34-38]. As seems, many consider ED as taboo and shameful to disclose in front of any authorized clinical supervisors. This mental state should not persist as it may make the ED patient suffer embarrassment in his social life. This underlying disorder requires proper education and knowledge about the ailment. As mentioned earlier, ED can be treated efficaciously with the current treatment options but cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (*e.g.*, hypogonadism and hyperprolactinemia), which can again be cured with specific treatments.

To appropriately counsel patients with ED, physicians must be fully well-versed with all the prevailing treatment possibilities. In this framework, physician-patient (partner) dialogue is indispensable throughout the management of ED. The assessment of treatment selections must ponder patient and partner satisfaction and other QoL (quality of life) aspects and efficacy and safety.

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CONFLICT OF INTEREST: NIL

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