Pathophysiology of Erectile Dysfunction

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Erectile dysfunction (ED) is a major problem in a life of the modern men. It affects 10–25 % of middle-aged and elderly men. ED is the failure to achieve erection, ejaculation, or both. Normal erectile function requires the involvement and coordination of multiple regulatory systems and is thus subject to the influence of psychological, hormonal, neurological, vascular, and cavernosal factors. An alteration in any of these factors may be sufficient to cause erectile dysfunction (ED), but in many cases a combination of several factors is involved [1]. Some conditions such as diabetes, atherosclerotic, and drug-related causes account for 80 % of causes of ED in elderly.

Evidence suggests that ED may result from three basic mechanisms:

1. Failure to initiate (psychogenic, endocrinologic, or neurogenic)
2. Failure to fill arteriogenic (atherogenic)
3. Failure to store adequate blood volume within the lacunars network (veno-occlusive dysfunction)

Psychological factors are involved in a significant number of cases of erectile dysfunction alone or in combination with organic causes. An important psychogenic factor related to erectile dysfunction is performance anxiety (fear of failure during intercourse).

There is a lot theory explaining psychological factors in erectile dysfunction have described multiple developmental, cognitive, affective, and interpersonal factors that predispose men to sexual dysfunction [2]. At present, psychogenic erectile dysfunction is thought to be primarily related to a group of predisposing, precipitating, and maintaining factors.

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3.1 Neurogenic Erectile Dysfunction

Certain neurological disorders are frequently associated with erectile dysfunction, including multiple sclerosis, temporal lobe epilepsy, Parkinson's disease, stroke, Alzheimer's disease, and spinal cord injury [3].

Events that disrupt central neural networks or the peripheral nerves involved in sexual function can cause ED. Evidence suggest that this form of ED has been termed "neurogenic impotence" [4].

The etiologies of neurogenic ED can be classified as:

- Peripheral (peripheral ED)
- Spinal (sacral-peripheral ED, suprasacral-central ED)
- Supraspinal (suprasacral ED)

3.1.1 Peripheral ED

Peripheral ED can be secondary to the disruption of sensory nerves that bring local information to the brain and contribute the afferent arm of reflex erection or to the disruption of autonomic nerves which mediate arterial dilation and trabecular smooth muscle relaxation.

3.1.2 Erectile Dysfunction in Spinal Cord Injury

Patients with lesions above the sacral parasympathetic center maintain reflexogenic erection. In these patients, minimal tactile stimulation can trigger erection, although of short duration requiring continuous stimulation to maintain erection. If the lesion is incomplete patients can receive input from psychogenic erection and maintain erectile function. Patients with significant lesions affecting the sacral parasympathetic center do not have reflex erections and have severe ED [5].

3.1.3 Erectile Dysfunction After Radical Pelvic Surgery (Supraspinal)

The neurologic lesion occurs in the pelvic plexus or in the cavernosal nerves located in the posterolateral aspect of the prostate. Maintenance of erectile capacity with nerve-sparing procedures varies between 35 and 68 % depending on the surgical technique, the clinical and pathological staging of the tumor, and the age of the patient [5]. Recovery of erectile function after radical pelvic surgery can be slow over the course of 12–18 months. Intracavernosal administration of vasoactive agents improves the probability of recovering erectile function, probably by preventing prolonged ischemia.

However, recent advances in surgical techniques have significantly lowered the incidence of post-pelvic-surgery erectile dysfunction [6].

3.2 Atherosclerosis and Erectile Dysfunction

Most important risk factors are connected with penile arterial insufficiency, including atherosclerosis, hyperlipidaemia, hypertension, diabetes mellitus, cigarette smoking, and pelvic irradiation.

Consistency of evidence association of ED to systemic vascular diseases is clear. There is notice a high prevalence of ED in patients having cardiovascular disease (CAD), peripheral arterial disease, and cerebrovascular disease [7]. The prevalence of ED looks to be increased with severity of vascular disease. Patients with lesions in two or more coronary arteries had worse erectile function than patients with normal coronary arteries or single vessel CAD. However, cardiovascular diseases are also prevalent among patients with ED. Furthermore, CAD has been revealed in patients reporting ED without any other symptomatology of vascular disease [8]. ED has also been associated to the presence of peripheral atherosclerotic lesions. Among patients with ED, 66.4 % presented atherosclerotic lesions, while lesions were only present in 36.5 % of patients without ED. In rabbit's chronic ischemia provoked by atherosclerotic stenosis of the proximal iliac artery is also associated with functional changes in the distal part of the penile vasculature such as nitric oxide synthase (NOS) activity. Neurogenic contractions were potentiated, while endothelium-dependent and neurogenic NO-mediated relaxations were reduced in cavernosal tissue. Reduced NOS activity and impaired endothelium-dependent and neurogenic NO-mediated relaxation of cavernosal tissue have been confirmed in a rabbit model of cavernosal ischemia without hyperlipidemia. An elevation of the cavernosal content of endogenous inhibitors of NOS was proposed to be responsible for these effects.

Inman and colleagues in their studies suggested that erectile dysfunction shares the same risk factors as CAD, with endothelial dysfunction being an important underlying pathological change in both diseases. Other potential mechanisms involved in the development of endothelial dysfunction that can lead to erectile dysfunction and CAD include a dysfunctional L-arginine NO pathway, increased peripheral sympathetic activity, vascular structural alterations leading to decreased vascular dilatation capacity, and increased specific [9].

Evidence from studies of Montorsi suggested that inflammatory phenomenon might be related to the caliber of the blood vessels. Whereas the penile artery has a diameter of 1–2 mm, the proximal left anterior descending coronary artery is 3–4 mm in diameter. Thus, an equally sized atherosclerotic plaque developing in the smaller penile arteries would more likely compromise flow, presenting itself as an erectile dysfunction complaint much earlier than if the same amount of plaque developed in the larger coronary artery, causing angina. Inadequate venous occlusion is another important cause of vasculogenic erectile dysfunction [9]. Inadequate venous occlusion can occur as a result of the development of large venous channels draining the cavernous tissue. It might also be caused by severe degenerative, functional, or anatomical changes in the tunica albuginea, such as those that occur in Peyronie's disease [10].

The present Princeton III Consensus guidelines recognize erectile dysfunction as a strong predictor of CVD. This association between CVD and erectile dysfunction was confirmed in a study that reported that erectile dysfunction is a potent predictor of adverse cardiovascular events in high-risk cardiovascular patients [11].

Recent findings that erectile dysfunction is a strong predictor of CAD and that the development of symptomatic erectile dysfunction might precede the occurrence of a cardiovascular event by 2–3 years have led to stricter measures during the assessment of patients who present with poor erections [12, 13]. A strong recommendation is that all men with erectile dysfunction who are free from any cardiac symptoms should be considered to be cardiac (or vascular) patients until proven otherwise (Fig. 3.1).

3.3 Hyperlipidemia and ED

It is an important association of ED and hyperlipidemia which has been found in several clinical studies. Most of them suggest that hypercholesterolemia at baseline was also shown as a predictor of ED. High concentrations of low-density lipoprotein seem to be related to ED, although low levels of high-density lipoproteins have been shown to be predictive of ED [15].

The selective action of the endothelial NO/cGMP pathway in hypercholesterolemia could be due to increased superoxide production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase or to increased plasma levels of asymmetric dimethylarginine, an endogenous inhibitor of NOS [16].

3.4 Hypertension and ED

High blood pressure is an independent risk factor for development of ED [17, 18]. Cardiovascular complications following hypertension such as ischemic heart disease and renal failure are associated with an even higher prevalence of ED.

Hypertension affects blood vessels by shear stress, which can lead to endothelial abnormalities such as an altered production and activity of vasoactive substances. It has been proposed that in hypertension, the increased blood pressure per se does not induce an impairment of erectile function; therefore, it is thought that the resultant dysfunction could be caused by the associated arterial stenotic lesions [19].

In hypertensive population, ED was associated to older age, longer duration of hypertension, and a more severe hypertension. ED was also related to the antihypertensive therapy [20].

Together with high blood pressure, it should be emphasize that some endocrinological disorders and hormone irregularity can lead to ED.

Endocrinological erectile dysfunction thru androgens plays important parts in enhancing sexual desire and maintaining adequate sleep-related erections but have a limited effect on visually induced erections. It is spot that testosterone is important in the regulation of the expression of NO synthase (NOS) and PDE5 inside the penis [21]. Testosterone deficiency or hypogonadism has been recently associated with cardiovascular morbidity and mortality. Hyperprolactinemia leads to sexual dysfunction, due to low testosterone concentrations. Increased prolactin concentration leads to the inhibition of gonadotropin-releasing hormones, which, in turn, decreases the secretion of luteinizing hormone, which is responsible for testosterone secretion [22].

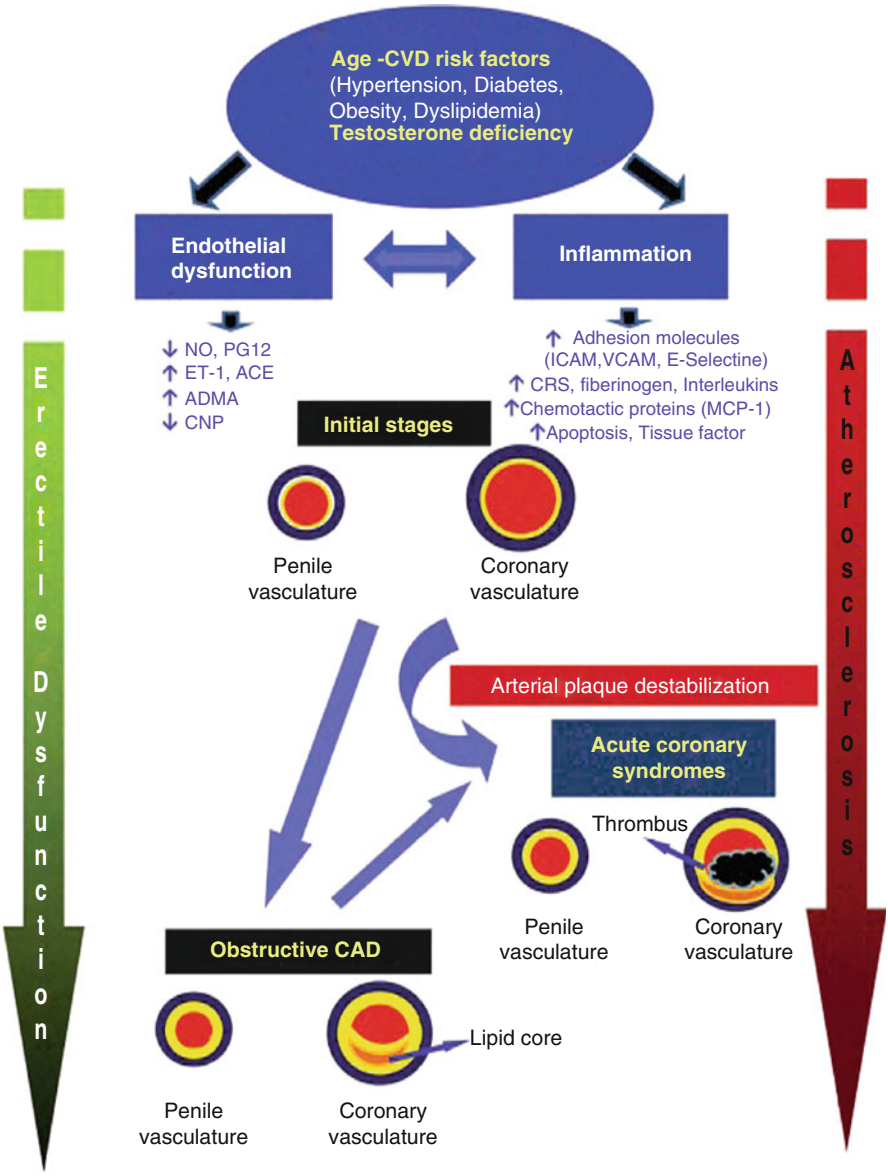

Fig. 3.1 Pathophysiological links between endothelial dysfunction, inflammation, testosterone deficiency, and acute or chronic coronary artery disease (Modified with permission by Vlachopoulos et al. [14]). *ACE* angiotensin-converting enzyme, *ADMA* asymmetric dimethylarginine, *CAD* coronary artery disease, *CNP* C-type natriuretic peptide, *CRP* C-reactive protein, *ET-1* endothelin-1, *ICAM-1* intercellular adhesion molecule, *MCP-1* monocyte chemotactic protein-1, *NO* nitric oxide, *PGI2* prostaglandin, *VCAM* vascular cell adhesion molecule

3.5 Cigarette Smoking and ED

Cigarette smoking is an important independent modifiable risk factor and it appears to have a deleterious effect on penile hemodynamic integrity. Mannino showed an odds ratio (OR) of 1.4 for smokers vs. nonsmokers. Some researchers furthermore demonstrated an OR of 1.7 and also that the risk of ED increases with duration of this habit [23]. Cigarette smoking showed also to increase the age-adjusted risk of ED in addition to increasing the relative risk for antihypertensive medications, cardiac drugs, and systemic illness as diabetes mellitus (50 vs. 45.4 % of complete ED, smokers vs. nonsmokers, respectively). The authors reported that there are strong parallelisms and shared risks among smoking, CAD, atherosclerosis, and ED [7]. Clinical and basic science studies provide strong indirect evidence that smoking may affect penile erection by the impairment of endothelium-dependent smooth muscle relaxation. They also confirmed that the association of ED with risk factors such as CAD and hypertension appears to be amplified by cigarette smoking [24].

From a pathophysiological point of view, nicotine may inhibit smooth muscle function or the neurovascular mediators, such as prostacyclin, causing many types of hemodynamic alterations. Hypercoagulability and increased platelet aggregation, the release of fatty acids and catecholamines, or direct toxic effects on the vascular endothelium have also been considered as possible mechanisms. Recently, literature data showed that smoking may act as a risk factor for ED by reducing high-density lipoprotein (HDL) and increasing fibrinogen concentrations [25].

3.6 Increased Vasoconstriction and ED

Enhanced basal and myogenic tone has been observed in arteries from hypertensive rats [26]. It is unclear whether enhanced myogenic constriction reflects a primary pathological defect contributing to the hypertensive state or a secondary adaptive process protecting the exchange vessels from elevated pressures [27]. Although the role of myogenic tone in the penile vasculature for erection remains to be clarified, the increased vasoconstriction could contribute to decreased arterial inflow and erectile response [28].

Enhanced adrenergic activity keeping the penile smooth muscle contracted is expected to result in ED. Sympathetic nerve activity accompanies hypertension in man and hypertensive animals [29]. However, in corpus cavernosum from spontaneously hypertensive rats, the content of sympathetic neurotransmitters was found to be unchanged [30]. Neither the contractions evoked by the ά1-adrenoceptor agonist, phenylephrine, nor the contractions induced by electrical field stimulation were enhanced in arteries or erectile tissue from renal hypertensive compared to normotensive rats.

In view of these findings, it is unlikely that changes in the peripheral sympathetic neuro-effectors junction or responsiveness to ά-adrenoceptor agonists play a role for the decreased erectile function observed in hypertensive rats [31].

3.7 Impaired Neurogenic Vasodilatation and ED

Immunohistochemical and functional studies of isolated penile small arteries indicate that NO is the main neurotransmitter mediating nonadrenergic noncholinergic relaxations to electrical field stimulation [32].

In patients with essential hypertension, endothelium-dependent vasodilatation elicited by infusion of agonists such as acetylcholine, bradykinin, or flow is diminished [33, 34].

There is a lack for studies addressing whether endothelium-dependent vasodilatation in the penile circulation is altered in hypertensive men.

3.8 Diabetes and ED

Diabetes mellitus type 2 is the second most common risk factor for erectile dysfunction, which in turn develops in 50–75 % of diabetics. The prevalence of ED is three times higher in diabetic men (28 % vs. 9.6 %), occurs at an earlier age, and increases with disease duration, being approximately 15 % at age 30 rising to 55 % at 60 years [35]. Diabetes mellitus may cause ED through a number of pathophysiological changes affecting psychological function, central nervous system (CNS) function, androgen secretion, peripheral nerve activity, endothelial cell function, and smooth muscle contractility [36].

In diabetic patients, insulin is thought to enhance nitric oxide synthase (NOS) activity by increasing transport of L-arginine into the cell and furnishing greater quantities of the essential cofactor NADPH. These effects are reversed in the insulin lack or insulin resistance of diabetes. Plasmatic concentration and vascular content of L-arginine are reduced in diabetic rats [37]. Arginase is an enzyme that competes with NOS for the 30 substrate, L-arginine. The inducible form of the enzyme, arginase II, is overexpressed in corpus cavernosum from diabetic patients, where inhibition of arginase restores NOS activity. Intracellular availability of L-arginine in diabetic cavernosal tissue could be reduced not only by transport impairment but also by excessive metabolization through arginase pathway.

The ratio of reductase cofactors NADH/NAD + is increased in diabetes. This reduces the levels of NADPH, an essential cofactor for NOS, and increases the levels of calcium-elevating second messengers such as diacylglycerol and protein kinase C (PKC) thus increasing smooth muscle contractility [38].

3.9 Chronic Renal Failure and ED

Men suffering chronic renal failure (CRF) requiring renal replacement therapy have a high prevalence of sexual dysfunction (20–50 %) [39]. Many of the pathophysiological effects of persistent uremia can potentially contribute to the development of ED including disturbance of the hypothalamic-pituitary-testis sex hormonal axis, hyperprolactinemia, accelerated atheromatous disease, and psychological factors [40].

Uremia results in a decrease in bioavailable NO in erythrocytes. Sarioglu and coworkers demonstrated that a chronic uremic state resulted in impaired nerve and endothelial-mediated relaxation of rabbit cavernosal smooth muscle while relaxation induced by NO donors or purinergic activation was preserved [41].

Cavernosal vascular function in men undergoing renal replacement therapy showed that 80 % had both arterial insufficiency and veno-occlusive dysfunction. A link with possible impairment of the NO/cGMP pathway relating to failure of cavernosal relaxation is provided by the finding of increased serum levels of endogenous inhibitors of NO synthesis in uremic patients [42].

3.10 Drug-Induced Erectile Dysfunction

Treatment using higher doses of a thiazide showed a significant increase in ED compared to placebo [43]. Addition of a thiazide to existing treatment with propanolol or methyldopa also increased the prevalence of ED, while this effect did not occur when the thiazide was combined with an ACE inhibitor [44]. Data from a large UK trial showed that twice as many men taking thiazides for treatment of mild hypertension reported ED compared to those treated with propanolol or placebo, this being the commonest reason for withdrawal from the bendrofluazide arm of the study [45]. In the Treatment of Mild Hypertension Study (TOMHS), the prevalence of ED at 2 years in men taking low-dose thiazide was twice that of both the placebo group and those on alternative agents [46].

Psychotropic drugs are among the most common drug classes involved in the development of erectile dysfunction. In a first place, antidepressants are the most common psychotropic drugs associated with significant rates of erectile dysfunction, including the selective serotonin reuptake inhibitors and venlafaxine. Antipsychotics such as risperidone and olanzapine have the highest likelihood of all psychotropic drugs of causing erectile dysfunction [47].

In conclusion, several mechanisms related with ED are well done, described, and known. Despite the fact that some conditions joined with ED increase risk for cardiovascular disease, we need some more evidence to have clear picture on how to bring a gap between potential in distinctions in pathophysiology of ED.

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