3 Erectile Dysfunction: From Pathophysiology to Clinical Assessment

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3.1 Penile Erection

Penile erection is a complex phenomenon characterized by the equilibrium of the neurological, vascular, hormonal, and muscular compartments [1]. In normal condition, penile erection requires coordinated involvement of intact central and peripheral nervous systems, corpora cavernosa, and spongiosa, normal arterial blood supply, and venous drainage [2].

Generally, erection is associated with several psychological and physical changes: heightened sexual arousal, full testicular assent and swelling, dilatation of the urethral bulb, an increase in glans and coronal size, cutaneous flush over the epigastrium, chest, and buttocks, nipple erection, tachycardia and elevation in blood pressure, hyperventilation, and generalized myotonia [3].

3.1.1 Anatomy

We can divide the penis into three parts: root (radix), body (shaft), and glans [4].

The root is the proximal part of the penis located in the urogenital triangle. It consists of two muscles (ischiocavernosus and bulbospongiosus) and the crura and the bulb of penis which represent proximal expansions of the erectile tissues.

The body of penis is enveloped in skin and in three fasciae (dartos, buck, and tunica albuginea) [5].

The body of the penis contains three erectile tissues: the two corpora cavernosa and the corpus spongiosum. Corpora cavernosa consists of bundles of smooth muscle fibers, collagenous extracellular matrix, endothelial cell-lined sinuses, helicine arteries, and nerve terminals. Penis anatomy is represented in Fig. 3.1.

Each corpus cavernosum is wrapped by the tunica albuginea. The tunica albuginea is a membrane that covers and protects the corpora cavernosa. It consists of an inner and an outer fascial layer, the first circular and the second longitudinal. The corpora cavernosa lies in the dorsal part of the penis, while the corpus spongiosum lies in the ventral groove between them.

The corpus spongiosum houses the urethra. It has a proximal dilation that projects into the root of penis.

The glans is the most distal part of the penis. It is a sensitive structure at the end of the body of

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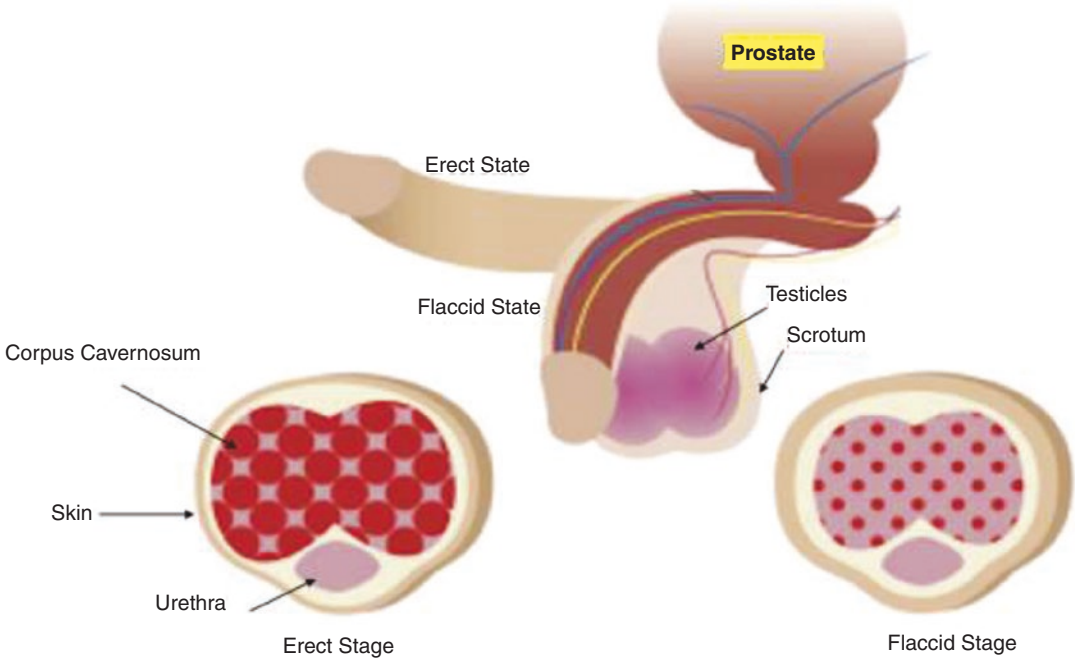

Fig. 3.1 Simple anatomy of the male reproductive system

penis which gets its shape from the bulbous expansion of the corpus spongiosum.

The glans is covered by a fold of skin that covers called prepuce [6].

3.1.2 Innervation

The penis is characterized by autonomic (sympathetic and parasympathetic) and somatic (sensory and motor) innervation system. The autonomic system regulates the neurovascular events occurring during erection and detumescence. The somatic system is responsible for sensation and the contraction of the bulbocavernosus and ischiocavernosus muscles. From the neurons in the spinal cord and peripheral ganglia, the sympathetic and parasympathetic nerves merge form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum to affect the neurovascular events during erection and detumescence [6].

From peripheral nerve fiber, the impulses reach the spinal erection centers and while some follow the ascending tract (resulting in sensory perception), others activate the autonomic nuclei to induce penile erection. The sympathetic system originates from T10-T12, and the chain ganglia cells projecting to the penis are located in the sacral and caudal ganglia. The parasympathetic system arising from neurons in the intermediolateral cell columns of S2-S4 is carried by cavernous nerves from the peri-prostatic nerve plexus. In S2-S4, it has been described the Onuf's nucleus, identified as the center of somatomotor penile innervation. Onuf's nucleus is a particular group of neurons located in the ventral part the anterior horn of the sacral spinal cord. It is involved in many functions as the maintenance of micturition and defecatory continence, as well as muscular contraction during orgasm. It contains motor neurons and is the origin of the pudendal nerve.

The Onuf's nucleus regulates external sphincter muscles of the anus and urethra. In this connection, the ischiocavernosus and bulbocavernosus muscles are involved into in penile erection and ejaculation [7].

3.1.3 Vasculature

The penis receives arterial supply from three sources originated by internal pudendal arteries: dorsal arteries of the penis, deep arteries of the penis, and bulbourethral artery [8]. The first supply the fibrous tissue surrounding the corpora cavernosa, corpus spongiosum, spongy urethra, and penile skin [4]. The second supply the erectile tissue of the penis, while the arteries of the bulb of the penis supply the bulbous part of the corpus spongiosum, urethra, and bulbourethral gland. The penile skin is supplied by superficial and deep branches of the external pudendal arteries.

The venous system is characterized by the deep dorsal vein of the penis which receives blood from the cavernous spaces. The superficial dorsal vein which drains blood from the skin and subcutaneous tissue of the penis. Regarding the lymphatic system, the penis skin and all the perineum drain into superficial inguinal nodes. The intermediate and proximal parts of the urethra and cavernous bodies drain into the internal iliac lymph nodes, and the distal spongy urethra and glans penis drain to the deep inguinal nodes.

3.1.4 Erectile Process

The erectile process involves specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls [1]. In the flaccid state, there is a tonically contraction of these structures. The relaxing of smooth muscle resulting in increase of intracavernosal pressure that leads to compression of the subtunical venules against the tunica albuginea [9]. This reduces venous drainage from the corpora cavernosa and increases pressure within the corpora. Three types of erection have been described: nocturnal, that follows the rapid eye movement sleep periods; reflexogenic due to genital stimulations; and the central or psychogenic related to many stimulations trigger points (imaginative, visual, auditory, olfactory, gustatory, tactile, etc.) Many central transmitters are involved in the erectile control such as dopamine, acetylcholine, nitric oxide (NO), oxytocin, and adrenocorticotropin/α-melanocyte-stimulating hormone which have a facilitatory role, serotonin with either facilitatory or inhibitory, and enkephalins with inhibitory role [10]. According to several studies, it is know that the central supraspinal systems controlling sexual arousal are localized in the limbic system (e.g., olfactory nuclei, medial preoptic area, nucleus accumbens, amygdala, and hippocampus) and hypothalamus (paraventricular and ventromedial nuclei). In particular, amygdala, medial preoptic area (MPOA), paraventricular nucleus (PVN), the periaqueductal gray, and ventral tegmentum have been described as the most important structures involved in the central control of the male sexual response [11].

Erection is mediated by a spinal reflex, which involves different central and peripheral neural and/or humoral mechanisms [12]. This reflex is initiated by recruitment of penile autonomic and somatic afferents, and it is regulated by supraspinal influences related to visual, olfactory, and imaginary stimuli. Erection is regulated by a balance between pro- and anti-erectile mediators. Acetylcholine is the most important neurotransmitter for ganglionic transmission, vascular smooth muscle relaxation, and release of NO from endothelial cells. Nitric oxide (NO) is a potent relaxant of peripheral vascular smooth muscle, and its action is mediated by cGMP. It is synthesized from endothelium via eNOS and by nitrergic nerves via nNOS. It is produced from endogenous L-arginine by NO synthase (NOS) located in the sinusoidal endothelial cells and by the NANC activated by electrical or chemical stimulation [9]. NO pathway is reported in Fig. 3.2.

Nitric oxide through the activation of guanylate cyclase stimulates the production of cGMP. cGMP activates the potassium channels and inhibits calcium entry into the cell. When intracellular calcium concentration is low, light chains of myosin are dephosphorylated and this induces corporal smooth muscle relaxation. Smooth muscle contraction and relaxation is regulated by sarcoplasmic free Ca^{2+}. Norepinephrine and prostaglandin F2a activate receptors on smooth muscle cells to increase inositol triphosphate and

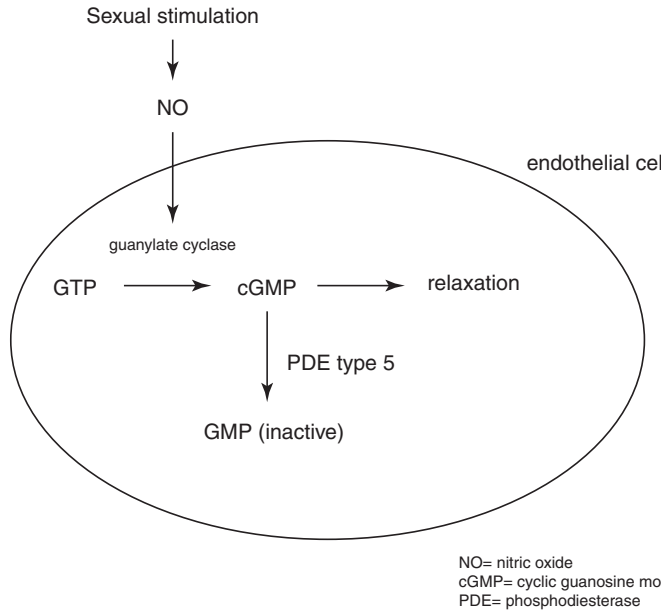

Fig. 3.2 Physiology of erection

diacylglycerol. This resulting in the release of calcium from intracellular stores and influx from extracellular space. The interaction between Ca^{2+} and calmodulin exposes sites of interaction with myosin light-chain kinase with phosphorylation of myosin light chains and exits in muscle contraction. Relaxation of the muscle is related to a decrease of free Ca^{2+} in the sarcoplasma. Calmodulin dissociates from myosin light-chain kinase and inactivates it. NO, cyclic GMP (cGMP), and cAMP are inhibitory pathways through phosphorylation. Cyclic AMP (cAMP) and cGMP are the second messengers involved in smooth muscle relaxation. They activate cAMP- and cGMP-dependent protein kinases, through several mechanisms due to calcium influx and muscle relaxing [1].

NO is involved in the initiation of erection through activation of nNOS, and in attainment of erection through PI3K/Akt-dependent phosphorylation of eNOS [13].

The penile erectile tissue plays a primary role in the erectile process. In the flaccid state, the penile tissue is moderately contracted with a low flow of blood for nutritive purposes. This is also evidenced by the cold weathers in which blood PO_2 decreases and tissue contraction raises [14].

All this changes when the sexual stimulation comes on. As a consequence of the sexual stimulation, the neurotransmitters release results in the relaxation of this smooth muscles and the following events take place:

- Dilatation of the arterioles and arteries by increased blood flow
- Trapping of the incoming blood by the expanding sinusoids
- Compression of the subtunical venular plexuses between the tunica albuginea and the peripheral sinusoids, reducing the venous outflow
- Stretching of the tunica to its capacity, which occludes the emissary veins between the inner circular and the outer longitudinal layers and further decreases the venous outflow to a minimum
- An increase in PO_2 (to about 90 mmHg) and intracavernous pressure (around 100 mmHg), which raises the penis from the dependent position to the erect state (the full-erection phase)
- A further pressure increase (to several hundred millimeters of mercury) with contraction of the ischiocavernosus muscles (rigid-erection phase)

3.2 Pathophysiology of Erectile Dysfunction

Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain penile erection sufficient to permit satisfactory sexual performance [15].

Erectile dysfunction may affect physical and physiological health and has a strong impact on quality of life and relationships. It is recognized as a possible early sign of coronary artery and peripheral vascular disease. Therefore, physicians should ask male patients about sexual health in order to identify potential life-threatening underlying conditions such as cardiovascular disease [16, 17]. ED is known to have psychological as well as organic causes. Non-organic erectile dysfunction is also known as psychogenic or adrenaline-mediated erectile dysfunction (noradrenaline-mediated or sympathetic-mediated erectile dysfunction). It has not been well studied but is an important factor to consider when evaluating and managing men with this condition [18].

Stress, depression, and anxiety are generally defined as heightened anxiety related to the inability to achieve and maintain an erection before or during sexual relations, and are commonly associated with psychogenic erectile dysfunction [19].

Erectile dysfunction possibly generates from any process that impairs either the neural or the vascular pathways that contribute to erection. Neurogenic erectile dysfunction is caused by a deficit in nerve signaling to the corpora cavernosa [20]. Such deficits can be secondary to, for example, spinal cord injury, multiple sclerosis, Parkinson's disease, lumbar disc disease, traumatic brain injury, radical pelvic surgery (radical prostatectomy, radical cystectomy, and abdominoperineal resection), and diabetes. Upper motor neuron lesions (above spinal nerve T10) do not result in local changes in the penis but can inhibit the central nervous system (CNS)-mediated control of the erection. By contrast, sacral lesions (S2–S4 are typically responsible for reflexogenic erections) cause functional and structural alterations owing to the decreased innervation [21]. The functional change resulting from such injuries is the reduction in NO load that is available to the smooth muscle. The structural changes center on apoptosis of the smooth muscle and endothelial cells of the blood vessels, as well as upregulation of fibrogenetic cytokines that lead to collagenization of the smooth muscle. These changes result in veno-occlusive dysfunction (venous leak). Vascular disease and endothelial dysfunction lead to erectile dysfunction through reduced blood inflow, arterial insufficiency, or arterial stenosis. Vasculogenic erectile dysfunction is by far the most common etiology of organic erectile dysfunction [22]. Many men assume that erectile dysfunction is a natural consequence of aging. But, despite age stands as an independent risk factor for ED, about one-third of 70-year-old men report no erectile difficulties. Thus, physicians should not automatically assume that erectile dysfunction is anyway attributable to aging.

Risk factors for developing erectile dysfunction include tobacco use, obesity, sedentary lifestyle, and chronic alcohol use. These factors are believed to make hormonal changes that could easily lead to lower testosterone levels and result in impaired endothelial function [23–25].

Several studies have suggested that chronic inflammation and circulating inflammatory markers affect systemic endothelial function [26]. Chronic inflammation may, therefore, represent a link between ED and cardio vascular diseases (CVD). ED onset and severity are associated with increased expression of markers of inflammation. Markers and mediators such as C-reactive protein (CRP), intercellular adhesion molecule 1, interleukin (IL)-6, IL-10, and IL-1B, and tumor necrosis factor alpha (TNF-α) were found to be expressed at higher levels in patients with ED. In addition, endothelial and prothrombotic factors such as von Willebrand factor (vWF), tissue plasminogen activator (tPA), plasminogen activator inhibitor 1 (PAI-1), and fibrinogen are also expressed at higher levels in ED patients [27, 28]. Androgens play an important role in both penile and vascular health, with cellular targets located in both endothelial and smooth muscle cells [29–32].

Androgens promote endothelial cell survival, inhibit proliferation and intimal migration of vascular smooth muscle cells, and reduce endothelial expression of pro-inflammatory markers [33]. Within the penis, low androgen levels are associated with apoptosis of endothelial and smooth muscle cells as well as with pathologic structural remodeling [34]. Besides, both hypo- and hyperthyroidism can lead to erectile impairment. Also, people diagnosed with hypertension, mellitus diabetes, dyslipidemia, and depression have an increased risk of developing erectile dysfunction. The metabolic syndrome also known as syndrome X and insulin resistance syndrome is the term that consists of a cluster of disease states abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance ± glucose intolerance, proinflammatory state, and prothrombotic state. Coronary artery diseases and ED share similar risk factors such as hypertension, diabetes mellitus, smoking, and hypercholesterolemia, and many of these factors are part of MetS [35].

MetS may cause ED through multiple mechanisms. All components of MetS are frequently found in the obese population. Abdominal obesity promotes insulin resistance that is associated with hyperinsulinemia and hyperglycemia [36]. It may also lead to an abnormal lipid profile, hypertension, and vascular inflammation, all of which promote the development of atherosclerosis. Endothelial dysfunction leads to a decrease in vascular nitric oxide levels, with resulting impaired vasodilation; the increase in free radical concentration also leads to atherosclerotic damage. In light of these common pathways, MetS could be a strong risk factor for ED as well as ED might be a harbinger of cardiovascular diseases [18, 37]. Some drugs and medicines, for example, α-blockers, benzodiazepines, β-blockers, clonidine, digoxin, histamine H2-receptor blockers, ketoconazole, methyldopa, monoamine oxidase inhibitors, phenobarbital, phenytoin, selective serotonin reuptake inhibitors, spironolactone, thiazide diuretics, and tricyclic antidepressants can cause erectile dysfunction although the exact mechanisms are not always known [15]. The most common iatrogenic cause of erectile dysfunction is radical pelvic surgery [22]. Generally, the damage that occurs during these procedures is primarily neurogenic in nature (cavernous nerve injury) but accessory pudendal artery injury can also contribute. Pelvic fractures can also cause erectile dysfunction in a similar manner, owing to nerve distraction injury and arterial trauma [22]. Finally, patients with erectile dysfunction are more likely to also have premature ejaculation, lower urinary tract symptoms associated with benign prostatic hypertrophy (BPH), and overactive bladder compared with the general male population [38].

3.3 Diagnosis

The basic work-up of a male patient seeking medical care for erectile dysfunction needs to include an evaluation of all the risk factors mentioned. Physician should investigate medical and sexual history and physically examinate the lower genitourinary tract, the penis, and testicles. Then, hormonal blood levels should be examined (i.e., testosterone, prolactin, LH, and FSH).

Given the personal and social implications of sexual dysfunction, assessing sexual history is not an easy task. Hence, expert-guided, validated, and standardized sexual inventories, structured interviews, and self-reported questionnaires, can help both inexperienced and seasoned clinicians to address sexual health and related conditions. The severity of erectile dysfunction is often described as mild, moderate, or severe according to the five-item International Index of Erectile Function (IIEF5) questionnaire, with a score of 1–7 indicating severe, 8–11 moderate, 12–16 mild–moderate, 17–21 mild, and 22–25 no erectile dysfunction. The EDITS questionnaire evaluates the erectile dysfunction treatment outcomes. The physical examination of patients includes evaluation of the chest (including heart rhythm, breathing, and signs of gynecomastia (enlargement of the breasts)), penis, prostate and testes, and the distribution of body hair. Small testes and prostate, depending on patient age, mammary glands growth could imply an underlying hypogonadism. Increased pulse rate (tachycardia) might suggest hyperthyroidism, whereas reduced

pulse rate (bradycardia) might be evident in men with heart block (arrhythmia), hypothyroidism or in those who use certain drugs (for example, βblockers). Diminished or absent pulses in the various arteries examined could be indicative of impaired blood flow caused by atherosclerosis. The evaluation of the penis in the flaccid condition might show the presence of Peyronie's disease (involving palpable fibrous plaques), phimosis, or frenulum breve that can all contribute to erectile dysfunction.

Few biochemical and hormonal parameters are of extreme importance as well as levels of cholesterol, triglycerides, fasting glucose, and glycosylated hemoglobin (HbA1c) are key determinants of cardiovascular and metabolic risk stratification [22].

US is the imaging method of choice for initial evaluation of the penis because it can assess anatomy and dynamic blood flow. There are three principal US modalities to evaluate the penis. The first is gray-scale or B-mode US that evaluates the penile anatomy and nonvascular abnormalities, such as plaques, fibrosis, tunica albuginea defects, masses, and fluid collections. The second color Doppler US, allows simultaneous display of moving blood superimposed on a gray-scale image. It is used for the assessment of vascular flow and its direction. The third modality, spectral Doppler US, displays blood flow velocity over time as a waveform, so it is a graphic representation of the flow. It allows evaluation of the speed and direction of the flow.

The main role of imaging is to differentiate vascular from nonvascular causes. Currently, Doppler US is used to investigate arterial or venous defects in patients suffering from ED with no response to PDE-5. ED is also a consequence of pelvic surgery (prostate, bladder, and rectal cancer surgery), and it may also be consequence of vascular or neural injuries [39, 40]. Doppler US is also used to confirm organic damage before penile prostheses [41].

Rigiscan has represented an important tool in the differentiation between psychogenic ED and organic ED. It is a non-invasive diagnostic instrument that assesses male nocturnal penile tumescence and rigidity by making repetitive measurements of radial rigidity at the base and tip of the penis. Rigiscan has proved to be the preferential choice in distinguishing psychogenic ED from organic ED. It has more advantages over penile color-doppler US [42].

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